
GUIDELINES ON THE PREVENTION AND CONTROL OF CONGENITAL HYPOTHYROIDISM



DIVISION OF NONCOMMUNICABLE DISEASES
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I. General Principles for the Formulation of National Programmes for
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1. INTRODUCTION

Untreated, congenital hypothyroidism has devastating effects on the growth and development of infants. A deficiency in circulating thyroxine is the biochemical defect that causes this disorder. The deficiency in thyroid hormone can be the result of no thyroid gland, incomplete gland development, or inability to synthesize thyroxine because of iodine deficiency. The early detection and treatment of congenital hypothyroidism is essential to prevention of severe irreversible mental retardation and physical deformities. Some features of untreated hypothyroidism are similar to those of cretinism which exists in endemic goiter regions of the world. The diagnosis and treatment of congenital hypothyroidism must happen before three months of age for therapeutic effectiveness. Early clinical diagnosis is difficult, and before newborn screening, most cases of infant hypothyroidism were not detected before three months of age¹.

In 1973, in Canada, the first mass screening programme for congenital hypothyroidism was initiated². A pilot screening project was first conducted in association with the existing newborn screening operation for inborn errors of metabolism, phenylketonuria (PKU) and galactosemia. The system for mass screening was quickly adopted because of the routine collection of dried blood spots from newborns, the development of sensitive immunoassays, and the in place logistics for follow-up and treatment of the other disorders.

In the early 1960's, regional programmes were developed for population screening for PKU by using blood collected on filter paper from heel sticks of newborns. These programmes developed not only adequate processes for specimen collection and analysis, but also follow-up systems for complete patient management for detected individuals. Modifying radioimmunoassays for serum thyroid function tests to permit the use of small volumes of eluted whole blood from routinely collected dried blood spots triggered the emergence of population screening for hypothyroidism. Initially, screening centres used radioimmunoassays (RIA) for thyroxine as the primary screen and a secondary RIA screen for thyrotropin (thyroid-stimulating hormone [TSH]) on all specimens with low thyroxine values. Screening centres in the USA have continued the use of the combination screen, while primary TSH screens with isotopic and nonisotopic immunoassays are used in Europe and Japan. The primary TSH screen does not detect secondary hypothyroidism. Some early pilot programmes utilized cord serum and cord blood dried on filter paper to screen effectively for congenital hypothyroidism³; however, these cord blood programmes were somewhat cumbersome and unadaptable logistically to population screening.

Newborn screening programmes for congenital hypothyroidism have spread rapidly in industrialized nations. Seven to nine million newborns are screened per year in these nations⁴. The incidence frequency for the disorder is similar among these screening programmes, 1 in 4,000 - 6,000. Congenital hypothyroid screening is gradually being adopted by developing nations, with effective programmes having been initiated in Brazil, Mexico, China and some African nations⁴.

Congenital hypothyroidism screening programmes and the mechanistic design will greatly differ with each country. Numerous national aspects, political climate, economics, medical facilities, and transportation systems will naturally influence the overall design and implementation of the screening programme. Programme implementers in each country must evaluate their specific

resources and needs. This document can only provide the general guidelines and the suggested minimal requirements for the implementation of a screening programme. The guidelines should not be viewed as rigid requirements, but as an itemized list or model to direct an orderly and comprehensive planning process.

Regardless of the variables, it is possible to delineate some common components and their impact. An adequate screening programme for congenital hypothyroidism should include the complete participation of the population at risk, an education component for notification of parents and the public sector about newborn screening, adequate specimen collection, reliable and timely performance of the screening tests, prompt follow-up of individuals identified by positive test results, accurate diagnosis by confirmatory tests, and appropriate counselling and treatment of patients.

2. SITUATION ANALYSIS

Rationale for Screening

The clinical signs are not sufficient to readily permit easy detection of affected newborns (inadequate production of thyroid hormone) for treatment. Failure to timely diagnose and treat will result in irreversible damage to the infant. If the nation, parents, and society are to be spared from the consequences of this disorder, early detection and treatment is the key. A sound programme involving reliable laboratory testing and intervention with medication is essential to the prevention of adverse congenital hypothyroidism outcomes.

Population Characteristics

The overall incidence frequency varies among existing screening programmes with an average incidence rate of 1:4,500. The incidence rate in the USA is 1:3,600 to 1:5,000, in Europe 1:3,000, and in Japan 1:5,700. The incidence among black populations appears to occur at a lower rate with 1:10,000 to 1:17,000 and higher among Hispanic populations with a rate of 1:2,700⁵. Females with the disorder outnumber males by a ratio of 2 to 3:1⁵. No programme has identified a seasonal variation.

Adverse Outcomes

Indications are that without newborn screening, mortality may exist from failure to diagnose and this may be related to the retarded patient's treatment by society. Developmental disabilities vary depending on the extent of the thyroid deficiency, with IQs ranging from 55 to 85 with a mean value of 80. Physical disabilities also are related to the extent of deficiency and may involve low metabolic rate, poor growth, constipation, goiter, and poor peripheral circulation⁵.

Available data indicate that with accurate screening and prompt appropriate treatment, mortality is not an issue. Whether developmental disabilities are present is still being debated. No physical disabilities occur.

Principal Information

Numerous obstacles must be overcome to initiate a congenital hypothyroidism screening programme and much information gathered to support development of the programme design.

- (a) Government support, policy, and financial resources.
- (b) Education and support of the local medical community.
- (c) Education of the hospital staff (specimen collection sites).
- (d) Training for adequate specimen collection.
- (e) Laboratory resources and training of staff.
- (f) Equipment needs for laboratory tests.
- (g) Central laboratory and/or local laboratories for testing.
- (h) Logistics of specimen transport (central/local laboratory).
- (i) Coordination of laboratories if multiple test sites.
- (j) Quality Assurance programme for laboratory.
- (k) Development of follow-up centre for affected newborns.

- (l) Training of public health nurses for patient tracking and confirmatory specimen collection.
- (m) Data collection and physician notification facilities.
- (n) Develop a record keeping system (if possible computerized) for all specimens, outcomes, notifications, confirmatory specimens, and initiated treatment and outcomes.
- (o) Availability of a paediatric endocrinologist for consultation and an epidemiologist.

A flow diagram must be developed to illustrate each step of the designed programme and to identify the responsible person(s) at each step along with the address and telephone number. A lead person, responsible for the complete programme, must be designated before any programme-design work is done. A second person must be designated as the quality assurance coordinator who will monitor the programme to ascertain the promptness of data turnaround and treatment of affected infants. The quality assurance coordinator will also monitor the laboratory quality control and carry out proficiency evaluations of the testing laboratory. These two individuals should coordinate and develop the congenital hypothyroidism screening programme design and pilot testing of its operation. The design of the screening operation as a centralized laboratory and follow-up centre will be highly dependent upon the availability and reliability of the transportation system.

An advisory committee (a multidisciplinary team) should be organized consisting of the newborn screening programme director, representatives from the medical community, representatives from the public sector, and where appropriate, a representative from the legal sector. The role of the advisory group is to function as a liaison between the government, medical community, and the general public to oversee and ensure the financial support, public relations, and quality of programme operations. An annual report for the screening programme should be developed through the programme and the advisory committee for distribution to the user community.

The size of the screening laboratory will vary depending on the resources available and transportation system of the geographical area covered. A central laboratory that can process 40,000 to 150,000 specimens/year has been recommended for quality assurance and cost benefit aspects. A laboratory screening 40,000 specimens/year will detect sufficient newborns with congenital hypothyroidism to maintain an appreciation of their contributions to prevention of adverse outcomes due to congenital hypothyroidism disorders. Such a workload also ensures optimum utilization of manpower, laboratory equipment, and reagents.

