

# Screening of Newborns for Congenital Hypothyroidism

Guidance for Developing Programmes



**IAEA**

International Atomic Energy Agency

SCREENING OF NEWBORNS  
FOR CONGENITAL HYPOTHYROIDISM

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# SCREENING OF NEWBORNS FOR CONGENITAL HYPOTHYROIDISM

GUIDANCE FOR DEVELOPING PROGRAMMES

INTERNATIONAL ATOMIC ENERGY AGENCY  
VIENNA, 2005

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## FOREWORD

Congenital hypothyroidism is a condition that, if left untreated, can cause lifelong human suffering as a result of severe mental retardation and deficiency of growth. With the involvement of the IAEA, screening programmes to detect congenital hypothyroidism in newborn infants have been introduced successfully in a large number of countries. The cornerstone of these programmes is accurate and reliable screening methods involving isotope techniques and simple medical treatment.

The suffering — and heavy social and economic burden — caused by congenital hypothyroidism prompted many countries to institute a formalized screening programme directed at newborns, just as a vaccination programme has become an integral part of child health care. In many other countries however, this type of formalized service has not yet been established. For these countries, the implementation of a neonatal screening programme will bring about a considerable improvement in child health care. It is hoped that the guidance in this publication will be especially useful to the signatories of the United Nations Convention on the Rights of the Child.

Several factors that prevail in a country — the climate, political environment, economic development, level of health care and the transportation system — have an influence on the overall operational systems, design and implementation of a screening programme. As such, the design of such a programme will differ greatly from country to country. Nevertheless, neonatal screening programmes have many elements in common. This book draws on the IAEA's experience in this area over more than a decade, and on the results of a regional technical cooperation programme on neonatal screening for congenital hypothyroidism in East Asia (IAEA Project RAS6032). This publication provides guidance aimed specifically at implementing and sustaining programmes for the screening of newborn infants.

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## PREFACE

Congenital hypothyroidism (CH) is a treatable deficiency of the thyroid hormone that causes severe mental retardation and growth deficiency if it is not detected and treated early. Undetected at or near birth, CH clinically manifests itself too late for treatment to completely eliminate the mental and growth retardation that result. In many newborns, CH may be diagnosed late or go completely undiagnosed, resulting in unnecessary health, economic, and social burdens for the family. Treatment is simple, inexpensive, and effective. With early detection and treatment, infants usually develop normally without mental handicaps and become productive members of society.

Interest in the screening of newborns by the IAEA stems from the following: (1) CH can be detected through tests that use radioisotopes; (2) the condition is of relatively high prevalence, particularly in developing countries where iodine deficiency exists; and (3) testing and treatments are simple, inexpensive, and effective. Worldwide, the incidence of CH is 1 in every 3000 births. In iodine deficient areas, the incidence has been reported to be as high as 1 in 600 births.

Because of the success of the screening of newborn infants in eliminating the effects of CH in screened populations, the IAEA began assisting developing States in establishing neonatal screening programmes early in the 1990s. Since that time, a number of developing neonatal screening programmes have received IAEA support and many Member States have been able to establish neonatal screening programmes, some of which are rapidly becoming self-sufficient. Once established, the screening of newborns offers the opportunity to use the same infrastructure and specimens already collected to detect and treat other severely debilitating conditions. Using radiochemical testing, congenital adrenal hyperplasia (CAH) and cystic fibrosis can be detected, and up to 40 different disorders can be detected with other techniques that are available for screening.

The screening of newborns for CH identifies newborns presymptomatically and provides the opportunity to improve the life of affected children and their families. A well-established newborn screening infrastructure provides the opportunity to expand case detection to other serious conditions, thus increasing the potential for saving lives, preventing mental retardation, preventing physical disabilities, and improving the health and well-being of society.

This publication stemmed from the IAEA Regional Programme for Neonatal Screening for Congenital Hypothyroidism in East Asia (RAS 6/032). It was prepared by experts and reviewed by project directors in the region to provide guidance for the development of screening programmes for newborns. It is primarily focused on screening for CH, but it also provides background information and practical implementation ideas to assist in establishing and sustaining a comprehensive screening system for newborns. It provides information for screening policy decisions, gives examples of experiences in developed and developing programmes, explains the intricacies of developing and sustaining a complete screening system for newborns, and provides information for assessing the quality of the system developed.

The IAEA would like to thank Schleicher and Schuell, Inc., for granting permission to use their posters and figures depicting the proper method for collecting and handling blood specimens, and also for permitting their translation for local requirements.



## **Part 1**

### **INTRODUCTION**



## 1.1. NEWBORN SCREENING

### 1.1.1. Definition

The term ‘newborn screening’ is used to describe various types of tests that are done during the first few days of a newborn’s life. Screening separates those who *might* have the disorder from those who *probably do not* have the disorder. In contrast, diagnostic testing is performed to establish the presence of a condition. Newborn screening that is properly timed and performed has the potential for preventing catastrophic health outcomes, including death [1]. The conditions under which screening is conducted vary. They are usually influenced by factors such as prevalence (population characteristics), testing and treatment availability, outcome, geography, economics (including cost and cost effectiveness), transfer of science and technology, and politics. In general, the barriers to newborn screening are the same whether the programme is in a developing nation or a more developed one, and they include:

- (1) **Education** (awareness and understanding of health practitioners, politicians and the public);
- (2) **Finances** (funding for education, testing, diagnosis and treatment);
- (3) **Logistics** (delivery of testing, follow-up and treatment services);
- (4) **Politics** (decisions concerning degree of government involvement including programme purpose, system organization, financing and personal privacy);
- (5) **Culture** (sensitivity to ethno-cultural issues concerning both medical care and parenting).

*Newborn screening refers to tests given within the first few days after birth for certain conditions that cause severe health problems if they are left undetected.*

*Barriers to successful implementation of screening are the same whether the programme is in a developing nation or in a more developed one.*

The specimen that is used in the screening of newborns is usually blood taken from a heel stick or heel skin puncture, although certain programmes that limit their screening to specific disorders that are not affected by maternal contamination may sometimes use cord blood that has been taken from the umbilical (see Appendix I for a discussion on various types of newborn screening specimens). In either case, the specimen obtained can be absorbed onto a specially manufactured filter paper collection device, thereby facilitating its transport to a distant laboratory.<sup>1</sup> Blood placed onto the paper is air dried and transported to a testing laboratory soon after collection either by mail or courier. In this way, it has been possible to efficiently and effectively centralize testing services. Centralization takes advantage of economies of scale and more accurate case recognition: as the number of analyses increases, so does

---

<sup>1</sup> In the USA, this “filter paper collection device” is actually an approved medical device regulated by the Food and Drug Administration.



the actual number of cases recognized. Advanced newborn screening programmes now include screening for up to 40 health disorders using state of the art technologies such as tandem mass spectrometry (MS/MS) and second tier testing with DNA. Utilization of costly testing equipment has been facilitated by the ability to easily transfer analytical specimens via the filter paper card procedures developed by Dr. Robert Guthrie (see below), thus encouraging the use of regional laboratories for cost containment and improved testing quality.

In some cases, the term ‘newborn screening’ may also refer to a more comprehensive testing for newborns which includes testing for congenital hearing loss in addition to biochemical testing.

### **1.1.2. Background and programme development**

*Dr. Robert Guthrie (1916–1995) is considered the ‘father’ of newborn screening. He pioneered the use of filter paper for collecting blood specimens and developed an inexpensive newborn screening test for PKU in the early 1960s.*

Newborn screening began in the 1960s with the work of Dr. Robert Guthrie, a researcher in the USA. Guthrie developed a bacterial inhibition assay (BIA) for phenylalanine in order to detect phenylketonuria (PKU), an inborn error of metabolism leading to severe mental retardation [2]. The test could be performed on a 5 mm diameter sample of dried blood punched from a filter paper collection card. Blood was easily collected on the card by pressing (‘sticking’) the pricked heel of a newborn against a filter paper for collecting blood and allowing blood drops to be absorbed. Once dried, the card was easily transported to the testing laboratory. Within a few short years, laboratory techniques for detecting other biochemical markers of debilitating conditions from small amounts of blood or serum extracted from filter paper punches as small as 3 mm (~1.5 µL of serum is extracted from a 3 mm whole blood punch) were of sufficient sensitivity and specificity to allow expansion of the screening process to conditions such as CH, CAH sickle cell diseases, and others.

Since most inherited health disorders depend on population frequencies, expanding screening often provides an opportunity to improve cost effectiveness. In the early days of screening in the USA, Europe, Australia and New Zealand, PKU was the primary screened health disorders and exhibited an incidence of 1:15 000 in Caucasians. Adding simultaneous screening for CH improved cost effectiveness since the incidence of CH was almost fivefold higher (about 1:3500). Thus, during the 1980s, most newborn screening programmes expanded to include screening for CH (usually in developed countries). Newborn screening for CH also became a priority in countries without large Caucasian populations, such as in Asia. Since the incidence of CH is markedly increased in areas where the soil and food are poor in iodine, newborn screening for CH also began to emerge in developing countries, where iodine deficiency was a recognized problem.

Guthrie’s idea of providing a transport mechanism (special uniformly manufactured filter paper) for specimens to be sent to a remote testing facility provided a simple mechanism for stabilizing and

transporting specimens. This technique sufficiently simplified sample collection and transport to the point that mass population screening of newborns became feasible. Low priced, high quality testing is a necessity for successful screening. Large number of specimens are necessary in order to acquire the testing experience necessary to properly identify abnormal testing results for these relatively rare conditions. Established newborn screening programmes have found that centralized laboratory testing on large numbers of specimens provides the highest and most cost effective quality of testing, least analytical variability, and greatest ease of data handling and evaluation. It is generally agreed that to be most effective, newborn screening laboratories should test at least 30 000 specimens annually [3]. Screening programmes that are in the initial stages of operation, by necessity, begin by testing low number of specimens. When the centralized testing volume becomes so large that quality and service are diminished, then decentralization into regional laboratories (at least 30 000 specimens per year) is usually the most effective testing strategy. Multiple small volume laboratories (if they are allowed to be established) have consistently been found to hinder screening implementation by fragmenting testing services and generally providing lower quality testing results and higher costs.

In order to provide the timely testing needed to confirm the diagnoses and begin treatment within a time frame that maximizes positive health outcomes, the screening system must be highly organized and prepared to meet the needs of affected newborns and their families. Screening identifies newborns at increased risk and should not be equated to diagnosis. Clear protocols to facilitate diagnosis and treatment should exist and a defined system of follow-up and continuation of treatment must be included. Screening programmes should be designed so that the necessary screening tests can be performed within 1 to 3 working days of sample receipt and within 7 to 10 days of birth. To accomplish rapid turnaround of testing results, laboratory test results that indicate an increased risk for a disorder should be followed by telephone or personal contact with the infant's health care practitioner within hours of the availability of the result. Written reports of all screening tests (including normal results) should be returned to the submitting facility within 10 to 14 days of sample submission. Specimens that are unsatisfactory for testing should be dealt with on a priority basis, in a manner that is similar to the processing of positive testing results, since time to treatment is critical and a repeat sample must be obtained quickly if screening is to be effective.

*Screening identifies patients 'at risk' and should not be equated with diagnosis.*

### **1.1.3. Policy evolution**

With the emergence of newborn screening for inborn errors of metabolism in the 1960s, public health policies were developing

regarding which conditions to include in screening and on what basis they should be chosen. The World Health Organization (WHO) took a leadership role in organizing international discussions on this issue. The first of the international discussions on newborn screening was in 1967, when a WHO Scientific Group on Screening for Inborn Errors of Metabolism was convened to consider the technical and ethical aspects of newborn screening including “whether and how newborn screening programmes could improve the health of mankind.” The recommendations of that group of experts provide the general guidance used by most developing newborn screening programmes today (see Table 1 [4]).

TABLE 1. GENERAL RECOMMENDATIONS FOR NEWBORN SCREENING [4]

- 
- Appropriate techniques and methods should be developed for screening general populations as well as high risk groups for certain inborn errors of metabolism.
  - Automatic procedures should be developed for the analysis of samples and handling of data.
  - The long term storage of biological specimens should be studied.
  - Large scale pilot studies should be made to evaluate and compare screening methods.
  - Selected populations should be investigated to obtain data on the frequency of these disease and traits.
  - Multidisciplinary groups should be set up to study the short term and long term social and biological consequences of screening programmes.
  - In each proposed screening programme, a careful estimate should be made of the cost of the programme and of the personnel, facilities, and equipment required.
  - Central laboratories specialized in screening procedures should be created on a regional basis and those that already exist should be assisted.
  - Specialized regional centres should be set up for the study and the management of patients or, if such centres exist, they should be expanded.
  - Collaborative studies should be undertaken to evaluate the investigation and management of patients.
  - International cooperation should be enlisted for the exchange and training of personnel, the exchange of information and materials, and the comparison of methods and results.
- 

The traditional criteria used for the screening of newborns are given in Table 2 [5].

Wilson and Jungner [5] also developed criteria for test selection in population screening at about the same time and these have been generally applied to newborn screening programmes over the years. These early criteria have been reviewed and debated since they were published and have led to comments in a number of reports by other professional groups including, among others, the US National Research Council [6], the US Institute of Medicine [7], the American Academy of Pediatrics (AAP) [3, 8], the Human Genetics Society of Australasia

*Wilson and Jungner developed criteria for population screening as part of a WHO conference in 1968. These criteria continue to guide most newborn screening programmes today.*

TABLE 2. PRINCIPLES OF EARLY DISEASE DETECTION [5]

---

- The condition sought should be an important health problem.
  - Facilities for diagnosis and treatment should be available.
  - There should be a recognizable latent or early symptomatic state.
  - There should be a suitable test or examination.
  - The test or examination should be acceptable to the population.
  - The natural history of the condition, including development from latent to declared disease, should be adequately understood.
  - There should be an agreed policy on whom to treat as patients.
  - The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
- 

(HGSA) (<http://hgsa.com.au/policy/ns.html>), and the United Kingdom National Screening Committee (<http://www.doh.gov.uk/nsc/>).

The AAP has also played a leadership role in newborn screening over the years, first by endorsing the concept of newborn screening in 1965, and then by publishing a large number of policy statements and fact sheets pertaining to newborn screening disorders [9]. In order to emphasize the role of the paediatrician in the newborn screening process, goals for paediatricians were also published [10] and these have provided a model for paediatric involvement in other countries. Obstetricians also have a critical role in providing information about screening to prospective parents, and guidance on the role of the obstetrician in the newborn screening process has recently been published [11].

A recent Task Force on Newborn Screening, organized by the AAP in cooperation with several other interested governmental and non-governmental organizations (NGOs) in the USA, published guidance for future public health activities that involve newborn screening that can serve as a prototype for comparable programmes, including those in developing nations [3]. The basic assumptions upon which their report was based can serve as guidance for newborn screening programmes in general (see Table 3). In addition, the blueprint for future activities provides guidance for government activities for developing a long term plan of action (see Table 4).

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TABLE 3. BASIC ASSUMPTIONS OF THE AAP TASK FORCE ON NEWBORN SCREENING [3]

---

- Infants should benefit from and be protected by newborn screening systems.
  - Using previously defined (WHO) criteria for inclusion of a screening test, not all conditions are good candidates for newborn screening.
  - Newborn screening is a system and every newborn should receive appropriate and timely services.
  - Newborn screening is an essential public health prevention activity requiring service integration for affected newborns.
  - State public health agencies have responsibility for assessment, assurance, and policy development.
  - The newborn screening system must be clinically, socially, and ethically acceptable to the public and health professionals.
  - Every newborn should have a medical home.
  - All newborns should have access to screening according to nationally accepted criteria regardless of their location.
  - Parents have a right to information about newborn screening, the right to refuse testing, and the right to privacy protection.
  - Increased newborn screening programme coordination and uniformity will benefit families, health care professionals and public health agencies.
  - Parents and consumers must be involved in policy making and programme implementation.
- 

TABLE 4. BLUEPRINT FOR THE FUTURE — AAP TASK FORCE ON NEWBORN SCREENING [3]

---

“The Task Force believes that public health agencies (federal and state), with health professionals and consumers, should continue a process that will:

1. Better define public health responsibilities for federal and state public health agencies;
  2. Develop and disseminate model state regulations to guide implementation of state newborn screening systems (including disease and test selection criteria);
  3. Develop and evaluate innovative testing technologies;
  4. Design and apply minimum standards for newborn screening activities (e.g., sample collection, laboratory quality, sample storage, and information systems);
  5. Develop and disseminate model follow-up, diagnosis and treatment guidelines, and protocols for health professionals and other participants in the newborn screening system;
  6. Design and evaluate model systems of care with services and supports from infancy to adulthood that are consistent with national guidelines for children with special health care needs (i.e. family centered, community based, and coordinated systems of care);
  7. Design and evaluate tools and strategies to inform families and the general public more effectively;
  8. Fund demonstration projects to evaluate technology, quality assurance, and health outcomes.”
-

### 1.1.4. System for newborn screening

Newborn screening is *not* just a laboratory test. Over the past 40 years, newborn screening has evolved into a **system** that relies on smooth integration of the efforts of a number of individuals and processes. This newborn screening system is comprised of six essential components [3, 11–13], each of which will be discussed in more detail in a later section:

- (1) **Education** (health professionals, parents, the general public and politicians);
- (2) **Screening** (proper timing and specimen collection, transport, laboratory testing and reporting);
- (3) **Early follow-up** (abnormal test notification, tracking and confirmatory testing);
- (4) **Diagnosis** (clinical and biochemical evaluation);
- (5) **Management** (counselling, treatment monitoring and long term follow-up);
- (6) **Evaluation** (outcome monitoring and quality assurance throughout the system).

*System for newborn screening:*

- *Education;*
- *Screening;*
- *Early follow-up;*
- *Diagnosis;*
- *Management;*
- *Evaluation.*

It is this system that must be the focus of infrastructure development in establishing a new programme. In order to ensure the highest level of screening quality, all system components should be included in an overall quality assurance plan. In addition, all system components should have their own, specifically developed, quality indicators. The smooth integration of newborn screening system components must develop locally within individual geographical, economic and political constraints. The creation of an appropriate and functioning newborn screening system presents a challenge that requires dedication and perseverance of the organizer(s) in order to succeed. Traditionally, programme oversight is a responsibility of the public health department or the health ministry; however, coordination and cooperation with academic centres and private partners (confirmatory laboratories, medical centres, third party payers (e.g. insurance companies) and other NGOs is essential for the success of the overall system. The critical points in developing the system for newborn screening are given in the summary below and will be discussed further in the sections that follow.

### 1.1.5. Summary

The critical points in the development of an infrastructure for the screening of newborns include the following:

- **Education.**

Education of professionals, policy makers, and parents is one of the most essential components of any newborn screening programme.
- **Screening.**
  - Specimen collection should occur within the first few days of life.
  - Specimens are collected from the heel (or the umbilical cord if taken at birth).
  - Specimens should be collected on a specific and valid filter paper made for the process.
  - Key demographic data of the newborn must be correctly documented.
  - Specimen collection procedures require rigorous supervision and monitoring to avoid errors.
  - Specimens must be transported efficiently and rapidly to minimize damage to the sample.
  - The recall rate should be adjusted to keep the programme viable.
  - TSH or T4 (or a combination) may be used as the primary screening test.
- **Early follow-up.**
  - Rapid recall and complete follow-up for all newborns must occur with positive screening test results.
- **Diagnosis.**
  - Diagnostic serum tests are required on all newborns with positive screening test results.
- **Management.**
  - Immediate thyroxin replacement therapy is essential in a newborn identified with CH.
  - Close follow-up of children and good compliance with replacement therapy are crucial for normal mental development.
  - Other diagnostic tests are required to determine the cause of CH.
- **Evaluation.**
  - Monitoring, quality assurance, and periodic audits are necessary to evaluate every aspect of the newborn screening system.

1.2. CONGENITAL HYPOTHYROIDISM

1.2.1. Background

Simply put, CH is inadequate thyroid hormone production in newborn infants. Thyroxin (thyroid hormone (T4) — 3,5,3',5'-tetraiodo-L-thyronine), an iodine containing hormone which is produced and secreted by the thyroid gland, is an important regulator of metabolic rate in the body and plays a critical role in brain and bone growth in infancy and early childhood. Untreated, CH has devastating effects on growth and development of infants. The biochemical defect in CH is a deficiency in circulating T4, and can result from absence of thyroid gland (aplasia) or structural abnormalities of the gland (dysplasia and hypoplasia), abnormal location of the gland (ectopic gland), or inability to synthesize thyroxin because of an inborn error of the metabolism of the thyroid gland (dyshormonogenesis). Percentages of specific aetiologies vary from country to country. The following ranges of aetiologies have been reported: ectopic thyroid, 35–42%; thyroid agenesis, 22–42%; and gland in place defects, 24–36%. Although a few cases of thyroid dysgenesis have been described resulting from gene mutations, there is no common link to explain the aetiological background in the majority of cases [14]. Table 5 gives a summary of the various causes of neonatal hypothyroid dysfunction with approximate birth prevalence.

*Congenital hypothyroidism is a deficiency of the circulating thyroid hormone at birth. It causes mental and growth retardation. Early clinical detection may be difficult since symptoms often do not exist.*

TABLE 5. CAUSES AND BIRTH PREVALENCE OF NEONATAL THYROID DYSFUNCTION [15–17]

Disorder	Prevalence
<b>Permanent disorders</b>	
(1) Thyroid dysgenesis (agenesis, hypoplasia, ectopia)	1:4500
(2) Thyroid dyshormonogenesis	1:30 000
(3) Hypothalamic–pituitary hypothyroidism	1:100 000
(4) Generalized resistance to thyroid hormone	Very rare
<b>Transient disorders</b>	
(1) Transient hypothyroxinemia (mainly premature infants)	1:200
(2) Transient primary hypothyroidism (common in areas of iodine deficiency)	Variable
(3) Transient hyperthyrotropinemia (predominantly in Japanese populations)	Very rare



Congenital hydrothyroidism has long been recognized as a cause of mental retardation. Endemic cretinism was the early term used to describe clusters of infants with goitre and cretinism within a defined geographical area. Hypothyroidism secondary to iodine deficiency was eventually found to be the cause of endemic cretinism. In the 1930s, it was found that goitre and cretinism could be prevented by an adequate dietary intake of iodine, and iodination of salt became a standard way of providing dietary iodine. Thus, the iodination of salt was established. Despite tremendous international efforts, iodine deficiency still exists in some parts of the world, including parts of developing East Asia.

Thyroid hormones are catalysts in oxidative reductions and their biosynthesis involves the active accumulation of inorganic iodine in the thyroid gland. The oxidized iodine is bound to tyrosine residues of thyroglobulin, the major protein of the thyroid gland, and thyroxine likely develops when two di-iodinated tyrosine residues link [18]. Thyroxine is stored in the thyroglobulin molecule until proteolytically released and secreted into circulation by exocytosis. It is essential that thyroid hormone deficiencies are detected early and that replacement therapy is started as soon as possible in the newborn's life. If CH goes undetected and untreated during this critical growth period, it progresses to lethargy, poor feeding, constipation, prolonged jaundice, hypothermia, growth retardation, and neurological damage [19, 20]. Because newborns with undiagnosed CH are generally passive, they are often thought to be 'good babies' and this contributes to their delayed diagnosis. The net result is irreversible brain damage. Children with untreated CH have been shown to have a median IQ of approximately 80, with 40% below 70 [20].

Prior to the introduction of systematic screening of newborns to detect congenital diseases, diagnosis of CH was based on clinical findings. This led to delays in treatment, which could only be initiated when the infants were three to six months of age or older [21, 22]. The clinical signs of CH are not usually sufficient to allow for easy detection in affected newborns. For example, in a study of one week old infants [23], few of the discriminating characteristics of CH (decreased linear growth and delayed skeletal maturation for gestational age, jaundice, enlarged tongue, abdominal distention, umbilical hernia, mottled skin, enlarged fontanelle, and muscle hypotonia) were noted. These signs, when present, were generally non-specific and some infants had none of these disease characteristics.

*The goal of newborn screening for CH is to begin treatment by one month of age.*

The goal of newborn screening is to detect CH and begin treatment before the infant reaches one month of age. Studies show that by detecting CH at birth or shortly thereafter, and by beginning thyroid replacement therapy with L-thyroxine (usually as the sodium salt) within the first few weeks of life, hypothyroid infants can be expected to grow and develop normally with only minor problems [24–26] except for

babies who are severely hypothyroid at birth whose mothers also have hypothyroidism. Major improvements in mental development have been shown to result from early diagnosis and appropriate treatment of newborns with CH [27], and arguably may completely overcome the negative effects of the hypothyroidism. Developmental delays have been shown in children that were not adequately treated during the first years of life [28]. The intelligence scores of children who have been detected with CH through newborn screening and have been appropriately treated will typically be within limits, although slightly lower compared with that of normal children [27]. Only occasionally have some children shown developmental delays in later childhood, and a small percentage have shown persisting impairments in the language, neuromotor [27, 29, 30], and perceptomotor areas [31]. Such difficulties appear to be more evident in children with thyroid aplasia or severe hypothyroidism at the time of diagnosis [27].

### **1.2.2. Prevalence of congenital hypothyroidism**

#### *1.2.2.1. Around the world*

The prevalence of CH around the world, varies across different population groups. Likewise, the predominant disease aetiology also varies. As newborn screening programmes have proliferated, CH prevalence has slowly increased with better methods of case detection and increased disease awareness in screened populations. Globally, the prevalence of CH approaches 1:3000, with substantially higher prevalence in iodine deficient areas, sometimes in excess of 1:900. Table 6 [32–46] summarizes world data from studies of screened populations in which at least 15 cases have been detected.

Racial and ethnic differences in the prevalence of CH vary across populations. For example, the prevalence among Japanese is approximately 1:7600, while in Israel it is about three times higher (Table 6). Variations in prevalence have also been reported within various populations. In the USA, for example, African-Americans appear to have a CH prevalence about half that of Caucasians, while Hispanics have a rate about 40% higher and Native Americans may have an even higher rate (see Table 7). Studies in the UK [47] and South Africa [42] found that CH appears to be several times more prevalent in children of Asian (including Indian) ancestry; however, a recent study in India indicates a prevalence of approximately 1:2630 among people there. Studies have also found a higher prevalence (approximately 2:1) of CH among females. Recent research has shown that much of this discrepancy may be attributed to differences in thyroid ectopy and are gender related.

