J Inherit Metab Dis (2007) 30:490–506
DOI 10.1007/s10545-007-0687-7

NEWBORN SCREENING

# Newborn screening in the Asia Pacific region

**Carmencita D. Padilla · Bradford L. Therrell**

Received: 21 May 2007 / Submitted in revised form: 7 June 2007 / Accepted: 8 June 2007 / Published online: 23 July 2007


**Summary** The success of blood spot newborn screening in the USA led to early screening efforts in parts of the Asia Pacific Region in the mid-1960s. While there were early screening leaders in the region, many of the countries with depressed and developing economies are only now beginning organized screening efforts. Four periods of screening growth in the Asia Pacific region were identified. Beginning in the 1960s, blood spot screening began in New Zealand and Australia, followed by Japan and a cord blood screening programme for G6PD deficiency in Singapore. In the 1980s, established programmes added congenital hypothyroidism and new programmes developed in Taiwan, Hong Kong, China (Shanghai), India and Malaysia. Programmes developing in the 1990s built on the experience of others developing more rapidly in Korea, Thailand and the Philippines. In the 2000s, with limited funding support from the International Atomic Energy Agency, there has been screening programme development around detection of congenital hypothyroidism in Indonesia, Mongolia, Sri Lanka, Myanmar and Pakistan. Palau has recently contracted with the Philippine newborn screening programme. There is little information available on newborn screening activities in Nepal, Cambodia, Laos and the other Pacific Island nations, with no organized screening efforts apparent. Since approximately half of the births in the world occur in the Asia Pacific Region, it is important to continue the ongoing implementation and expansion efforts so that these children can attain the same health status as children in more developed parts of the world and their full potential can be realized.

Communicating editor: Georg Hoffmann

Competing interests: None declared

C. D. Padilla
Department of Pediatrics, College of Medicine,
and Institute of Human Genetics, National Institutes
of Health, University of the Philippines Manila,
Manila, Philippines

C. D. Padilla (✉)
Institute of Human Genetics, National Institutes of Health,
University of the Philippines Manila, 625 Pedro Gil Street,
Ermita Manila 1000, Philippines
e-mail: cpadilla@upm.edu.ph

B. L. Therrell
Department of Pediatrics, University of Texas Health
Science Center at San Antonio, San Antonio, Texas, USA

B. L. Therrell
National Newborn Screening and Genetics Resource Center,
Austin, Texas, USA

**Abbreviations**

| | |
|---|---|
| CAH | congenital adrenal hyperplasia |
| CDC | Centers for Disease Control and Prevention |
| CF | cystic fibrosis |
| CH | congenital hypothyroidism |
| DOH | Department of Health |
| GAL | galactosaemia |
| G6PD | glucose-6-phosphate dehydrogenase |
| HIS | histidinaemia |
| HOM | homocystinuria |
| IAEA | International Atomic Energy Agency |
| ICMR | Indian Council for Medical Research |
| IMR | infant mortality rate |
| IRT | immunoreactive trypsinogen |
| JAMW | Japanese Association for Maternal Welfare |

| | |
|---|---|
| JSMS | Japanese Society for Metabolic Screening |
| PKU | phenylketonuria |
| MSUD | maple syrup urine disease |
| NSW | New South Wales |
| MS/MS | tandem mass spectrometry |
| NBS | blood spot newborn screening |
| NIH | National Institutes of Health |
| PT | proficiency testing |
| QA | quality assurance |
| QC | quality control |
| $T_4$ | thyroxine |
| TSH | thyrotropin (thyroid-stimulating hormone) |
| UNICEF | United Nations Children's Fund (formerly United Nations International Children's Emergency Fund, |
| WHO | World Health Organization |

## Introduction

In most economically developed countries, blood spot newborn screening (NBS) using biochemical markers to detect certain congenital conditions is a public health activity aimed at the early identification and treatment/management of affected newborns. Screening of newborns with non-chemical methods for other congenital defects, such as hearing loss, is also emerging as a public health priority. Early identification of these conditions is crucial, since timely intervention can lead to significant reductions of morbidity, mortality and associated disabilities in affected infants (American Academy of Pediatrics 2000). In countries with depressed and developing economies, particularly those in Africa and Asia, NBS and other infant screening is either not yet a priority or is just emerging as a priority. This paper will focus on NBS in the countries of the Asia Pacific Region, a region of vastly differing newborn screening priorities. While newborn hearing screening is growing, and in some cases is integrated into the blood spot screening programme, it will not be discussed here.