The collective information and its comprehensiveness will vary with each situation, and the programmes will evolve differently for each level of initiation. If newborn screening for other disorders is already in place, congenital hypothyroidism screening should flow smoothly into the existing operation. Examining the screening operations in other regions or countries of similar size may be useful in promoting the implementation of a congenital hypothyroidism screening programme. The list mentioned under "Principal Information" should guide the programme's comparative evaluation.

3. OBJECTIVES AND TARGETS

The long-term objective of any congenital hypothyroid screening programme is to establish a quality programme that provides not only laboratory testing but follow-up treatment and prevention of disorders associated with this defect. The aim of the programme is to provide these services to the total newborn population for identification and treatment of congenital hypothyroidism as effectively as medically possible. The programme planners must establish that detection alone is not the outcome of screening. The follow-up phase to the health care community must ensure the appropriate medication is available and treatment is monitored and maintained.

Operating a sound screening system for congenital hypothyroidism will drastically reduce or eliminate the adverse effects of congenital hypothyroidism and improve the quality of life for the parents and the affected newborn. Of course, congenital hypothyroidism screening must be viewed in the context of the national priority of health needs and assessed in regard to delivery of the most benefits for cost and resources on a national basis.

The initial target should be a systematic inventory of resources available and additional manpower and financial resources required to develop a congenital hypothyroidism screening programme. The inventory may well direct how the programme is designed and the extent of the start-up cost.

Congenital hypothyroid screening falls into a category of high priority among health problems in general: public concern for the problem, effects on economic productivity, community motivation, importance in terms of disability, availability of highly effective solution, effectiveness of prevention treatment, emotional stress to families, and gain in prestige of health administration.

The first goal should be the initiation of a screening programme associated with high birth rate centres or regions to develop impact statements for the area. This programme could then gradually be expanded to meet national needs.

4. APPROACHES

There are five basic focal points to achieve programme operation and these may be examined as a phased approach to programme operation:

Education

Numerous educational pamphlets for parents have been developed by the presently operating screening programmes and these are available as guides or for modification to meet the needs of the new screening programme. These pamphlets are directed to the parents at several levels of sophistication and in several languages. The theme is to inform the parents of the tests and the positive aspects of testing to reduce emotional anxieties and to ensure complete participation for all newborns. The development of these educational materials for parents are essential to operation of the programme.

Specimen Collection

Primary method is whole blood collected from a heel stick of newborn onto filter paper at the birth location; a second method, though not widely used but still viable, is cord blood applied to filter paper or direct analysis of cord serum. A national standard has been developed and published that is applicable to all techniques involving collection of blood on filter paper⁶.

Laboratory Methods

Radioimmunoassays, enzyme-linked immunoassays, or fluoroimmunoassays are in use for measuring the analytes for screening tests. Tests are available in kit format from commercial sources or may be developed from bulk reagents by the laboratory.

Follow-up Services

Tracking systems are applied to follow specimens from receipt by the laboratory through results of testing, notification and collection of confirmatory specimens, and notification of attending physician or paediatric endocrinologist. Computer systems have been developed for this purpose, although manual systems are used effectively in some programmes.

Medical Therapy

The treatment for an infant with congenital hypothyroidism is L-thyroxine in amounts sufficient to produce a serum level in the high normal range. A programme of routinely monitoring the thyroxine and TSH levels must be maintained for effectiveness of therapy. Laboratory services must be available for measuring these analytes in serum. Some transient hypothyroidism may be detected through the screening process and would not require permanent treatment.

Screening Programme Modes

Combination Thyroxine and TSH Screen

A programme is designed using a primary thyroxine assay with dried blood spot punches and a floating cutoff based on daily mean values of the screened

population, and followed by a TSH assay in duplicate on all specimens below the designated thyroxine cutoff value (lower tenth percentile). The TSH assays use a fixed cutoff value of 20 to 30 $\mu\text{IU/mL}$ (depending upon commercial kit in use) for presumptive classification. All presumptive positive infants (low thyroxine value coupled with high TSH value) are recalled for examination and complete thyroid analysis by the physician or endocrinologist. A minimal false positive rate is tolerated to ensure adequacy of the screening process (reduce risk of false negative classifications). The combination screen is used by large centralized screening operations, primarily in the USA.

TSH Screen

The programme uses a primary TSH assay on dried blood spot punches with a fixed cutoff value of 20 $\mu\text{IU/mL}$ (may vary slightly with programme and test kit). In most programmes, no thyroxine screen is performed. These programmes are used in Europe and Japan; and in most cases, the daily specimen load per laboratory is smaller than those in the USA. The timing of sample collection is usually in excess of three days in programmes utilizing the primary TSH testing. False positive rates are somewhat comparable. TSH analysis alone misses detection of secondary hypothyroidism.

Cord Blood Screen

The programme uses either cord serum in serum assays or cord blood applied to filter paper for thyroxine and TSH assays. Since cord blood systems are not easily adaptable to mass screening and the specimen is not suitable for PKU screening, this system is rarely used.

Filter Paper Collection Matrix

Special paper specifically designed and monitored for its effectiveness for newborn screen must be used. This paper, although routinely referred to as filter paper, is not generic. The punches usually 1/8, 3/16 or 1/4 inch in diameter equate to a volumetric measurements with all the associated accuracy factors^{6,7}.

Sampling Time

Optimal time for specimen collection is three to seven days after birth. Because of early discharge or other factors, it is desirable to collect a specimen while the infant is available. Early collection may increase the false positive rate, but this risk is preferred over the risk of failure to be screened. The congenital hypothyroid infant will not be missed by the early specimen collection. Some programmes recommend that a second specimen be collected for testing on all newborns at two to four weeks to ensure adequacy of screening⁸.

Selecting the screening mode will be dependent upon the variables associated with the particular screening programme. The performance of the primary TSH or combination tests have been equally effective. Resources available and size of the screening operation are factors which must be considered in the selection process.

5. ACTIVITIES

An exact agenda cannot be developed to cover all circumstances for implementation of the congenital hypothyroidism screening operation. Programmes may differ in design without impacting its effectiveness. Each situation will differ based on resources, transportation, centralization or lack of birthing locations, and interactions with the physicians. It is impossible to establish time frames in any realistic sense because of the variety of levels of entry into the newborn screening process. Programme sizes will vary from numerous laboratories coordinated by a central health authority to a centralized test facility. Numerous variations will exist from both of these situations. Ideally, the screening facility should be centralized for conservation of resources. The presented information will serve as a guide to cover the critical aspects of all congenital hypothyroidism screening activities and provide some perspective of the time frame.

Government Policy

The support of a government health agency and its policies is important to the initiation and operation of a newborn screening programme. The development of well-defined government guidelines for all phases of the screening system can be an effective means of reducing errors and designating responsibilities for defined authority. The cooperation of the medical community in developing countries is frequently required to obtain favourable reception of the programme because of the other high priority health needs affecting infant morbidity and mortality; e.g., malnutrition, infections, and diarrheas. Government intervention may be necessary to overcome lack of cooperation. Without political decisions by health authorities for both financial commitments and adequate health policies, screening programmes for congenital hypothyroidism will start and die, and never become a nationwide programme. Negotiations must be carried to the body of the health organization providing them with information to support congenital hypothyroidism screening.

