CHALLENGES AND OPPORTUNITIES IN ESTABLISHING AND MAINTAINING NEWBORN SCREENING SYSTEMS

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Abstract. Newborn screening began in the early 1960s and during the four decades it has existed, has become a recognized vital public health prevention program. It has evolved conceptually from a laboratory test for a single disorder, phenylketonuria, to a comprehensive 6-part public health system of education, screening, follow-up, diagnosis, management, and evaluation. Newborn screening in different countries has been successful because of the efforts of a single individual or group of individuals interested in improving the health of children. Newborn screening has been shown to successfully detect serious disorders before symptoms appear and to significantly reduce the morbidity and mortality that might result if left undetected and untreated, yet there have been (and continue to be) obstacles to implementing newborn screening programs. The obstacles are the same for developed or developing programs and include: (1) adequate financing, (2) technology implementation, (3) program logistics, (4) cultural sensitivity, (5) education, and (6) political support. All newborn screening programs must exist within the limitations of their local environment in this regard. Each program confronts these barriers in its own way and various examples of overcoming barriers are discussed including linkages to immunization programs, regional planning, program advocacy, and legislation.

INTRODUCTION

Newborn screening began in the early 1960s with the work of Bob Guthrie (Guthrie and Susi, 1963). During the four decades that it has existed, newborn screening has become recognized as a vital public health program that can prevent death and mental retardation. It has evolved conceptually from a laboratory test for a single disorder, phenylketonuria (PKU), to a comprehensive 6-part public health system involving education, screening, follow-up, diagnosis, management, and evaluation (Therrell, 2001; Pass *et al*, 2000). Where newborn screening has been successful, it began with the efforts of a single individual or group of individuals interested in improving the health of children. Its success depended on the efforts of the dedicated workers who function within the system.

Despite the benefits of newborn screening in (1) detecting and treating serious disorders before symptoms appear, and (2) significantly reducing the morbidity and mortality that might result if these disorders were left undetected and untreated, there have been (and continue to be) obstacles to implementing newborn screening programs. These obstacles are basically the same whether the program is in a developed or developing country, and they primarily involve (1) adequate financing, (2) technology implementation, (3) program logistics, (4) cultural sensitivity, (5) education, and (6) political support. All newborn screening programs must exist within the limitations of their local environment in this regard. This paper discusses some of the experiences in developing programs and reviews the status of newborn screening in various parts of the world.

SCIENCE BACKGROUND

The technique of collecting blood on filter paper cards and submitting the samples to a remote laboratory for analysis was Guthrie's innovative way of providing a viable mechanism for mass population screening. Despite the potential benefits that were obvious to him and a few others working to prevent mental retardation at the time, it took several years for newborn screening to become accepted and mandated in public health systems across the country. It took even longer for more efficient and more sensitive laboratory testing techniques to result in expanded screening for disorders other than PKU. Throughout the 1960s, most newborn screening research activities were centered in Guthrie's laboratory and focused on inborn errors of metabolism (Guthrie, 1964). At the same time, automated punching procedures were also evolving to speed the sample preparation process. Development of the Phillips' quadratic punching machine provided a means of simultaneously preparing 4 samples for analysis from a single filter paper dried blood spot

(DBS) thus allowing screening laboratories to efficiently expand their testing protocols.

During the 1970s, other researchers became interested in the possibilities of detecting different disorders through newborn screening. Micro-tests for other disorders, either known or thought to be, of relatively high prevalence in newborns were developed and made commercially available including: congenital hypothyroidism (CH) (Dussault and Laberge, 1973; Dussault *et al*, 1974;1976), congenital adrenal hyperplasia (CAH) (Pang *et al*, 1977) and sickle cell diseases (SCD) – includes all clinically significant sickling disorders and is not limited to sickle cell anemia (S,S-Disease) (Garrick *et al*, 1973). The combination of automated punching and sensitive and specific DBS screening tests led to widespread program expansion during the 1970s and 1980s. Microcomputers also became available in the 1980s and the larger screening programs began to utilize computerization to manage their high sample volumes. Laboratory information systems evolved into comprehensive patient case management systems that included automated result reporting, bar coded sample tracking, and voice response result reporting. The combination of automation and improved efficiency in managing patient testing information resulted in faster result reporting, case detection, and treatment (Therrell, 1982; Therrell and Brown, 1988).