*Around the world, the incidence of CH is about 1:3000, but this number is significantly higher in iodine deficient areas. Incidences vary in different population groups.*

TABLE 6. PREVALENCE AT BIRTH OF CH IN SELECTED POPULATIONS

Country	Study period	Screened	Cases	Prevalence	References
Australia	1977–1985	1 812 683	436	1:4151	[32]
Austria	1985–1988	346 185	63	1:5495	[33]
Belgium	1985–1988	360 264	109	1:3305	[33]
Canada	1973–1983	874 000	209	1:4182	[34]
Czechoslovakia	1982–1984	773 593	136	1:5688	[33]
Denmark	1981–1982	224 189	76	1:2950	[33]
Finland	1985–1988	246 189	58	1:4254	[33]
France	1985–1988	3 216 596	750	1:4289	[33]
Germany	1985–1988	1 148 415	279	1:4116	[33]
Greece	1985–1988	412 714	135	1:3057	[33]
Hong Kong	1984–1995	451 391	145	1:3113	[35]
Hungary	1985–1988	306 265	56	1:5469	[36]
Israel	1985–1988	393 304	1647	1:2473	[33]
Israel (West Bank)	1990–1994	49 694	24	1:2070	[37]
Italy	1977–1991	5 018 241	1151	1:3047	[33, 38]
Japan	1979–1985	8 846 297	1151	1:7686	[39]
Korea, Rep. of	1991–1992	147 098	34	1:4326	[40]
Kuwait	1981–1987	86 910	25	1:7686	[41]
New Zealand	Up to 1983	228 783	47	1:3475	[42]
Norway	1985–1988	215 124	68	1:4868	[33]
Oman	1991–1995	36 000	16	1:2200	[43]
Portugal	1985–1988	431 536	98	1:4403	[33]
Saudi Arabia	1985–1991	44 033	21	1:2097	[44]
Singapore	1981–1999	>500 000	–	1:3000	[45]
Spain	1985–1988	1 400 279	433	1:3234	[33]
Sweden	1985–1988	413 616	131	1:3157	[33]
Switzerland	1985–1988	314 599	85	1:3701	[33]
Netherlands	1985–1988	1 601 603	481	1:3330	[33, 46]
United Kingdom	1985–1988	2 784 603	840	1:3315	[33]
USA	1991–2000	40 214 946	13 213	1:3044	[1]

### 1.2.2.2. East Asia

In East Asia, screening for CH has been progressively expanding. The IAEA has been actively involved in regional development of CH screening since 1999, when it launched its regional technical cooperation project, RAS 6/032, “Regional Screening Network for Neonatal Hypothyroidism”. The prevalence of CH in East Asia reportedly varies from 1:1000 to 1:7336 births (Table 8 [48–54]). However, reports limited to iodine deficient areas indicate incidences as high as 1:600. Thus, the reported number of babies born yearly with CH in the region is approximately 40 000, and this presents a significant public health problem.

*Approximately 40 000 babies are born each year with CH in the developing nations of East Asia.*

TABLE 7. PREVALENCE AT BIRTH OF CH ACCORDING TO RACIAL/ETHNIC GROUP IN CERTAIN STATES OF THE USA

Racial/ethnic group	Screened	Cases	Prevalence	Reference
<b>California</b>				
Caucasian	1 497 971	359	1:4172	[48]
African-American	249 415	23	1:10 844	
Hispanic	1 042 518	367	1:2841	
<b>Georgia</b>				
Caucasian	337 746	93	1:3632	[49]
African-American	196 873	22	1:8949	
<b>Texas</b>				
Caucasian	668 736	198	1:3377	[1]
African-American	171 069	25	1:6843	
Hispanic	398 604	161	1:2476	
<b>New Mexico</b>				
Hispanic	66 610	28	1:2379	[1]
Native American	21 010	18	1:1167	

### 1.2.3. Detection of congenital hypothyroidism

As noted previously, CH is caused by an inadequate level of the T4 hormone in circulation in the metabolism of newborn infants. The hypothalamus produces the thyrotropin-releasing hormone (TRH), which causes the release of thyrotropin (thyroid stimulating hormone (TSH)) from the pituitary gland. In turn, TSH stimulates the thyroid

*CH can be detected by screening for TSH, T4, or free T4. Using combinations of the tests can lower the recall rate.*

TABLE 8. PREVALENCE AT BIRTH OF CH AS RECORDED IN IAEA PROJECTS IN EAST ASIA

Country	Study period	Screened	Cases	Prevalence	Reference
Bangladesh	2000–2002	12 341	6	1:2042	[50]
China (Tianjin)	1982–2001	543 192	84	1:6467	[51]
Indonesia (Bandung)	2000–2002	15 824	6	1:3469	[50]
Indonesia (Jakarta)	2000–2002	13 200	1	(Overall)	[50]
Korea, Rep. of	1991–1999	1 431 791	330	1:4339	[52]
Malaysia	2000–2002	319 807	36	1:3029	[50]
Mongolia	2000–2002	3785	3	1:3057	[50]
Pakistan	2000–2002	2500	3	1:1000	[50]
Philippines	1996–2003	272 547	83	1:3284	[53]
Thailand	1996–2001	1 425 025	430	1:3314	[54]
Vietnam	2000–2002	9 451	4	1:2500	[50]

gland to produce T<sub>4</sub>, which is converted to the active form of triiodothyronine (T<sub>3</sub>). Feedback to the hypothalamus and pituitary gland regulates the synthesis of the TSH and consequently, the production of T<sub>4</sub> [55]. The foetal T<sub>4</sub> pool includes a maternal contribution from the mother since T<sub>4</sub> crosses the placenta [56] and there is also a significant TSH concentration surge during the first few hours after birth [57]. When T<sub>4</sub> is decreased, TSH secretion increases through stimulation from TRH. Proteins in serum effectively bind circulating T<sub>4</sub> such that only about 1% exists in the ‘free’ form. The free T<sub>4</sub> (FT<sub>4</sub>) reflects the bioavailability of T<sub>4</sub> and determines the metabolic status of the infant. ‘Total T<sub>4</sub>’ is the sum of the bound and free fractions. Currently, a newborn screening FT<sub>4</sub> kit of sufficient sensitivity and specificity for newborn screening is not widely available, although such a kit is reportedly in use in the Republic of Korea. Consequently, screening programmes are left to choose between using total T<sub>4</sub>, TSH, or a combination of the two for their screening methodology.

The question of whether to use TSH or T<sub>4</sub> as the initial screening test has raged for years, ever since screening to detect CH in newborns began. While a decrease in T<sub>4</sub> concentration is the earliest available laboratory manifestation of CH, both TSH and T<sub>4</sub> testing have proved to be effective screening methods for detecting CH in newborns [58]. The screening tests commercially available for TSH were initially (in the 1970s) more expensive and less sensitive than T<sub>4</sub> tests, requiring larger blood specimens (i.e. multiple 3 mm punches). Today, both TSH and T<sub>4</sub> kits cost approximately the same and the sensitivities and

specificities are similar. Example testing protocols using both TSH and T4 as initial tests are shown in Appendix I and a more complete discussion of the testing methodologies can be found in the subsection on laboratory testing in Section 2.2.2. These protocols are only shown as examples and the actual testing values should be adjusted to fit the local programme on the basis of testing experiences. Different testing methods will produce different cutoff levels. In any case, a similar testing protocol should be outlined so that the methods used are clear to all persons who are involved in conducting the screening.

Proponents of initial screening with TSH point to less analytical variation and fewer false positive results than are found with initial T4 screening [59]. However, most published reports on TSH testing have relied on testing performed after day 3 of life (the usual protocol in Europe and Japan) and only limited data have been published concerning the utility of TSH screening at earlier ages [46, 60]. While TSH is likely a better diagnostic test than T4, it is subject to a biological surge that occurs shortly after birth, peaks at around between 6 and 12 hours, and diminishes over the next 24–48 hours [57]. The effect of this surge must be considered when choosing the analytical testing procedure. The range of expected TSH results for newborns screened early (within the first 24 hours after birth) is not easily determined because of the biological variability in the timing and level of the surge. The lack of a definite range of expected values within the surge period creates a higher likelihood of false positive screening results when TSH is the initial screening analyte. For this reason, initial T4 screening is often considered as an alternative procedure in screening populations where blood specimens must, of necessity, be collected early (less than 24 hours of age) in a high number of newborns. In such cases, TSH is often used as a second level test to reduce the numbers of patient results requiring follow-up testing. Proponents of initial T4 testing also argue that initial screening with T4 allows for detection of secondary hypothyroidism, which is not possible with initial screening for TSH since the TSH levels in secondary hypothyroidism are not usually elevated.

*TSH screening is more specific and is best performed on specimens collected after 24 hours of age.*

*T4 screening is less affected by age at the time of specimen collection and can detect secondary CH.*

#### 1.2.4. Summary

The critical points in the identification of CH, and its prevalence, are as follows:

- CH is due to a deficiency in circulating thyroxin.
- Untreated CH is a cause of severe mental retardation.
- Early detection and treatment that starts within the first month of life can prevent mental retardation due to CH.
- World data have shown that the birth prevalence of CH is approximately 1:3000.

- The birth prevalence of CH may be higher in East Asian countries (as high as 1:600) when compared with Europe or the USA, (given that the birth prevalence of CH is higher in iodine deficient areas, many of which are in East Asia).

## **Part 2**

# **BASIC ASPECTS IN THE SCREENING OF NEWBORNS WITH EMPHASIS ON THE DETECTION OF HYPOTHYROIDISM**





## 2.1. DEVELOPMENT OF INFRASTRUCTURE FOR THE SCREENING OF NEWBORNS

An essential aspect of developing a programme for the screening of newborns is planning and establishing an infrastructure that can implement and sustain the screening system with its six components (education, screening, early follow-up, diagnosis, management and evaluation). A highly motivated newborn screening team can facilitate this process. The first step in developing the infrastructure is to understand what is necessary to make newborn screening work and then to define the responsibilities for each component. Throughout the planning process it is important to consider the availability and cost of technology that will be used as part of the testing and follow-up process. Quality indicators should also be considered for each operation and should be developed into a quality assurance plan that covers the entire system. One mechanism for understanding and developing the system is to diagram the flow of the screening process. A typical flow diagram for newborn screening is presented in Fig. 1.

In this diagram, the first steps shown are demographic data entry and specimen collection. However, before these steps can effectively be taken, it is necessary to provide an education programme to help the specimen collector, the parents, and the health care providers understand the purpose for and expectations behind newborn screening. Similarly, the responsibilities and operations for each component of the

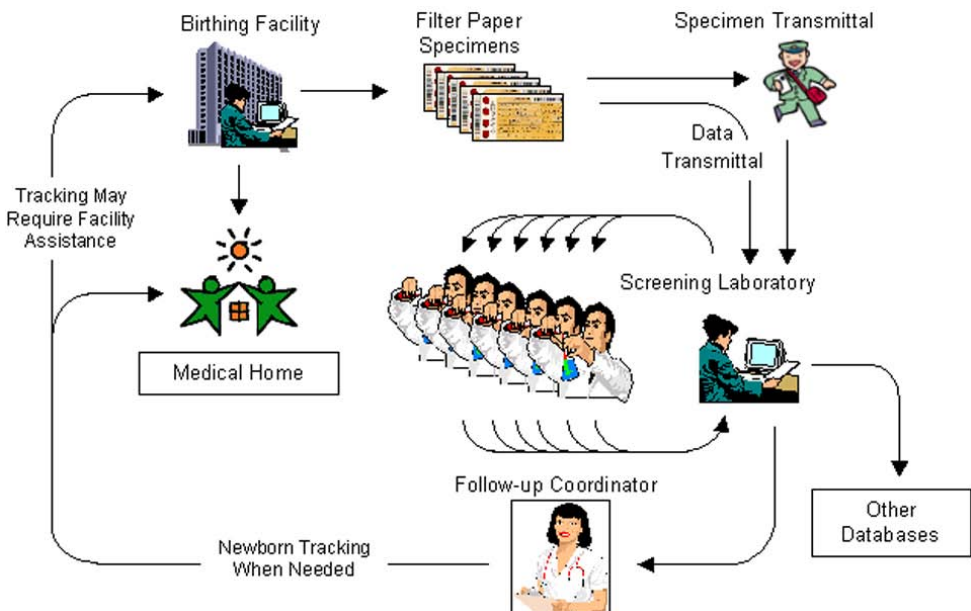


FIG. 1. Flow diagram for a typical system for the screening of newborns.

system must be fully defined and understood, including the roles and responsibilities of the personnel involved; this also requires education and training. In this sense, this simplistic diagram showing the mechanics of a system for the screening of newborns provides a basis for more detailed development.

## 2.2. COMPONENTS OF THE SYSTEM FOR THE SCREENING OF NEWBORNS

The components of the screening system have been previously described. They are: education, screening, early follow-up (and outreach), diagnosis, management and evaluation (and assurance). This section provides a more in-depth discussion of each of these components.

### 2.2.1. Component 1 — Education

*Education on  
newborn screening  
must be provided to:*

- *Parents,*
- *Professionals,*
- *Policy makers.*

Education is perhaps the most essential component in the initial stages of the development of a newborn screening programme. Not only must health professionals be educated in the benefits and operation of newborn screening as a preventive public health programme, they must also understand their roles in it. Parents and the public at large must also understand the preventive health measures which are encompassed in the newborn screening activities.

#### 2.2.1.1. Professional education

From the outset, for a screening system to succeed, professional health practitioners must be involved in its development. Even though the successful implementation of the newborn screening programme will most likely depend on the efforts of a few individuals interested in infant health, family and societal benefits, health professionals will be responsible for the implementation of the programme and ultimately for successful outcomes as a result of early diagnosis and treatment. Efforts must be made to gather pertinent educational materials (professional literature, video and/or audio tapes, newspaper articles) to share with physicians, nurses, midwives, and other health professionals so that they will understand the programme and lend their support.

Many articles have been published about the benefits of newborn screening since the 1960s. Articles that can be most persuasive in the local environment should be collected in the form of an information sourcebook for sharing, as needs arise. Sometimes sourcebook information can be useful in the form of newspaper articles, at other times it may be important to have professional articles available. In either case, the idea is to have information available in an easily

accessible format along the lines of a notebook or binder with articles encased in transparent sheeting.

Participation in seminars and local, regional, and national professional society activities also provides excellent venues for professional education. Use of outside experts can often provide the additional information and interest needed to gather the local professional support needed to sustain programme activities. Care should be taken to involve specialists whenever possible, since screening will ultimately lead to the need for specialty clinical services (e.g. paediatric endocrine expertise). As the programme progresses, consideration should be given to developing a manual in support of newborn screening activities that is directed at health care professionals. This manual should provide a clear picture of the role of the professional in the system, with flow diagrams about system functions and individual responsibilities, and answers to questions about the programme. Many examples of such programme manuals exist and can be found on the Internet (linkages to many newborn screening programmes and materials can be found through the US National Newborn Screening and Genetics Resource Center (NNSGRC) web site: <http://genes-r-us.uthscsa.edu>).

In order to ensure adequate and appropriate blood specimens for laboratory testing, educational materials must be distributed on collection techniques and the responsibilities of the person who submits specimens. A detailed standard on blood collection techniques on filter paper has been published in the USA (NCCLS LA4-A4) along with an educational videotape, and this may be appropriate to use in English speaking settings. Otherwise it can serve as a model on which to base a local standard. Creation of an instruction sheet for specimen collection should be a consideration of any newly starting programme. Training workshops to discuss responsibilities and demonstrate proper specimen collection techniques will likely be needed before the programme begins, and periodic continuing education will be needed to meet the needs in relation to personnel turnover at the various collection centres and hospitals. One of the items often overlooked in calculating programme costs is the need for ongoing professional education to ensure proper specimen collection. Examples of educational posters on specimen collection are provided in Appendix IV. Many programmes have used these posters for distribution to collection facilities who in turn have posted them in critical locations within the facility (e.g. nursery and laboratory walls).

*Information manuals can provide physicians with pertinent information about their screening responsibilities.*

*A national standard for blood collection with the aid of filter paper exists in the USA and can serve as a model.*

## 2.2.1.2. Parent education

Parent information must be brief, informative and in simple language. Any pictures should be relevant. Pre-natal education is preferable.

In order to assist parents in understanding the importance and need for newborn screening, ongoing education is necessary. One of the easiest ways of providing basic education to parents is through a simple programme brochure or programme information sheet. Pamphlets which explain the newborn screening programme, its requirements and its importance, should be developed. Such pamphlets are best distributed to expectant mothers through gynecologists, midwives, in public health maternity clinics and through pre-natal training classes, if available. They should also be available at hospitals as part of any general information on newborns given to the mother.

Programmes have also found it useful to have pamphlets available to explain individual disorders for patients diagnosed with specific conditions such as CH. In most cases, information pamphlets are best developed in cooperation with specialists and are distributed to parents through their physician during the diagnosis process. It is not necessary to reinvent these pamphlets since many programmes have already prepared them and are willing to share them. Some are available through newborn screening web sites and may be easily accessed through the NNSGRC web site: <http://genes-r-us.uthscsa.edu>. Care should be taken that any pamphlets developed should take into account



FIG. 2. Sharing information on the screening of newborns with mothers as part of post-natal care education.

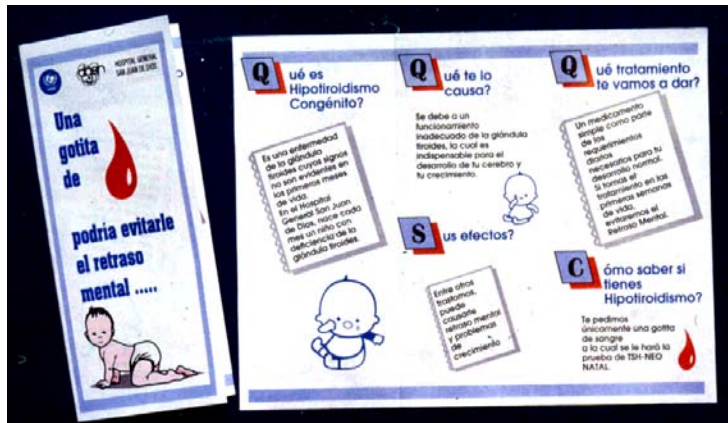


FIG. 3. An example of simple information about screening for CH.

the existence of a low literacy rate (less than 4th grade) among readers, and they should be culturally and medically appropriate. Information provided should seek to dispel the concept of 'fault' that might exist when inherited conditions are the topic under consideration.

### 2.2.1.3. Education of policy makers

One of the biggest challenges facing newborn screening programmes is adequate and appropriate education of policy makers. It will usually fall to the programme manager to make a special effort to involve and educate any policy makers who might be important to self-sustainability of the programme. Outside experts can provide assistance in this area by personal visits and letter writing. It is essential that the programme take a proactive role in addressing policy maker education. Since most policy makers are totally unfamiliar with the consequences of the untreated or delayed treatment of disorders in newborn screening programmes, it is often helpful to provide graphic illustrations of the catastrophic consequences of undetected and untreated disorders. Often the tendency is to provide pictures of healthy newborns as evidence of the worthwhile nature of the programme, but it is sometimes more effective to show pictures of the tragic results of not having an effective newborn screening programme in place. Parents can also provide important programme advocacy when educating policy makers.

*Policy makers are important to sustain programmes and must be educated about prevention and benefits to family and society.*

It is important to document programme successes and to cultivate parent advocates for convincing policy makers of the importance of the screening programme. It is also essential that the concept of a newborn screening system be conveyed, since there is sometimes misunderstanding among policy makers who tend to perceive newborn screening as simply a laboratory test. Sometimes this results in inadequate attention to the need for a comprehensive newborn screening system that serves the screening population with effective education and follow-up, and appropriate medical service delivery.

Cost and financing will invariably be a concern of policy makers and it will be important to have considered programme costs and developed comparisons with other programmes that may already be in place. As pilot data are developed, it will be essential to keep records of the numbers of newborns confirmed with CH and thus prevented from a life of mental handicap. Likewise, it will be prudent to develop costs for care of untreated CH cases so that cost-effectiveness of the programme can be discussed. These costs should include costs to the family for items such as days away from work for patient care. Policy makers should be aware of the organizational development of the programme and the steps to institutionalizing it including: developing pilot data, creating a centralized infrastructure, beginning local and/or regional projects, expanding local projects into a national network, and institutionalizing the programme at the national level, including adequate quality assurance measures.

## 2.2.2. Component 2 — Screening

### 2.2.2.1. Collection activities

*Screening includes:*

- *Collection activities;*
- *Specimen delivery;*
- *Laboratory testing;*
- *Result reporting.*

The process of screening begins well before specimens reach the laboratory. Proper timing and collection of the screening specimens are crucial. The obstetrician/midwife should provide information and advice about testing prior to delivery, but if this has not been possible, it will be necessary to give some basic information about testing at the hospital after delivery. It is important to allow parents the opportunity to consent to the testing and to supply them with sufficient information about the programme to allow them to make an informed decision about screening. The person who is responsible for obtaining consent must be knowledgeable about the programme.

Persons assigned to collect blood specimens (attending physicians, residents, nurses, midwives, and medical technologists) play a vital role in the screening system. They will often be the ones providing initial information, answering questions, and collecting a proper specimen for screening. If they collect an unacceptable or poor quality specimen, it places an unnecessary burden on the screening and follow-up system. Unnecessary repeat testing causes needless trauma to the infant, anxiety to the infant's parents, and delay in the detection and treatment of an affected infant. The confidence of the public, policy makers and health professionals in a programme for the screening of newborns is dependent on a fast and accurate process. Quality laboratory testing cannot be accomplished with poor quality specimens. Additionally, it is important to note that iodine can have a compromising effect on testing for CH. Care should be taken at the time of delivery not to use iodine or iodine containing antiseptic solutions if alternatives are available (or in cleaning the umbilical cord if umbilical cord blood is to be used).

With regard to specimen collection (heel stick — filter paper), while it is possible to use umbilical cord blood for newborn screening, its use for other newborn screening tests is severely limited. Blood from the umbilical cord is generally not the specimen of choice for most newborn screening programmes. The collection of blood from the umbilical cord is discussed in Appendix III.

## Timing

In order for newborn screening to be effective, a specimen must be taken within the first few days after birth and the testing and diagnosis must be completed in time to make a significant difference in health outcome. With CH, this means that the patient should begin treatment within one month after birth. Therefore, specimen collection and initial testing should occur within the first week of life. In some programmes, it has been effective to combine the responsibility for the collection of specimens for newborn screening with immunizations if a birth immunization is required. If the birth occurs outside of the hospital and an immunization is required, then collecting a newborn screening specimen at the time of immunization may provide a mechanism to more effectively reach those babies that are born outside of a hospital setting.

Practically speaking, the timing for specimen collection is highly dependent on hospital discharge policies. The best time for collection of a specimen for CH testing has been reported to be around 72 hours of age. This is the time needed for the newborn's metabolism to stabilize and adjust to its new environment. If screening involves TSH testing, then collecting a specimen after 24 hours of age is particularly important to minimize the number of false positive tests that occur due to the physiological surge in TSH during the first hours after birth. Screening 24 hours or more after birth will also minimize false negative results for some of the metabolic tests for newborn screening that are dependent on dietary challenges. If a large number of newborns are expected to be screened before 24 hours of age, then strong consideration should be given to using T4 as the primary screening test, since T4 is more stable during this time period. There is no rigid rule regarding the maximum length of time after which specimens should not be collected, but it must be remembered that a specimen collected too late will defeat the purpose of newborn screening. For this reason, it is strongly recommended that all newly born babies undergo screening by seven days of age. In some countries such as the United Kingdom, a visiting nurse collects the specimen at the time of the first home visit in the first days after birth.

## Transfers and special circumstances for collection

Infants who are transferred from one facility to another, and who had not been screened at the birthing facility, must be properly screened at the second facility. A programme policy that provides guidance in such circumstances needs to be drawn up. Generally, the person who attended the birth is responsible for ensuring that the second facility is informed of the screening status of the baby. The second facility is then responsible for screening. In either case, appropriate documentation of the screening circumstances should be kept by both facilities.

*For effective CH screening:*

- *Testing should occur within one week of birth.*
- *Diagnosis and treatment should occur within one month of birth.*

*Policies should ensure that transferred newborns also receive screening.*



Babies who are on intravenous (IV) fluids only, total parenteral nutrition (TPN), non per orem (NPO), or special diets may be screened in the usual manner; however, the feeding status of the newborn who has been tested should be transmitted to the testing laboratory. Diet will not affect CH testing results; however, metabolic tests performed from the same specimen may be affected. Newborns on TPN, for example, may have elevated phenylalanine values.

If a newborn is to receive a blood transfusion, a valid specimen may only be collected before the transfusion. If the baby cannot be screened prior to transfusion, another specimen should be collected four months after the transfusion in order to ensure that the baby's blood (and not the donor's) is tested.

Screening can be performed on premature infants, although caution must be taken in interpreting the results. It is recommended that a preliminary screen be done by seven days of age on all newborns; even if the baby is in intensive care [10]. If metabolic screening is performed on a baby in intensive care in addition to CH screening, a second screen is suggested between 24 and 36 hours after the baby has begun regular feeding. Premature infants can be expected to present with reduced thyroxin levels and elevated 17-hydroxyprogesterone levels. Antibiotics, which may have been administered to a premature infant, can affect certain galactosemia and PKU test results.

Card for collection of specimens and demographic data

FIG. 4. Special filter paper forming part of a sample data card for specimen collection.

In addition to containing an absorbent piece of special filter paper on which to collect a blood specimen, the card for specimen collection should contain a space for collecting pertinent demographic information about the patient (Fig. 4). These data should be minimal and concise, and useful for patient identification, patient location for follow-up, and programme evaluation. Since the special filter paper costs more than regular paper, it is less expensive if a small piece of the special filter paper is attached to the information portion of the form rather than printing all of the demographic information on the filter paper itself. Commercially, this is called ‘tip on’ and is done with a special gluing process.

*Cards for specimen collection are specially prepared and should be handled carefully.*

Other, less sophisticated, methods can be used, including stapling and taping, but it is important that the specimen and the

demographic information do not become separated. Many programmes use a serial number to identify both the filter paper portion and the demographic portion of the collection form, and this serial number can also be used as part of an inventory system when forms are distributed to birthing facilities. In computerized systems, this serial number can also be an important patient identifier, allowing linkages between databases, including birth certificates. The reader is referred to standard NCCLS LA4-A4 in the USA for more details on the specimen collection form and required data. Tables 9 and 10 provide guidance on the type of data that needs to be collected.

When filling in the demographic information, a ball-point pen with blue or black ink should be used for best results. The person filling

TABLE 9. COLLECTION DATA USUALLY CONSIDERED ESSENTIAL

- 
- Baby's name (or baby of (parent's name))
  - Date of birth
  - Weight at birth
  - Date of collection
  - Name of mother or father (whichever is best for identification — may vary depending on country)
  - Mother's contact address (indicate street, city, etc., to aid in getting correct information — may include phone number)
  - Name of health care provider and telephone number (optional — mobile phone)
- 

TABLE 10. COLLECTION DATA USUALLY CONSIDERED OPTIONAL

- 
- Time of birth
  - Time of collection
  - Patient identification number (e.g. medical record number)
  - Gestational age
  - Submitter's identification and address (optional: birth facility and address when birth facility is different from submitter)
  - Expiration date of device for specimen collection
  - Feeding status (e.g. breast, bottle, breast and bottle, soy, NPO, TPN)
  - Health status (normal, premature, sick, on antibiotics, transfused, other — may give combinations)
  - Parents' telephone number
- 

in the form must legibly print all entries so that the receiving personnel can read them, and the data must be accurate and complete. It is essential that the demographic data match the baby from whom the specimen was collected.