Routine Procedures

All expectant mothers are provided with pamphlets that explain what the screening procedures involve and their purpose. Filter paper and patient data forms are designed for specimen collection kits and provided to all individuals who deliver newborns. Whole blood specimens are collected at birthing centres or locations by the attending physician (or midwife, etc.) within three to seven days after birth on collection paper by heel puncture, air dried for at least two hours, and then transported to the testing laboratory⁶. The specimens are mailed or transported to the testing laboratory within 24 hours of collection. The specimen collection forms must have an attachment for reporting all information relative to the infant, the parents, and the physician, and a description of the procedure for appropriate collection of adequate specimens⁶. Logistical mechanisms are in place for prompt delivery of the specimen to the laboratory. The specimens are logged into a record system, verified as adequate specimens, and passed to the testing facility. The appropriate screening protocol is followed for analysis of the samples and presumptive positive specimens identified. The physician and/or parents are notified for collection of a repeat specimen and retesting where necessary. Diagnosis is confirmed by serum testing and treatment is initiated. Turnaround time from collection of specimen to treatment must be less than three months, ideally less than one month. The treated infant is monitored for satisfactory response and is

followed for maintenance of treatment. Testing records are kept on all identified congenital hypothyroid infants for periodic evaluations and measurements related to successful outcomes.

Laboratory Structure

The facilities should be developed after inventory of existing laboratories with capabilities for immunoassays for thyroid hormones. The organizational components include areas for specimen receipt and recording, specimen punching, analytical test preparation, and for appropriate instruments for selected immunoassay type, and a data reporting and quality control verification section. Initial utilization of an existing laboratory facility with experience in immunoassays is recommended. Size of the screening effort will somewhat direct the laboratory structure and location.

Training

The director of the screening programme should be trained in an experienced screening laboratory of similar screening capacity and resources. Laboratory personnel should be trained to perform immunoassays using dried blood spots. The staff of the screening laboratory should be provided with information on the overall screening process and the significance of their effort. Staff involved in the follow-up process should be trained to ensure location and treatment of detected infants. The training needs of personnel are highly specialized, requires extensive time, is costly, and will probably involve on-site experience at a newborn screening facility outside the country. Owing to the timely nature of treatment, the programme must have cross training of staff in order to carry out its functions in the absence of particular personnel.

Confirmation Testing

Identified presumptive congenital hypothyroid infants should be confirmed with liquid serum tests for thyroxine, TSH and other thyroid function tests. The infant is recalled for collection of the serum specimen and initiation of treatment by a physician aware of treatment and testing for endocrine disorders. Confirmation testing is necessary because of false positive screening results, possible screening mistakes, and transient hypothyroidism (especially in regions of iodine deficiency). Treatment must not be delayed pending results of the confirmation testing. Adverse results have not been reported for treatment of a normal infant with thyroxine medication. Delay of treatment can be harmful. The serum test may be performed in another laboratory that routinely analyzes for these analytes.

Quality Assurance

The mechanism of setting acceptable standards of operation and monitoring the maintenance of performance from specimen collection to data reporting and treatment is a complete quality assurance system. Standards of practice should be written for the laboratory outlining the best practice, potential errors, and corrective actions. One measure of quality performance is the time frame between specimen collection and its receipt to the identification and treatment of the hypothyroid infant. The analytical laboratory should maintain quality control specimens, charts, and if possible, participate in an external exchange of quality control specimens or in a quality control programme.

Medical Treatment

The recommended level of thyroxine is 10 to 15 μg per kilogram of body weight per day⁹. The serum should be periodically tested for thyroxine and TSH levels to ensure that a circulating level of thyroxine is maintained in the high normal range. Re-examination should be carried out every two to four weeks after treatment begins and at least every three months for the first year. A dosage schedule has been proposed based upon age. Thyroxine is inexpensive and does not interfere with the routine of the family. The infant should be evaluated for response to medication by examination of the intellectual and physical development.

Developing Advisory Committee

A committee comprised of a variety of professionals associated with newborn activities is an excellent mechanism to maintain support of the medical community and for assisting in gaining financial support from the government. The committee serves as a quality assurance factor to provide external review and critique of the screening programme activities. Such a committee should be established before formation of the screening programme. Physician participation helps in obtaining the cooperation and adherence to recommended guidelines by other physicians and mediators of birthing services. Regular meetings must be scheduled and topics discussed relative to the status or current problems of the screening programme. Newsletters can be developed by the committee to provide public relations and to garner broader support for the programme.

Education of Parents

Pamphlets in easy-to-read or picture format which explain all the aspects of screening and the positive outcomes should be provided to all childbearing women. Pamphlets in easy-to-read, question/answer format should be given to parents of presumptive congenital hypothyroid infants when recalled for further testing. This information, along with counselling, will relieve anxieties and residual fears of the parents of congenital hypothyroid children and provide positive information for community discussions.

Legal Aspects

Errors in the screening process will occur and have happened for many reasons. The missed congenital hypothyroid child and his parents may have legal grounds for compensation. Lawsuits occur in many industrialized nations; however, in government supported screening programmes in developing nations, lawsuits may not be an issue. Regardless, maintaining excellent records and documenting quality assurance procedures is the best way to establish sound operation of the screening process for any legal ramifications.

Pilot Testing of Programme

The designed programme should be field tested in one location to ascertain any problems before attempting a full-scale operation. The pilot testing should be phased in with increasing numbers of specimens to the anticipated maximum output for the pilot test site. Flow charts for the programme and an examination of the performance of each step is important to measure successful operations and to easily trace the problems. The phasing process allows the

analysis and improvements in the activities in a gradual process. The phasing levels for the test area can be reasonably achieved in two to three months. The expansion of the programme to other areas can be accomplished in an evolving process over the succeeding nine months. A full-scale national programme can be accomplished in a year or less, depending on the variables of the particular situations.

6. MONITORING AND EVALUATION

The primary evaluation of the programme will be developed as a feasibility assessment from the outcomes of the pilot or expanded screening programme. The feasibility will be highly dependent on the local conditions. The purpose of the pilot programme is to determine the potential for implementation of a screening programme; therefore, its success is a direct measure of the feasibility. Success is measured by outcome and process evaluations in the same manner as for the expanded or operational programmes.

Outcome measurements are the best means of monitoring performance of the congenital hypothyroidism screening programme. The target of providing screening to all newborns can be assessed from the number of specimens processed and the number of births. The determination of the incidence frequency in the population will yield a measure of the impact of the programme. Disease registers and the examination of the status of treated hypothyroid infants detected by the screening programme will provide a measure of the successful operation in meeting programme objectives for prevention.

Sound record keeping practices are essential to monitoring and evaluating the programme. These records provide collected data for deriving incidence/prevalence rates under various conditions and among high risk population groups. The data will be obtained from various conditions and high risk population groups. The data will be obtained from the information on the specimen collection forms, the results of laboratory tests, and follow-up procedures. It is essential that uniform and accurate records be maintained.

Monitoring the time required for the affected infant to be detected and treated is a critical evaluation indicator. Failure to detect and treat the congenital hypothyroid infant within the three month time frame indicates a failure in the programme.

Several process indicators may be examined to measure the flow of the operation. The quality of the specimens collected must be checked to direct the identification of training needs and to ensure adequate specimens are provided to the testing laboratory. An assessment of the time required from collection of specimen to receipt by the laboratory measures the reliability of the specimen transportation process. Participation of the laboratory in one of the international quality control programmes will provide a blinded evaluation of the analytical performance of the laboratory and give an indication of its comparability to other screening programmes. The records maintained on the follow-up of presumptive positive infants will show an evaluation of the time span required to establish contact with the infant's parents and carry out confirmatory testing. These same records will also permit the determination of false positive rates for measurement of the effectiveness of the laboratory methods and decision levels, and potentially, the transient hypothyroid incidence rates. The flow chart of the programme operation can be used to facilitate the process evaluation and the reliability of the personnel at each step. Process evaluations are not direct indicators of impact, but provide administrative and accounting measures, and show ways to improve efficiency.