The history of newborn screening is relatively short, beginning with the pioneering work by Guthrie in the early 1960s. His discovery that phenylketonuria (PKU) could be detected from dried blood spots collected on filter paper and transported to a testing laboratory opened the way for mass screening in newborn populations (Guthrie 1962; Guthrie and Susi 1963). Today, this technique for obtaining and analysing specimens from newborns is used to detect dozens of congenital conditions, including metabolic and infectious diseases, in screening programmes around the world (Therrell 2001). During its 45-year history, successful NBS has evolved into multidimensional systems sustainable through the integrated efforts of concerned individuals and defined processes. A successful NBS system is now generally considered to include six essential elements: (1) *education* (of health professionals, parents, the general public and politicians); (2) *screening* (proper timing and specimen collection, transport, laboratory testing and reporting); (3) *early follow-up* (including abnormal test notification, tracking and confirmatory testing); (4) *diagnosis* (through clinical and biochemical evaluation); (5) *management* (including counselling, treatment monitoring and long-term follow-up); and (6) *evaluation* (through system-wide quality assurance and outcome monitoring) (American Academy of Pediatrics 2000; Pass et al 2000; Therrell 2001; McCabe et al 2002). System sustainability depends on the smooth integration of all system components within the bounds of local (jurisdictional) geographic, economic and political constraints.

Creating an infrastructure that will sustain the NBS system is necessarily the focus of programme development as screening is implemented. To ensure high-level screening quality, all system components must be part of system-wide quality assurance using measurable indicators for each component (Therrell and Hannon 2006; Therell et al 1992). Thus, it is important for developing programmes to consider how they will monitor and evaluate programme impact. Traditionally, programme oversight is a public health responsibility that resides in the jurisdiction of the public health department or the health ministry; however, coordination and cooperation with academic centres and private partners (confirmatory laboratories, medical centres, third-party payers (insurance companies), and other non-government organizations) are essential for the success of the overall system. Establishing the necessary collaborations within the government of the developing countries has proved to be one of the biggest challenges in establishing successful and sustainable NBS in many parts of the region.

Of the 134 million babies born throughout the world, about half (67 million) (UNICEF 2007) are born in the Asia Pacific Region. The Asia Pacific Region (see Fig. 1) includes countries varying widely in size from very small countries (Singapore, New Zealand) to extremely large countries (China and India). It includes both economically developed (Japan, Taiwan,


**Fig. 1** The Asia Pacific region

Korea, Singapore, Australia, New Zealand) and economically developing countries (the rest of the Asia Pacific Region). Many challenges have faced and continue to face Asia Pacific countries in implementing newborn screening, including differences in language and culture, extremes in geography (large numbers of islands and many mountainous regions), poor economies, and unstable governments. In many of the developing countries of the Asia Pacific Region, the numbers of births outside of hospitals approaches 80%. Despite these challenges, NBS has existed in some areas of the region since the mid-1960s, and it continues to develop in many of the countries in the region that have depressed and developing economies. There are currently more developing programmes than developed programmes within the region. The challenges facing the developing programmes are in many ways similar to those of the developed programmes, and the lessons learned over time should provide a significant advantage in rapidly implementing and refining new programmes.

## Methods

In order to better understand the various challenges facing developing NBS programmes in the region and to document the history of the developed programmes, a survey was distributed between July and September 2006 to persons identified as knowledgeable about NBS within their country. Potential respondents were identified through an informal network that exists within the region that includes participants in both the Asia Pacific Regional Meetings of the International Society for Neonatal Screening and the International Atomic Energy Agency's Regional NBS Project.

The specific objectives of the survey were to: (1) review the current status of newborn screening programmes within the Asia Pacific Region; (2) identify the critical factors affecting full population coverage for national NBS; and (3) identify issues and challenges confronting individual NBS programmes. Questions elicited the following NBS programme information: the year newborn screening started; the panel of screening conditions then and now; the annual birth rate; the percentage of newborns currently screened; the method for financing NBS; the cost of NBS; a description of policies governing the programme; the party(ies) responsible for advocacy; future plans; and major obstacles to full population coverage.

Representatives from 16 countries responded to the survey including: Australia, Bangladesh, China (Hong Kong and the rest of China), India, Indonesia, Japan, Korea, Malaysia, Myanmar, New Zealand, Philippines, Singapore, Sri Lanka, Taiwan, Thailand and Vietnam. Additional information was obtained through literature searches and personal interviews. Data from the NBS programmes in Mongolia and Pakistan were obtained from IAEA Regional Meeting reports. In all cases, the information obtained and reported here was referenced to published articles whenever possible.