In the 1990s, DNA extraction techniques were applied to DBS (McCabe *et al*, 1987) and some newborn screening programs began using DNA tests as second tier screening to improve testing specificity for disorders such as sickle cell diseases (Descartes *et al*, 1992) and cystic fibrosis (Gregg *et al*, 1993). Technological improvements in instrument sensitivity and increased throughput also led to the use of coupled mass spectrometers (tandem mass spectrometry – MS/MS) for detecting other rare metabolic disorders from DBS (Chace *et al*, 1993). Research in both DNA and MS/MS continues today with the goal of providing more efficient and effective ways of conducting newborn screening. The ability to simultaneously analyze small amounts of blood for large numbers of comparatively rare disorders has created dilemmas for some newborn screening programs. Because of limited public health funding and a lack of curative treatment for some of the detectable disorders, decisions about which disorders to include in population-wide mandated screening have led to complex decision making and policy development (Therrell, 2001). Additionally, later onset disorders, like type I diabetes, can now be detected through newborn screening, and this raises the issue of where (or whether) diabetes screening and other late onset disorders that may be detected at or near birth fit in a newborn screening program. The lack of national standards for newborn screening in the US has recently led the federal government, Health Resources and Services Administration (HRSA), to fund contracts to explore the feasibility of national guidance and policy development for newborn screening including consent, testing panels, and fairness of cost distribution.

In some screening programs, expansion has also included infectious disease testing. The newborn screening program in New York, for example, provides testing for HIV, and the programs in Massachusetts and New Hampshire include testing for toxoplasmosis. Toxoplasmosis is also included in the screening panel in some of the developing programs in Latin America. Newborn screening programs are also expanding in areas beyond biochemical testing. Currently, the most widespread of these is newborn hearing screening (National Institutes of Health, 1993). While methods for detecting hearing loss in newborns have been available since the early 1960s, and some have advocated universal newborn screening since that time (Downs and Sterritt, 1964), it is only recently that the technology has allowed for such screening with acceptable false positive and minimal false negative screening rates. Over 30 states now require newborn hearing testing and legislative proposals to require it exist in almost all others (American Academy of Pediatrics, 2000).

In order to encourage program linkages and data integration with other infant health programs such as hearing, immunizations and birth certification, HRSA has provided grant funding to qualifying state programs. This funding is beginning to impact the development of integrated data systems in a number of state public health departments, and some states are deeply involved in developing comprehensive integrated data management systems. The anticipated result is decreased duplication of data entry efforts with a corresponding decrease in associated costs and data manipulation errors, and wider availability of patient information to service providers. Internet-based data handling is also evolving and with it, concerns about protecting patient privacy. Privacy issues are also present in considerations involving potential uses of residual blood specimens remaining after the newborn screening tests have been completed. Data linkages, issues of privacy, and ethical, legal and social issues in newborn screening are discussed elsewhere in this journal (Therrell, 2003a, b).

POLICY BACKGROUND

Newborn screening policies have been a concern eversince PKU screening began expanding around the

world. The first international meeting to discuss the science of screening and to develop policies governing it occurred in 1966 in Dubrovnik, Yugoslavia, and subsequently the World Health Organization (WHO) sponsored several discussions on newborn and other population screening issues. From these meetings came the screening criteria suggested by Wilson and Jungner (World Health Organization, 1968; Wilson and Jungner, 1968) that have been used by most policy makers in developing newborn screening systems. The appropriateness of the criteria for disorder (test selection) have been debated over the years (Frankenburg, 1974; National Research Council, 1975; Andrews *et al*, 1994; American Academy of Pediatrics, 2000) but have remained essentially intact as the principal criteria used by programs in considering disorders to be included in newborns screening panels. The Wilson and Jungner criteria are under review again, in light of the new technologies available in newborn screening, as part of the HRSA contract with the American College of Medical Genetics (ACMG) to propose national newborn screening policies on disorder selection.