The evaluation and monitoring of false positive rates are extremely important in preventing problems. High false positive rates can jeopardize the success of the programme by producing increased anxiety among the population,

overloading the follow-up component of the programme, and reducing the creditability within the medical community.

An internal review and evaluation of the programme is an important function performed by the advisory committee or some local medical group. An external review and evaluation of the pilot programme by a group of experts can be valuable for assessment of the programme design and operation. Periodic reviews of the established programme by internal and/or external review groups are useful.

7. COSTS

The cost of resources, equipment, and personnel covering all aspects for the implementation cannot be estimated for each of the possible iterations in programme designs for the many circumstances. Numerous local factors will interact in the cost estimates of each programme. The screening strategy selected, follow-up logistics, numbers of repeat specimens, and the state of the national economy are some major factors contributing to the variable cost. An itemized cost for each component should be developed using the flow chart of the screening programme design and the inventory of existing resources. Training cost for personnel should be included in cost projections. Reliable estimates can be computed from the pilot programme testing for country-wide screening cost. Of course, the cost per disorder is greatly reduced when additional tests are added to the screening programme, i.e., PKU, sickle cell disease (SCD), galactosemia, etc., resulting in many components of the screening process being shared.

Several studies have examined the cost-effectiveness of newborn screening for congenital hypothyroidism in the USA^{10,11}. These cost-benefits in most cases are based on an estimated burden to society with institutional care of the mentally retarded child. All studies demonstrated substantial savings to society, disregarding the non-measurable contributions of a better quality of life for the child and family. The US Office of Technology Assessment¹² indicates that the savings are US\$93,000 per detected case when compared to no screening and the cost-effectiveness dramatically increases with expanded programmes covering tests for additional disorders.

The average cost for some of the analytical components has been estimated for programmes in the USA with specimen collection cost at US\$6.00¹⁰, cost per laboratory test at US\$1.50⁵, and costs per specimen screened ranging from US\$4.00 to US\$8.00¹⁰. The component cost will vary for each screening programme and country, with some items being less or more expensive in developing nations; but these data provide some perspective on operational cost. Centralization of the screening programmes will contribute significantly to reductions in operational cost by decreasing the number of laboratories, requirements for trained personnel, laboratory equipment, and redundancy in many fixed cost components.

Based on the reported experiences in the congenital hypothyroidism screening programme in Brazil¹³, even developing nations where malnutrition and infectious diseases are major causes of infant morbidity and mortality, the cost for newborn screening is practically insignificant compared to other health expenses and their preventive measures for adverse effects are more easily achieved.

8. MANAGEMENT AND OBSTACLES

An interactive management system developed around the personnel flow diagram for the screening programme is highly recommended for cooperative understanding of roles. The primary supervisors should be highlighted in the organizational diagram. Operating the screening programme smoothly requires daily involvement with each component. An effective means of maintaining quality management of the components is by having written standards of practice with detailed procedures for the specific parts and designated responsibilities. A trouble shooting guide that is developed by the programme as it encounters problems and their solutions is an evolving aid in ensuring the management process that repeat problems are recognized and resolved efficiently. A programme coordinator should have overall responsibility for operation of the programme; however, each staff member must feel the significance of his or her function. Periodic meetings of the programme staff during which the accomplishments of the programme are reviewed and problems discussed is a valuable tool. Since the workload of the screening programme is continuous and time of treatment is critical, a cross-training system for personnel is an effective motivational tool and a fail-safe management resource. The advisory committee should be asked to review any major management decisions.

In developing countries, the local transportation and mail system may be the major obstacle to overcome in developing newborn screening programmes, especially for cost-effective centralized operations. The logistics of getting a specimen to a laboratory, obtaining repeat specimens, locating presumptive positive infants, and obtaining treatment while achieving all aspects in a timely manner is dependent upon the efficiency and reliability of the transportation networks¹³. Ensuring that medication is readily available to the infants undergoing treatment may be a critical obstacle, since the benefits of screening efforts are dependent on maintaining therapy, especially for highly mobile populations with poor tracking systems. These problems may determine the extent and size of the screening programmes in many countries. A second obstacle after receipt of financial support for the programme will be maintaining the support through changing government officials and stability of the specific government entities. One developing country has experienced this problem with complete termination of the programme with changes in the political climate and then trying to restart the newborn screening effort when the attitudes shifted. In some areas of extremes of illiteracy and many ethnic groups, the education of families and expectant mothers regarding the advantages for screening and treating infants will require a dedicated effort¹³.

9. COLLABORATION

When developing and planning a national congenital hypothyroidism programme it is important to coordinate these activities with medical and voluntary organizations and other health agencies in the country.

Presently, congenital hypothyroidism screening programmes are operational in about 30 countries¹⁴. Cooperative interactions have been experienced among all the screening programmes in terms of training assistance, exchange of materials, and consultative assistance. The international network of screening programmes is a highly interactive group, and collaboration with new programmes are welcomed and encouraged. The use of these existing programmes will help prevent struggling with many problems that have already been encountered somewhere in the world. The limitations of resources makes it essential that efforts be directed toward these valuable information sources. Many of these programmes are willing to share copies of their procedures and standards of practice for modification or use as is. International and regional societies of newborn screening hold meetings periodically at which recent data and emerging problems and technologies are discussed. Since the exchange of information and problems is essential to any new programmes, the director of the congenital hypothyroidism screening programme should attend these meetings when possible.

Internationally, several proficiency evaluation programmes exist for congenital hypothyroid screening. These programmes encouraged collaboration and comparative information exchange on laboratory and test performance¹⁵. The national programme at the Centers for Disease Control in Atlanta, Georgia, USA, has provided dried-blood spot reference materials and protocols for preparation of quality control materials to several countries, and have also assisted some countries in establishing their own national proficiency evaluation systems¹⁶. The International Society for Newborn Screening has held discussions on formation of committees to organize international quality control efforts for newborn screening. The international newborn screening community maintains an environment of sharing to help develop high quality screening programmes through their numerous collaborative efforts.

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II. General Principles for the Formulation of National Screening Programmes
for Congenital Hypothyroidism in the USA

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1. INTRODUCTION

The technique whereby whole blood collected from newborns onto filter paper as a specimen source to test for phenylketonuria (PKU) was introduced 28 years ago¹. The introduction of this new technique led to the implementation of newborn population screening programmes in the USA for inborn errors of metabolism. The dried blood specimen permitted the development of simplistic systems for logistical operation of centralized laboratory screening programmes. These screening programmes became well established over the next 10 years, primarily in the State public health laboratories. With the resolution of numerous problems of specimen transportation, laboratory analysis, data turnaround, follow-up of detected newborns, confirmatory testing, and treatment of affected infants the programmes evolved into reasonably smooth operations. These programmes established the experience base for operational testing of new laboratory methods pursuing the early detection of affected infants in a cost-beneficial manner for many newborn disorders requiring early treatment for prevention of adverse effects.

Congenital hypothyroidism was known to cause severe physical and mental disabilities before newborn screening². The finding that early treatment of this disorder produces significant improvements in outcome and that the frequency of occurrence was greater than the rate for PKU created the momentum for mass newborn screening for congenital hypothyroidism³. In 1973, the first population screening for congenital hypothyroidism was started in the USA⁴ and occurred as an addition to the existing newborn screening operation for PKU. Based on the experience of this pilot programme, population screening for congenital hypothyroidism was pursued with intensity by the newborn screening laboratories in the USA.