The specimen collection portion of the form should be large enough to allow the necessary blood specimen to be collected. An appropriate number of preprinted circles can assist the specimen collector in obtaining a sufficient amount of blood. If printed, these circles should be broken or dotted on one side of the filter paper (optionally, the circles can be printed on both sides of the filter paper). A dotted or dashed outline for the circle is preferred, since difficulties have been encountered with solid lines acting as a 'dam' and preventing free flow of the specimen outside of the circle when there is excess blood. For purposes of illustration, the US national standard NCCLS LA4-A4 requires a circle of a diameter of 1/2-inch (13 mm). This diameter requires approximately 75  $\mu\text{L}$  of blood to extend to the circle edges while 100  $\mu\text{L}$  of blood spreads slightly beyond the edges of the circle. The example collection device shown in Fig. 4 has been

produced by the company that manufactures most of the filter paper materials for developed programmes. It is shown here merely as an example for consideration. The area at the lower right has been reserved for newborn hearing information, which is rapidly being added to many newborn screening programmes.

### Source of blood

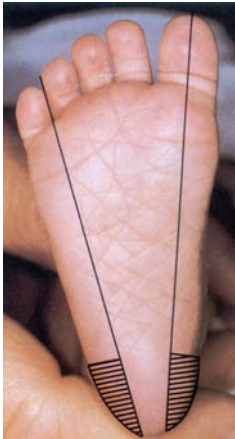


FIG. 5. Heel stick collection site — hatched areas are safe for puncture site

**Heel** — Blood collected from the heel is preferred for newborn screening and should be collected from the most medial or lateral portion of the plantar surface of the heel. ‘Medial’ is defined as closest to the mid-line of the body; ‘lateral’ is defined as away from the mid-line of the body; and ‘plantar surface’ as the walking surface of the foot (the cross-hatched area in the diagram shows the preferred collection site). Previous puncture sites or the curvature of the heel must not be used. A detailed discussion of the proper procedures for collecting blood specimens on filter paper is given in Appendix II.

**Others (see discussions in Appendices II and III)** — Umbilical cord blood, venous blood (dorsal hand vein or umbilical venous catheter specimens), and arterial blood

(umbilical arterial catheter specimens) might be appropriate for special situations.

### Errors in the collection of specimens

In addition to improperly matching accompanying information on a newborn to its specimen card, a number of other common collection errors can lead to invalid specimen collection cards (see Appendix V for picture charts). The most common problems include:

- Contamination — the blood collection portion of the card has contacted a foreign substance such as oil, ink, powder or water.
- Serum ring — usually due to excessive squeezing of the heel during collection — appears as yellow coloured ring surrounding the dried blood spot.
- Moisture (causing bacterial contamination or mould) — the specimen has not been air-dried appropriately for at least 4 hours — the blood specimen is characterized by a bright red colour instead of brown, or contains mould that is visible.

#### Collection errors:

- Contamination;
- Serum ring;
- Specimen not dry;
- Insufficient blood;
- Supersaturation;
- Torn surface;
- No specimen.

- Insufficient specimen — circles are not completely filled or saturated.
- Supersaturation — blood appears layered or of variable density on observation.
- Excessively rough or torn surface of spot — collector was not careful in using capillary tube or used the tube as a paintbrush to ‘spread’ blood within the preprinted ring.
- No specimen — does not contain any blood — usually due to collection oversight or mix-up with another specimen.
- Missing information — laboratory quality assurance requires certain data and the data are missing due to collector’s oversight.

### Pain prevention during sampling

#### *Simple interventions to reduce pain:*

- Oral glucose solutions;
- Sucrose solutions;
- Milk;
- Non-sucrose sweet solutions;
- Oral pacifiers;
- Gentle stroking and reassurance;
- Spring loaded lancing device;
- Local anaesthetic creams.

Even though many newborns will not exhibit outward symptoms of pain during the heelstick procedure, a number of studies have demonstrated that pain may be in fact be experienced [61–64]. Research has shown that even short term pain can have lasting negative effects [65], and this has led many to develop strategies to alleviate any pain that might result from diagnostic and therapeutic procedures in newborns. Treating pain in the newborn is desirable not only for ethical reasons, but because in certain circumstances, pain can lead to decreased oxygenation, haemodynamic instability, or increased intracranial pressure [66]. Fortunately, studies in newborns have reported simple and benign pain interventions that may be used in conjunction with newborn screening heelsticks. These include the use of oral glucose solutions [67], sucrose solutions [68, 69], milk [70], non-sucrose sweet tasting solutions [71], oral pacifiers [72, 73], gentle stroking and reassurance [74], spring loaded lancing devices [74, 75], and use of local anaesthetic creams like EMLA [74] or lidocaine (lignocaine) [76, 77]. A limited number of comparative studies are also available [78, 79]. In cases where topical anaesthetics are used, care should be taken to ensure that there is no interference with the laboratory testing procedure by consulting with the screening laboratory.

#### 2.2.2.2. Laboratory testing

*Laboratory tests should be sensitive and specific with low recall. See Appendix I for CH testing flow diagrams.*

Laboratory testing plays a key role in the newborn screening process, since the testing results determine whether or not the baby is at risk for the condition being screened. It is critical to remember that laboratory testing for screening purposes is different from diagnostic testing, and screening is expected to produce some false positive test results. There should be no false negatives if at all possible. In this connection, the goal of continuous programme evaluation is to identify improvements that will continue to minimize false positives without allowing for any false negatives. Additionally, it is essential that

adequate quality assurance steps be in place to ensure testing accuracy. Testing should include negative and positive controls, and appropriate internal and external proficiency testing should be part of the system.

Initially, it may be appropriate to set conservative cutoff values to ensure that no babies are missed. But as soon as data are available that will allow for statistically valid cutoff changes, they should be adjusted to lower the recall rate. Most CH programmes that screen newborns at 2–3 days of age tolerate a recall rate of between 0.5% and 21% (most of these recalls are false positives). It is essential that laboratory testing that is of a high quality and is stable be a focus of any infrastructure development. Similarly, it is important that testing results be reliable and efficiently delivered to the submitter so that appropriate follow-up can be carried out. Operating procedural manuals must be in place and followed, and proper documentation of all aspects of laboratory operation must exist.

### Transport of specimens

When specimens have been collected and dried properly, they should be transported to the testing laboratory as efficiently as possible. Since heat and humidity can adversely affect many of the tests performed on dried blood spots, the transport system should seek to minimize these environmental variables. In countries where the postal system is not efficient, alternative transport should be sought. Courier services such as FedEx and DHL are often very efficient in this role. If choices exist between motorcycle courier and air-conditioned vans, the latter are likely a better choice. The laboratory should be capable of operating throughout the week and reporting results within 2–4 work days after receipt of a specimen.

*Transport of specimens should be efficient (rapid) and batching should be discouraged. Temperature control is preferred.*

### Testing protocol

The choice of whether to use T4 (more specific) or TSH (more sensitive) as the initial screening test for CH screening often rests with the ability of the programme to collect the blood specimen when the infant is 24 hours old or older. In the USA, where hospital discharge often occurs within the first 24 hours after birth, the preferred screening method has been to use T4 followed by TSH on a percentage of abnormal T4s; whereas in Europe and Japan, where screening occurs at a later time, TSH has been the method of choice. Either method can be effective if properly implemented [58].

*Testing protocols:*

- TSH as primary screen;
- T4 as primary screen;
- Both T4 and TSH.

Newborn screening identifies patients at increased risk and by definition may not detect 100% of cases, regardless of the screening protocol. Clinicians must continue to be aware of signs and symptoms and should not become complacent when newborn screening is in place.

*TSH is elevated in the first few hours after birth. Testing during this period is unreliable.*

*TSH as the primary screen:* In cases where TSH is used in the initial screening test, most programmes assay specimens against a fixed cutoff (20–35  $\mu\text{LU/mL}$  (serum) depending on the characteristics of the reagents in use and statistical testing history of the programme) in order to determine those presumed to be at risk for CH. In some cases, particularly in populations where there are large numbers of specimens taken prior to 24 hours of age (TSH surge period), a certain small percentage of specimens with the most elevated levels (usually the upper 3%) may be selected for retesting and rescreening with T4 in order to lower the rate of false positive reports and unnecessary follow-up (see example flow diagram in Appendix I). Follow-up procedures similar to those listed above for initial T4 screening are followed. In some programmes (e.g. in Japan and the United Kingdom), specimens are taken a few days after birth when TSH is considered to be stable and, therefore, no additional thyroxin screen is usually performed.

Newborns with an abnormal TSH are considered to be presumptively positive for CH and are vigorously followed until the screening results are resolved. Care must be taken to set testing cutoffs at a level such that excessive false positive results do not occur. Whenever false positive screening results are excessive, the physician community will lose interest in the programme and can become a critical opponent of the screening process. This is particularly critical in cases where samples are taken close in time to the TSH surge period. If collection at this time cannot be avoided, then an adjustment to the cutoff level based on time of collection should be considered using accumulated data from the programme.

*T4 testing is less specific but not affected as much in the first 24 hours after birth.*

*T4 as the primary screen:* In cases where T4 is used in the initial screening test, secondary screening by TSH on a certain percentage of newborns with low T4 has been most effective at increasing sensitivity and specificity of the screening procedure. Thus, it is common in such cases to use either a cutoff on the basis of daily mean values or a fixed percentage of the screened population, usually the lower 10% of each assay, to select the initial suspect group for additional testing. This group is resampled from the original screening card (as a quality control check) and analysed (usually in duplicate) for TSH concentration (see the flow diagrams in Appendix I). Often the T4 is repeated at this time (usually in duplicate) to better define those specimens with abnormal T4 concentrations (usually the lower 5% to 10% of the mean of the duplicates resulting in the lower 0.5%-1% of the day's specimens (lower 10% of the lower 10% = lower 1%)). Interestingly, while T4 assays are often judged against variable cutoffs based on percentiles or daily means, TSH assays are usually judged against fixed values set

from 20 to 35  $\mu\text{LU}/\text{mL}$  (serum), depending upon commercial kit and statistical testing history, for presumptive classifications.<sup>2</sup>

Newborns with an abnormal level of both T4 and TSH are presumed to be positive for CH and are vigorously followed until the screening results are resolved. Those with either an abnormal level of T4 or of TSH are also considered at increased risk for CH and a repeat specimen is requested to resolve the discrepant original findings. In such cases, additional serum testing may be necessary for final resolution. A minimal false positive rate (usually between 0.5% and 1.0%) is tolerated in T4/TSH screening in order to ensure adequacy of the screening process (i.e. to reduce the risk of false negative classifications).

*Combined testing with TSH and T4 can reduce recalls.*

### **2.2.3. Component 3 — Early (short term) follow-up**

For hospitals and physicians, early (sometimes called short term) follow-up of normal patients begins with specimen collection and ends with a valid screening result that is documented in the medical record. For abnormal or potentially abnormal patients, early follow-up begins with detection of an abnormal or unsatisfactory result and ends when either a satisfactory screening result or confirmatory test results are known, and the affected infant is receiving appropriate treatment. The newborn screening system must ensure rapid and complete follow-up and resolution of any positive screening test result.

There are usually two levels of follow-up, depending on the risk of abnormal consequences as a result of the laboratory testing results. Newborns at highest risk of severe consequences usually require confirmatory serum testing and/or clinical evaluation and should be followed up by telephone or personal visit. Those at lesser risk may be contacted by less urgent means, for example, a letter requesting another filter paper test. Many programmes maintain standard recall letters into which may be inserted the patient's name and physician or parent contact information. Such letters should be carefully worded and periodically updated as programme information changes. The information contained in contact letters will vary from programme to programme depending on the follow-up procedures and the degree of involvement of subspecialists. If clinical advice is included, clinicians current in the treatment of the condition should review the wording of the recall letters.

*Early follow-up ensures rapid diagnosis and treatment, and the urgency is dependent on screening test results.*

In all cases, good documentation of steps taken in follow-up is essential. Such documentation should support written follow-up

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<sup>2</sup> The International Society for Neonatal Screening suggests using (serum) or (blood) to indicate whether or not the units refer to serum equivalents or to whole blood, which has only about half as much serum in newborns (average haematocrit = 55).



TABLE 11. INTERPRETATIONS OF INITIAL NEWBORN SCREENING RESULTS FOR CH [12]

Screen results	Probable cause	Clinical manifestations	Special evaluation/ care required
T4 low, TSH high	Primary hypothyroidism	Severe	Diagnostic evaluation <sup>a</sup>
	Maternal antibodies	None	
	Maternal medications (PTU, Iodine)	None	
T4 low, TSH normal	Hypothyroidism possible	None to severe	Rescreen, if confirmed, consider diagnostic evaluation <sup>a</sup>
	Pituitary/hypothalamic disorder	Severe	
	Prematurity	None	
	TBG deficiency	Variable	
	Secondary hypothyroidism	Variable	
T4 normal, TSH high	Hypothyroidism possible	None to severe	Diagnostic evaluation <sup>a</sup>
	TSH surge	None	
TSH very high (with or without low T4)	Primary hypothyroidism	Severe	Diagnostic evaluation <sup>a</sup>
	TSH surge	None	

<sup>a</sup> See Table 12.

protocols that are realistic and aimed at accomplishing programme goals. When individuals who are participating in the process are identified in the documentation, names should be used, rather than initials.

#### 2.2.4. Component 4 — Diagnosis

*Diagnosis must be timely and should include an evaluation by a paediatric subspecialist if one is available.*

Once the screening tests have been completed and the results are known, it is important for babies who are presumptively at risk for a disorder to have confirmatory testing performed. Specialty physicians (paediatric endocrinologists in the case of CH) serving as advisers can best delineate the appropriate confirmatory and diagnostic tests for newborn screening programmes. In countries where paediatric endocrinologists are not available, physicians with a special interest or experience with CH should be asked for assistance. In the case of CH, published guidance on follow-up treatment is available (see Ref. [12]). These guidelines address not only the interpretation of screening results of T4 and TSH testing (Tables 11 and 12), but also suggest diagnostic procedures (Table 10).<sup>3</sup>

<sup>3</sup> Guidance for certain other disorders is also contained in Ref. [12], including galactosemia, phenylketonuria, CAH and sickle haemoglobinopathies.

TABLE 12. TESTS FOR CH (PRIMARY) [12]

CH (primary)	Diagnostic tests
Core tests and procedures	Serum total T4, T3 uptake, free T4 or T4 index, TSH <sup>a</sup>
Supplemental tests and procedures	Serum TBG <sup>a</sup> Anti-thyroid peroxidase and anti-thyroid globulin antibodies Ultrasound imaging of thyroid <sup>123</sup> I or <sup>99</sup> Tc thyroid uptake and scan Bone age Molecular evaluation of thyroid dysgenesis and inborn errors of thyroid hormone synthesis

<sup>a</sup> T4: thyroxin; T3: tri-iodothyronine; TSH: thyroid stimulating hormone; TBG: thyroid binding globulin.

## 2.2.5. Component 5 — Management

### 2.2.5.1. Medical management

It is essential that the newborn screening programme enlists the aid of competent physicians (specialists, paediatricians, family practitioners) in developing recommendations for medical management in the programme. Exact recommendations about diagnostic tests, result interpretation, prescribed medications, and follow-up testing to monitor outcomes are best left to specialty care providers.

In general, treatment for CH consists of hormone replacement, utilizing synthetic hormone in pill form. The pill can be crushed, then administered in a small amount of water/formula or breast milk and should not be mixed with soy formula since soy interferes with biological absorption of the L-thyroxin (levothyroxin = synthetic T4). Once started, the medication will usually be taken daily for life because T4 is essential for all of the body's functions. The average starting dose for L-thyroxin in a newborn is usually 25–50 µg/d or 10–15 µg/kg of body weight so that the T4 and TSH levels are normalized by one month of age, but dosages may differ in different settings. A local specialist should determine final dosages. Dosages are dependent upon the individual needs of the child and may increase to 150 µg/d or more as the child grows. Overtreatment is characterized by hyperactivity. Blood tests are required regularly to ensure normalization of hormone levels. Initially, frequent tests are necessary until there are normal thyroid hormone levels (patient is euthyroid).

Sometimes, establishing and maintaining the correct dose takes some effort. Typically, the need for T4 increases during periods of rapid growth. During times of rapid growth (such as the newborn period, infancy and puberty), T4 and TSH must be monitored frequently so that

*Medical management should be closely monitored to ensure proper patient compliance and desired health outcome.*

*Treatment for CH is lifelong and treatment compliance should be periodically monitored.*

the proper dosage of thyroxin can be determined. Children are usually seen every two–three months for the first three years. The goal of medical management is to elevate the serum T4 to approximately 10  $\mu\text{g}/\text{dL}$  within the first two weeks following diagnosis and to maintain the T4 levels in the middle to upper half of the normal range (approximately 12.5  $\mu\text{g}/\text{dL}$ ) for the first years of life. TSH levels should generally be below 20  $\mu\text{g}/\text{dL}$  within 2–4 weeks of starting treatment, and then maintained within the normal reference range for infants. Treatment/management for CH is safe, simple, and effective, but successful treatment depends on continued daily medication and thyroid hormone monitoring.

Most children diagnosed with hypothyroidism by newborn screening will require lifelong thyroxin treatment. On rare occasions, a child may be found to no longer need thyroxin treatment. In these cases of transient hypothyroidism the child does not require increased doses during the growth spurts, and has normal levels of T4 and TSH when thyroxin is discontinued. In cases where transient hypothyroidism is suspected, the child is usually taken off treatment for a short time (usually two weeks) between two and three years of age and re-evaluated with appropriate biochemical testing.

As an example of a protocol for the management of this disorder, the New England Congenital Hypothyroid Collaborative suggests that T4 and TSH measurements on serum should be carried out as follows for growing children (see the Massachusetts newborn screening web site: <http://www.umassmed.edu/nbs/screenings/disorders/hypothyroidism.cfm>):

- (1) At two weeks following any change in therapy;
- (2) Every 1–2 months during the first year of life;
- (3) Every 2–3 months from 1 to 3 years of age;
- (4) Every 3 months until the child's growth is complete.

Once growth is complete, the following thyroid test schedule is also suggested:

- (1) When signs and/or symptoms of hypothyroidism or hyperthyroidism exist;
- (2) Annually if dose, weight, and clinical condition are stable;
- (3) Six weeks after a change in dose;
- (4) Frequently during pregnancy (ideally, as soon as a pregnancy is detected as the dose of thyroxin may need to be increased during pregnancy).

### 2.2.5.2. Long term follow-up

Long term follow-up begins with the confirmation of a diagnosis of CH and continues throughout the life of the individual. It is important for newborn screening programmes to collect programme evaluation data by monitoring the long term outcome of individuals who, through screening, have been identified with the disorder of CH. These data provide a mechanism for determining the effectiveness of newborn screening diagnoses compared with clinical diagnoses, and should provide information on which to base programme changes. In this respect, long term follow-up is actually an essential part of the evaluation process of the system (discussed as component 6 of the newborn screening system). Long term follow-up data is a critical need for most developed newborn screening programmes and so it is important that health professionals who are developing programmes plan for this need. Without outcome data, it is impossible to accurately assess the performance of the programme, and thereby to convince others (e.g. policy makers) of its value.

*Long term follow-up (reporting) helps ensure optimal health outcome and can be used to evaluate the screening programme.*

One mechanism for accumulating long term outcome data is through annual inquiries, either to the treating physician, to the consulting specialist (if one exists), or to the parent. Some programmes have used birthday cards as a way of softening the data gathering experience. Others have developed data sheets that have been used by treating physicians as part of the medical record and submitted periodically to the newborn screening coordinating office. Since long term follow-up of treatment outcomes will invariably require funding if it is to be done correctly, it is suggested that this be a consideration of any deliberations on programme costs [3].

### 2.2.5.3. Specimen management (blood spot storage, access and use)

The most obvious and valid reason for retaining a specimen obtained in a newborn screening programme is for quality assurance for the testing process. If a question about testing results arises a short time after testing, then the original specimen can be reanalysed to answer any question (i.e. particularly with respect to false negatives). However, verification of original testing results for CH (and most other conditions) is valid only if the specimen has been properly stored and adequate control specimens are available [80]. Thus, careful attention to storage details is essential.

Other reasons for retaining residual specimens include: legal accountability (e.g. a screening was performed and performed correctly), future DNA testing, new method evaluations and comparisons, epidemiological or other public health surveys, special health related studies for patient or family, and forensic studies. There are also reasons for discarding residual specimens shortly after testing,

including: lack or uncertainty of analyte stability, cost of storage, unavailability of suitable storage space, no mechanism for easy retrieval, no quality assurance system to ensure integrity of stored specimens and the lack of parent consent for future testing. A more detailed discussion of the issues surrounding retaining, storing, and using residual newborn screening specimens has been published [81], and these matters were included in the discussions of the AAP Task Force on Newborn Screening [3].

*Residual blood spots used for screening are useful for laboratory QA and may provide important samples for research. Policies must provide for appropriate privacy safeguards.*

It is becoming widely recognized that whole blood absorbed into filter paper and then dried offers viable specimens for DNA analysis. Thus, residual newborn screening specimens have the potential for storage as a comprehensive ‘bank’ of biological information on the population of newborns screened. Such storage banks already exist in Denmark [82], the US military and several developed newborn screening programmes around the world. If a residual blood specimen is retained, it should be stored carefully and appropriately for an intended purpose. The duration of storage should meet the defined purpose. Retention should be based on scientifically valid arguments regarding need, analyte stability, potential use, and technical storage issues (including storage environment and method of retrieval).

Following the completion of newborn screening, residual blood specimens will remain, and the testing laboratory and the screening programme must consider the ultimate disposition of these specimens. A written management policy that defines storage conditions, access, and uses for these specimens should exist. If specimens are to be stored in the long or short term, then the policy should outline environmental parameters for storage including temperature, humidity, and light conditions. The policy should include defined procedures for access to and use of specimens, along with a procedure for their ultimate destruction.

### **2.2.6. Component 6 — Evaluation**

The purpose of newborn screening is to identify all newborns at risk for a disorder in a population of apparently healthy newborns. It is a delicate balance between selecting the fewest newborns ‘at risk’ for a condition without missing any true cases. In some cases the testing performed will be quantitative and in some cases qualitative, but in all cases it is necessary and prudent to have a carefully developed quality assurance (QA) system in place. As part of this system, good documentation of patient records and long term patient outcomes are essential components. Without information on the outcomes of patients detected with CH and treated, it is impossible to accurately know whether or not the operational system is accomplishing its mission.

Within the newborn screening system, a laboratory QA is essential to document that the analytical testing procedures are appropriate. However, QA in the laboratory is only one part of overall QA for newborn screening. Steps should be taken to ensure that all parts of the newborn screening system are functioning properly and that their quality is also assured. It is possible and appropriate to design QA so that the screening system is monitored from the point of collection through, and including, specimen submission, test analysis, result reporting, patient follow-up, confirmatory testing, diagnosis, and health outcome. Periodic audits of the system should be undertaken and the results shared with appropriate staff. Correction of any deficiencies detected should be documented and included in operational activities and manuals.

*System evaluation provides for continuous improvement and should include audits of various system components.*

### 2.2.7. Summary

The components of a newborn screening system are as follows:

- Component 1 — Education.
  - Professional education
  - Parent education
  - Education of policy maker.
- Component 2 — Screening.
  - Specimen collection
  - Laboratory testing.
- Component 3 — Early follow-up.
- Component 4 — Diagnosis.
- Component 5 — Management.
  - Medical management
  - Long-term follow-up
  - Specimen management.
- Component 6 — Evaluation.



**Part 3**

**QUALITY ASSURANCE  
FOR THE NEWBORN SCREENING SYSTEM**





### 3.1. INTRODUCTION

Newborn screening is a system with six component parts: education, screening, early follow-up, diagnosis, management and evaluation [12, 83]. It may be viewed more simply as a pre-analytic, analytic, and post-analytic system in which laboratory analysis is preceded by pre-analytic education and specimen collection/submission followed by post-analytic follow-up, diagnosis, education, treatment and outcome evaluation. It is a system that functions within local geographical, economical and political constraints, and seeks to smoothly and seamlessly integrate sample collection, laboratory analysis, follow-up, diagnosis and treatment. For a newborn screening system to be of high quality, there must first be a well understood infrastructure, the individual parts of which have well defined responsibilities with identifiable performance indicators. This section provides a general description of the infrastructure for a newborn screening system, identifies some of the performance indicators that may be used for developing a quality assurance plan, and discusses the objectives and components of such a plan.

*Newborn screening is a system.*

### 3.2. INFRASTRUCTURE

#### 3.2.1. Individual and collective responsibilities

Responsibility for assuring and improving the quality of newborn screening services lies with every individual working within the screening system. In order to develop a meaningful QA system, a clear understanding of individual and collective responsibilities within the newborn screening system is necessary. Typical responsibilities for various stakeholders (programme manager, health care practitioner, birthing facility, laboratory, follow-up team, treatment team, and parents/guardians) in the newborn screening system are given below.

*Components of the local newborn screening system should be identified, and the responsibilities defined.*

##### 3.2.1.1. Programme manager (administrator)

Responsibility begins with planning the various aspects of the screening system and ends with overseeing, evaluating, and continuously improving overall system operations. Several areas of responsibility exist.

## Scope of programme manager responsibilities

*The programme manager coordinates components within the newborn screening system. Central administration is essential.*

*Oversight/coordination of administration:* For the purposes of programme administration, there is usually a central administrative office or secretariat. In such cases, the programme manager usually serves as the principal administrator and as such, has general responsibility for overall office operations and personnel management. Included are such functions as personnel recruitment and selection, programme policy formulation, general office management, supply and equipment coordination, ordering and maintenance, public relations and programme advocacy, event planning (including training workshops, regional/national seminars, etc.) and other appropriate programme planning. Where computerization is a part of programme administration, the programme manager has a responsibility to ensure its effective and efficient operation, including system integrity and backup. The programme manager also has general responsibility to ensure that a comprehensive quality assurance system is in place and that emergency contingencies are planned. If reimbursement is an issue, the programme manager must ensure that a proper accounting system is established with adequate cash flow for programme stability. Quality indicators for coordination of administration include personnel evaluations, documented inventories of equipment and supplies, periodic reports of public relations/education activities, accounting records, and other records related to administrative oversight and documentation of computer problems and responses.

*Laboratory coordination ensures timely reporting and documentation of quality.*

*Oversight/coordination of the laboratory dedicated to newborn screening:* While daily management of the laboratory and other programme operations are generally the responsibility of technical supervisors, the programme manager coordinates all activities within the newborn screening system, including the basic responsibilities of the laboratory. Laboratory oversight is particularly important, since laboratory activities interrelate with receipt of specimens from birthing facilities, reporting of all laboratory testing results, follow-up of abnormal and unsatisfactory specimens, coordination of confirmatory testing, and patient education. If authorized release of laboratory testing results is a requirement, the programme manager is responsible for either performing this duty or ensuring that it is properly accomplished. In combination with senior laboratory staff, the programme manager ensures that testing time schedules are met, that operating manuals are current with periodic documented reviews, that all appropriate laboratory records are in order, and that patient results are reported timely and accurately. The programme manager also oversees training activities to ensure that employees are up to date in their knowledge of screening procedures and cross-trained where necessary, and that backup contingencies exist for personnel or reagent shortages and equipment malfunctions. Quality indicators include, inter alia,

documentation of personnel training, manual reviews, reporting timeliness, reporting accuracy.