Since 1965, the American Academy of Pediatrics (AAP) has taken an active role in newborn screening policy development (American Academy of Pediatrics, 1965). In addition to outlining the role of the pediatrician in newborn screening, various committees have produced a number of valuable position statements and fact sheets related to newborn screening disorders (American Academy of Pediatrics, 1996). In 1999, the US Maternal and Child Health Bureau responded to congressional interest in newborn screening programs by providing financial support for a Newborn Screening Task Force convened by the AAP to: (1) review the issues facing state newborn screening systems, and (2) make recommendations. As part of the process, the Task Force convened 5 multidisciplinary working groups to outline federal and state government responsibilities for establishing and maintaining a national newborn screening agenda. The 5 groups focused on: (1) newborn screening and its role in public health; (2) medical home and systems of care; (3) economics of screening; (4) ethical, legal, and social issues; and (5) research, surveillance, and assessment issues. Their working assumptions, concerns, and recommendations for an "agenda for action" are described elsewhere (American Academy of Pediatrics, 2000; Therrell, 2003).

Publication of the Task Force Report elicited a press release response from the March of Dimes Birth Defects Foundation (MOD) in which all state newborn screening programs were encouraged to mandate screening for 8 disorders (in addition to hearing): PKU, congenital hypothyroidism, congenital adrenal hyperplasia, galactosemia, sickle cell diseases, biotinidase deficiency, maple syrup urine disease, and homocystinuria. This was followed later by a published commentary in which testing cost was identified as an unnecessary element in newborn screening policy decisions (Howse and Katz, 2000). MOD also took the position that newborn screening (even for rare diseases) should be conducted on every newborn, "as long as its early discovery makes a difference to the child." Newborn screening programs were encouraged to abandon currently available testing procedures in favor of new ones "if the latter achieves a greater precision and offers a shorter turnaround time, no matter what the cost differential." Subsequently the MOD has added screening for MCAD deficiency to its list of universally mandated newborn screening disorders.

STATUS OF NEWBORN SCREENING IN THE UNITED STATES AND OTHER COUNTRIES

Newborn screening is a routine part of newborn care in almost all developed countries. In North America, there is not a national program in either Canada or the United States but screening exists in all US states and all Canadian provinces. Because of the lack of a national law, there are 51 separate newborn screening programs in the United States (including the District of Columbia), each with its own newborn screening law. Programs also exist in the US jurisdictions of Puerto Rico, the Virgin Islands, Guam and Saipan. Each state has a law mandating newborn screening (or the offering of newborn screening), and each has different lists of disorders included in screening (American Academy of Pediatrics, 2000). The only tests that are included in all state programs are PKU and CH. Galactosemia and sickle cell disease screening are included in most state programs, but there are few other similarities between the programs. In Canada, the numbers of newborn screening disorders included in provincial programs are generally fewer than in most US programs, however PKU and CH are also universally included. In both the US and Canada, some state and provincial programs have recently begun expanded newborn screening for fatty oxidation, organic acid and certain amino acid disorders using state-of-the-art MS/MS. In Mexico, there is a national newborn screening law requiring universal screening for CH and PKU (Vela *et al*, 1999), but screening implementation varies throughout the states. For this reason, Mexico is still considered to be a developing newborn screening program.

In the Caribbean and Central America, newborn screening exists in Cuba and Costa Rica, and is developing in Guatemala and Colombia. Among other Latin American countries, Chile and Uruguay have

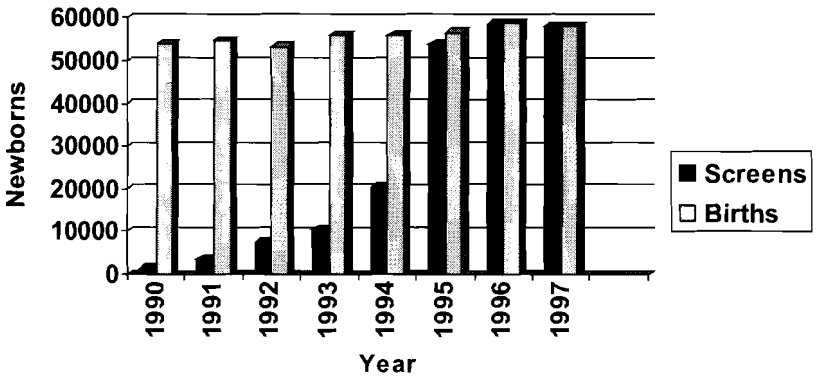

Fig 1. Comparison of newborns screened with births in Uruguay, 1990 – 1997.