The first congenital hypothyroid screening protocol required the use of immunoassays for thyroxine and thyrotropin (thyroid-stimulating hormone [TSH])^{4,5}, the primary and secondary screening tests, respectively. The use of the two tests in tandem was thought to be ideal for cost, reliability, turnaround of data, and quality control for high volume centralized laboratories. The fact that the thyroxine and TSH analytes were measured by radioimmunoassays for which the PKU laboratories had little or no experience and equipment impeded somewhat the initiation of testing. In 1975, the first screening programmes in the USA for congenital hypothyroidism were in the States of Oregon and Massachusetts each of which provided services for several regional States. These initial programmes applied assay methods using reagents and protocols developed by the laboratory. When the reliability of these assays was established, commercial kits quickly became available. The availability of experienced laboratories, training for isotopic assays, commercial test kits, and government funding for pilot programmes yielded the resources for the spread of this screening across the country. Numerous early arguments were heard regarding private versus public health sector screening of newborns in many of the States.

The introduction of congenital hypothyroidism screening to the dried blood specimen contributed substantially to increased efforts for centralization of screening laboratories. A wide diversity of approaches by State screening programmes exist in the USA based around the universal scheme of a primary thyroxine test followed by the secondary TSH test. These screening programmes may be carried out by the State laboratory, by contracted laboratories within

the State, by agreement with another State's laboratory, by private laboratories in the State, or by the combined efforts of private and State laboratories.

Screening by numerous private laboratories within a State is strongly discouraged, and such systems exist in only a few States. Most State programmes involve laboratories screening more than 40,000 newborn specimens per year. Two large centralized State screening facilities handle more than 250,000 specimens per year. The mechanistic designs within each State screening operation have some individualistic practices. Regardless of the approach by the State, virtually all newborns within the USA are effectively screened for congenital hypothyroidism.

2. SITUATION ANALYSIS

Objectives for the Nation

In 1980, the US Department of Health and Human Services issued as a 1990 objective for the nation that virtually all newborns should be provided neonatal screening for metabolic disorders for which effective tests and treatments are available, e.g., PKU and congenital hypothyroidism⁶. The mechanisms for achieving this objective were established and included technical assistance and cooperative measures. In the early 1970's, only 3% of the population was screened for congenital hypothyroidism and by 1985 every State and the District of Columbia had programmes in routine operation. The successful implementation of these programmes was greatly due to the provision of federal funding in 1976 for State genetic services programmes.

Justification for Screening

Screening is the presumptive classification of a specimen by the application of rapid inexpensive test. The screening test sorts the study population into the categories of presumptive positives and negatives with a reasonable rate of false positive results and no false negative classifications. A screening test is not intended to identify diagnoses. Positive results in the screen indicate who is referred for confirmatory testing and physician follow-up. Screening tests may be implemented for populations when treatments can be justified for prevention of severe disorders.

The clinical signs of congenital hypothyroidism are inadequate to yield easy detection of affected newborns (deficient production of thyroid hormone) for treatment. Failure to timely identify and treat will result in irreparable physical and mental damage to the infant². The consequences of this disorder and the ease of treatment supported that population screening should be implemented for early detection and treatment for all newborns in the USA. A sound programme involving reliable laboratory testing and intervention with medication was established for prevention of adverse outcomes from congenital hypothyroidism.

Incidence Characteristics

The overall incidence of congenital hypothyroidism varies among ethnic groups in the USA with an average incidence rate of 1:4,500 with a range of 1:3,600 to 1:5,000⁷. The incidence in black populations is lower with 1:10,000 (Georgia) to 1:17,000 (Texas)⁷. A higher incidence rate is seen for the Hispanic populations with a rate of 1:2,700⁷. Females with this disorder in the USA outnumber the males by a ratio of 2 to 3:1⁷. No seasonal variation has been reported by any programme for congenital hypothyroidism, and no high at-risk group has been found.

Disease and Adverse Outcomes

The neonatal hypothyroid disease seen in the USA has been called sporadic cretinism, a congenital biochemical or anatomical defect of the thyroid that causes a circulating thyroxine deficiency⁸; however, the disease is actually congenital hypothyroidism, not cretinism. The outcomes of the untreated hypothyroid newborn in the USA resembles those for cretinism. In the majority of the infants with congenital hypothyroidism the cause is an anatomical defect

of the gland that occurs at random among newborn population⁸. Early detection and therapy is necessary for improved intellectual and physical prognosis. Evidently, with medication, the developing brain in the first three months of life has the ability or sufficient redundancy to recover from the in-utero hypothyroid experience⁸.

Without newborn screening mortality may occur for failure to diagnose, and developmental and physical disabilities will vary depending on the extent of the thyroid deficiency. Even with effective and well-managed newborn screening programmes, occasionally a missed case of congenital hypothyroidism occurs.

Although no evidence exists to show that mental deficiencies occur in the detected hypothyroid infant treated within a three month time frame, some concern exists as to whether full potential is achieved. In the New England screening programme, treated hypothyroid infants do show lower psychomotor scores at 12 months, but do not differ in overall IQ at three to five years of age. By six years of age, these children appear normal in intellectual function but somewhat slower than average in motor performance speed⁹. The children with congenital hypothyroidism who were identified and treated may still develop some minor deficiencies even with appropriate treatment.

Organization and Management

Most State screening programmes are similar in structure and general operation, although many minor aspects are different. It is not possible to cover the subtle difference for all programmes. The flow chart below is the generic description for the organization and management scheme.

PHASE I: Collection Site

- Educational pamphlet to expectant mothers
- Specimen collection guide
- Newborn dried blood specimen
- Information on infant
- Specimen collection log
- Transportation of specimens/routine mail

PHASE II: Laboratory

- Specimen validity
 - Inadequate/new specimen requested
- Thyroxine test
 - Apply cut-off criteria
 - Thyroxine normal - report
- Thyroxine low
- TSH test
 - TSH normal/low thyroxine - request new specimen
 - TSH elevated - refer for primary hypothyroidism
- New Specimen - repeat thyroxine/TSH scheme
 - Thyroxine normal - report
- Thyroxine low
- TSH test
 - Thyroxine low/TSH normal - refer for secondary/tertiary hypothyroidism
 - Thyroxine low/TSH elevated - refer for primary hypothyroidism

PHASE III: Follow-up

Notification of physician/parents by telephone and letter
Confirmation testing/medication
Follow-up on notification
Counselling/parental education
Registry - Tracking

The size of the screening laboratory varies from small States of 8,000 to 20,000 specimens per year to central laboratories that can process 40,000 to 250,000 specimens per year. The centralized programmes are recommended because of quality assurance and cost-benefit ratios. The management team consists of the laboratory director, screening laboratory director, and the child and maternal health director. Laboratory quality control and proficiency evaluations are carried out at the national level by the Centers for Disease Control located in Atlanta, Georgia. An advisory committee which includes the newborn screening programme director, representatives from the medical community, representatives from the public sector, and where appropriate, a representative from the legal sector, serve as external consultants and as a review board for public relations and quality of programme operations. An annual report for the screening programme is produced by the management team for distribution to the user community.

3. OBJECTIVES AND TARGETS

The aim of the programme is to provide services to the total newborn population for identification and treatment of congenital hypothyroidism as effectively as medically possible. The target is that these services must be provided to all newborns in the USA by 1990⁶. The long-term objective for the congenital hypothyroid screening programme is to ensure that quality newborn screening programmes provide not only laboratory testing but follow-up treatment and prevention of disorders associated with this thyroid deficiency. The programmes operate under the rule that detection alone is not sufficient. The follow-up phase to the health care system ensures the appropriate medication is available and treatment is monitored and maintained. Operation of these sound screening systems for congenital hypothyroidism have drastically reduced or eliminated the adverse outcomes due to this disorder. Consequently, the quality of life for parents and newborn has improved.

Congenital hypothyroid screening falls into a category of high priority among health care priorities in general: among the reasons are public concern for the problem, effects on economic productivity, community motivation, importance in terms of disability, availability of highly effective solution, effectiveness of prevention treatment, and emotional stress to families.