*Oversight/coordination of follow-up activities:* Appropriately trained health programme specialists, nurses, or genetic counselors generally manage follow-up activities. The programme manager serves to coordinate activities of the follow-up staff (whether in the laboratory or in a separate unit) to ensure that all the testing results that require follow-up actions are pursued to completion and that they interrelate with other aspects of the screening system. The programme manager ensures that written protocols exist for all situations that require follow-up and that these protocols are current, realistic and subject to periodic, documented reviews. In instances where public relations activities are needed to better coordinate follow-up services with physicians or hospital staff, the programme manager may be required to fulfil this role. If the programme manager is qualified medically, he/she may assist with ensuring appropriate medical management of patients who do not have, or cannot afford, a proper medical 'home'. Preferably, this function is one of care coordination between local physicians and subspecialty care providers, rather than direct patient care. Where possible, and with appropriate patient privacy safeguards, a registry of confirmed cases allows for long term evaluation and possible patient support contacts — such a registry may best be coordinated by the programme manager. Quality indicators include documented times from birth to physician contact for confirmatory testing and from birth to diagnosis, documentation of periodic reviews and updates of written protocols for follow-up, documentation of responses to inquiries regarding patient care and documentation of patient registry availability and usage.

*Follow-up coordination includes adherence to written protocols with clear end points.*

*Oversight/coordination of educational activities:* There are many areas within the newborn screening system that can include education, and the programme manager has the general responsibility of ensuring that educational needs are met wherever they are needed. This can include educational activities directed at public, professional, and political associations, and may include such activities as preparation of brochures or other printed materials, videotapes, audiotapes, posters, seminars, training workshops, public service announcements, radio/television interviews, and other education/advocacy activities. It is particularly important in some settings that personal attention be paid to educating political and/or religious leaders in order to gain community support for the programme. Likewise, educating physicians about their role in the programme and the way they can interface to assist in programme implementation and improvement can often aid in integrating of the screening programme smoothly into local medical practice. As disorders are detected and the creation of parent support groups is possible, the programme manager can aid in establishing such groups and assisting in their educational needs. It may also be useful to establish internal staff discussions or other means of education for

*Educational activities must address the needs of:*

- The general public,
- Professionals,
- Policy makers.

associated staff, for example, in the discussion group club of a local journal. Quality indicators can include items such as documentation of the availability and use of the various educational materials available or documentation of participation in various educational functions (including number and job responsibilities of attendees).

*Research needs include protocol evaluation, new procedures and improved knowledge of diseases.*

*Oversight/coordination of research activities:* From time to time, research activities relating to newborn screening data or procedures will arise and the programme manager will generally be responsible for overseeing and coordinating such activities. For example, it is appropriate to periodically review data relative to diagnosed cases and to compare them with the recall rate and analytical cutoff values in order to assess whether or not cutoff levels need adjustment. New testing methods that are best evaluated by comparison with existing methods may be available. Periodic evaluation of testing sensitivity and specificity may provide useful information for improving the programme. Varied epidemiological studies of programme data may provide a better understanding of the natural history of the screened disorder. Also, because residual blood remaining after testing provides the potential for a DNA database on all newborns, the programme manager should be actively involved in policy development regarding the storage, access, and use of these specimens. Quality indicators can include items such as documented research policies, documented reports of various research studies or related activities or documented actions taken as a result of a research activity.

### 3.2.1.2. *Health care practitioner/birthing facility*

*For the health care practitioner or birthing facility, responsibility begins with the birth of the newborn (or entry of an infant into the practitioner's care) and ends when the practitioner knows and has documented the newborn screening results in the patient's medical record.*

Responsibility begins with the birth of the newborn (or entry of an infant into the health care practitioner's care) and ends when the practitioner knows and has documented the newborn screening results in the patient's medical record.

Scope of responsibilities of the health care practitioner/birthing facility

*Educating and instructing parents:* Education is primarily an obstetrics practitioner and birthing facility responsibility handled through the distribution of programme literature and responding to parent questions before the birth of their infant. Thus, one of the essential items that must be available is educationally and culturally appropriate programme literature. Literature availability and usage can be monitored as a quality indicator.

*Ensuring that every newborn is screened:* The AAP has published guidelines to paediatricians stating that it is the responsibility of every paediatrician to know the screening status of every patient in their care [10], and this appears to be universally applicable to paediatricians,

family physicians, and others providing health care to the newly born. Birthing facilities providing newborn screening should have a tracking system that ensures screening and receipt of results for every newborn, and transmittal of these results to treating physicians. The protocol should include specific written instructions for screening and follow-up that include procedures to be followed in case of early hospital discharge or hospital transfer. Expected turnaround times for results of blood tests and reporting procedures should be monitored as quality indicators.

*Obtaining written consent or dissent (when testing is refused):*

The health care provider should obtain a signed (and witnessed) consent (opt in) or dissent (opt out) form (depending on local rules, regulations or laws) for inclusion in the infant's medical record. This written documentation will afford the birth facility and the practitioner some legal protection, particularly if the infant is affected with a disorder that might have been detected through newborn screening and the parents declined testing. The numbers of newborns opting in or out of screening and their reasons for doing so can be used as quality indicators of the consent (or dissent) process.

*Collecting and submitting valid specimens and data:* It should be the responsibility of the health care provider at birth to collect specimens in accordance with programme rules and regulations and to ensure that adequate specimens with correct information are sent in a timely fashion to the testing laboratory. Attention should be given to sending all specimens from the birthing facility no later than 24 hours after they are collected. Specimens are usually sufficiently dry within four hours of collection for packaging and transport. The number of unsatisfactory specimens reported by the testing laboratory, the time from birth to collection, and the time from collection to laboratory reporting can be used as quality indicators.

*Receiving, evaluating, and assisting in communicating test results to parents:* The birthing facility that submits the specimen for screening should maintain written documentation of all completed test results, and these should be transmitted to the newborn's health care provider and ultimately to the parent or guardian of the newborn. The screening laboratory should routinely provide the results of tests for screening to the submitting facility soon after testing is complete. In the case of abnormal or unsatisfactory results, a more rapid contact protocol should be used so that confirmatory testing can be completed quickly. Rapid result transmittal from the testing laboratory relies on accurate identification (on the collection card) of the submitter and the health care provider for the newborn. Records of returned screening results on all newborns and the time it took from specimen collection until test results were received and transmitted to physicians (or parents) can be used as quality indicators.

*Test results should be communicated privately and followed up with appropriate confirmation.*

*Taking prompt follow-up action in the event of an abnormal or unsatisfactory result:* Health care practitioners have a responsibility to

rapidly follow up any abnormal results or inadequate specimens. This role should be coordinated with follow-up personnel from the newborn screening programme, and may involve appropriate medical consultants. Follow-up responsibilities include informing parents of test results in a sensitive and intelligent way, and arranging for appropriate diagnostic and confirmatory tests. When confirmatory tests indicate the need for treatment, this should be pursued and documented. The percentages of requests for recall tests that have been satisfactorily resolved and the time for their resolution can be used as quality indicators.

### 3.2.1.3. Laboratory

Laboratory responsibility begins with the receipt of a screening specimen and ends when all tests have been completed, results reported, quality control documented, and abnormal or unsatisfactory results communicated to the appropriate follow-up person. (In programmes where remote electronic data entry may be available, laboratory responsibility begins with receipt of the demographic data from the facility, prior to the arrival of the specimen.)

#### Scope of laboratory responsibilities

*Laboratory responsibility begins with receipt of a screening specimen and ends when all tests have been completed, results reported, quality control documented, and abnormal or unsatisfactory results communicated to the appropriate follow-up person.*

*Accurately documenting all laboratory activities involving screening specimens:* Some countries may have regulatory requirements in place for laboratories, and these may dictate some of the laboratory activities that relate to newborn screening. When developing programmes in places where laboratories are not subject to regulatory requirements, it is advisable to draw up laboratory standards or requirements to ensure best laboratory practices for the screened population. The testing laboratory should have good records that document its performance, including records of: specimen receipt, proper instrument operation, test results (including raw data and analytical interpretation), analytical quality control linked to patient specimens, final testing disposition (including copies of written or electronic result reports), and communications of abnormal and unsatisfactory results. Documentation of communications should include date, time, person giving information, and person receiving information (telexes should include documentation of receipt, often by return telex). All of these reports may be used as quality indicators. Any corrective actions should also be documented.

*Determining and enforcing criteria for specimen adequacy:* Quantity and quality standards for blood specimens should be established by the testing laboratory and appropriately communicated to the persons who submit specimens for screening. Specimen acceptability criteria should be included in materials provided to health

care providers. Schleicher & Schuell, Inc. (one manufacturer of filter paper for blood collection devices, located in Keene, New Hampshire, USA) distributes posters in various languages illustrating both the appropriate collection technique and the appropriate appearance of the dried blood spots (see Appendices III and IV). Collection diagrams are also included in the NCCLS blood collection standard and the Thailand Newborn Screening Programme has developed a collection poster in the Thai language (see Appendix III). The numbers of inadequate specimens and instances where incomplete patient information was received can be tallied and used as quality indicators. Some programmes have used these data to create monthly summary reports to send to all birthing facilities as a means of publicly acknowledging successes and challenges.

*Ensuring that each specimen is tested in a timely manner:*

Laboratories that carry out the tests on blood specimens must ensure that, once received, specimens are tested quickly, so that the benefits of early newborn screening can be realized. Most laboratories set three–four working days as a maximum processing time with a maximum of seven days from specimen receipt to reporting, [1, 12, 83] and accomplish this turnaround within seven days. In developing programmes with poor specimen transport systems, remote submitters, and various other local impediments, it may not be possible to meet these turnaround times. Nevertheless, the time in the testing laboratory itself should be minimized, wherever possible. While CH treatment can be started as late as one month and still be effective, other disorders may be life-threatening within a few days after birth, including galactosaemia, congenital adrenal hyperplasia, and some other metabolic conditions. Programmes should not add such disorders until their programme infrastructure can accommodate turnaround needs. Records of the length of time that specimens reside in the screening laboratory should be used as quality indicators and times in excess of predetermined limits indicate a situation that must be evaluated and corrected.

*Timely and accurate laboratory testing is essential.*

*Ensuring and documenting appropriate quality assurance:*

Good laboratory practice is essential and quality must be assured at every step of the local process. In order to assess analytical performance, external proficiency testing (PT) is essential and should be required in all newborn screening laboratories. Results and corrective actions (if needed) should be documented (see Ref. [84]) for a listing of programmes available around the world. In order to realistically assess the screening laboratory, PT specimens should be analysed in a manner identical to that used for patient specimens. Records of proficiency testing results, analytical problems encountered, and corrective actions taken, can be used as quality indicators.

*Ensuring that for every specimen, a timely report is transmitted:*

For each specimen, the facility that collects the specimen should keep a record which shows that the specimen has been transmitted and that a result has been received. The testing laboratory should document



receipt of all specimens and transmittal of a timely result for each. The testing laboratory must report all of its testing results as quickly as possible. This is especially true for presumptive positive findings and unsatisfactory specimens. In developing programmes, cellular telephone and telefax of abnormal and unsatisfactory results may be the most efficient method for rapidly transmitting testing results. Laboratories should actively attempt to improve the quality of specimens submitted. This can be done by monitoring the number of unsatisfactory specimens received as a quality indicator and developing an educational process targeted at those facilities that routinely submit large numbers of unsatisfactory specimens.

#### 3.2.1.4. *Follow-up individual or team*

*Individual or team follow-up responsibility begins with receipt of an abnormal or unsatisfactory report from the laboratory and ends when the infant has been proven to be not affected, affected and receiving appropriate medical management, or 'lost to follow-up'.*

Individual or team follow-up responsibility begins with the receipt of an abnormal or unsatisfactory report from the laboratory and ends when the infant has been proven to be not affected, affected and receiving appropriate medical management, or 'lost to follow-up' (following exhaustive completion of all established protocols).

#### Scope of follow-up responsibilities

*Resolving abnormal results quickly and effectively:* Case detection and enrollment in appropriate medical management are the **primary and most important** responsibilities for follow-up staff. Written protocols and flow sheets should be in place (usually developed in concert with the screening laboratory and medical consultants) and followed. Follow-up protocols must be realistic, as opposed to idealistic, and lead to the resolution of presumptive cases within a specified and appropriate time frame. Invariably, some cases will be lost to follow-up after reasonable contact efforts have been made. The follow-up protocol should specify the amount of effort that should be made before a case is classified as 'lost to follow-up'. Records that reflect compliance with this protocol should be kept. The numbers of cases lost to follow-up and time records for completed follow-up should be used as quality indicators.

*Following up unsatisfactory specimens:* The follow-up of unsatisfactory specimens is another critical element of the follow-up system, even though collection of a satisfactory specimen is a responsibility of the submitter. Tracking of repeat specimen collection, in cases where initial specimen quality or quantity is unsatisfactory, is a follow-up responsibility. In such cases, the submitter should be immediately contacted and asked to supply a proper specimen. In cases where the newborn is no longer at the submitting facility, a responsibility to collect a proper specimen remains, and this will likely become a shared project of the programme follow-up coordinator and the submitter. Follow-up of unsatisfactory specimens should be similar

to that for presumptive positive test results with similar documentation. The numbers of unsatisfactory specimens submitted may serve as a quality indicator.

*Assisting in educating health care providers:* Education is an important screening programme responsibility most often assumed by follow-up personnel. Nonetheless, laboratory staff can also assist in carrying out this responsibility. A good practitioner education programme should involve more than the distribution of educational materials. It should include regular in-service training or workshops on all aspects of the programme. Educational visits to birthing facilities can often provide special opportunities for personalized exchanges of questions and answers between programme and facility. One measure of the effectiveness of submitter education is the number of unsatisfactory specimens submitted. In cases where consent is a facility responsibility, the numbers of patients who choose to reject screening may be an indicator of the need for in-service education at the facility on the value of screening.

*Assisting the programme manager in overall programme evaluation:* The goal of programme evaluation is to provide an effective and efficient newborn screening programme. Follow-up personnel usually maintain the responsibility of assisting in evaluating all of the programme through periodic reviews of outcome data. A detailed discussion of short term and long term follow-up and quality assurance can be found in later sections of this manual. It is essential that thoughtful measures be developed that will lead to meaningful evaluations of all parts of the newborn screening system so that the programme can be improved. Treatment quality indicators ultimately involve patient outcomes, and periodic long term outcome data should be accumulated for this purpose. Patient outcome is the ultimate measure of programme quality.

*Follow-up personnel are usually responsible for educational programme evaluation.*

### 3.2.1.5. Treatment teams

(This term usually refers to subspecialty provider(s) caring for the special needs of children, but may also include private care practitioners.) Treatment team responsibility begins with receipt of an abnormal result or referral of the infant, either by follow-up personnel of the programme or private physicians, and ends with documentation that the infant is (or is not) affected and is (or is not) being treated.

*Treatment team responsibility begins with receipt of an abnormal result or referral of the infant, either by follow-up personnel of the programme or private physicians, and ends with documentation that the infant is (or is not) affected and is (or is not) being treated.*

#### Scope of treatment team responsibilities

*Providing medical advice to the newborn screening programme:* In the event of presumptive positive results, it is advantageous to have specialty consultation (e.g. by an endocrinologist) available for the private physician. A medical specialist/consultant for the programme

can help correlate the infant's clinical status and laboratory test results and provide suggested courses of action for the local treating physician. Considerations about treatment can be made while awaiting confirmatory testing results. Specialists can also advise the screening programme in such matters as normal ranges, cutoff values, and follow-up protocols.

*Providing diagnostic services and/or initiating treatment:* Ideally, affected newborns and their families should receive the services of a paediatric subspecialist, with an initial visit occurring as soon as possible, in some cases prior to confirmatory laboratory test results. Treatment, if necessary, should begin as soon as feasible (for CH, no later than one month after birth). As noted previously, treatment for CH is simple, effective, and inexpensive.

*Providing ongoing treatment and follow-up to affected children:* Cost of treatment may be an issue in many developing programmes. It is important to have national insurance and local insurance plans recognize the need for insurance coverage of treatment. Long term treatment and outcome monitoring is a joint responsibility of the treating physician and the parents. Treatment protocols can be outlined in coordination with specialty guidance. Examples of treatment protocols for CH are given in Section 2.2.5 of this manual on medical management.

*Collecting and sharing outcome data for long term programme evaluation:* Periodic review of patient outcome data and information is important in order for the programme administrators to evaluate the overall value and cost-benefit of the programme. Outcome parameters vary by disease. It is most important to know whether or not the newborn continues in disease management and to have available, on the basis of biochemical testing, evidence of appropriate compliance with the treatment regimen. Physical and mental development data are important for most disorders, along with morbidity and mortality information. Designing and obtaining meaningful outcome databases is one of the most difficult tasks for newborn screening programmes, but it is essential if proper programme evaluation is to be accomplished. Partnership between the newborn screening programme and private practitioners is essential if long term outcome data are to be obtained.

### 3.2.1.6. Parents/guardians

*Parents and guardians must ensure that newborns receive appropriate and timely testing.*

Once the newborn screening programme is established, parents and guardians also have responsibilities in relation to their newborn.

#### Scope of parent and guardian responsibilities

*Ensuring that their newborn receives appropriate and timely testing:* Parents should inquire about the newborn screening programme

from their physician, midwife, or hospital and should seek to make informed decisions about whether or not to obtain the testing. If finances are an issue, then long range planning for payment during the pregnancy should be considered. If there is insufficient information available locally about the programme, parents should seek to obtain additional information from other sources.

*Ensuring adequate follow-through if any further testing is required:* In cases where either unsatisfactory or abnormal screening results are obtained, the parent or guardian has a responsibility to see that the appropriate follow-up actions are completed.

*Ensuring patient compliance with medical management in diagnosed cases:* Parents or guardians should ensure to the best of their ability that medicines or other treatments are obtained and medical recommendations followed in order to ensure that their child benefits from early testing and diagnosis. In cases where public services are available to assist the family, these should be obtained.

*Contributing follow-up and outcome information back to the programme:* Parents and guardians have a responsibility to give information back to the programme so that programme administrators can adjust the programme to best meet the needs of the patients. This is a shared responsibility with the treating physician and is necessary in order to foster continuous quality improvement for the programme.

### 3.2.2. Summary

The responsibilities of the various stakeholders of a newborn screening system are summarized below:

- Programme manager
  - Oversight/coordination of administration;
  - Oversight/coordination of the laboratory dedicated to newborn screening;
  - Oversight/coordination of follow-up activities;
  - Oversight/coordination of educational activities;
  - Oversight/coordination of research activities.
- Health care practitioner/birthing facility
  - Educating and instructing parents;
  - Ensuring that every newborn is screened;
  - Obtaining written consent or dissent (when testing is refused);
  - Collecting and submitting valid specimens and data;
  - Receiving, evaluating and assisting in communicating test results to parents;
  - Taking prompt follow-up action in the case of an abnormal or unsatisfactory result.

- Laboratory
  - Accurately documenting all laboratory activities involving screening specimens;
  - Determining and enforcing criteria for specimen adequacy;
  - Ensuring that each specimen is tested in a timely manner;
  - Ensuring and documenting that appropriate quality assurance is practised;
  - Ensuring that for *every* specimen, a timely report is transmitted.
- Follow-up individual or team
  - Resolving abnormal results quickly and effectively;
  - Following up unsatisfactory specimens;
  - Assisting in educating health care providers;
  - Assisting the programme manager in overall programme evaluation.
- Treatment teams
  - Providing medical advice to the newborn screening programme;
  - Providing diagnostic services and/or initiating treatment;
  - Providing ongoing treatment and follow-up to affected children;
  - Collecting and sharing outcome data for long term programme evaluation.
- Parents/guardians
  - Ensuring that their newborn receives appropriate and timely testing;
  - Ensuring adequate follow-through if any further testing is required;
  - Ensuring patient compliance with medical management in diagnosed cases;
  - Contributing follow-up and outcome information back to the programme.

### 3.3. DEVELOPING QA GUIDELINES

#### 3.3.1. General guidelines for performance improvement

*Quality indicators should be developed and periodically evaluated to monitor ongoing programme improvements.*

The reason for developing and evaluating (or auditing) quality indicators is to improve the overall quality of the newborn screening programme. When unacceptable quality or performance is discovered, a plan must be in place to correct this. Thus, it is beneficial to have written protocols for evaluating QA indicators and resolving issues that might arise from the audit process. Such QA protocols can either be included as part of an operations manual for a specific programme function (such as follow-up for abnormal CH test results, laboratory testing for thyroxin, specimen check-in) or as a separate QA manual for the larger

system (e.g. laboratory, follow-up). Simple incidence reporting forms should be developed to document any QA problem encountered, the immediate corrective action taken, and the long term solution that will prevent the problem from recurring. The ‘QA Incidence Reports’ should be periodically reviewed at staff meetings in order to ensure that staff are aware of potential problems and their solutions. A limited number of solutions can usually solve most QA problems and these include:

- Education and/or training;
- New or revised policies;
- Staffing or schedule changes;
- Equipment or facility changes.

Problem resolution will ultimately be measured in terms of its effectiveness. Once the QA process has detected and corrected a problem, periodic spot checks should be conducted to ensure that the problem has been completely resolved. Good communication between management and staff are essential to continue a valid quality assurance system. This section outlines some of the details to consider in working with QA in laboratory and non-laboratory settings, and it will be followed by a section with other examples of potential quality indicators that might apply to the various parts of the newborn screening system.

*Quality assurance should apply to both laboratory and non-laboratory processes.*

### 3.3.1.1. Laboratory services

The analytical methods used in the newborn screening laboratory should be of sufficient sensitivity and specificity with adequate quality control to ensure maximum disease detection with minimal false negative results (i.e. test results within normal limits despite the fact that the newborn has the condition of interest). Low false positive rates (i.e. test results outside of normal limits despite the fact that the newborn does not have the condition of interest) are necessary to prevent overburdening of the follow-up system. Laboratory services should be centralized whenever possible. It has been repeatedly demonstrated in developed programmes that a laboratory must have a sufficient number of specimens for analysis in order to maintain testing proficiency (because of the relative rareness of the conditions of interest) and to realize economies of scale relating to equipment and supply purchases. Guidelines published in the USA suggest that a minimum of 30 000 specimens need to be processed annually to achieve these goals. Indeed, similar experiences have been observed in East Asia. In Thailand, initial attempts to allow testing in many local hospitals were counter-productive for the reasons already noted and because personnel turnover created an additional burden on the system that adversely affected the quality of results. Currently, the Thailand screening programme has established four regional screening laboratories with the National Institutes of Health, providing quality oversight for all testing and follow-up.

*Screening laboratory services should be centralized to the extent possible for better quality control and lower costs.*

*Laboratory performance standards should exist.*

Laboratories that perform screening should adhere to professional guidelines and best practices according to local standards. It is important to utilize professionally trained personnel wherever possible, and to develop training programmes so that staff development is ongoing. Within the laboratory, it is important to provide cross-training and mentoring. Since newborn screening procedures will be new to most laboratory staff members, development of training materials and procedure manuals is extremely important. Where local laboratory quality guidelines do not exist, such guidelines must be developed. Many examples of quality guidelines exist for laboratories that are involved in the screening of newborns, particularly in developed programmes, and these should be obtained as examples from which to create appropriate local guidance. Contact with other programmes can be established through the International Society for Neonatal Screening (<http://www.isns-neoscreening.org>).

*Newborn screening laboratories should successfully participate in a quality external proficiency testing programme.*

Successful participation in an external proficiency testing (PT) programme using the same specimen matrix (dried blood on filter paper) is essential for demonstrating the credibility of the procedures used in the screening laboratory [85]. A number of such programmes exist internationally including the US Newborn Screening Quality Assurance Program (NSQAP) ([http://www.cdc.gov/nceh/dls/newborn\\_screening.htm](http://www.cdc.gov/nceh/dls/newborn_screening.htm)) (Figs 6 and 7), and the United Kingdom National External Quality Assessment Service (UKNEQAS) (<http://www.ukneqas.org.uk/>). Programmes also exist in France, Germany, Japan, Republic of Korea and New Zealand. Usually these programmes require quarterly reports on unknown specimens distributed to programme participants. If no programme can be found for a particular analyte of interest and/or matrix in use, documented testing reliability should be demonstrated on specimens exchanged with other well-established laboratories in the field. PT specimens should be analysed and reported in a manner identical to that used for patients if PT is to be truly meaningful.

As part of its QA programme, the screening laboratory must document analysis, frequency of quality control specimens and appropriate use of standards (or calibrators traceable to a primary standard). It must also develop appropriate expected ranges. Such limits may be tedious to define, however, their importance cannot be overemphasized. In many cases, manufacturers' suggested limits for expected values may be conservative to the point that they can cause excessive false positive results and jeopardize programme credibility. It is strongly recommended that screening laboratories carefully validate manufacturers' suggested ranges or develop their own expected range(s) using statistically valid testing procedures. Similarly, manufacturers' analytical values for controls and/or standards should be validated using local testing protocols before being routinely used in assays. Once an assay is initially established, such validations can be easily performed through parallel testing with previous lots of standards or controls.



FIG. 6. Staff of the US Centers for Disease Control preparing proficiency testing materials.



FIG. 7. Staff of the Thailand National Institutes of Health preparing proficiency testing materials.

External PT with specimens blinded to the analyst is one proven mechanism for evaluating the quality of the screening laboratory. A blinded specimen of this type can also be used to check other parts of the system. For example, the New Zealand (Australasian) PT Programme will prepare PT materials on individual collection forms so that these may then be mailed to the screening laboratory in much the same way as a patient specimen. Some programmes have used this mechanism to check the system from point of collection through result reporting. Care must be taken, however, to track the specimens to ensure that the testing results are not accidentally reported to a patient.

As the laboratory testing part of the newborn screening system matures, it will become incumbent on the national programme to provide for PT internally. The preferable model is to provide production and oversight of PT at a national centre. Currently there are two national/provincial programmes that have developed such programmes in cooperation with the US Centers for Disease Control (CDC), one in Shandong Province, China, and one at the National Institutes of Health in Bangkok, Thailand. Initially, PT specimens from the CDC are provided to the national oversight centre in sufficient quantities for distribution to all local/regional screening laboratories. Results are reported back to the oversight centre for comparison with participant results in the CDC programme. If corrective actions are needed, consultation and technical assistance is provided locally. As the capability of the oversight centre increases, the intent is to produce local PT materials that can be validated by CDC and used in a manner similar to the CDC proficiency programme (i.e. a national proficiency testing programme overseen by a single credible oversight centre).