national programs while Argentina and Brazil both have national laws but only limited screening (Therrell and Aznarez, 1998). Ecuador, Paraguay, Peru and Venezuela are just beginning to screen. The program in Uruguay provides an interesting model of integrating newborn screening into an ongoing national immunization program at or near birth. In Uruguay, newborn screening began in the early 1990s and the number of screened newborns steadily increased (Therrell and Aznarez, 1998). In September 1994, a ministerial decree by the Health Minister required screening of all newborns for CH. While the decree contributed to increased screening, it was integration into the ongoing tuberculosis immunization program that ultimately led to coverage of 95% of all newborns in 1995 and essentially 100% coverage in subsequent years. By using immunization program staff who were responsible for BCG immunizations at birth to collect newborn screening samples and submit them through the network already in place for transferring immunization supplies, national coverage was almost immediate (see graph in Fig 1) (Aznarez, personal communication, 1999). This screening model may be applicable to other developing countries requiring BCG or other immunizations at or near birth since an infrastructure for universal newborn coverage already exists. Immunization programs also provide a mechanism by which out of hospital births (particularly in remote areas) may be included in newborn screening (since in most immunization programs, a high percentage of such births receive their immunizations on schedule). Timing may present a challenge since, to be effective, treatment for PKU and CH should begin within the first 3 weeks after birth, and even earlier for some of the other disorders that may be included in some developing newborn screening systems.

In Western Europe, newborn screening exists in almost all countries, similar to North America, with the exception that most of the programs are national. In Eastern Europe, screening programs are still developing with programs expanding in the Czech Republic, Poland, Russia, Belarus, Latvia, Lithuania, Estonia and Croatia, among others. Screening is less advanced in the African continent with programs developing in Tunisia, Nigeria, Ghana, Egypt and South Africa. In all developing programs, education of the Health Ministry and other political decision makers regarding the benefits of newborn screening is critical. The South African Health Ministry recently issued its policy guidelines (South Africa Department of Health, 2001) for genetic disorders, birth defects and disabilities in which it states that, "...populations can be screened...according to provincial needs...for treatable disorders such as PKU." This reference to newborn screening is the first official recognition of newborn screening by the South African government and provides an example of the difficulty of implementing a screening program in a developing country.

Newborn screening is also still in the developing stages in Western Asia and the Middle East. While screening has been available for some time in Israel, parts of Turkey, Oman and Saudi Arabia, it is only just beginning in Jordan, Syria, Lebanon, Iran, and Kazakhstan. It is particularly interesting that a great many of the technical details concerning the use of MS/MS in newborn screening have resulted from the work of Rashed in Saudi Arabia (beginning with training experiences in the US) (Rashed *et al*, 1995), but newborn screening is only now beginning to expand there with influences on neighboring countries (who are utilizing the laboratory facilities in Saudi Arabia through contractual arrangements).

In Australasia, newborn screening began in the 1960s. Both the New Zealand and Australian programs have evolved in a similar manner to those in the US and both programs included multiple screening disorders (Webster and Essex, 1996; Wilcken, 1999). The program in Australia is divided across five regions, each with its own program rules, screening disorders and administration. The New Zealand program administers an international proficiency testing and quality assurance program that provides testing materials to a large number of programs around the world. In combination with the CDC, the Australasian proficiency testing program has been instrumental in improving international newborn screening laboratory standardization (Webster *et al*, 1999).