4. APPROACHES AND ACTIVITIES

The basic programme design in the USA utilizes the combination screen of thyroxine and TSH assays. A national standardized programme design for screening does not exist in the USA and no written formal standard for operation is available. Each State has taken the basic concepts and set up their own design modelled from the Oregon and Massachusetts programmes (Northwest and New England regionals). Surprisingly, most programmes are similar in structure, function, and results. The common components of these programmes will be addressed.

Government Legislation

Of the 50 States having newborn screening programmes for congenital hypothyroidism, 48 States and the District of Columbia have legislative statutes governing newborn screening, one State has no statute, and one State has a statute stating that the screening is voluntary¹⁰. The statutes in 48 States direct that screening of all newborns in the State is mandatory for congenital hypothyroidism (or in generic terms): some States define no acceptable reasons for parental objection; in the majority of the States, religious grounds are acceptable justification; and, in a few States, the parents may object for any reason. Many of the States permit objections for some reason, but very few statutes require that the parents be informed of their consent rights or right to refuse. Most statutes specify by regulations or guidelines the specifications for the type of laboratory. Some statutes require that the screening programmes must participate in a proficiency evaluation programme. Statutes vary as to who has responsibility for ensuring that the specimen is collected; however, most statutes deal only with hospital births where the physician or the birth attendant carry the burden of responsibility¹⁰.

Education

Each State screening programme has designed pamphlets to inform parents about hypothyroidism and the infant, and to cover the aspects of newborn screening in general. The pamphlets are written for the parents at a moderate educational level and are available in different languages in States with large populations who do not read in English. The pamphlets for hypothyroidism are designed in a question-and-answer format; e.g., "What is congenital hypothyroidism?", "Where is the thyroid gland and what does it do?", "Could my baby have inherited hypothyroidism from me?", "What would cause the thyroid gland not to work properly?", etc. These pamphlets are provided to the pregnant women by the person or facility providing prenatal care: hospitals, physicians and midwives within the State.

Specimen Collection

An approved national standard exists for blood collection on filter paper for newborn screening programmes¹¹. The standard delineates in detail how to collect and what is an adequate specimen. In general, a specimen is considered inadequate if the full panel of tests cannot be done with the submitted specimen. This standard in a picture format is provided to all collection centres, physicians, and other appropriate individuals. Each State has a specimen collection card consisting of an information section with attached filter paper. The information attachment request the specifics relative to the birth, the parents, and physician or birthing attendant. The recommended

collection method is whole blood taken from a puncture of the newborn's heel by direct blotting of the blood droplet into the circles outlined on the filter paper. Some State cards have specific instructions for collection and processing outlined on the reverse side of the non-filter paper portion of the specimen collection card. The blood spots are dried at ambient temperature for at least two hours and mailed to the laboratory within 24 hours of collection.

Time of Specimen Collection

Specimens are collected on the State specimen collection form, primarily at hospitals, within an optimal range of three to five days after birth. If the newborn is to be discharged from the hospital or birthing centre before this criteria is met, the specimen must be obtained immediately prior to discharge. A second specimen is collected from this infant between seven to 14 days of age. Premature or sick infants may have the collection delayed as late as seven days. Transfused infants must have a second specimen collection two to four weeks following transfusion. A few States recommend that a second specimen be collected on all newborns at two to four weeks to ensure adequacy of screening¹².

Specimen Collection Matrix

The filter paper used for the specimen collection is Grade 903 manufactured by Schleicher and Schuell, Inc. (Keene, NH 03431). This collection paper is specifically designed and monitored for its effectiveness for newborn screening and is used by all screening programmes in the USA. The absorbency of serum in a 1/8 inch (0.32 cm) punch equates to a volumetric measurement with all associated accuracy factors¹³. The variability of each manufactured lot of Grade 903 filter paper is monitored by the National Infant Screening Quality Assurance Programme at the Centers for Disease Control in Atlanta, Georgia, before it is distributed to the screening programmes^{11,13}.

Laboratory Routine

The specimen number and patient information are recorded into the record-keeping system (computer) of the laboratory and screened for adequate collection. A second specimen is immediately requested for inadequate specimens and a record maintained of the responsible collection facility to direct training efforts if frequent inadequate specimens are submitted by a particular collection centre. The combination of immunoassays for thyroxine and TSH are applied in a tandem process to the screening of the specimen. All the laboratories use complete assay kits purchased from one of several manufacturers. A thyroxine assay is performed using a 1/8 inch punch taken from the dried whole blood specimen. Analytical results are sorted to normal and abnormal thyroxine based on a cut-off criteria (action level) assigned by the screening laboratory. The cut-off decision differs with State laboratory: some use a fixed value of 6 $\mu\text{g}/\text{mL}$ thyroxine, some use the lowest 10% of the values, and some use a floating cut-off based on two standard deviations below the daily (or geometrical) mean of the screened population. Specimens falling in the abnormal category are re-analyzed in duplicate and those specimens repeating as abnormal are submitted for TSH analysis in duplicate using 3/16 inch punches. The TSH assays use a fixed cut-off value of 20 $\mu\text{IU}/\text{mL}$ (a few States use 25 or 30 $\mu\text{IU}/\text{mL}$) for abnormal classification. The specimens determined to have presumptive positive results are referred to the designated individual for

follow-up services. A false positive rate of 2 to 5% is tolerated to reduce the risk of false negative classifications.

Interpretation of Test Results

If low thyroxine and elevated TSH values are obtained for a specimen, the result is classified as presumptive primary hypothyroidism and the physician of record is immediately notified by telephone and letter. The information is also recorded into a follow-up file to ensure that the infant has been located and is in the physician's care. If the thyroxine value is low and the TSH normal, a repeat specimen is requested. If the outcome remains the same on repeat testing, the specimen is classified as presumptive non-primary hypothyroidism. The information is recorded and the physician notified. The majority of the primary hypothyroid infants have TSH values greater than 80 μ IU/mL. Several non-primary hypothyroidism conditions are associated with abnormal (low) thyroxine values: secondary hypothyroidism, low thyroid binding globulin levels, maternal drugs (lithium, iodides), prematurity, severe illness, idiopathic transient hypothyroidism, and maternal thyroiditis. Most of these disorders usually are transient in nature. Secondary hypothyroidism occurs at a frequency of about 1:60,000 resulting from pituitary or hypothalamic disorders². Low thyroxine values are frequently observed in low birth weight infants with TSH values normal or slightly elevated and usually return to normal as nutritional status improves. Abnormal classifications with the dried blood spot specimen are not considered diagnostic and confirmation testing must be done using venipuncture serum.

Follow-up Services

The State maternal and child health groups associated with the screening laboratory perform a key role in administering follow-up programmes for notification of physician and/or parents for ensuring all presumptive positive infants are located and re-tested. In some cases their services are used to obtain repeat specimens and to monitor the compliance for specimen submission. Parental counselling is provided to minimize the anxiety that these requests for repeat and confirmation specimens might cause. The outcome of each presumptive positive is expected to be resolved by the follow-up process within 30 days after notification of test results by the laboratory. Computer systems are used to keep track of repeat specimen requests, notification and collection of confirmatory specimens, and notification of parents, attending physician or paediatric endocrinologist. Paper copies are used to document telephone calls, date, person contacted, action taken, and are verified by the signature of the coordinator. A network of paediatric specialists located statewide is maintained to provide consultation to physicians regarding management of hypothyroid infants. The State health departments maintain a listing of all infants that have been diagnosed with congenital hypothyroidism through their screening programmes.