*Larger national screening programmes should develop a central oversight programme for screening laboratories, complete with PT and periodic audits.*



### 3.3.1.2. *Non-laboratory elements*

*Quality assurance is also necessary outside of the laboratory. It should be used for improvement and not punitively.*

Often, laboratory QA and laboratory PT are mistakenly viewed as the extent to which programme evaluation (audit) is possible. However, many elements outside of the laboratory can be easily monitored and used to evaluate different elements of the screening system. For example, the quality of specimens received can be judged using criteria that have been established for specimen acceptability, and this can be used as an indicator of a submitter's ability to collect specimens. The completeness of demographic data can be evaluated, the time required to receive repeat specimens can be monitored, and the time from birth to treatment can be monitored along with the intervening steps. Quality indicators should not be monitored solely for punitive action, but rather, for evaluating and improving the system. Documentation of compliance with established criteria and the corrective actions taken when failures occur are essential components of the quality assurance process.

Setting and monitoring criteria for the time necessary to achieve certain follow-up activities can be used as the basis for a QA (evaluation) programme for follow-up. Documentation of the results of monitoring quality indicators should be maintained and periodic audits should be carried out to complete the evaluation process. Flow charts for follow-up activities should exist with time limitations as part of the overall quality assurance process and these should be included in an operations manual. For example, if it is desirable to have identification and treatment achieved by 21 days of age, then this becomes a quality indicator to be monitored. Examples of other measurable items include the time from receipt of the specimen until results are reported, and the time from birth until treatment is started. A manual of standard operating procedures (SOPs) that defines follow-up responsibilities should include realistic, attainable time lines, and corrective actions in case there are failures in achieving the goals.

*Outcome data are essential to determine the value of the programme.*

Evaluation of the diagnosis and treatment process can be accomplished using information obtained from physicians and parents. Many programmes have accomplished this process by using simple questionnaires that are periodically completed either by the parents, the physicians, or both. In some cases, programmes have found that this process works better when used as a birthday or other holiday greeting. Some of the data that might be included in such collection and evaluation efforts have been previously listed and include:

- Age at definitive diagnosis and initiation of treatment (if appropriate);
- Simplified clinical profiles of patients under treatment;
- Number of hospitalizations for disease related reasons;
- Compliance with treatment protocols;

- Long term outcome and functionality of patients (e.g. schooling, employment, psycho-social adaptation, reproductive success);
- Treatment costs.

It is also important that educational information about suspected conditions be available at the time of follow-up, and the extent to which such information is available and distributed can be monitored as a measure of programme success in this area. From time to time it may be necessary to hold focus groups with both professionals and with parents to assess the value of educational materials provided and make improvements. Examples of materials for this type of post-analytical education are available on many web sites from developed programmes and the American College of Medical Genetics is currently developing models of such materials that may prove valuable to developing programmes.

### **3.3.2. Summary**

The critical points in developing a screening laboratory for newborns that is of high quality are as follows:

- A manual of procedures for the laboratory that includes quality assurance guidelines must exist;
- Testing should include internal specimen tracking and monitoring, and documenting quality assurance of laboratory actions;
- Facilities and resources must include adequate instrumentation, appropriate consumable supplies, instrument maintenance and calibration;
- Staffing must include adequately trained personnel;
- Filter paper cards used for specimen collection should be the same as those used for quality control and kit calibration materials;
- Date (time) of specimen collection, date (time) of receipt in laboratory, and date (time) of reporting must be rapid and monitored, and corrective actions must be taken when these tasks are not done in time;
- Quality of assay performance should include monitoring reagent quality, success in internal and external assay quality assessment, and result validation before release;
- Laboratory reporting should occur in a timely fashion for all tests, with particular emphasis on rapid reporting of presumptive positive tests;
- A system of clear communication that ensures the proper transfer of the test reports to the appropriate person must exist to ensure rapid follow-up.

The critical points in developing a programme that is of high quality outside of the laboratory are as follows:

- A follow-up procedure manual that includes flow diagrams must exist for necessary actions and QA.
- Follow-up staffing must include adequately trained personnel.
- Tracking should include defined follow-up actions before considering a case 'lost to follow-up' and these should be as extensive as practical.
- Educational materials explaining the programme should be available to parents before and after delivery as needed, to explain the condition (for positive tests).
- In cases where testing results are positive, educational materials should be available to physicians that describe what immediate actions need to be taken and provide additional resources for further reference.
- A system for providing follow-up patient information (outcome progress) from the programme should be established and used to evaluate programme activities.

### 3.4. QUALITY INDICATORS

#### 3.4.1. Introduction

*Quality assurance should be an overriding concern throughout the newborn screening system.*

It was noted in the previous section that the overall objective of QA for newborn screening is to ensure the highest quality for the services provided. Creation of a QA plan, a QA manual and selection of appropriate quality indicators are essential to the process of programme evaluation [84, 85]. An effective QA system includes identifying (auditing), documenting, and correcting problems. Overall, good QA leads to continuous improvement in the quality of the newborn screening system. Some of the basic programme components that must be assured in order for the newborn screening system to succeed include:

- A competent staff;
- Appropriate education throughout the system;
- Effectiveness of specimen processing;
- Appropriateness of analytical testing;
- Accuracy, reliability, and speed of testing and reporting;
- Efficient and effective confirmatory testing;
- Rapid availability of appropriate diagnostic services;
- Appropriate long term outcome.

The concept of dividing the screening process into three stages: pre-analytical (education and specimen collection), analytical (laboratory testing), and post-analytical (follow-up, diagnosis, education, management and evaluation) has been introduced. Any QA programme that is developed for the screening of newborns should be comprehensive and cover these pre-analytical, analytical, and post-analytical components of newborn screening. In some cases, particularly with the laboratory, it may be appropriate to have monthly or bi-monthly QA meetings focused on specific methodology improvements. With other programme functions, such as timeliness of follow-up, formal QA evaluations may be effectively performed less frequently due to the lower numbers of events being monitored.

*Responsibilities within the newborn screening system may be logically divided into three general categories:*

- *Pre-analytical,*
- *Analytical,*
- *Post-analytical.*

### 3.4.2. Examples of quality indicators

#### 3.4.2.1. Pre-analytical processes

Includes review and monitoring of any activity occurring prior to testing the specimen. Items that might be monitored for QA include:

- At the birthing facility
  - Number of parents who refused screening and the reasons why;
  - Number of newborns screened compared with the number of births;
  - Accounting practices, including the number of delinquent collections and speed of internal payments between birthing facility and parent and testing laboratory;
  - Records showing specimens submitted and results received with appropriate documentation of follow-up actions;
  - Time from specimen collection and submission until receipt of results;
  - Legibility of data accompanying submitted specimens;
  - Number of unsatisfactory specimens returned for retesting.
- At the screening laboratory
  - Number of demographic data errors categorized by the person who submitted them;
  - Number of unsatisfactory specimens, categorized by reason for their unacceptability and facility that submitted them;
  - Records of specimens submitted and results received for each newborn;
  - Timeliness of specimen collections (i.e. accounting of number of specimens collected too early);
  - Time from specimen collection until receipt at screening laboratory;
  - Documentation of appropriate staff training (including formal education completed and credentials) and cross-training;

*Pre-analytical processes occur in obstetric offices, at birthing facilities and in the laboratory.*

- Written operating procedures for all laboratory testing and related activities with appropriately annotated updates and supervisory reviews;
- Documentation of preventive maintenance schedules and preventive maintenance for instruments in the laboratory;
- Temperature records and related actions when out of compliance with QA standards, for refrigerators, incubators, and other temperature sensitive laboratory equipment;
- Checking that all reagent vials/flasks are labelled and that the date they were opened is noted on the label.

#### 3.4.2.2. Analytical processes

This includes the review and monitoring of activities associated with actual laboratory testing. Items that might be monitored for QA include:

- Only at the screening laboratory
  - Written manual of procedures with appropriate documentation of annual supervisory review and periodic updates, as needed;
  - Documentation of individual assay validity through tabulation and analysis of selected assay parameters, including such items as slope of analytical curve, distribution of specimen results, variation in selected counting standards (in radiometric testing) and inter-assay and intra-assay variability of standards and controls;
  - Validation of analytical concentrations for assay controls and standards being used;
  - Assay validation data when new reagent or other assay variables change, including new controls and standards (i.e. through parallel analytical runs);
  - Documentation of acceptability of external variables possibly affecting testing (e.g. temperature of reagents, background radiation and current activity of testing reagents in radiometric testing, proper instrument functioning);
  - Documented accuracy of computer generated reports (e.g. random checking);
  - Documented review of analytical results by supervisory personnel prior to final release;
  - Documented transmittal and receipt of presumptive positive and unsatisfactory reports to follow-up personnel (e.g. phone logs, fax logs, fax receipts).

*Analytical processes occur at the screening laboratory.*

### 3.4.2.3. Post-analytical processes

This includes review and monitoring of any activities that occur after specimen testing. Items that might be monitored include:

- At the screening laboratory
  - Acceptability of laboratory turnaround time (monitored by checking the date of receipt of the specimen and comparing it with the date of the result report);
  - Quality and usefulness of report including: legibility, readability, expected results, explanatory notes and test results;
  - Appropriate storage of residual specimens and ability for them to be retrieved in a timely, efficient, and accurate manner;
  - Appropriate record keeping of analytical results, controls, and standards in place based on local requirements.
  
- Outside the screening laboratory
  - Timeliness of laboratory reporting to physician for both normal and abnormal findings (monitored by checking date of report);
  - Adequacy of reporting procedure (monitored by checking date of receipt of the specimen and comparing it with the date of the result report);
  - Availability and degree of distribution of educational, factual information directed at professionals and parents about conditions reported as not normal;
  - Timeliness of confirmatory testing (from date of birth to time of testing);
  - Timeliness of diagnosis (from date of birth — however, the natural history of some forms of the condition detected may make final diagnosis difficult and slow);
  - Compliance with treatment (subjectively by asking parent or physician; objectively by assessing outcomes);
  - Number of presumptive positive or unsatisfactory findings for which follow-up is incomplete;
  - Number of diagnosed conditions resulting despite screening;
  - Number of diagnosed conditions for which screening was not performed.

*Post-analytical processes occur at the screening laboratory, at physician's offices and in diagnostic laboratories.*

### 3.4.3. Summary

Laboratory quality indicators include:

- Analytical/reporting turnaround time;
- False positive rate;
- False negative rate;
- Performance in external PT programme(s);
- Available/updated operating manual;

- Trained/cross-trained personnel;
- Record keeping:
  - Maintenance,
  - Analytical performance,
  - Patient records (physician contact, etc.) ,
  - Corrective actions.

Non-laboratory quality indicators include:

- Number of reason for rejected specimens;
- Number of reason for parents opting out (in);
- Recalled patients ‘lost’ to follow-up;
- Educational materials available/provided;
- Time in transit for specimens/reports;
- Time from birth to diagnosis/treatment;
- Extended follow-up:
  - Compliance with medication/management,
  - Morbidity/mortality data,
  - Overall health outcome,
  - Costs (for cost–benefit comparisons).

**Part 4**

**IMPLEMENTING AND SUSTAINING  
THE SCREENING PROGRAMME**





#### 4.1. INTRODUCTION

Successful newborn screening programmes usually begin with the efforts of an interested individual or group of individuals concerned with improving a particular aspect of children's health. They succeed in bringing about improvement through the continued efforts of dedicated persons working to build and maintain the system that provides the needed service(s). In all cases, newborn screening exists in unique political, cultural, and economic circumstances. Newborn screening must be responsive to its environment. This is true both in developing and developed countries.

*Newborn screening is a system that must be responsive to local:*

- *Politics;*
- *Culture;*
- *Geography;*
- *Economics.*

Ultimately, a successful newborn screening system results from the collaborative efforts of different sectors of the local society. These sectors can be classified broadly as government organizations, non-governmental organizations and individuals. Successful newborn screening programmes have demonstrated that team efforts and partnerships, along with realistic planning and education, are critical to successfully implementing a national newborn screening system. The success of any public health programme usually hinges on two important aspects. First, it must be beneficial and acceptable to its target audience and second, it must be a collaborative partnership between many different sectors of society. Key to implementing and sustaining an efficient and effective screening system for newborns are (i) understanding the importance of screening for the health of all children and (ii) personal dedication to this cause. Certain critical points that must be considered in developing and sustaining a successful newborn screening programme are summarized in Table 13.

#### 4.2. ADVOCACY

Many new public health programmes have succeeded in the past in part due to active public advocacy efforts aimed at target clients and the public in general. In order for the screening of newborns to be successful, people must know about this practice, accept that it is medically effective and that the system is efficient. Therefore, it is important to take advantage of every opportunity to educate and inform. In order to ensure that sufficient emphasis is placed on public relations, it may be advantageous to assign a staff member to this responsibility. Many examples of successful public relations activities exist among newborn screening programmes and it is not necessary to 'reinvent the wheel' in order to obtain a number of useful examples of outreach activities that can be adapted to the local situation.

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**TABLE 13. CRITICAL CONSIDERATIONS IN DEVELOPING A SUCCESSFUL AND SUSTAINABLE NEWBORN SCREENING PROGRAMME**


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- An individual or group that champions newborn screening (screening for CH).
  - Preliminary screening activities that develop supportive data such as a pilot or regional screening project, and preliminary infrastructure development.
  - Education and influence of policy makers (Ministry of Health, politicians) to include newborn screening (screening for CH) as a routine programme in the national health service.
  - Use of the media and other public relations efforts to boost support and coverage for newborn screening activities.
  - Creation of a mechanism to fund routine newborn screening (screening for CH).
  - Development of national coordination for the established programme by the Ministry of Health — i.e. by ensuring advisory, monitoring and audit roles.
  - Recognition and development of a method for continuous evaluation and improvement.
- 

#### 4.2.1. Experts

*External experts can be used to increase programme knowledge and visibility, particularly with high level policy makers.*

In developing a newborn screening programme, health care officials should consider the use of external experts to assist in presenting programme information at professional meetings whenever possible. In addition to local screening programme advocates, external experts with newborn screening programme experience can often be useful in ‘spreading the word’ and answering technical questions. If there is a particular developed country that has more influence over medical decision making at the local level, health care officials might want to obtain expert consultants from that country. The International Society for Neonatal Screening and the US National Newborn Screening and Genetics Resource Center can provide important professional contacts in this regard.

Sponsorship and organization of national meetings in which newborn screening is explained and the local programme logistics are discussed in detail have also been effective in many countries. In developing programmes, the health ministry is usually an important political and organizational ally to include in national meetings in which newborn screening is discussed. It is sometimes prudent to support and assist the Ministry of Health as the primary sponsor of both national and local newborn screening events. If there is a national health plan, it is important to work at including newborn screening in the plan. For example, the Ministry of Health in the Philippines recently supported the introduction of legislation that resulted in a national law requiring the offering of newborn screening there. The Ministry of Health in South Africa recently released a national genetics plan in which the future of newborn screening for genetic conditions was acknowledged as a possibility, despite limited programme support in previous years.

This acknowledgement presents the developing programme in South Africa with the hope that, by developing pilot data on newborn screening, the Government will support the screening programme and thereby contribute to the improved health outcomes that result.

#### 4.2.2. Recognition

Awards that acknowledge the cooperation and leadership of professional individuals and organizations can also be effective public relations tools. This type of activity has been particularly useful in the Philippines, where many examples of such endeavours exist. Most notably, awards have been presented to hospital directors for display in their offices and hospital foyers, acknowledging and recognizing the hospital's participation in varied newborn screening activities. Recognition can initially acknowledge institutional cooperation with the programme and then become increasingly more descriptive and meaningful as the programme advances. In some cases, hospital banners, poster displays, or prominently displayed announcements have been strategically used to advertise the programme. Other types of public relations materials have also been used to routinely make parents aware of the programme including items such as pins, descriptive magnets, pencils and pens. While these items may not be free, often commercial sponsors are willing to assist with the expenses involved (see Appendix VI).

*Recognition of individuals and groups can play an important part in gaining support within the community.*

#### 4.2.3. Media

It is prudent for the programme to develop educational information early and to provide this information to the news media whenever possible. In most countries, a significant percentage of the population can be reached through various public media. Care should be taken to cultivate media representatives who will advocate for the programme. A press release or brochure can be very useful in spreading programme information among the written press. Radio and television opportunities should not be overlooked. Both of these media are usually available to health prevention programmes and reach the majority of the population. Advocacy for newborn screening has been advanced through press conferences, magazine and newspaper articles, radio and television public service announcements, and topical shows. Many television and radio stations are willing to air public service announcements at little or no expense. Health professionals and parents can be very effective proponents of the programme and can also be effective in influencing the media. Videotape(s) can be produced with programme information and used in media advertisements when opportunities arise.

*Media exposure can promote programme awareness.*

Radio exposure, especially in developing countries, assures broader information coverage since the population is more likely to

have access to the radio. In the Philippines and Thailand, for example, newborn screening has been promoted on several occasions through radio interviews and informational presentations. In Thailand, a national symposium on newborn screening featured the Minister of Health, who held a widely publicized press conference with visiting expert consultants answering technical questions. In Guatemala, the dedication of a newborn screening laboratory provided an opportunity for an interview on a local radio that described the new facility and its usefulness in newborn screening. The media have also played a role in some cases where patients that needed follow-up services were difficult to locate. There have been several instances where radio appeals to the public for assistance in locating patients resulted in timely follow-up confirmation and/or treatment for a serious condition identified through newborn screening.

#### **4.2.4. Government organizations**

*Government organizations can provide support through established support and networks.*

If the programme is accepted as a government responsibility, advocacy efforts can be broad. The government agency responsible for physician and health related professions can be asked to include topics related to newborn screening in the curricula of health allied courses (such as medicine, nursing, and midwifery). Government organizations, such as the Ministry of Health, can be asked to develop and conduct non-formal education courses such as seminars for midwives, or prenatal training for prospective mothers. Where national legislation is considered helpful, newborn screening advocates will likely be important players in developing legislation and encouraging legislators to support passage of the legislation. In some developing countries, government assistance has often included the use of government facilities for educational seminars and workshops. In the Philippines programme, banners were installed free of charge in pedestrian overpasses in Manila, with the approval of the local government leadership. Government nurses have been utilized in China to spread the word about screening by riding on the back of open trucks and using bullhorns to announce the programme. Government funds have been used for producing simple brochures or comic books giving basic information about newborn screening. In Thailand, Government funds were helpful in supporting visits of Thai health officials to developed programmes outside of Thailand.

#### **4.2.5. Non-governmental organizations**

*Non-governmental organizations can provide support through increased public awareness.*

Members of NGOs or the private sector can also be important partners in establishing a successful newborn screening programme through their command of local customs, their understanding of local issues and their local experience outside the governmental setting. The non-governmental sector includes academic institutions,

non-government health professionals, insurers, professional societies, hospital administrators, civic organizations, the media, sectarian and religious groups, parents' and patients' organizations, and the general public. Non-governmental organizations have an important advocacy role. Health professionals in private hospitals and other non-governmental academic institutions can be useful in promoting newborn screening among their peers. Private academic institutions can assist in advocacy and the development of materials for education. Professional societies can advance newborn screening through policy statements and other professional activities and advocacy. For example, the AAP has impacted newborn screening in the USA and throughout the world through its various policy statements, fact sheets, task force reports and general advocacy among its paediatrician members. In the USA, NCCLS has been active in publishing guidance on procedures relating to the collection of specimens and data standardization for newborn screening.

Awareness campaigns conducted by professional societies can create a lasting impact among their members and the public since these societies are generally regarded as opinion leaders in health. Inclusion of newborn screening in their professional educational activities and positive endorsements can markedly improve the acceptability of newborn screening by the public, politicians and other health professionals. In the Philippines, the Philippine Pediatric Society (PPS) and the Philippine Obstetrical and Gynecological Society (POGS) were instrumental in organizing the newborn screening programme in Metro Manila that is now expanding throughout the country. Advocacy among hospital administrators was another critical step in advancing Philippine newborn screening, and it has also been a useful component of other developing systems for the screening of newborns.

Public service organizations such as the Lions Club and Rotary International have also played an important role in advancing newborn screening in some countries. In several instances, these organizations provided funding for such items as informational materials, laboratory equipment, laboratory facilities and services for charity patients. UNICEF provided support funding for the production and distribution of informational brochures on newborn screening in at least one country and the March of Dimes Birth Defects Foundation has provided financial support for expert speakers at some national meetings on newborn screening in developing programmes.

Sectarian and religious groups can also have a significant influence on the population and their acceptance or rejection of principles of screening can be influential in the attitude of the public. Integration of newborn screening concepts in religious activities such as pre-nuptial seminars for couples can help in promoting an understanding of the significance of newborn screening. Informing future parents about newborn screening can also provide them with an

opportunity to save money for the payment of a newborn screening fee, if this is required.

#### 4.2.6. Parents

*Parents can be important advocates of a newborn screening programme.*

Parents (private citizens) can also make significant contributions to the success of newborn screening. Once parents understand the advantages of newborn screening, particularly if they experience its success first hand through a child detected and treated as a result of a programme, they usually become dedicated advocates for programme acceptance in the community. They can help immensely in creating a demand for newborn screening in communities or hospitals that may be sceptical about the programme. As an example, the programme in Thailand has created an advocacy/informational videotape in Thai that describes in detail, with family examples, the value of newborn screening in the northern iodine deficient regions of the country. In the USA and some other developed countries, parent support or advocacy groups have played a crucial role in lobbying for government and other support for screening activities. One parent support group in the USA has even established a national newborn screening awareness week in which it widely publicizes the benefits of successful and comprehensive newborn screening. In the Philippines, a support group of parents helped with a newborn screening awareness campaign held in October 2000. And, in China, a parent support group has been influential in explaining the value of screening to pregnant mothers and prospective parents.

#### 4.2.7. Health professionals

*Health professionals must understand their role and receive appropriate recognition.*

General physicians, paediatricians, obstetricians, health administrators, and other private practitioners also have an important role to play in advocacy for the screening of newborns. It is essential that health professionals be made aware of the existence and importance of the newborn screening programme. They should be given information on the history of the programme, the rationale for its existence, programme benefits to individual newborns, families and society, the financial strategies involved and future plans for the programme. The availability of information and education allows advocates to be informed and to provide information to others. It is the education and understanding of a few key individuals that can often determine the acceptance or rejection of newborn screening as a routine medical activity in local hospitals. In addition to the usually strategy of providing talks at professional meetings, workshops and seminars, the programme in the Philippines has found increased advocacy through organizations such as the national nursing society, the National Academy of Science and Technology, and local medical societies. Similar successes have been demonstrated in Thailand, Republic of

Korea, Indonesia and throughout East Asia. Training and awareness seminars not only provide educational opportunities, they strengthen the advocacy of those who get involved.

#### 4.3. INFRASTRUCTURE

Because a national programme for the screening of newborns is usually formulated within the government sector, it necessarily must conform, at least partially, to a government infrastructure that already exists. Ideally, newborn screening may be added to an existing health programme such as maternal and child health, where it can take advantage of an already established framework. It is likely that other government infrastructures can be utilized to provide assistance to the programme as it is being developed. For example, the Ministry of Health often oversees government hospitals and has a system of health clinics and nurses in place. This infrastructure has the potential for rapidly providing a mechanism for spreading newborn screening opportunities throughout the country, including remote areas. Without access to such an infrastructure, a newborn screening system that is in the initial stages of formation is destined to take a longer time to develop, as a similar system will have to be reinvented.

There may be other government programmes that can provide assistance to newborn screening if their purpose is to improve public health service and systems of care. For example, birth or near-birth immunization programmes may provide a mechanism for collecting and transporting newborn screening specimens by using immunization programme personnel already in place as specimen collectors. Similarly, the transport networks used for immunization supplies might be available for the transport of specimens for the screening of newborns. In some settings, educational activities for existing child health programmes might be modified slightly to include educational components on newborn screening. Health records systems already in place might be simply modified to include newborn screening in individual health records, without the need to develop a new and parallel system. Government transport systems may already exist for other purposes and these could serve as mechanisms for the transport of specimens for newborn screening. It is important to take advantage of any available government networks and personnel that can be utilized for screening activities rather than trying to provide similar, and often duplicative, systems.

*Partnering with the national immunization programme should be considered for newborns in distant/difficult locations.*



#### 4.4. POLICY MAKING

*Government support is important for programme sustainability.*

Government is responsible for ensuring the health and survival of the population it serves. Government can include legislative bodies (the national or federal assembly, congress, senate, or parliament), government agencies (different departments or ministries such as those dealing with health, nuclear or atomic energy, or education), and local organized leadership (state or province, city, town, and village). The roles played by the government and governmental organizations in promoting, establishing and sustaining newborn screening systems are essential to the survival of these systems.

The United Nations Convention on the Rights of the Child (<http://www.unhchr.ch/html/menu3/b/k2crc.htm>) requires signatories to “recognize the right of the child to the enjoyment of the highest attainable standard of health” [Art. 24(1)]. In ensuring this right, parties are to take appropriate measures to “diminish infant and child mortality” [Art. 24(2a)] and to “ensure the provision of necessary medical assistance and health care to all children with emphasis on the development of primary health care” [Art. 24(2)]. A large number of countries have ratified or are in the process of ratifying, this convention. The screening of newborns, in this regard, is a major step forward in primary health care for all children: this is a compelling argument that can serve to persuade the government policy makers of the need and benefits of newborn screening.

Government usually maintains the public’s health through policies that may be established as governmental proclamations, laws, policies, administrative orders, or policy related rules and regulations. Properly developed and administered health policies include assignment of responsibilities for health programme implementation and administration at all levels of operation. Health programmes that result from government policies ultimately lead to plans of action that develop organizational structures for the programme at all levels, including implementation at the local level. In addition to developing a financial strategy for administering the system, health plans usually define roles and responsibilities of each part of the organization and outline the steps necessary for programme implementation.

In some successful newborn screening programmes in developed countries such as the USA, successful universal (full population) implementation of newborn screening required passage of laws, while in other countries it became the national standard of medical care without the necessity of a law. It is important to note that even in China, with over 20 million newborns annually, a national mandate now exists encouraging the gradual development of a newborn screening programme to improve the health outcome of newborns as part of the law governing the health of mothers and their children. In Thailand, there is a national public health policy that supports newborn screening and provides insurance coverage as part of the maternity package of the

national health insurance programme. In Uruguay, there was a presidential proclamation that declared that all newborns should undergo newborn screening. In the Philippines, there is a Department of Health administrative order calling for the nationwide implementation of newborn screening and a national law was recently enacted requiring health care workers to make newborn screening available to all newborns.

Non-governmental organizations can also have an impact at various levels on policy making for newborn screening. For example, it has been suggested that newborn screening as a service to patients should be included in the regulations towards accreditation and renewal of private hospital licences in at least one country. At the hospital level, the hospital administrator and/or the medical director can issue directives that directly affect the implementation of newborn screening in that hospital. Since most developing programmes encompass a large number of hospitals that do not belong to the government, it is important to identify a contact person at each birthing facility who can assume responsibility for the organization and implementation of the programme within that facility. As newborn screening advisory committees are organized, it is important to include representation by NGOs and professional societies in these committees. In this way, the programme can obtain multidimensional input into its policy making decisions.