Newborn screening in Eastern Asia has also been comparatively slow to develop despite early screening availability in Japan. This has been primarily caused by poor economic and social conditions. The first Asian newborn screening program began in Japan in 1965 and now almost 100% of Japanese newborns are screened for PKU, maple syrup urine disease (MSUD), homocystinuria (HCY), galactosemia (GAL), CH and CAH (Naruse, 1999). The first international newborn screening policy meeting that included a significant amount of discussion on endocrine disorders (in addition to metabolic disorders) was held in Tokyo in 1981. It was also at the encouragement of Dr Naruse that the International Society for Neonatal Screening (ISNS) was formed along with its journal, *Screening* (no longer in publication), dedicated primarily to newborn screening articles. Naruse and his colleagues in Sapporo also hosted the first Asian Pacific Regional Meeting of the ISNS in 1993, and this has subsequently led to a total of four such regional meetings until now.

Other Asian newborn screening programs began to develop in the late 1970s with limited screening in Taiwan. In 1985, the Taiwan Department of Health established nationwide mass screening for CH, PKU, HCY, GAL, CAH, and G6PD deficiency (Chen, 1994). In Hong Kong, newborn screening for G6PD deficiency and CH started in 1984 and the coverage is almost 100% (Lam, 1994; Lo and Lam, 1999), and in Singapore the history of screening is similar having begun in 1965 with G6PD screening and expanded to CH screening in 1981 with nationwide coverage in 1995 (Joseph *et al*, 1999). In Korea, the Ministry of Health and Social Affairs adopted nationwide newborn screening in 1991 and by 1998 screening for PKU and CH were offered nationally to all newborns with screening for GAL, MSUD, HCY, and histidinemia (HIS) optional if the parents agreed to the additional expense (Lee, 1994). Limited testing by MS/MS for other metabolic disorders is also now available (Lee, personal communication, 2001). In Thailand, newborn screening began with a pilot in Nan Province in northern Thailand where iodine deficiency existed and goiters were prevalent in a high percentage of the population. The pilot data showed an incidence of CH of about 1:900 and one case of PKU was also detected. Today, screening is available nationwide with approximately 85% of all newborns participating in the government-sponsored program. Pilot testing for CAH is ongoing in provinces where high numbers of cases have been clinically documented. In addition to four large regional laboratories, the Thailand Ministry of Health sponsors a quality assurance oversight program at the National Institutes of Health in Bangkok, which is developing in cooperation with, and similar to, the program at the CDC in the US (Charoensiriwatana, personal communication, 2000).

In China, with over 20 million births annually, neonatal screening is available only in a limited number of cities (Gu *et al*, 1999). The Maternal and Child Health Rules (Article 24, June 1, 1995) encourage local public health departments to develop programs for, "...physical check-up, preventive inoculation...and...healthcare services such as the screening of newborn babies." Most screening includes both PKU and CH, but in some areas there is optional screening for GAL and HIS. In the Shandong Province, a provincial quality assurance program covers over 90% of the screening laboratories there (Wang, personal communication, 2001). It includes quarterly analysis of proficiency testing samples provided by the CDC. The samples are repackaged, submitted to the local laboratories, analyzed, and the results tabulated by the Shandong Health Department. If poor performance is found, then technical assistance is provided. This program serves as a model for other provinces and countries developing national or provincial quality assurance programs. It utilizes cooperation with a developed program to meet initial program needs with the goal of eventually becoming self-sufficient. In the Philippines, with approximately 1.5 million births annually of which only 30% are born in hospitals, newborn screening began in 1996 with 24 hospitals in Metro Manila and has now expanded to over 150 hospitals screening for 5 disorders (PKU, CH, CAH, GAL, and G6PD deficiency) and covering approximately 10% of all newborns (Padilla and Domingo, 2002). Programs are also starting in Vietnam, Malaysia, Indonesia, Bangladesh, Mongolia, Myanmar, Lao PDR, Pakistan, and India.

THE FUTURE

The future of newborn screening is promising. With the completion of the Human Genome Project, technological advances and knowledge are already

impacting newborn screening and this will continue. We must carefully consider the consequences of all public health policies related to genetics and newborn screening. Genetic awareness is increasing and there will be a corresponding growth in demand for predictive testing and genetic screening. We must be careful to protect individual privacy and to maintain a public health focus. Public health administrators should actively educate themselves and others about genetic issues. There is an excellent opportunity to provide leadership in establishing new programs and we must not let it pass. Regulations, policies, and laws should be readied in order to address potential issues such as accessibility, confidentiality, and discrimination. Newborn screening has been shown to be an effective way of improving infant health and outcome. We are all entitled to equitable health care and productive, healthy lives.