Confirmation Testing and Evaluation

Presumptive congenital hypothyroid infants identified by screening must be confirmed with venipuncture serum for thyroxine, thyroid binding globulin, triiodothyronine uptake, and TSH. The infant is recalled for collection of approximately 2 mL of the serum, examination and initiation of treatment. These serum tests are necessary because of false positive results, possible screening mistakes, and transient hypothyroidism. The evaluation involves a complete

physical examination, X-rays of the knee and ankle for estimation of bone age, a thyroid scan with isotopic iodine, and the clinical thyroid test battery. Treatment is not delayed for results of this testing. The screening programme may or may not be responsible for coordinating diagnostic services or treatment for infants with abnormal screening results. Delay of treatment can be harmful; and if results indicate normal conditions, medication can be easily withdrawn. The serum tests are performed by the State laboratory or by a clinical laboratory selected by the physician. Re-examination of the infant should be administered after two to four weeks of treatment.

Medical Therapy

The recommended treatment is oral L-thyroxine at an amount sufficient to bring the serum level of thyroxine into the high normal range, 25-50 $\mu\text{g}/\text{day}$ for term infant and 8-10 $\mu\text{g}/\text{Kg}/\text{day}$ for pre-term infants. The circulating thyroxine level should be maintained in the 8-11 $\mu\text{g}/\text{dL}$ range for the first year of life^{7,14}. A routine programme for monitoring the thyroxine, triiodothyronine, and TSH levels is carried out at three month intervals. Neurological development evaluations are made at the follow-up visits. The circulating TSH concentration may remain abnormal despite treatment. The treated child is checked for response to medication by examination of the intellectual and physical development. Transient hypothyroidism is detected by the testing process and when confirmed, does not require continued treatment.

Quality Assurance

The congenital hypothyroid screening laboratories have analyzed their programmes and developed levels of acceptable performance for each step. Each programme has developed flow charts for the processing of specimens from receipt to confirmation to assure quality control is maintained throughout the operation. Standards of practice have been written for the laboratory outlining the best practice, potential errors, and corrective actions. The time frame is monitored periodically from specimen collection and receipt to the identification and treatment of the hypothyroid infants to determine effective programme operation. Periodically, in some State programmes, the laboratory director will produce simulated specimens and infant information for the specimen collection form and send these faked specimens through the screening process as a proficiency testing operation.

A two-component national external quality assurance programme is operated by the Centers for Disease Control in Atlanta, Georgia, for all screening laboratories^{15,16}. This programme provides laboratories with dried blood spot quality control materials for thyroxine and TSH assays. These quality control materials are provided at three levels for thyroxine and TSH: negative, borderline, and positive classifications. Sufficient materials are provided to each laboratory for routine use. These quality control specimens provide the laboratory with a second level of control beyond the kit or laboratory control specimens, and transcend changes in test kit lots and other control materials. Quality control charts are kept for each test for the daily analytical performance in the laboratory. The national quality assurance programme provides, on a quarterly distribution, a panel of blind coded dried blood spots that simulate normal and presumptive hypothyroid infants for proficiency evaluation. The proficiency evaluation specimens provide an external check on the ability of the laboratory to identify and classify abnormal and normal specimens. Quarterly reports are developed using coded identifiers for the

laboratories and distributed (within 30 days after receipt of their data) to the screening laboratories indicating performance of all laboratories.

Training

The State laboratories maintain training films and literature on procedures for satisfactory specimens for hospital employees involved in specimen collection. The screening programmes can provide bench training in laboratory procedures to each other upon request. Most laboratories rotate personnel in the laboratory as much as possible to provide cross-training and to assure that in employee absence or resignations the screening operation is not jeopardized. Formal training sessions are periodically offered by some States laboratories in new technologies and tests. At the national newborn screening conference, question-and-answer workshops are organized so that participants can discuss problems and issues associated with congenital hypothyroid screening.

Advisory Committee

The programmes in the USA have formed committees of varying composition to assist the congenital hypothyroid screening programme in resolving administrative problems, critiquing of proposed programme changes, and carrying out public relations activities with the public and private health providers. These committees are usually composed of individuals from the technical and lay communities and provide a broad base for public support of programme activities. A paediatric endocrinologist is usually a member of the committee to represent the congenital hypothyroidism component. The committee members may be selected and appointed by the health commissioner for the State or by the screening laboratory director. Occasionally special task forces are also organized with specific technical expertise to assist the committee with unusual educational, financial, social, or medical issues impacting the newborn screening programme. One of the primary functions of the advisory committee is to help develop and review guidelines and regulations for compliance and legal issues. The committee meets at scheduled times to discuss topics relative to the status or current problems of the screening programme. A committee secretary keeps detailed minutes of the meetings and recommendations from committee sessions.

Legal Aspects

Newborn screening programmes for congenital hypothyroidism, although well designed with many quality assurance steps, are not infallible. Several cases of congenital hypothyroidism are known to have been missed since screening for this disorder began in the USA¹⁷. Infants whose disease is undiagnosed and their parents are entitled to compensation for this failure. In the programme a legal counsellor is involved in many discussions of programme operations. The programme personnel and all providers of health care in the screening system are made aware of the scope of their legal responsibilities and liabilities¹⁸. The cost of litigation or its threat is enormous for missed cases and the settlements, regardless of their outcomes, have created much discussion over the advantages and/or elimination of newborn screening in its present form¹⁸. Written guidelines and regulations for programme operation are reviewed by legal counsel to ensure clarity and explicit delineation of responsibilities to minimize negligent performance. The guidelines are not idealized concepts, but are practical statements in a handbook of operational procedures with defined limits of responsibility¹⁸.

In many States the screening programme personnel carry insurance to cover them in the event of a lawsuit. At least one State has developed a self-insurance mechanism for dealing with missed cases by applying part of the fee-for-services charged for newborn screening to a special fund account. Records must be kept for a period of time determined by the statute of limitations by the State. This limit has been set as high as 28 years in some States¹⁸. All the States make an effort to maintain excellent records, registries on all detected infants, and documented quality assurance procedures with actions taken to demonstrate sound operational practices of the screening system.

Research

Investigations have been conducted to examine the possible role of TSH as the primary screen, thyroxine as a secondary screen, and TSH as the total screen for State programmes. The validity of such possible iterations has not been resolved or accepted. Research efforts are also being directed toward the development of rapid enzyme-linked immunoassays, in microtiter plate configurations, for thyroxine and TSH. This effort includes a modification of the automated punching devices to handle the microtiter plate. These technologies may eliminate isotopes in congenital hypothyroid testing in the USA as well as direct the laboratory screening process to greater automation and conservation of the newborn specimen for use in new tests under consideration and awaiting discovery.

5. MANAGEMENT AND EVALUATION

Diagrammatic flow or organization charts are used by the State screening programmes to describe all phases of the programme and the specific individuals responsible for each unit. This provides a management overview and clear delineation of responsibilities for management, giving each manager a scope of the complete system and the important linkage of his/her role. The general management scheme is a programme director, a laboratory chief, a director of follow-up from maternal and child health, physician consultants for treatment issues, and in some programmes, a State epidemiologist. The State programmes have written comprehensive procedural manuals for each part of the congenital hypothyroid screening system and these are referred to as the standards of practice. Each year these standards or practice are reviewed and updated as necessary.

Computers are a vital part of congenital hypothyroidism screening in the USA. Most States use computers for patient and programme tracking and for maintaining the database of demographic information. Infants with presumptive positive laboratory results are maintained in a separate database until diagnosed. Complete patient histories on all diagnosed cases are kept including documentation of follow-up contacts and the results of annual medical reviews. The computer files are used to generate daily activity charts for ensuring follow-up and treatment of detected hypothyroid infants. The systems link the laboratory and follow-up activities. A modular microcomputer network has been employed in some programmes to provide the necessary capabilities to ensure accurate and efficient tracking from submission of newborn specimens through diagnosis and treatment¹⁹. Numerous programme evaluations are available through statistical tabulations of various types of data collected and maintained in the computer files¹⁹. It is usually the responsibility of the screening programme to keep long-term records of the screening results and actions following identification of affected infants.