*Non-governmental support is also helpful in sustaining programme interests.*

#### 4.5. IMPLEMENTATION

In order to be sustainable, newborn screening must be developed as a comprehensive system. Formal recognition and institutionalization of the newborn screening programme within the public health system is one of the most important steps in implementing and sustaining newborn screening. To accomplish this, it is likely that public–private partnerships will be necessary if maximum programme efficiency is to be obtained. Where government support is available, integrating newborn screening into existing public health and other public service programmes can facilitate implementation.

As an example of the utilization of existing government programmes, it is often possible to build on other programmes to create networks for collecting and transporting specimens, recalling potentially positive patients for confirmatory testing, ensuring proper management of detected disorders, and monitoring patient outcome. Academic centres may be helpful in providing expertise for the preparation of training and educational materials, and for managing and treating patients that have been identified with a disorder through screening. Often academic institutions and private laboratories with a disorder can provide follow-up laboratory services for confirming the

*Newborn screening must be implemented as a system in a way that will lead to its sustainability.*

presence or absence of disorders and for monitoring treatment and/or compliance with treatment.

*Prompt recall is critical.*

Prompt recall of patients with a suspected disorder which has been identified through screening is one of the critical parts of the system because such patients are usually asymptomatic and early detection and treatment is essential to optimal outcome. Health clinics that belong to the government and are public, in tandem with outreach programmes, provide a means of patient contact that can be particularly useful in both rural and urban settings. In the urban environment, government clinics and hospitals are usually available to the majority of the population and they should be utilized as part of the follow-up system. In rural areas, public health nurses, local clinics, and an informal health network usually provide the necessary follow-up.

*Integration with child health programmes should be considered.*

Building on the synergies of other government health programmes for infants and children can sometimes provide a unique opportunity for faster and broader programme development. For example, programmes that include actions such as vaccinations that begin at or near birth are often well established and reach most newborn populations in developing countries. Adding newborn screening to vaccination programme activities has successfully aided programme implementation and outreach in at least one developing country. Utilizing immunization staff and networks already in place for vaccine delivery allowed for full newborn screening coverage within a very short time. While this model may not work in every setting, it offers an opportunity to reach babies born in remote areas where an established 'near birth' immunization is already effectively established and sustained.

*Subspecialists should be considered.*

In order to succeed, it is important that subspecialty care (e.g. paediatric endocrinology in the case of CH) be available in order to assist with proper diagnosis and patient management. Subspecialty care may be available at, or in conjunction with, government hospitals or medical centres or in the private sector. In cases where a subspecialty provider is desired but not available, it may be necessary to rely on a physician who has had experience with such cases in his(her) training, or who has a special interest in the condition of concern. Subspecialty care and availability can be a challenge in a developing country, but it is an integral part of the newborn screening system and must be a continuing consideration. Likewise, pharmaceuticals used for treatment may be difficult to obtain in a developing country and it may be necessary to cultivate relationships with suppliers outside the country in order to implement and sustain the treatments necessary to take advantage of the screening system.

*Education at all levels is essential.*

Education about newborn screening and the medical implications of early biochemical testing must also be available to the public and the health care community. Continuing education must also be a priority for programme managers as they seek to work through their own programme difficulties: 'train the trainer' workshops in developing

regions are one example of effective educational training. For education within a developing programme, it is prudent to obtain training videotapes and literature from developed programmes — these can serve for developing local educational materials. Many materials of this kind exist around the world. Once developed, it is a simple matter to update materials periodically for sustainability. Eventually it may be possible to include newborn screening as a part of the education curriculum in formal training programmes for health care workers and physicians, including medical schools.

Logistics are a major concern in most developing programmes and agencies: in this regard, organizations that handle transport and communication can be asked to assist in establishing and sustaining a logistically sound newborn screening system. For example, it may be possible to develop special shipping arrangements with courier, bus and postal services. Likewise, special telephone, telefax, or other telecommunication arrangements and fees may facilitate result reporting. In instances where immediate (emergency) testing follow-up is needed, government police may be able to assist and several examples of such assistance exist. In at least one programme in the USA, the agency in charge of locating missing persons assisted in locating babies for critical follow-up when their address proved to be fictitious or outdated.

*Programme logistics cannot be overlooked.*

Public-private partnerships have played a valuable role in establishing and sustaining successful newborn screening programmes around the world. Concerned businesses have sponsored important organizational and educational meetings and conferences, and some have even incorporated newborn screening into their social action agenda by paying the screening costs for some charity patients. Often, private businesses have paid expenses for experts from developed programmes to assist developing ones. Contributions from private companies have supported scientific visits of staff from developing programmes as they seek to transfer knowledge from more developed programmes.

*Public-private partnerships may be important to overall programme success.*

In many cases, private laboratories have also played an important role in confirming screening test results and providing diagnostic testing to assist with diagnoses. It has been demonstrated repeatedly that laboratory testing for screening purposes that is centralized and processes a high volume of specimens is more efficient than hospital testing that processes a smaller volume of specimens and that it provides higher quality results for patients. However, private laboratories or hospital laboratories sometimes anticipate that low volume testing can improve their profitability and thus, they attempt to establish low volume newborn screening laboratories. Such laboratories have the potential for fragmenting the screening system by generally providing lower quality service at higher costs, and not contributing to the national data collection effort to evaluate the screening process. Nonetheless, partnerships with such laboratories for the provision of confirmatory

testing services on serum can provide a viable alternative for them to work in parallel with laboratories for newborn testing; these kinds of partnerships prevent unnecessary competition with the national programme.

*Confirmatory testing must be of high quality.*

The availability of quality confirmatory testing is often assumed by the managers of the screening programme and little thought is given to monitoring the quality of this testing. Consideration should be given to ensuring quality systems for confirmation facilities. For example, in thyroid screening, laboratories and nuclear medicine facilities that provide confirmatory testing (e.g. thyroid profiles, bone scans) should have the appropriate credentials to ensure quality services. External PT is another way of assessing performance and is as important for a confirmatory laboratory as it is for a laboratory that is dedicated to newborn screening. In cases where appropriate confirmatory testing is not readily available, the programme should develop a listing of available service providers in other locations and assist in obtaining any needed testing services.

#### 4.6. FINANCIAL IMPLICATIONS

*Screening should be available to all infants.*

In most cases where newborn screening is a national or local government mandate, a portion of the government health budget is allocated to support the programme. However, in some cases, national or local government budgets do not include funding for the screening of newborns and the programme is left to obtain funds through other means. Many developing programmes find that a fee is necessary when the programme is starting up in order to defray the expenses of testing. While some may view a newborn screening fee as unnecessary or too expensive, the fee charged is usually significantly less than the cost of most other pre-natal activities. Relative to other health care costs, newborn screening is considered inexpensive in most settings. In order to encourage screening, a plan should be developed to encourage prospective parents to save for it. Altruistic organizations or local governments may also participate in programme financing in order to lower or eliminate costs. Alternatively, it may be of benefit to educate prospective grandparents on the value of screening, and they may in turn assist in paying or contributing to the payment of any fee that may be required. Ideally, no one should be refused screening because of their inability to pay, but this idealistic goal usually can be reached only after the programme is established and costs can be supplemented with some sort of government or insurance assistance. It is important for the newborn screening programme to develop local financing models and advocate for their use.

*Sound budgeting must support all programme components*

*Financing should cover all aspects of the screening system.*

A comprehensive listing of all system expenses should be maintained and used for budgetary planning. System funding should cover screening laboratory costs, follow-up services (including

education and counselling), computerization, advisory committee meetings, and QA site visits to screening laboratories and birthing facilities. System funding may include supplemental payment for some of the costs relating to treatment if local circumstances permit this (e.g. drugs, foods). Two primary fee collection mechanisms exist: (1) direct bill to the birthing facility following testing and (2) billing for collection cards that are purchased prior to screening. The former requires that the programme pay for itself pending payment after testing, while the latter can be established in such a way as to have the collection kits paid for in advance of testing. When fees for newborn screening are collected from the sale of laboratory collection kits, care must be taken to make the fee comprehensive so that non-laboratory costs are also covered. In all cases, sound accounting principles should be followed in establishing the fee. Any monies generated from newborn screening fees should first be used to pay for programme expenses before they are used for any other purposes. In some cases in programmes in the USA, funds collected from screening fees have gone into general revenue accounts of the government for redistribution to the programme, and this has invariably led to the use of these funds for other government programmes that may not have had sufficient funding. This practice detracts from programme improvement and should be avoided if at all possible.

Because adequate funding is essential for a programme for the screening of newborns, a great deal of effort must usually be expended in developing necessary costing data and financial planning. Additionally, in cases where fees are necessary, a sound billing and collection system must be developed and implemented. Some programmes have found that billing hospitals for testing after it is completed, without an efficient collection system, results in postponed payments that eventually cause the programme to encounter financial difficulties. Good advance planning can help avoid this problem.

#### 4.7. NATIONAL COORDINATION

It is often the case that implementing and sustaining a newborn screening system requires the help of advisors. Strong leadership is critical and usually falls initially to the person or persons who have advocated most strongly for the programme. Eventually it is necessary to include others to assist in decision making for the programme, and this requires wisdom and tact. Most developed screening programmes have a newborn screening advisory committee of some type, not only for advice, but also for professional assistance and advocacy. Aside from technical expertise, the advisory committee might also include individuals who can adequately represent professional and community groups interested in or impacted by newborn screening.

*A State's health ministry should ultimately assume national coordination and oversight.*

As the programme develops, so can the advisory committee. Whilst initially, it may be advisable to work with a small 'core' group of organizers in order to define the infrastructure needs and programme development approaches, it is usually prudent to invite local physicians knowledgeable in treatment of the conditions included in screening programme. They can play a key role in developing programme guidance and gaining acceptance and cooperation of other community physicians. It may also be useful to include representatives from public health, parent advocates, obstetricians, and others who might have a role in the screening process, such as insurers and hospital administrators. Carefully chosen, the members of the advisory committee can gather the appropriate input and external support necessary to progressively develop a comprehensive programme. Depending on local customs, it may also be beneficial to develop formal committee guidance including a formal committee charge and meeting rules. Most programmes have benefited from published minutes of committee meetings that are circulated widely among the interested newborn screening community.

If the newborn screening programme develops outside of the health ministry, for example in an academic setting, it will eventually be prudent for it to move there given its impact on public health. In this case, care must be taken to maintain already established momentum. This may mean that the initial administrative head of the programme needs to continue to serve in this role through the transition to a recognized health ministry programme. It will likely be most effective if there is sharing of advisory responsibilities until stability is achieved and the programme is sustainable. At this point, the health ministry can assume full responsibility and oversight.

#### 4.8. EVALUATIONS AND AUDITS

*Evaluation is essential to programme improvement and should cover all programme components.*

In order to show that the screening of newborns to detect congenital disorders is a valuable health programme, it is necessary to obtain incidence and outcome data. The incidence data are required to show that there is a need for screening to prevent negative health outcomes and the outcome data are required to show that the programme is working. Once data have been collected, they can be used to establish cost effectiveness and importance for public health. In some settings, the government has provided an impetus for programme evaluation through budgetary restrictions that are tied to the outcome of the programme. Sometimes the creation and maintenance of birth defect registries that include patients who have undergone newborn screening has been a useful resource for monitoring long term programme benefits. In addition to providing a reference source from which to extract periodic outcome information, the creation and maintenance of registries of this type have been used to assist in organizing parent support groups. In this way there is family-to-family support and an

opportunity for the programme to provide family assistance on a more personal level. An assessor benefit of parent support groups can be programme advocacy to convince policy makers of the importance of institutionalizing and of continuing support for newborn screening.

The programme needs to be evaluated inter alia by reviewing the various data that have been compiled, in order to identify strategies for improving the entire newborn screening system. This method of evaluation is particularly recognized and utilized in the laboratory setting, but should also be applied to the programme in whatever ways are available. For example, testing data can be used to monitor the extent to which screening is expanding and may be useful in determining the location of satellite laboratories so as best to serve the population being screened. It is prudent to develop cost effectiveness and financing studies using programme data to facilitate government understanding and support for the screening of newborns, both nationally and universally.

*Data are essential for evaluation.*

Academic institutions, as part of their research agenda, can provide assistance in programme evaluation. Epidemiologists and statisticians have been used to develop incidence data from programme records and these data have in turn been used to provide a basis for recommending that certain disorders be screened. Health economists have often been involved in determining cost effectiveness of various newborn screening strategies. Ethicists have played a role in developing issues relating to consent and have been involved in issues relating to the storage and use of blood specimens after these have been utilized for the newborn screening process. Parents and representatives of professional and community groups have often been included in advisory committees to newborn screening programmes to ensure that these are serving the needs of the community.

#### 4.9. SUSTAINABILITY

Developing programmes can build on over four decades of experience in organizing successful newborn screening systems. Experience shows that the obstacles and challenges that face developing programmes remain, but the errors made previously by others need not be repeated. It is essential that collaborations be established with developed and other developing programmes so that time, energy and resources will not be wasted. Additionally, consideration should be given to the possibilities of expanding the disorders that are to be detected through screening by building on the infrastructure that is already developed within the screening programme. Examples of developed and developing programmes exist locally and around the world. Programme and personal collaborations can occur over the Internet, through contacts at international meetings, and through personal interactions. Furthermore, signatories to the United Nations



Convention on the Rights of the Child are “to undertake to promote and encourage international co-operation with a view to achieving progressively the full realization of the right recognized in the present article” (i.e. access to health care services that reduce infant and child mortality and provide improved primary health care for the child) (Art. 24(4)).

*Newborn screening is a public health programme and must benefit the public.*

Newborn screening is ultimately a public health programme. If the programme is initially supported through grants or contracts within the nuclear energy agency in the country, as with many IAEA projects, then collaboration between the nuclear agency and the health ministry is essential to the long term success and sustainability of the programme. Likewise, collaboration with the education ministry or the academic affairs ministry is usually necessary if university medical schools and hospitals exist within the coverage area. In countries with large religious groups, collaborations with religious leaders will likely prove beneficial. Religious institutions are in the position to provide strong programme advocacy in such settings. Because government funding and/or insurance coverage will likely be a pressing need in most programmes, it is useful to build relationships with government officials and insurance industry representatives. Similarly, in order to achieve the maximum exposure at the local level, collaborations between the programme and the media, concerned parents, and local non-government organizations can prove to be extremely beneficial. For example, Rotary International gave considerable support to the building of a new laboratory facility that would be engaged in newborn screening and immunizations in one Latin American country, and there are numerous examples of press releases, radio and television interviews, and newspaper advertisements in many countries that show the results that can be achieved when several groups of stakeholders work together.

Throughout East Asia, Latin America, West Asia, the Middle East and Africa, there are many newly developing programmes. IAEA projects exist throughout these regions and regional meetings have had a positive impact on exchange of ideas, planning, and success. Local collaborations are usually the result of the efforts of one or two local programme leaders. They result initially from the need for a broader base of support for programme implementation and they expand with time in order to sustain and expand these efforts. Collaborations with nurses, midwives, paediatricians, family physicians, obstetricians, appropriate subspecialists, and other health care workers are essential if newborn screening is to survive. Active participation in professional meetings is one of the most effective means of improving and expanding collaborations.

On an expanded international level, there are a number of avenues that may be used to achieve collaboration. IAEA technical cooperation projects have allowed administrators and technical staff from developing programmes to visit developed programmes in the USA, United Kingdom, Australia and other countries. Experts from developed programmes have also visited in developing programmes to provide technical evaluation and expert advice. Similarly, training fellowships have allowed technical staff from developing programmes to visit and train in developed programmes. From such training and visitation experiences, programmes have learned to avoid the mistakes of others and have developed successful implementation strategies and best practices to aid in their own process of programme development. Often experts from developed countries have been principal speakers at national meetings and training workshops. Additionally, these experts have helped to educate local professional and governmental officials through seminars and personal visits. Periodic regional meetings in cooperation with the International Society for Neonatal Screening (ISNS) are held in which there are active exchanges of ideas and experiences. Regional ISNS meetings are routinely held in the Asia-Pacific region and in Latin America. Active national newborn screening societies also exist, including in the Philippines, Brazil and a number of European countries. In each instance, a major goal is to increase local and regional collaborations to aid in improving newborn screening.

*Developing programmes should work toward sustainability by taking advantage of 'lessons learned' from other programmes.*

#### 4.10. OTHER ISSUES

##### 4.10.1. Legal considerations

Because newborn screening is intended to prevent catastrophic health consequences that can result from undetected and untreated conditions, cases that are detected late, either inside or outside of the screening system, have the potential for giving rise to lawsuits for negligence. Newborn screening is designed to detect all cases that exhibit biochemical abnormalities at the time of screening while keeping the number of 'false positive' cases as low as possible to reduce case detection costs, maintain physician confidence, and avoid the anxiety that accompanies retesting. In order to minimize legal exposure, the system should have well defined, realistic procedures in place and ensure that they are performed accordingly. Wherever possible, documentation should exist that confirms that all policies and procedures have been followed.

*Legal consequences must be considered.*

In some situations, it has been beneficial to have a law requiring screening, or the offering of screening, for every newborn. In such cases, care should be taken to ensure that the law is sufficiently prescriptive to ensure the sustainability of the programme, but not overly prescriptive so that procedural flexibility does not exist. For

example, if screening conditions are a part of the law, then the law must be changed whenever it becomes necessary to add or subtract screening conditions. If, on the other hand, the law describes a mechanism by which rules and regulations can be made independent of changing the law, then screening conditions can be part of the rules and regulations that are developed. In this way, programme changes may be enacted through changes in rules and regulations rather than through changes in the law. Wherever possible, funding should be provided by the government and should be sufficient to cover all aspects of the programme. If a national insurance programme exists, newborn screening should be included, usually as part of the maternity coverage. Examples of State laws, rules and regulations in the USA may be found at the web sites of the newborn screening programme of individual States (for links see <http://genes-r-us.uthscsa.edu>).

#### **4.10.2. Computerization**

*Computerization can offer increased efficiency. Planning is essential.*

Computerization of newborn screening programmes is usually considered to be cost effective and can provide improved system control and case management. Since programme administrators must monitor the entire newborn screening system, computerization can provide a valuable management tool. Similarly, computers have proven useful in laboratory tracking and case management. Justifications for computerization include more efficient public service through time savings, improved accuracy, and more extensive data assessment for programme evaluation and improvement. It is usually not necessary to develop new or elaborate systems, since a number of commercial programmes tailored to newborn screening are available. Likewise, some newborn screening programmes that have developed computer systems with public funds may willingly share their systems with others. In such cases, minimal modification may be required to accommodate local needs.

With careful thought and planning, implementation of a newborn screening computer system can improve many aspects of the screening programme [86]. Computer systems do not usually decrease the number of programme personnel since oversight, data entry, and management functions are required; however, programme staff can usually be more efficiently utilized to accomplish expanded or increased numbers of tasks within equivalent time periods once computers are in place. Ideally, a fully computerized newborn screening system includes laboratory data transmittal from the point of collection and includes laboratory data management, result reporting (to the submitter and to the follow-up coordinator), documentation and creation of follow-up communications, documentation of follow-up contacts on abnormal results (laboratory to follow up, follow-up to physician, and extended follow-up), medical records for diagnosed patients, disease registries, administrative reports, and linkage to birth records. Programme

evaluation reports can be built in, as can quality assurance reports (see Sections 3.3 and 3.4).

#### 4.11. CHALLENGES

This publication was developed to provide comprehensive information on establishing and sustaining a newborn screening programme for the detection of CH. Listed below are some of the challenges that must be overcome if the programme is to become functional and sustainable. Using this summary as a checklist may assist in providing a measure of progress in planning and implementing a new screening programme. If difficulties are encountered in overcoming one or more of the challenges presented, programme managers are urged to seek help from the sources given throughout this manual. Establishing a newborn screening programme is not easy, but the personal satisfaction and improved health of the nation provide the rewards that will keep you working.

*Challenges can be overcome!*

The range of challenges to overcome in developing a newborn screening programme include:

- Creating a plan and vision for development, implementation and sustainability of the newborn screening programme.
- Organizing a group(s) of persons dedicated to the successful implementation of screening for newborns.
- Providing education to the medical community and gaining their support.
- Obtaining pilot data to validate the value of the screening programme.
- Ensuring adequate resources for laboratory testing, including appropriate staff and training.
- Developing a central laboratory facility for screening.
- Providing necessary training for the adequate and appropriate collection of specimens.
- Providing for the logistics of the transport of specimens to the testing laboratory.
- Establishing a follow-up system for presumptive positive findings.
- Ensuring the availability of an adequate follow-up tracking system and of appropriate confirmatory testing.
- Developing a system for appropriate diagnosis and treatment.
- Developing and disseminating educational materials for the general public.
- Establishing a record keeping system (computerized if possible) for all newborns who are offered testing including: consent/dissent documentation, specimen date(s), testing outcomes, result notifications, information on confirmatory testing, and treatment

documentation including periodic results of patient compliance with treatment and health outcomes.

- Considering and developing a comprehensive quality assurance programme for the system, including listings of quality indicators, procedures for monitoring, and monitoring results (along with a record of corrective actions).
- Providing external proficiency testing for the screening laboratory.
- Developing detailed operating manuals and flow diagrams for all parts of the system, including descriptions of procedures for quality assurance.
- Obtaining government and financial support for the programme, including inclusion in maternal benefits or other appropriate health insurance programmes.
- Developing and enacting an overall evaluation and improvement plan for the newborn screening system.

#### 4.12. SUMMARY: CRITICAL INGREDIENTS FOR PROGRAMME SUSTAINABILITY

The critical ingredients required for the sustainability of a newborn screening programme include:

- Active public advocacy efforts directed at:
  - Experts;
  - Media;
  - Government and NGOs;
  - Parents;
  - Health practitioners;
- Integration in existing government infrastructure;
- Issuance of policies on newborn screening;
- Public–private partnerships;
- Funding for newborn screening;
- National coordination;
- Evaluation and audit.

**Part 5**

**APPENDICES**



# Appendix I

## EXAMPLES OF PROTOCOLS FOR NEWBORN SCREENING LABORATORY TESTING FOR CH

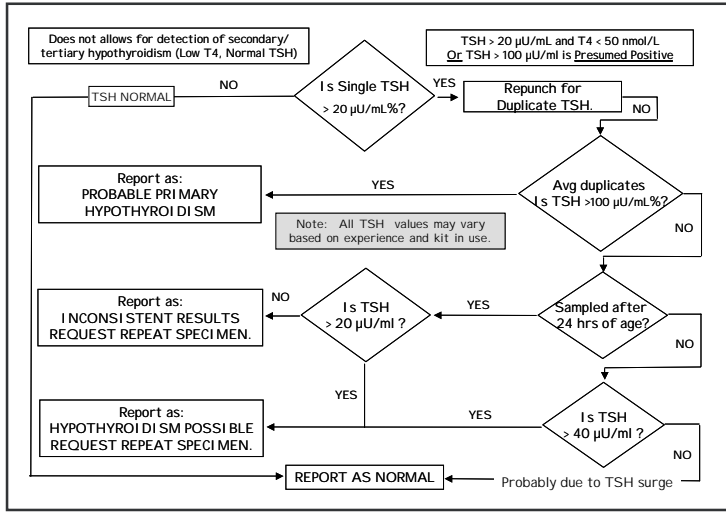


FIG. I.1. Example of a TSH (only) screening protocol.

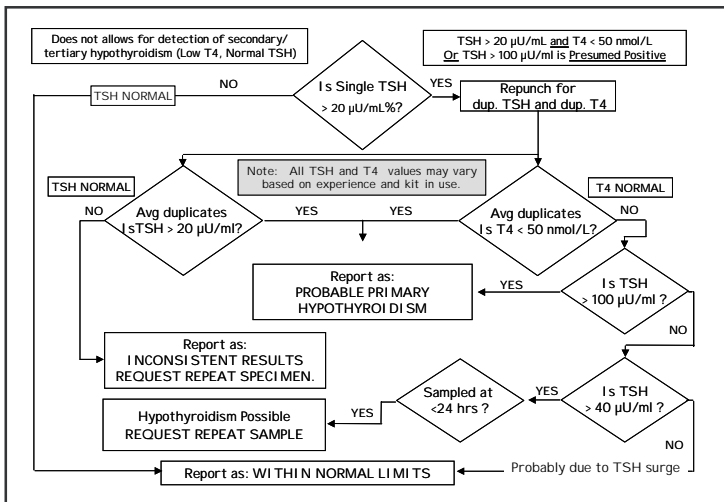


FIG. I.2. Example of a TSH+T4 screening protocol.



EXAMPLE OF PROTOCOLS FOR NEWBORN SCREENING

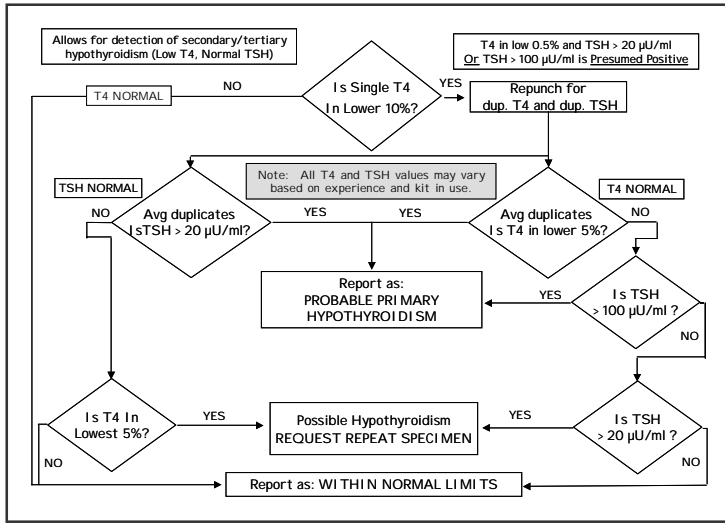


FIG. I.3. Example of a T4+TSH screening protocol.

## Appendix II

### METHOD FOR COLLECTING A BLOOD SPECIMEN ON FILTER PAPER

#### II.1. COLLECTION OF A SPECIMEN ON FILTER PAPER

##### II.1.1. Heel stick procedure

The heel stick provides convenient and easy access to a blood specimen from the newborn and has a low risk of complications. It requires basic skills that are expected of any health professional who needs to draw a blood specimen.

- *Materials.* The materials needed include: a pair of clean gloves; a sterile lancet with tip of a length of less than 2.4 mm (approximately 2.0 mm); sterile cotton balls; 70% isopropyl alcohol; and a filter paper card (Fig. II.1). If there is an expiration date on the collection device (card), ensure that the expiration date has not passed.



*FIG. II.1. Material for collecting a specimen of blood.*

- *Preliminary preparation.* Complete the required patient information form using a ball-point pen as the ink of soft tip pens is not suitable for making copies. Do not use address imprint devices (or adhesive labels) unless the handling process ensures that patient information is not obscured and the blood collection area is not compromised. Do not use a typewriter or printer that might compress the paper. Avoid touching the filter paper collection area before, during, and after the collection of blood spots. Do not allow water, feeding formulas, antiseptic solutions, glove powder, hand lotion, or other materials to come into contact with the device for the collection of a specimen before or after use. Take all appropriate precautions including wearing powder-free gloves, changing gloves between infants, taking blood handling precautions, and disposing of

used lancets in a biohazard container for sharp objects. Confirm the identity of the infant and ensure accuracy of the demographic data on the card.