REFERENCES

American Academy of Pediatrics, Committee on Fetus and Newborn. Screening of newborn infants for metabolic disease. *Pediatrics* 1965; 35: 499–501.

American Academy of Pediatrics, Committee on Genetics. Newborn screening fact sheets. *Pediatrics* 1996; 98: 473-501.

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* 2000;106(suppl):383-427.

Andrews LB, Fullarton JE, Holtzman NA, Motulsky AD, eds. Assessing genetic risks. Implications for health and social policy. Washington D.C.: National Academy of Sciences, 1994.

Chace DH, Millington DS, Terada N, Kahler SG, Roe CR, Hofman LF. Rapid diagnosis of phenylketonuria by quantitative analysis for phenylalanine and tyrosine in neonatal blood spots by tandem mass spectrometry. *Clin Chem* 1993; 39: 66-71.

Chen JS. The organization of neonatal screening programs and international cooperation systems in Taiwan. In: Takasugi N and Naruse H (eds) New Trends in Neonatal Screening. Sapporo: Hokkaido University Press, 1994; 33-6.

Descartes M, Huang Y, Zhang YH, McCabe LL, Gibbs R, Therrell BL, McCabe ERB. Genotypic confirmation from original dried blood specimens in a neonatal hemoglobinopathy screening program. *Pediatr Res* 1992; 31: 217-21.

Downs MP, Sterritt GM. Identification audioimetry for neonates: a preliminary report. *J Aud Res* 1964; 4:69–80.

Dussault JH, Laberge C. Thyroxine (T4) determination in dried blood by radioimmunoassay: a screening method for neonatal hypothyroidism. *Union Med Can* 1973; 102: 2062-64.

Dussault JH, Coulombe P, Laberge C. Preliminary report on a mass screening program for neonatal hypothyroidism. *J Pediatr* 1974; 86: 620-4.

Dussault JH, Parlow A, Letarte J, Guyda H, Laberge C. TSH measurements from blood spots on filter paper. A confirmatory screening test for neonatal hypothyroidism. *J Pediatr* 1976; 89: 550-2.

Frankenburg WK. Selection of diseases and tests in pediatric screening. *Pediatrics* 1974; 54: 612-6.

Garrick MD, Dembure P, Guthrie R. Sickle cell anemia and other hemoglobinopathies: procedures and strategy for screening spots of blood on filter paper as specimens. *N Engl J Med* 1973; 288:1265-8.

Gregg RG, Wilford BS, Farrell PM, Laxova A, Hassemer D, Mischler EH. Application of DNA analysis in a population-screening program for neonatal diagnosis of cystic fibrosis (CF): comparison of screening protocols. *Am J Hum Genet* 1993; 52: 616-26.

Gu XF, Jun Y, Chen R-G. Neonatal screening of phenylketonuria and congenital hypothyroidism in China. *Southeast Asian J Trop Med Public Health* 1999; 30 suppl 2: 17-9.

Guthrie R, Susi A. A simple phenylalanine method for detecting phenylketonuria in large populations of newborn infants. *Pediatrics* 1963; 32: 338-43.

Guthrie R. Routine screening for inborn errors in the newborn: "inhibition assays", "instant bacteria" and multiple tests. In: Oster J, ed. Proc International Copenhagen Congress on the Scientific Study of Mental Retardation. Copenhagen: Statens Andssvage Forsong, 1964; 495-9.

Howse JL, Katz M. The importance of newborn screening. *Pediatrics* 2000; 106:595.

Joseph R, Lai YH, Gomez JM, Rajdurai VS, Sivasankaran S, and Yip YY. Newborn screening in Singapore. *Southeast Asian J Trop Med Public Health* 1999; 30 suppl 2: 23-7.