Annual reports are effective management and motivational tools of the newborn screening network and are developed outlining the results from the previous year of operation. These reports include the number of specimens analyzed, false positive rates, number of congenital hypothyroid infants detected, and the results from participation in external proficiency evaluations. Annual reports are distributed to the screening personnel, State legislature, medical community, local chapter of the Academy of Paediatrics, Family Practice Association, newborn nursery directors, and the advisory committee members to foster the feeling of cooperation among all participants and the significance of their overall achievements. These reports become a part of the permanent records for documentation of the programme activities.

Several critical indicators are used to evaluate and measure the success of congenital hypothyroid screening programmes: the number of infants screened, the number of births, the incidence rate, and the time lapse between specimen collection and treatment of affected newborn. Several State Programmes link the testing with birth certificates to monitor efficiency of complete coverage of the newborn population¹⁰. The frequency of inadequate specimens and the number of false positive results are monitored also for programme evaluation. These evaluation figures are not direct indicators of impact, but provide administrative and accounting measures, and help indicate areas for improved efficiency.

The participation of the screening laboratories in the quality assurance programme for congenital hypothyroidism testing offered by the Centers for Disease Control in Atlanta, Georgia, provides a periodic indicator of performance on a battery of blind coded specimens simulating disease and non-disease status. These proficiency evaluations give an independent evaluation of the analytical performance of the laboratory and an indication of its comparability to other screening programmes. The laboratories performing the confirmatory testing participate in proficiency testing services with the College of American pathologists for serum tests for thyroid profiles. The reports from these proficiency programmes provide an evaluation of performance for these laboratory components. The internal quality assurance system with set limits of acceptable performance for each step in the screening process is periodically reviewed to determine and record the number of events falling outside the established limits for satisfactory operation. These records provide the State programme with an itemized list of difficulties in the day-to-day operation and locate areas of needs for improvement or careful attention.

In some States, internal review and evaluation of the programme is an important role performed by the advisory committee or a local medical group. Requested external reviews by an experienced groups of experts are used by programmes to assess the effectiveness of operations and to identify potential problem areas. These periodic evaluation reviews of established State programmes are carried out by the Selected Panel on Newborn Screening from the Genetic Services Branch, Health and Human Services Administration and are useful critiques for improved operations and legal documentation.

6. SOURCES OF ERROR

A major misconception causing a potential source of error is the creation of a false sense of security in the medical community by the routine operation of a mandated screening programme. Because physicians incorrectly assume that congenital hypothyroidism has been definitely ruled out by the laboratory report, a decreased alertness for clinically symptomatic infants may occur⁷.

The missed case is a rare event. From the initiation of population screening for congenital hypothyroidism to 1983 in the USA, 33 missed cases of congenital hypothyroidism are known to have occurred, 1:500,000 screened newborns¹⁷. These missed cases were associated with all steps in the screening process, but the majority took place in the laboratory associated phases of the programme.

- 16% of the cases were missed in the specimen collection phase because of home delivery, specimen not received by the laboratory, premature newborn, congenital anomalies, inadequate specimen, and transfer of newborn to another hospital¹⁷. Some other potential sources of error identified for this phase are: parents refusal to permit heel stick for collection, discharge of newborn against medical advice, early discharge with specimen to be collected at physician's office, wrong name of newborn on collection form, specimen misplaced at hospital, specimen lost in mail, and delivery of specimen to wrong laboratory.

- 50% of the errors happened in the laboratory operation because of reading and transcriptional errors, improper cut-off values, switched specimens, wrong specimen pulled for repeat testing, normal first specimen, and abnormal results not recorded¹⁷. For half of the cases missed in the laboratory, the exact source of error by the laboratory are: failure of the quality control system, same specimen punched twice, delayed elevation of TSH, excessive false positive rate, and computer errors.

- The smallest number of errors occurred in the follow-up phases with 15% missed cases¹⁷. These misses were the result of specimen requested and not received, patient transfer to another physician, patient moved, no cooperation in follow-up, physician slow to follow-up and treat, and delayed reporting of test results. Other potential sources of error are computer entry errors, inability to locate physician, follow-up overloaded with false positive results that delay notification and tracking, failure to re-check on receipt of notification by physician, and other types of communication errors with physicians and parents. For some of the missed cases the source of the error could not be located, and some misses may be due to rare biological variations that yield normal results on initial screening².

7. COSTS

The State newborn screening programmes are funded by Federal, State, fee for services, and private sources. In the USA, the programmes perform screening for several disorders besides congenital hypothyroidism thereby reducing the overall operational cost. An increasing number of State programmes are charging a fee for services to offset the cost or totally support the programmes. 12 States have included in their programme regulations the authority to charge a fee for screening and treatment services²⁰. The fee ranges from US\$3-24 per newborn tested²⁰. The costs of screening services are usually reimbursable by insurance or public health agencies. In cases where the family cannot pay, the hospital or State screening programme must absorb the cost.

Several studies have examined the cost-effectiveness of newborn screening for congenital hypothyroidism in the USA^{21,22}. These cost-benefits are built around the loss in earning potential, time of necessary institutional health care of a retarded child, and the average life expectancy of the individual with the disorder. The studies have shown positive savings for society without the difficult-to-measure contributions of improved quality of life for the child and family. The US Office of Technology Assessment²⁰ determined that the savings is US\$93,000 per detected case compared with no screening and the cost-benefit increases substantially with programmes that screen for additional disorders and centralization of facilities.

Estimates of cost have been made on some of the components for the screening process in the USA. The cost for specimen collection is US\$6²¹ and cost per analytical test is US\$1.50⁷. The total operational cost per specimen screened ranges from US\$4-8²¹. The component and total prices vary somewhat for each State programme; however, these data give a general idea of the screening cost. Centralization of the screening programmes has yielded significant savings in operational expenses by reducing the number of laboratories, requirements for trained personnel, laboratory equipment, and redundancy in many fixed-cost components.

8. COLLABORATION

The External Quality Assurance Programme at the Centers for Disease Control in Atlanta, Georgia, besides distributing quality control and proficiency evaluation materials, serves as a focal point for the coordination of problem solving efforts for the screening programme. Each year the quality assurance programme receives numerous telephone enquiries regarding problems, and places these individuals in contact with other States having experienced similar problems. The annual report produced by the quality assurance programme presents a comparison of the performance of assay kits and screening laboratories in the USA. The report provides a database for the selection of commercial products and the assessment of techniques and goals for improved performance.

The Association of State and Territorial Laboratory Directors has appointed a national committee of laboratory directors to oversee coordination of State newborn screening programmes. One of the roles of this committee is to sponsor and select the site for a national conference. The National Newborn Screening Conference is held every 12 to 18 months with participation from all parts of the congenital hypothyroidism screening community. The conference offers a forum for collaboration and discussion of technical problems and methods for improved screening efforts.

Many of the centralized State screening operations and the large State programmes provide training courses for laboratory staff from other States. The Council of Regional Networks for Genetic Services coordinates efforts among the regions of the country for follow-up aspects, treatment, child and maternal health, and some programmes for quality assurance of confirmatory testing. This group meets annually to discuss general problems and issues and it has designated several subcommittees to address specific concerns.

The Infant Screening newsletter offers a method for the collaborative exchange of new ideas and results. This newsletter, originally a national publication, has expanded to the international screening community and is now the official publication for the International Society for Neonatal Screening²³. This publication has filled a communications gap for screening programmes by providing a source for publishing scientific articles specifically related to newborn screening activities.

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