- *Location of the heel stick.* Use either the lateral or medial plantar surface of the heel for the puncture site (Fig. II.2).



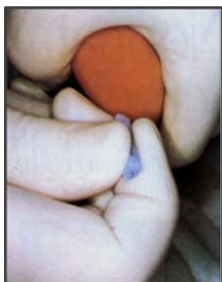
FIG. II.2. Hatched area indicates safe areas for puncture.

- *Heel preparation.* In order to increase blood flow, position the infant with feet below the heart. To increase blood flow, warm the puncture site with a piece of cloth (e.g. diaper) moistened with warm water (up to 42°C so as not to burn the skin), for three to five minutes (Fig. II.3). Heel warming devices are also commercially available. Once ready, clean the puncture site with a sterile cotton ball soaked in 70% isopropyl alcohol and allow to air dry.



FIG. II.3. Example of warming by wrapping a warm towel or diaper around the heel for 3–5 min.

- *Puncture.* Puncture the heel with a sterile lancet or with a heel incision device. Some have found that administering two consecutive punctures to the heel at sites within 1 mm of each other aids in providing an adequate amount of blood for the collection process. Any puncture device used should not exceed 2.0 mm in length [II.1]. A commercial incision device provides improved blood flow by creating a standardized incision 1.0 mm deep by 2.5 mm long. For safety, scalpel blades or needles should not be used as puncture devices since depth of puncture or incision cannot be easily controlled and may lead to unwanted contact with the heel bone (calcaneus).
- *Collection.* After the heel has been punctured, wipe away the first drop of blood with a sterile gauze pad or cotton ball and allow a large drop of blood to form (Fig. II.4). Intermittently apply gentle pressure to the heel with the thumb, and ease this pressure as

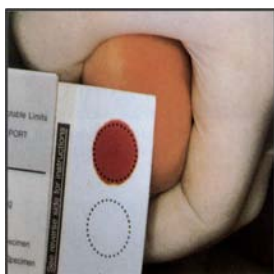


*Position a sterile disposable lancet or an automatic lancet at a slight angle to perform a swift clean puncture.*

*Wipe away the first drop of blood with dry sterile gauze.*

*FIG. II.4. Cleaning the puncture.*

drops of blood form. Avoid excessive milking or squeezing since this may cause specimen haemolysis or result in an admixture of tissue fluids with the specimen and might adversely affect test results. Gently touch the filter paper against the large blood drop and, in one step, allow a sufficient quantity of blood to soak through and completely fill one of the pre-printed circles on the filter paper. Do not apply layers of successive blood drops to the same printed circle since layering the blood onto partially dried spots can cause variable analyte concentrations and invalidate the testing results (Fig. II.5). Try to avoid pressing the filter paper against the puncture site. Apply blood to only one side of the filter paper. Examine both sides of the collection paper to ensure that the blood has uniformly penetrated and saturated the paper.



*Allow a second large drop of blood to form.*

*Lightly touch blood drop to filter paper.*

*Allow blood to soak through and completely fill circle.*

*FIG. II.5. Applying blood to the filter paper.*

- Repeat the process to fill all indicated areas of the card. If blood flow diminishes so that a circle is not completely filled, repeat the sampling technique using a new circle or, if necessary, a new blood collection card (Fig. II.6).



*Fill remaining circles with successive blood drops.*

*If blood flow slows, repeat procedure, selecting a different site and using sterile equipment.*

*FIG. II.6. Filling in the circles.*

- *Post-collection.* After collection, elevate the baby's heel above the heart while applying pressure to the wound with a sterile gauze pad or cotton swab until the bleeding stops. It is not advisable to apply adhesive bandages over skin puncture sites on newborns (Fig. II.7) [II.2].



FIG. II.7. Examples of heel skin puncture in (a) Brazil; (b) South Africa; and (c) China.

## II.2. ALTERNATIVE METHODS OF SPECIMEN COLLECTION

### II.2.1. Capillary tube

Although not the method of choice, specimens can be obtained by collecting blood from the heel skin puncture in sterile, heparinized capillary tubes. Phlebotomists who are unable to obtain adequate specimens from the traditional heel stick technique, and who have had extensive experience in capillary tube techniques, are sometimes more successful with this technique. Heparin is the preferred anticoagulant since EDTA is known to cause interference with some laboratory tests. The capillary tube collection method may also be used to transfer umbilical cord or venous blood onto filter paper.

Use a fresh capillary tube of appropriate volume (75  $\mu\text{L}$  or 100  $\mu\text{L}$  as dictated by the programme) for each circle on the screening card. Puncture the heel as outlined above and touch the tip of the capillary tube to the blood drop at the puncture site. Allow blood to flow into the tube by capillary action (fill rates may be improved by holding the tube in a near-horizontal position). After filling a capillary tube to the calibration mark, immediately apply the contents of that tube to the centre of a single, preprinted circle on the filter paper, completely filling the circle. Waiting too long before application will allow cells and plasma to separate. Apply blood to only one side of the filter paper. Do not apply several capillary specimens to the same circle, since caking or heterogeneous spreading may occur and adversely affect the results of the tests. To avoid damaging the fibres of the filter paper, avoid touching the paper with the capillary tube. Actions such as 'colouring in' the circle, repeated dabbing around the circle, or any action that might scratch, compress, or indent the paper should be avoided. Do not reuse capillary tubes. Repeat the collection procedure until the required number of uniform blood spots have been obtained.

### II.1.2. Dorsal hand vein

Although not the method of choice, direct filter paper application to filter paper of blood collected from needle puncture of the dorsal hand vein is possible [II.3]. Some programmes in

developing countries have chosen this technique because of difficulties in obtaining the appropriate supplies for proper heel sticks (namely, a lack of short point lancets) or because nursing personnel were more certain of the technique because of extensive experience. Blood should not be drawn from a hand into which intravenous fluids (including blood) are being or have been infused. The routine practice of dorsal hand vein collection is discouraged since it is more invasive than a heel stick and test results might be affected by blood from different vessel sources [II.4, II.5]. Select a winged blood collection set that is of the appropriate size (butterfly). Remove or shorten the length of the catheter so that blood can flow freely onto the circle on the filter paper and proceed using the standard paediatric procedures for venous collection.



*FIG. II.8. Procedure for the collection of blood from the dorsal hand vein, as practiced in the newborn screening programme in Thailand.*

### **II.1.3. Umbilical venous catheter or umbilical arterial catheter**

Although not the method of choice, blood collected from umbilical venous catheters (UVCs) or umbilical arterial catheters (UACs) is acceptable in extreme situations (e.g. for sick babies or babies with very low birth weight). It is reasonable to expect that some differences in analytic test may exist between blood taken from the heel and that obtained by umbilical catheters, although no studies have been reported. For this reason, repeat testing with blood from a puncture at the heel should be considered at a later time. Since UACs or UVCs are used to infuse antibiotics or other medicines, it is important that a small amount of blood (2.0–2.5 mL) be drawn from the line and discarded in order to clean it before blood is collected for testing purposes. After cleaning the line, collect blood in a syringe and immediately apply the appropriate volumes of specimen to the appropriate area on the collection card. It is important that the blood be transferred as quickly as possible to avoid blood clotting that might invalidate specimen testing.

### **II.1.4. Specimen drying and transport**

Once the specimen has been collected it should be dried horizontally (flat) on a non-absorbent open surface. It is important to keep the specimen horizontal to avoid migration of excess blood to one side of the circle, which can occur if the card is dried hanging vertically. Special racks are available for drying or can be easily constructed (see Fig. II.9). Filter paper cards must not be refrigerated, stored in drawers or closets, placed in plastic sleeves, nor exposed to intense heat or direct sunlight. The cards should also not be kept near any substance that emits fumes such as paint, varnish, aerosols, and insecticides. Care must be taken in handling the cards so that the blood spots are not touched or smeared accidentally. Depending on

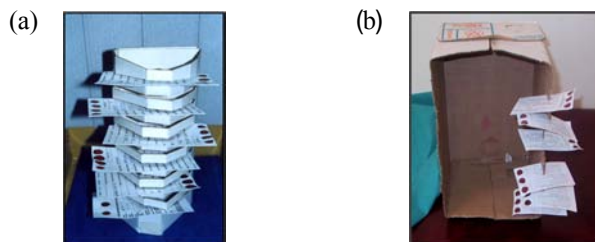


FIG. II.9. Examples of horizontal drying racks. (a) Commercial drying rack; (b) homemade rack in South Africa.

the local environment, specimens may take several hours to dry, so a minimum of 4 hours of air drying (ambient temperature of 15–22°C) away from direct sunlight should be required.

Since leaching (cross-contamination) between specimens can occur, direct blood spot to blood spot contact should be avoided. Before placing the specimens in a container or envelope for transport, each collection card should be rotated 180° from the collection card immediately above and below it so that the blood spots do not come in contact with one another. Specimen rotation is not necessary if physical barriers such as a sheet of paper separate the cards. Collection cards should be transported or mailed to the testing laboratory within 24 hours after specimen collection. Appropriate tracking records should be maintained. Daily courier transport of dried specimens is recommended whenever possible. Delays at collection sites should be avoided, and the shipping environment should be structured to maximize transport efficiency. Humidity and moisture are detrimental to stability of dried blood spot specimens and analyte recovery [II.6, II.7]. Use of sealed plastic bags or other shipping containers that are impermeable to air are not recommended since moisture may build up inside the envelope and cause bacterial contamination. Similarly, excessive heat should be avoided during transport, especially if it is excessive and prolonged. Specimens known to be biohazardous should be identified as such and transported with special precautions (e.g. a specially marked envelope inside the usual transport container) (Fig. II.10).

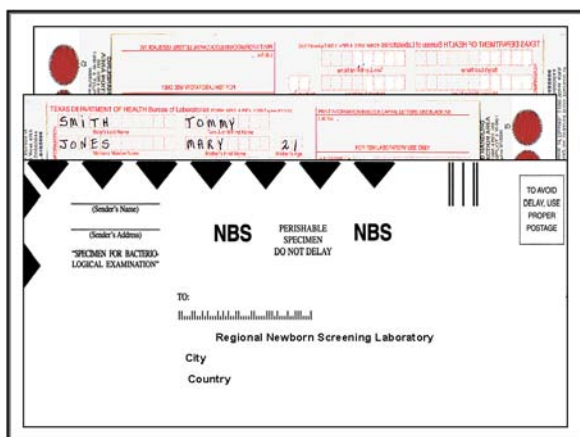


FIG. II.10. Illustration showing how the forms for the collection of specimens that have been dried are alternated before placing them into the envelope (within 24 h of collection) for transport to the screening laboratory.

**REFERENCES TO APPENDIX II**

- [II.1] BLUMENFELD, T.A., TURI, G.K., BLANC, W.A., Recommended sites and depth of newborn heel skin punctures based on anatomical measurements and histopathology, *Lancet* **1** (1979) 230–233.
- [II.2] MEITES, S., LEVITT, M.J., Skin puncture and blood collection techniques for infants, *Clin. Chem.* **25** (1979) 183–190.
- [II.3] CLAGG, M.E., Venous sample collection from neonates using dorsal hand veins, *Lab. Med.* **20** (1989) 248–250.
- [II.4] ANDERSON, D., HAMMON, D.K., “Use of dorsal hand vein specimens for newborn screening”, Proc. 8th National Neonatal Screening Symposium and the XXI Birth Defects Symposium, Saratoga Springs, 1991 (PASS, K.A., Ed.), ASTPHLD, Washington, DC (1992) 271–274.
- [II.5] LOEREY, F.W., CUNNINGHAM, B.C., Effect of specimen collection method on newborn screening for PKU, *Screening* **3** (1994) 57–65.
- [II.6] THERRELL, B.L., et al., Guidelines for the retention storage, and use of residual dried blood spot samples after newborn screening analysis: Statement of the Council of Regional Networks for Genetic Services, *Biochem. Molec. Med.* **57** (1996) 116–124.
- [II.7] LEVY, H.L., SIMMONS, J.R., MacREADY, R.A., Stability of amino acids and galactose in the newborn screening filter paper blood specimen, *J. Pediatr.* **107** (1985) 757–760.



**Appendix III**  
**COMPARISON BETWEEN**  
**VARIOUS BLOOD COLLECTION PROCEDURES**  
**FOR THE SCREENING OF NEWBORNS<sup>1</sup>**

III.1. BLOOD COLLECTION PROCEDURES  
FOR THE SCREENING OF NEWBORNS

**III.1.2. Possible methods of blood sampling, collection  
and transport of specimens for CH screening**

There are several methods possible for obtaining blood from a newborn when screening for CH. Each method has its advantages and disadvantages. Blood may be collected by heel skin puncture, from the umbilical cord, by venipuncture, or from a catheter. The specimen can either be placed onto special collection filter paper or submitted as a liquid. While any or all of these different sources have been used for obtaining screening specimens, it is preferable to use the heel skin puncture from the outset of programme development. Not only has the heel skin puncture specimen proven to be easiest to transport through drying onto filter paper cards, it has, in the long run, been proven to be stable, usable for multiple disorder screening without fear of excessive maternal contamination and the most reliable. Nonetheless, it may be that other ways to obtain blood specimens are more amenable to the local situation, hence the following considerations concerning the availability and utility of other techniques.

**III.1.3. Pros and cons of different methods<sup>2</sup>**

*Heel skin puncture*

Advantages

- Requires a small volume of blood;
- No maternal admixture problems, so the process can be extended for other conditions (e.g. metabolic disorders — PKU, galactosaemia, MSUD);
- Blood drop size can be regulated with appropriate lancets;
- Blood specimen can be collected at any time after birth;
- Patient demographic information is usually attached to the collection card;
- Transport of the sample is simple and easier, especially for home deliveries;
- Variable grades of staff can be trained and used for this technique;
- Relatively quick procedure that prevents problems with blood clots;
- Procedure can be incorporated into existing home visiting programmes for newborns;

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<sup>1</sup> Material in this section was taken in part from the Output Report of the IAEA RAS/6/032 Technical Trouble Shooting Workshop on Current Problems of Specimen Collection and Transport, Dhaka, Bangladesh, 11–15 November 2002.

<sup>2</sup> Adapted from the methods identified and reported by participants at the Bangladesh meeting.

- No serum separation is required;
- Long term storage is possible.

#### Disadvantages

- Proper collection can have technical considerations — warming the heel, type and depth of lancet, sufficient specimen volume — so some training is required;
- Collection card requires drying for 3–4 h away from direct sunlight;
- Collection card can more easily be contaminated from external sources such as powder, oil or alcohol;
- Parental anxiety at time of collection;
- Some pain may occur;
- Risk of infection if the procedure is done incorrectly;
- TSH surge after birth requires a delay of 24 h for the sample to be valid;
- Laboratory values may differ from those expected with venous specimens;
- Cross-contamination can occur between specimens placed in contact with each other;
- Sample consistency is harder to achieve;
- Requires micro-techniques for laboratory analysis.

### *Umbilical cord blood*

#### Advantages

- Blood is easy to collect and place on filter paper (using direct application or a syringe);
- Easy to get a large volume of blood or a large number of blood drops;
- Better parental acceptance of this technique since the baby is not involved;
- Allows blood collection if mother and baby are discharged rapidly;
- Earlier sample collection can lead to earlier testing and treatment;
- Other tests are valid (e.g. G6PD deficiency);
- Less intensive procedural training for blood collectors;
- Analytical methods for umbilical cord blood testing are standard serum methodology, if tubes submitted.

#### Disadvantages

- Cannot extend to screening for many other conditions due to contamination with maternal blood (e.g. metabolic conditions — PKU, galactosaemia, MSUD, etc.);
- Must be carried out immediately at birth (may be complicated by obstetric emergencies);
- False negatives are possible from maternal blood admixture;
- May require a needle and syringe or plastic dropper to control drop size on filter paper;
- Rapid clotting, hence collection following home or complicated deliveries may be difficult;
- Transport and storage of liquid blood from the umbilical cord is more difficult;
- May require separation of cells and serum;
- Requires micro-techniques in laboratory if the specimens are submitted on filter paper;

- Demographic information on the patient that is on the accompanying form may become separated or lost.

### *Venipuncture (open needle technique)*

#### Advantages

- May be more common for phlebotomists;
- Specimen may be placed on filter paper, where it offers the same advantages as the heel skin puncture.

#### Disadvantages

- Collection is significantly more technical, requiring trained staff (nurses);
- Parental anxiety and similar disadvantages as with the heel skin puncture;
- Risk of haematoma if the procedure is done incorrectly;
- Laboratory values may differ from those for capillary (heel skin puncture) samples;
- Transport and storage of liquid blood is more difficult;
- May require separation of cells and serum or plasma;
- Requires use of micro-techniques in the laboratory if the specimens are submitted on filter paper;
- Demographic information on the patient that is on the accompanying form may become separated or lost.

## III.2. METHOD FOR THE COLLECTION OF BLOOD FROM THE UMBILICAL CORD

### III.1.3. General precautions for blood collectors

- Practice universal precautions;
- Wash hands and wear clean gloves;
- Follow all local hospital procedures that apply;
- Handle and dispose of syringes and sharps (needles and lancets) in a safe manner;
- Maintain awareness of possible transmissible infections or health problems faced by the newborn (e.g. excessive bleeding).

### III.1.4. Collection of blood from the umbilical cord

Cord blood specimens must be collected within the first 5 min following birth if clotting and the TSH surge (occurring within 30 min after birth) are to be avoided. If the baby or the mother is experiencing difficulties following delivery, then attending to the baby or the mother should have first priority. If such situations occur, arrangements should be made to obtain a heel skin puncture sample at a later time according to the instructions of the programme. The specimen may either be blood applied to a newborn screening filter paper collection device and

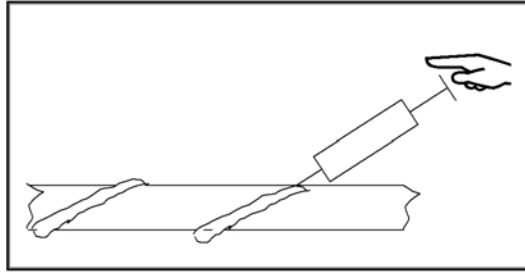


FIG. III.1. How to withdraw blood from the umbilical cord.

dried in the manner described in the procedures for the collection of heel puncture specimens, or serum (or plasma) collected as whole blood into suitable test tubes. Where serum or plasma samples are required, plastic tubes are preferable because they tolerate transport better. Glass tubes have the advantage of being reusable but are more likely to break during transport and processing. Sampling should occur after the umbilical cord has been cut and the collection site should be between the clamps or ties normally applied at delivery. Blood must not be drawn from the portion of cord still attached to the baby due to the serious risk of bleeding.

#### *Collection for use on filter paper*

This is a whole blood specimen, hence, the blood that is applied must not be clotted.

#### Equipment requirements for sample collection

- Filter paper card.
- Gloves.
- Sterile syringe and needle (or dropper).
- Special drying rack (if applying to a collection card made of filter paper).
- Sterile gauze.

#### Procedure

- Clean the collection site on the cord with sterile gauze.
- Place the cord on a clean flat surface.
- Obtain a syringe and attach the appropriate needle.
- Uncap the needle and insert the tip into a large cord blood vessel, approaching from the top of the cord and holding the needle and syringe approximately parallel with the cord or at a shallow angle (see Fig. III.1) and with the needle tip pointing away from the operator.
- Withdraw blood by pulling back on the plunger.
- Withdraw needle and syringe together from the cord.
- A minimum of 1 mL of blood should be collected.

- Remove the needle from the syringe (pushing blood through the needle will result in damage to the blood cells).
- Drop blood from the syringe directly onto the circle of filter paper, without bringing the syringe in contact with the paper.
- Control blood flow from the syringe (better control is maintained by using both hands and avoiding too much blood from being expressed).
- Allow only one drop to fill each circle on the filter paper. If several drops fall onto the same area, the amount of blood will be altered and a wrong result could be obtained. (See Section II.1 of Appendix II for additional details on collecting a specimen on filter paper.)
- Dispose of the needle in an appropriate and safe manner (a disposal container for the disposal of sharp objects is preferred). The needle need not be recapped.
- If applying the specimen to filter paper card, place drops into appropriate locations on card and proceed as noted earlier in the guidance for the collection of blood on filter paper.
- Follow the instructions for the labelling of specimens at the end of this section.
- If submitting serum or plasma, follow the prescribed separation procedures of the testing facility.
- If the tubes used for the collection of samples are submitted, carefully wrap them for shipment, attach appropriate identification to tube and demographic information sheet, and submit these items together to the testing laboratory.

#### Alternative procedure for collection

- (Blood can also be obtained directly from the cut end of the maternal portion of the umbilical cord.)

#### After cleaning

- Release the clamp or tie on the maternal part of the cord;
- Using a gloved hand, gently squeeze blood along the cord to the end;
- Drop the blood into a sterile gully pot;
- A minimum of 1 mL of blood should be collected;
- Use a syringe or dropper to transfer the blood onto filter paper;
- Drop blood from the syringe or dropper directly onto the circle of filter paper, without bringing the syringe or dropper into contact with the paper.

**Note:** Dropping the blood directly onto the filter paper from the end of the cord results in poor control of the amount of blood going onto the paper (usually too much spilling over the edge of the circle). This alternative can be used if there is no better option.

#### *Collection for serum or plasma in suitable tubes*

#### Equipment requirements for sample collection

- Suitable tubes;
- Gloves;

- Sterile syringe and needle (or dropper);
- Sterile gauze;
- A sterile gully pot.

#### Procedure

(**Note:** A larger amount of blood can more easily be obtained directly from the cut end of the maternal portion of the cord.)

- Clean the maternal part of the cord with sterile gauze to avoid contamination of the specimen with maternal blood.
- Follow the instructions for the labelling of specimens at the end of this section.
- After cleaning the cord, release the clamp or tie on the maternal part of the cord
- Using a gloved hand, gently squeeze blood along the cord to the end. ‘Milking’ should be gentle to avoid gross haemolysis of the blood sample.
- Drop the blood into a sterile gully pot.
- Re-clamp the cord.
- A minimum of 5 mL of blood should be collected.
- Directly transfer the blood from the gully pot into a suitable tube. This must be done before the blood clots (within one minute). Alternatively, use a syringe (without a needle) or dropper to transfer the blood from the gully pot into a suitable tube. Pushing blood through the needle will result in damage to the red blood cells.
- If an plain tube is used, keep the capped tube upright to collect serum. If a heparinized or gel separator tube is used, the blood should be mixed gently by inverting the capped tube five times. Other anticoagulants should not be used.

#### Notes:

- (1) It may be possible to drop blood from the end of the umbilical cord directly into the test tube, but this has been found to be difficult and messy. The procedure may be easier with the larger glass tubes than with the plastic ones.
- (2) In most normal deliveries, at least one clamp or tie is placed at the baby’s end of the cord so that the baby will not bleed when the cord is cut. Before cutting the cord, often a second clamp (instrument or tie) is placed to limit the mess made by blood loss from the remaining (maternal) portion of the cord as well as to secure the cord and placenta.

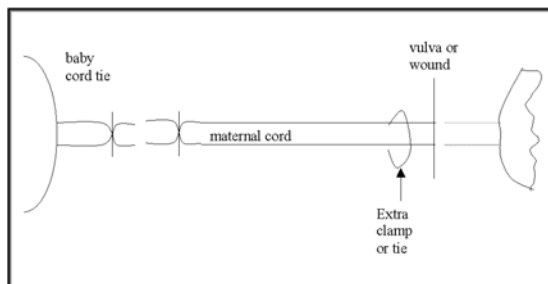


FIG. III.2. Securing blood from the umbilical cord.

- (3) An additional practice is suggested for the purposes of reducing the theoretical risk of admixture of maternal blood with cord blood as the placenta separates. As illustrated in Fig. III.2, this involves placement of a third clamp or tie near the vulva (for normal delivery) or placenta (Caesarian section) to isolate that part of the cord.

### *Labelling*

For filter paper cards


**(Note:** Blood collectors should understand the importance of the data written on the filter card.)

- Care must be taken to ensure that the blood sample collected is not mixed up with that of another baby; at all times make sure that the sample is correctly labelled to match the baby from whom it was collected.
- Fill out the requested data on the filter card. Make sure that all the data sections are complete and correct.
- Write legibly using blue or black ink, preferably with a ball-point pen. Fill in any matching hospital forms.
- Most programmes use the mother's name to facilitate repeat testing if a new sample from the baby is required.
- The correct address and phone number of the mother are very important to ensure proper follow-up.
- In case of multiple pregnancies, forms should be clearly labelled to identify the individual babies (twins, triplets).
- Avoid touching the filter paper circles while completing the information required. Do not contaminate filter paper circles with ink before blood collection.
- At the health facility where the samples have been collected, keep a list of all cards sent for testing.

For tubes

- Complete the laboratory investigation form.
- Tubes can be labelled and forms can be filled before blood collection. However, tubes that are labelled must match the laboratory forms. Care must be taken to ensure that the blood collected is correctly attributed to the baby from whom it has been collected. In the situation where pre-formed data labels are available, these should be attached to tubes and forms immediately after collection.
- Write legibly using blue or black ink, preferably with a ball-point pen. Fill in the forms to list the data that are required by the screening programme.
- Most programmes use the mother's name to facilitate repeat testing if a new sample from the baby is required.
- The correct address and phone number of the mother are very important to ensure proper follow-up.
- In case of multiple pregnancies, forms should be clearly labelled to identify the individual babies (twins, triplets).
- At the health facility where the samples have been collected, keep a list of all samples sent for testing.


**Appendix IV**  
**POSTERS DESCRIBING**  
**PROPER PROCEDURES FOR THE COLLECTION**  
**OF BLOOD SPECIMENS ON FILTER PAPER**  
*(in English and Thai)*




**1** Equipment: Sterile lancet with tip approximately 2.0 mm, sterile alcohol prep, sterile gauze pads, soft cloth, blood collection form, gloves.

# Neonatal Screening


## Blood Specimen Collection and Handling Procedure





**2** Complete ALL information. Do not contaminate filter paper circles by allowing the circles to come in contact with spillage or by touching before or after blood collection. Keep "SUBMITTER COPY" if applicable.



**4** Warm site with soft cloth, moistened with warm water up to 41°C, for three to five minutes.



**3** Hatched area (  ) indicates safe areas for puncture site.



**5.** Cleanse site with alcohol prep. Wipe DRY with sterile gauze pad.






FIG. IV.1. Blood collection on filter paper (Part 1) (reprinted with permission of Schleicher and Schuell, Inc., Keene, NH, USA).



**6** Puncture heel. Wipe away first blood drop with sterile gauze pad. Allow another LARGE blood drop to form.

**7** Lightly touch filter paper to LARGE blood drop. Allow blood to soak through and completely fill circle with SINGLE application to LARGE blood drop. (To enhance blood flow, VERY GENTLE intermittent pressure may be applied to area surrounding puncture site). Apply blood to one side of filter paper only.

**8** Fill remaining circles in the same manner as step 7, with successive blood drops. If blood flow is diminished, repeat steps 5 through 7. Care of skin puncture site should be consistent with your institution's procedures.