Lam STS. The organization of genetic screening programmes in Hong Kong – an overview. In: Takasugi , Naruse H, eds. New trends in neonatal screening. Sapporo: Hokkaido University Press, 1994; 29-32.

Lee DH. Neonatal screening in Korea. In: Takasugi N, Naruse H, eds. New trends in neonatal screening. Sapporo: Hokkaido University Press, 1994; 3-6.

Lo KK, Lam TS. Neonatal screening programme for congenital hypothyroidism in Hong Kong. In: Lam TS, Pang CP, eds. Neonatal and perinatal screening – The Asian Pacific perspective. Hong Kong: The Chinese University of Hong Kong, 1996; 145-8.

McCabe ERB, Huang S-Z, Seltzer WK, Law ML. DNA microextraction from dried blood spots on filter

paper blotters: potential applications to newborn screening. *Hum Genet* 1987; 75: 213-6.

Naruse H. Establishment of screening systems in East Asia. *Southeast Asian J Trop Med Public Health* 1999; 30 (suppl 2): 5-10.

National Institutes of Health, Consensus Development Conference Statement. Early identification of hearing impairment in infants and young children. *Int J Pediatr Otorhinolaryngol* 1993; 27: 215-27.

National Research Council, Committee for the Study of Inborn Errors of Metabolism. Genetic screening: programs, principles, and research. Washington, D.C.: National Academy of Sciences, 1975.

Padilla CD, Domingo CF for the Newborn Screening Study Group. Implementation of newborn screening in the Philippines. *Philippine J Pediatr* 2002; 31:2-10.

Pass KA, Lane PA, Fernhoff PM, *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 Ser-vices (CORN). *J Pediatr* 2000; 137: S1-46.

Rashed MS, Ozand PT, Bucknall MP, Little D. Diagnosis of inborn errors of metabolism from blood spots by acylcarnitines and amino acids profiling using automated electrospray tandem mass spectrometry. *Pediatr Res* 1995; 38: 324-31.

South Africa Department of Health. Policy guidelines for the management and prevention of genetic disorders, birth defects and disabilities. Pretoria: South Africa Department of Health, 2001.

Therrell BL Jr. Computerization in the newborn screening laboratory: an aid to data management. In: Naruse H, Irie M, eds. Neonatal Screening. Amsterdam: Elsevier Science Publishers, 1982; 455-60.

Therrell BL, Brown LO. Computerized newborn screening in Texas - A multiple microcomputer approach. *J Med Systems* 1988;12:115-120.

Therrell BL, Aznarez AA. Newborn screening in the Americas. *J Jpn Soc Mass-screening* 1998; 8 (suppl 1): 87-94.

Therrell BL. US Newborn screening policy dilemmas for the twenty-first century. *Molec Genet Metab* 2001; 74: 64-74.

Therrell BL. Ethical, legal and social issues in newborn screening in the United States. *Southeast Asian J Trop Med Public Health* 2003a; 43: 52-6.

Therrell BL. Data integration and warehousing: coordination between newborn screening and related public health programs. *Southeast Asian J Trop Med Public Health* 2003b; 43: 63-8.

Vela M, Gamboa S, Loera-Luna A, Aguirre BE, Perez-Palacios G, Velazquez A. Neonatal screening for congenital hypothyroidism in Mexico: experience, obstacles, and strategies. *J Med Screening* 1999; 6: 77-9.

Webster D, Essex C. Neonatal screening in New Zealand. *Br Med J* 1996; 312: 312.

Webster D, Dhondt JL, Hannon WH, Loeber G, Torresani T. Quality assurance and standardization: summary of the satellite meeting, Turku, Finland, 11-12 June 1999. *Acta Paediatr* 1999; 88 (suppl): 7-12.

Wilcken B. Neonatal screening in Australia. *Southeast Asian J Trop Med Public Health* 1999; 30 (suppl 2): 41-2.

Wilson JMG, Jungner F. Principles and practice of screening for disease (Public Health Papers No. 34). Geneva: World Health Organization, 1968.

World Health Organization Scientific Group on Screening for Inborn Errors of Metabolism. Screening for inborn errors of metabolism. *Wld Hlth Org Techn Rep Ser*, 1968;401:1-57.