**9** Dry blood spots on a dry, clean, flat non-absorbent surface for a minimum of four hours.

**10** Mail completed form to testing laboratory within 24 hours of collection.

Information provided by The New York State Department of Health  
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FIG. IV.2. Instructions for blood collection on filter paper (Part 2) (reprinted with permission of Schleicher and Schuell, Inc., Keene, NH, USA).




FIG. IV.3. Instructions in Thai for blood collection on filter paper, part of the Thailand newborn screening programme.

## Appendix V


### POSTERS ILLUSTRATING VALID AND INVALID BLOOD SPECIMENS ON FILTER PAPER

# Simple Spot Check


### Invalid Specimens:




1. Specimen quantity insufficient for testing.




2. Specimen appears scratched or abraded.




3. Specimen not dry before mailing.




4. Specimen appears supersaturated.




5. Specimen appears diluted, discolored or contaminated.



6. Specimen exhibits serum rings.




7. Specimen appears clotted or layered.



8. No blood.

### Valid Specimen




Allow a sufficient quantity of blood to soak through to completely fill the preprinted circle on the filter paper. Fill all required circles with blood. Do not layer successive drops of blood or apply blood more than once in the same collection circle. Avoid touching or smearing spots.

### Possible Causes:

- Removing filter paper before blood has completely filled circle or before blood has soaked through to second side.
- Applying blood to filter paper with a capillary tube.
- Touching filter paper before or after blood specimen collection with gloved or ungloved hands, hand lotion, etc.
- Allowing filter paper to come in contact with gloved or ungloved hands or substances such as hand lotion or powder, either before or after blood specimen collection.
- Applying blood with a capillary tube or other device.
- Mailing specimen before drying for a minimum of four hours.
- Applying excess blood to filter paper, usually with a device.
- Applying blood to both sides of filter paper.
- Squeezing or "milking" of area surrounding the puncture site.
- Allowing filter paper to come in contact with gloved or ungloved hands or substances such as alcohol, formula, antiseptic solutions, water, hand lotion or powder, etc., either before or after blood specimen collection.
- Exposing blood spots to direct heat.
- Not wiping alcohol from puncture site before making skin puncture.
- Allowing filter paper to come in contact with alcohol, hand lotion, etc.
- Squeezing area surrounding puncture site excessively.
- Drying specimen improperly.
- Applying blood to filter paper with a capillary tube.
- Touching the same circle on filter paper to blood drop several times.
- Filling circle on both sides of filter paper.
- Failure to obtain blood specimen.

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FIG. V.1. Description of valid and invalid blood specimens on filter paper (reprinted with permission of Schleicher and Schuell, Inc., Keene, NH, USA).

**채혈은 이렇게 도와주세요!**

검체 유무	검체 예	채혈시 주의 사항
간		<ul style="list-style-type: none"> <li>전과 후 간방울의 혈액이 형성되면 채혈지의 한쪽 변만 묻혀 뒷면까지 충분히 스며들도록 합니다.</li> <li>원이 완전히 채워지도록 합니다.</li> <li>같은 방법으로 다른 원을 채우도록 합니다.</li> </ul>
	<p>혈액량이 부족한 경우</p>	<ul style="list-style-type: none"> <li>전과 후 간방울의 혈액이 형성되기 전에 소량을 자주 채혈기에 묻히지 않아야 합니다.</li> <li>혈액이 원대에 충분히 흡수되기 전, 뒷면까지 흡수되기 전에 갈래지 않도록 합니다.</li> </ul>
불	<p>긁히거나 마모된 경우</p>	<ul style="list-style-type: none"> <li>혈액을 Capillary tube 혹은 기타 기구를 이용해서 채혈지에 흡수시키지 않도록 합니다.</li> </ul>
	<p>충분히 건조되지 않은 경우</p>	<ul style="list-style-type: none"> <li>음지에서 최소한 4시간 이상 건조시켜야 합니다.</li> <li>건조되기 전에 채혈지를 겹쳐 놓지 않도록 합니다.</li> </ul>
	<p>희석, 번개, 오염된 경우</p>	<ul style="list-style-type: none"> <li>혈액 채취 부위를 과도하게 압박하지 않아야 합니다.</li> <li>장갑을 낀 채, 맨손, 또는 알코올, 용액, 살균제, 염도오염, 파우더 등을 바르고 혈액채취 전후 채혈지 원 부위를 만지거나 오염되지 않도록 해야 합니다.</li> <li>채혈지에 직사광선이나 열을 가하지 않아야 합니다.</li> </ul>
적	<p>혈청고리를 보일 경우</p>	<ul style="list-style-type: none"> <li>채혈지의 동일한 원에 혈액을 반복해서 묻히지 않도록 해야 합니다.</li> <li>채혈 부위가 어떤 용액으로 오염되지 않도록 해야 합니다.</li> </ul>
	<p>올고 혹은 흠이진 경우</p>	<ul style="list-style-type: none"> <li>채혈지의 동일한 원에 혈액을 반복해서 묻히지 않도록 해야 합니다.</li> <li>채혈지 양면에 각각 혈액을 묻히지 않도록 해야 합니다.</li> <li>채혈기구를 이용하여 채혈지에 묻히지 않도록 해야 합니다.</li> </ul>
	<p>과도하게 스며든 경우</p>	<ul style="list-style-type: none"> <li>기구를 사용해서 과도한 양의 혈액을 채혈지에 묻히지 않도록 해야 합니다.</li> <li>채혈지 양면에 각각 혈액을 묻히지 않도록 해야 합니다.</li> </ul>

※ 본 자료는 매일유업(주) 협찬으로 제작하였습니다.

FIG. V.2. Description of valid and invalid blood specimens on filter paper, part of the newborn screening programme, Republic of Korea.



## Appendix VI

### EXAMPLES OF PUBLIC RELATIONS/EDUCATIONAL MATERIALS FROM THE IAEA SUPPORTED NEWBORN SCREENING PROGRAMME



FIG. VI.1. Public relations poster inside and sign outside a Regional Health Centre – Cebu, Philippines.



FIG. VI.2. Examples of public relations/educational materials available from the Thailand newborn screening programme.



FIG. VI.3. Thailand poster with 'before' and 'after' images which show the benefits of newborn screening. (The information sheet at the top of the left-hand picture can be folded down to show the poster at right.)



FIG. VI.4. Booklets aimed at explaining the programme to parents, newborn screening programme, Republic of Korea.



FIG. VI.5. Instructional videotapes, newborn screening programme, Republic of Korea.

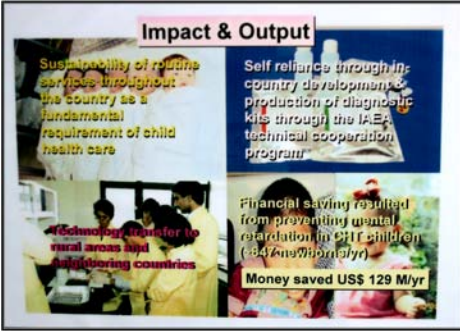


FIG. VI.6. Poster describing the benefits of the newborn screening programme, Thailand.



FIG. VI.7. Small poster placed on hospital bulletin board, Philippine newborn screening programme.



FIG. VI.8. Newspaper and magazine articles concerning the benefits of newborn screening, Philippine newborn screening programme.

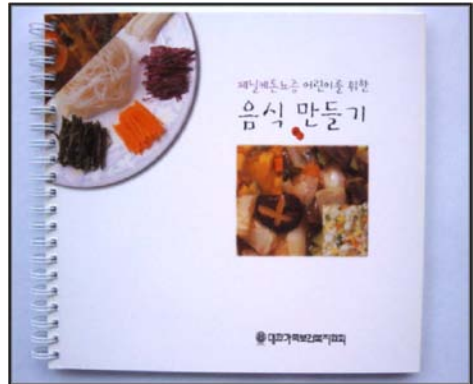
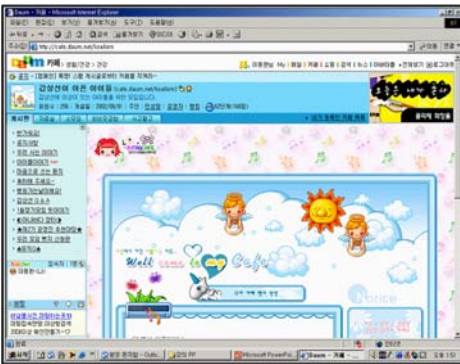


FIG. VI.9. Internet chat room (left) and cookbook (right) available as part of the newborn screening programme, Republic of Korea.



## REFERENCES

- [1] THERRELL, B.L., US newborn screening policy dilemmas for the twenty-first century, *Mol. Genet. Metab.* **74** (2001) 64–74.
- [2] GUTHRIE, R., SUSI, A., A simple phenylalanine method for detecting phenylketonuria in large populations of newborn infants, *Pediatrics* **32** (1963) 338–343.
- [3] AMERICAN ACADEMY OF PEDIATRICS, Newborn Screening Task Force, Serving the family from birth to the medical home — newborn screening: A blueprint for the future, *Pediatrics* **106** (2000) 383–427.
- [4] WORLD HEALTH ORGANIZATION, Scientific Group on Screening for Inborn Errors of Metabolism, Screening for Inborn Errors of Metabolism, World Health Org. Technical. Report Series **401**, WHO, Geneva (1968) 1–57.
- [5] WILSON, J.M.G., JUNGNER, F., Principles and Practice of Screening for Disease, Public Health Papers No. 34, WHO, Geneva (1968).
- [6] NATIONAL RESEARCH COUNCIL, Committee for the Study of Inborn Errors of Metabolism, Genetic Screening: Programs, Principles, and Research, National Academy of Sciences, Washington, DC (1975).
- [7] INSTITUTE OF MEDICINE, Committee for the Study of the Future of Public Health. The Future of Public Health, National Academy of Sciences, Washington, DC (1988).
- [8] AMERICAN ACADEMY OF PEDIATRICS, Committee on Fetus and Newborn, Screening of newborn infants for metabolic disease, *Pediatrics* **5** (1965) 499–501.
- [9] AMERICAN ACADEMY OF PEDIATRICS, Genetic Disorders and Birth Defects: A Compendium of AAP Guidelines and Resources for the Primary Care Practitioner, AAP, Elk Grove Village, IL (1997).
- [10] AMERICAN ACADEMY OF PEDIATRICS, Committee on Genetics, Issues in newborn screening, *Pediatrics* **89** (1992) 345–349.
- [11] LARSSON, A., THERRELL, B.L., Newborn screening: The role of the obstetrician, *Clin. Obstetr. Gynecol.* **45** (2002) 697–710.
- [12] PASS, K.A., et al., U.S. newborn screening system guidelines II: Follow-up of children, diagnosis, management and evaluation — statement of the Council of Regional Networks for Genetics Services (CORN), *J. Pediatr.* **137** (2000) 1–46.
- [13] McCABE, L.L., THERRELL, B.L., McCABE, E.R.B., Newborn screening: Rationale for a comprehensive, fully integrated public health system, *Mol. Genet. Metab.* **77** (2002) 267–273.
- [14] KLETT, M., Epidemiology of congenital hypothyroidism, *Exp. Clin. Endocrinol. Diabetics* **105** 4 (1997) 19–25.
- [15] FISHER, D.A., Effectiveness of newborn screening programs for congenital hypothyroidism: Prevalence of missed cases, *Pediatr. Clin. North Am.* **34** (1987) 881–890.
- [16] FISHER, D.A., Status report: screening for congenital hypothyroidism, *Trends Endocrinol. Metab.* **2** (1991) 129–133.
- [17] JOHN, R., Screening for congenital hypothyroidism, *Ann. Clin. Biochem.* **24** (1987) 1–12.
- [18] INGBAR, S.H., WOEBER, K.A., “The thyroid gland”, *Textbook of Endocrinology* (WILLIAMS, R.H., Ed.), Saunders, New York (1981) 177–247.
- [19] KLEIN, R.Z., Infantile hypothyroidism then and now: The results of neonatal screening, *Cur. Prob. Pediatr.* **15** (1985) 1–58.



- [20] GRANT, D.B., SMITH, I., FUGGLE, P.W., TOKAR, S., CHAPPLE, J., Congenital hypothyroidism detected by neonatal screening: relationship between biochemical severity and early clinical features, *Arch. Dis. Childhood* **67** (1992) 87–90.
- [21] ALM, J., LARSSON, A., ZETTERSTROM, R., Congenital hypothyroidism in Sweden, incidence and age at diagnosis, *Acta Paediatr. Scand.* **67** (1978) 1–3.
- [22] KLEIN, A., MELTZER, S., KENNY, F., Improved prognosis in congenital hypothyroidism treated before age three months, *J. Pediatr.* **81** (1972) 912–915.
- [23] VIRTANEN, M., Manifestations of congenital hypothyroidism during the first week of life, *Eur. J. Pediatr.* **147** (1988) 270–274.
- [24] ARONSON, R., EHRICH, R., BAILEY, J., ROBERT, J., Growth in children with congenital hypothyroidism detected by neonatal screening, *J. Pediatr.* **116** (1990) 33–37.
- [25] ROVET, J., EHRLICH, R., SORBARA, D., “Longitudinal prospective investigations of hypothyroid children detected by neonatal thyroid screening in Ontario”, *Advances in Neonatal Screening* (THERRELL, B.L., Ed.), Elsevier, Amsterdam (1987) 99–106.
- [26] GRANT, D.B., Congenital hypothyroidism: optimal management in the light of 5 years experience of screening, *Arch. Dis. Childhood* **72** (1995) 85–89.
- [27] ROVET, J.F., “Neuromotor deficiencies in six-year-old hypothyroid children identified by newborn screening”, *Proc. 8th National Newborn Screening Symp.*, 1991, Saratoga Springs, NY (PASS, K.A., Ed.), ASTPHLD, Washington, DC (1992) 378–381.
- [28] MURPHY, G.H., HULSE, J.A., SMITH, I., GRANT, D.B., Congenital hypothyroidism: physiological and psychological factors in early development, *J. Child Psychol. Psychiatr.* **31** (1990) 711–725.
- [29] ROCHICCIOLI, P., ALECANDRE, F., ROGE, B., “Neurological development in congenital hypothyroidism”, *Research in Congenital Hypothyroidism* (DELANGE, D., FISHER, D., GLIMOER, G., Eds), Plenum, New York **30** (1989) 1–8.
- [30] FUGGLE, P., GRANT, D.B., SMITH, I., MURPHY, G., Intelligence, motor skills and behavioural 5 years in early-treated congenital hypothyroidism, *Eur. J. Pediatr.* **150** (1991) 570–574.
- [31] VIRTANEN, M., SANTAVUORI, P., HIRVONEN, E., PERHEENTUPA, J., Multivariate analysis of psychomotor development in congenital hypothyroidism, *Acta Paediatr. Scand.* **78** (1989) 405–411.
- [32] CONNELLY, J., “Australian experience in neonatal thyroid screening 1977–1985”, *Advances in Neonatal Screening* (THERRELL, B.L., Ed.), Elsevier, Amsterdam (1987) 31–34.
- [33] EUROPEAN SOCIETY OF PEDIATRIC ENDOCRINOLOGY, Working Group on Congenital Hypothyroidism, *Epidemiological Inquiry on Congenital Hypothyroidism in Europe* (1985–1988), *Hor. Res.* **34** (1990) 1–3.
- [34] DUSSAULT, J., An update on screening for congenital hypothyroidism, *Thyroid Today* **8** (1985) 1–5.
- [35] LO, K.K., LAM, T.S., Neonatal screening programme for congenital hypothyroidism in Hong Kong, *Neonatal and Perinatal Screening: The Asian Pacific Perspectives* (LAM, T.S., PANG, C.P., Eds), The Chinese University Press, Hong Kong (1996) 145–148.
- [36] PETER, F., BLATNICZKY, L., KOVACS, L., TAR, A., Experience with neonatal screening for congenital hypothyroidism in Hungary, *Endocrinol. Exp.* **23** (1989) 143–151.
- [37] SACK, J., FELDMAN, I., KAISERMAN, I., Congenital hypothyroidism screening in the West Bank: A test case for screening in developing regions, *Hor. Res.* **50** (1998) 151–154.

- [38] SORCINI, M., BALESTRAZZI, P., GRANDOLFO, M.E., CARTA, S., GIOVANNELLI, G., The national register of infants with congenital hypothyroidism detected by neonatal screening in Italy, *J. Endocrinol. Invest.* **16** (1993) 573–577.
- [39] IRIE, M., et al., “Screening of neonatal hypothyroidism in Japan”, *Advances in Neonatal Screening* (THERRELL, B.L., Ed.), Elsevier, Amsterdam (1987) 41–47.
- [40] LEE, D.H., “Neonatal screening in Korea”, *New trends in Neonatal Screening* (TAKASUGI, N., NARUSE, H., Eds), Hokkaido University Press, Sapporo (1994) 3–5.
- [41] DAOUD, A., ZAKI, M., AL-SALEH, Q.A., TEEBI, A.S., AL-AWADI, S.A., Congenital hypothyroidism in Kuwait, *J. Trop. Pediatr.* **35** (1989) 312–314.
- [42] BERNSTEIN, R.E., OP’T HOF, J., HITZEROTH, H.W., Neonatal screening for congenital hypothyroidism: A decades review, including South Africa, *S. Afr. Med. J.* **73** (1988) 339–343.
- [43] ELBUALY, M., BOLD, A., DE SILVA, V., GIBBONS, U., Congenital hypothyroid screening: The Oman experience, *J. Trop. Pediatr.* **44** (1998) 81–83.
- [44] MAJEED-SAIDAN, M.A., JOYCE, J., KHAN, M., HAMAM, H.D., Congenital hypothyroidism: the Riyadh Military Hospital experience, *Clin. Endocrinol.* **38** (1993) 191–195.
- [45] JOSEPH, R., Mass newborn screening in Singapore, *Southeast Asian J. Trop. Med. Pub. Health* **34** 3 (2003) 89–90.
- [46] VERKERK, P.H., BUITENDIJK, S.E., VERLOOVE-VANHORICK, S.P., Congenital hypothyroidism screening and the cutoff for thyrotropin measurement: Recommendations from the Netherlands, *Am. J. Public Health* **83** (1993) 868–871.
- [47] ROSENTHAL, M., ADDISON, G.M., PRICE, D.A., Congenital hypothyroidism: Increased incidence in Asian families, *Arch. Dis. Childhood* **63** (1988) 790–793.
- [48] LOREY, F.W., CUNNINGHAM, G.C., Birth prevalence of primary congenital hypothyroidism by sex and ethnicity, *Human Biol.* **64** (1992) 531–538.
- [49] BROWN, A.L., FERNHOFF, P.M., MILNER, J., McEWEN, C., ELSAS, L.S., Racial differences in the incidence of congenital hypothyroidism, *J. Pediatr.* **99** (1981) 934–936.
- [50] INTERNATIONAL ATOMIC ENERGY AGENCY, Report of the East Asia Project Coordination and Planning Management Meeting, Workshop on congenital hypothyroidism: Quality assurance and validation (RAS 6/32, Tianjin, China 2002), IAEA, Vienna (2002) 10–12.
- [51] FANG, P.-H., GAO, S., “Neonatal screening for congenital hypothyroidism in Tianjin, China”, Report of the IAEA East Asia Regional Seminar for Policy Makers and Professionals on Congenital Hypothyroidism (RAS 6/32, Manila, 2001), IAEA, Vienna (2001) 77–91.
- [52] HAN, Y.J., LEE, D.H., KIM, J.W., Newborn screening in Korea, *Southeast Asia J. Trop. Dis. Pub. Health* **34** 3 (2003) 81–84.
- [53] NATIONAL INSTITUTES OF HEALTH — UNIVERSITY OF THE PHILIPPINES, Philippine Newborn Screening Program, Prevalence Update as of June 2003, N.I.H.–U.P., Manila (2003).
- [54] CHAROENSIRIWATANA, W., et al., Neonatal screening programme in Thailand, *Southeast Asia J. Trop. Dis. Pub. Health* **34** 3 (2003) 94–100.
- [55] FISHER, D.A., “The thyroid”, *Clinical Pediatric Endocrinology*, Revised Edition (KAPLAN, S.A., Ed.), Saunders, Philadelphia (1990).

- [56] VULSMA, T., GONS, M., VIJLDER, J., Maternal-fetal transfer of thyroxine in congenital hypothyroidism due to a total organification defect of thyroid agensis, *New Eng. J. Med.* **321** (1989) 13–16.
- [57] FISHER, D.A., KLEIN, A.H., Thyroid development and disorders of thyroid function in the newborn, *New Eng. J. Med.* **304** (1981) 702–712.
- [58] DUSSAULT, J.H., MORISSETTE, J., Higher sensitivity of primary thyrotropin in screening for congenital hypothyroidism: A myth? *J. Clin. Endocrinol. Metab.* **56** (1983) 849–852.
- [59] DELANGE, F., CAMUS, M., WINKLER, M., DODION, J., ERMANS, A.-M., Serum thyrotropin determination on day 5 of life as a screening procedure for congenital hypothyroidism, *Arch. Dis. Childhood* **52** (1977) 89–96.
- [60] BAUMGARTNER, J.H., HAIBACH, H., “Screening for primary hypothyroidism in Missouri using thyroxine and TSH assay for all specimens: A five-year experience”, *Proc. 11th National Neonatal Screening Symposium, Corpus Christi, Texas* (THERRELL, B.L., ALDIS, B.A., Eds), ASTPHLD, Washington, DC (1996) 39–42.
- [61] BARKER, B.P., RUTTER, N., Exposure to invasive procedures in neonatal intensive care unit admissions, *Arch. Dis. Childhood* **72** (1995) 47–48.
- [62] BROWN, L., Physiologic response to cutaneous pain in neonates, *Neonatal Network* **5** (1987) 18–21.
- [63] OWENS, M.E., TODT, E.H., Pain in infancy: Neonatal reaction to heel lancet, *Pain* **20** (1984) 77–86.
- [64] KABRA, N.S., UDAPNI, R.H., Evaluation of physiological and behavioral response to pain following heel prick with different techniques for dextrostix assessment in healthy preterm neonates, *Indian Pediatr.* **36** (1999) 1135–1141.
- [65] TADDIO, A., GOLDBACH, M., IPP, M., STEVENS, B., KOREN, G., Effect of neonatal circumcision on pain responses during vaccination in boys, *Lancet* **6-345** (1995) 291–292.
- [66] ANAND, K.J.S., HICKEY, P.R., Pain and its effects in the human neonate and fetus, *New Eng. J. Med.* **317** (1987) 1321–1329.
- [67] SKOGSDAL, Y., ERIKSSON, M., SCHOLLIN, J., Analgesia in newborns given oral glucose, *Acta Paediatr.* **86** (1997) 217–220.
- [68] RUSHFORT, J.A., LEVENE, M.I., Effect of sucrose on crying in response to heel stab, *Arch. Dis. Childhood* **69** (1993) 388–389.
- [69] BUCHER, H., et al., Sucrose reduces pain reaction to heel lancing in preterm infants: a placebo-controlled, randomized and masked study, *Pediatr. Res.* **38** (1995) 332–335.
- [70] BLASS, E.M., Milk-induced hypoalgesia in human newborns, *Pediatrics* **99** (1997) 825–829.
- [71] RAMENGI, L.A., GRIFFITH, G.C., WOOD, C.M., LEVENE, M.I., Effect of non-sucrose sweet tasting solution on neonatal heel prick responses, *Arch. Dis. Childhood* **74** (1996) F129–131.
- [72] FIELD, T., GOLDSOHN, E., Pacifying effects of non-nutritive sucking on term and preterm neonates during heelstick procedures, *Pediatrics* **74** (1984) 1002–1005.
- [73] CAMPOS, R.G., Rocking and pacifiers: two comforting interventions for heelstick pain, *Res. Nursing Health* **17** (1994) 321–331.
- [74] McINTOSH, N., VEEN, L.V., BRAMEYER, H., Alleviation of the pain of heelprick in preterm infants, *Arch. Dis. Childhood* **70** (1994) F177–181.
- [75] HARPIN, V.A., RUTTER, N., Making heel pricks less painful, *Arch. Dis. Childhood* **58** (1983) 226–228.

- [76] WEBSTER, U., Analgesic effect of lignocaine ointment on infant skin in neonates, *Acta. Paediatr.* **82** (1993) 791.
- [77] RUSHFORT, J.A., GRIFFITHS, G., THORPE, H., LEVENE, M.I., Can topical lignocaine reduce behavioral response to heel prick? *Arch. Dis. Childhood* **72** (1995) F49–F51.
- [78] BLASS, E.M., SMITH, B.A., Differential effects of sucrose, fructose, glucose, and lactose on crying in 1- to 3-day-old human infants: Qualitative and quantitative considerations, *Dev. Psychol.* **28** (1992) 804–810.
- [79] CARBAJAL, R., CHAUVET, X., COUDERC, S., OLIVIER-MARTIN, M., Randomised trial of analgesic effects of sucrose, glucose, and pacifiers in term neonates, *Brit. Med. J.* **319** (1999) 1393–1397.
- [80] WAITE, K.V., MABERLY, G.F., EASTMAN, C.J., Storage conditions and stability of thyrotropin and thyroid hormones on filter paper, *Clin. Chem.* **33** (1987) 853–855.
- [81] THERRELL, B.L., et al., Guidelines for the retention, storage, and use of residual dried blood spot samples after new born screening analysis: Statement of the Council of Regional Networks for Genetic Services, *Biochem. Molec. Med.* **57** (1996) 116–124.
- [82] NØRGAARD-PEDERSEN, B., SIMONSEN, H., Biological specimen banks in neonatal screening, *Acta Paediatr.* **88** 432 (1999) 106–109.
- [83] THERRELL, B.L., Newborn screening for congenital adrenal hyperplasia, *Endocrinol. Metab. Clin. North Am.* **30** (2001) 15–30.
- [84] WEBSTER, D., DHANDT, J.-L., HANNON, W.H., TORRESANI, T., Description of quality assurance programs in newborn screening, *Screening* **2** (1993) 219–228.
- [85] SLAZYK, W.E., HANNON, W.H., “Quality assurance in the newborn screening laboratory”, *Laboratory Methods for Neonatal Screening* (THERRELL, B.L., Ed.), American Public Health Association, Washington, DC (1993) 23–46.
- [86] THERRELL, B.L., Data integration and warehousing: coordination between newborn screening and related public health programs, *Southeast Asia J. Trop. Med. Public Health* **34** 3 (2003) 63–68.



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**Congenital hypothyroidism, when undiagnosed or if there is a lack of proper treatment management, results in an unnecessary health, economic and social burden. Formalized screening programmes to detect congenital hypothyroidism in newborn infants, and its timely treatment, can prevent lifelong human suffering caused by severe mental retardation. With the involvement of the IAEA, such screening programmes have been introduced successfully in a large number of countries. However, in many other countries, such programmes have not yet been established. This publication is intended to assist these countries in establishing and sustaining a comprehensive screening system for newborns. It draws on experience gained over more than a decade, and provides information for making sound screening policy decisions. It also describes how a newborn screening system should be set up, and offers guidance on assessing the quality of the system.**