## Discussion

In reviewing the materials provided by the various programmes and the published records of their activities, it appears that the history of screening in the Asia Pacific can be grouped into four primary periods of activity. In each period, a few more countries began screening and those already screening continued to expand.

### First Asia Pacific screening era

The first surge of screening activity occurred shortly after Guthrie introduced newborn screening in the USA in the 1960s. Prior to that time, many countries around the world, including some in the Asia Pacific, had been developing screening programmes for PKU using a commercially available ferric chloride urine screening test, Phenistix (Ames Laboratories, Ames IA, USA). Within the Asia Pacific Region for example, New Zealand nurses were performing screening tests on urine-impregnated napkins at the first home visit after birth, usually during the 2nd or 6th week of life (Houston and Veale 1971). In Japan, a 1963 study group of paediatricians, obstetricians and researchers in basic medicine, established by the Ministry of Health and Welfare, had begun a study of PKU using the Phenistix test to identify babies with PKU (Nozue et al 1983). And in Australia, urine testing was also used to screen for PKU beginning in New South Wales in 1964, achieving approximately 80% coverage (Wilcken et al 1980).

Urine screening was prone to false-negative results and proper specimen collection was not always easy or timely. For these reasons, many laboratories began blood spot testing for PKU soon after Guthrie's report (Guthrie and Susi 1963). In 1965, Guthrie spent nine months travelling around the world advocating his blood spot procedure (Guthrie 1992; Koch 1997). His travels to New Zealand resulted in one of the first national NBS programmes in the world. Other countries in the region also took an interest in screening including Australia and Japan (Veale and Houston 1978; Nozue et al 1983). Thus in the Asia Pacific Region, an initial wave of NBS programme implementation occurred in the mid- to late-1960s (see Table 1). This surge of NBS included New Zealand in 1966 and Australia in 1967, and pilot screening in Japan in 1967 (which led to a national programme in 1977). A screening pilot for G6PD deficiency using cord blood also began in Singapore in 1965, which became national in 1970. This cord blood screening programme was the basis for later expansion into a broader newborn screening initiative that included congenital hypothyroidism (CH).

#### *New Zealand*

In April 1966, the New Zealand health department instituted PKU screening for all newborns using the Guthrie bacterial inhibition test. From the beginning, New Zealand NBS included a core group of four bacterial inhibition tests for inborn errors of metabolism that included: PKU, homocystinuria (HCY), maple syrup urine disease (MSUD) and hereditary tyrosinaemia (TYR). Subsequently, screening tests for histidinaemia (HIS) and galactosaemia (GAL) were added (Veale and Houston 1978). In 1968–69, Guthrie spent a sabbatical year in New Zealand. During that time, he worked with Dr Arthur Veale to organize a Pacific Island newborn screening programme. Specimens were sent by air to the New Zealand screening laboratory from 10 island groups. Thus, New Zealand screening included all newborns in New Zealand (60 000 per year) and some newborns in Australian New Guinea, British Solomon Islands, Fiji, Western Samoa, American Samoa, Niue, Guam and Saipan

**Table 1** Programme demographics in Asia Pacific newborn screening programmes

| Jurisdiction | Program demographics | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | [b]Population, 2005 (000) | [b]Thousand births 2005 | [b]Infant mortality rate (under 1) 2005 | [b]Life expectancy at birth 2005 | Date NBS began | Reference for date screening began | Reported program coverage in 2006 | Cost or screening paid by | Cost in US$ |
| Australia | 20 155 | 250 | 5 | 81 | 1967 | Wilcken (1999) | 100% | Govt | 6.00 |
| Bangladesh | 141 822 | 3 747 | 54 | 64 | 1999 | Moslem et al (2003) | <1% | Govt | ? |
| Cambodia | 14 071 | 429 | 98 | 57 | – | – | ? | ? | ? |
| China | 1 315 844 | 17 310 | 21 | 72 | 1981 | Chen and Guo (1983) | 25% | Family | 5.50 |
| Hong Kong (China) | | | | | 1984 | Lo and Lam (1995) | 99% | Govt | 20.00 |
| India | 1 103 371 | 25 926 | 43 | 64 | 1980 | Devi and Naushad (2004) | <1% | Family | ? |
| Indonesia | 222 781 | 4 495 | 18 | 68 | 1999 | Rustama et al (2003) | <1% | Family | 2.50 |
| Japan | 128 085 | 1 162 | 2 | 82 | 1967 | Irie et al (1975) | >99% | Govt | 18.33[a] |
| Korea (South) | 47 817 | 457 | 3 | 78 | 1991 | Lee (1994) | 94% | Govt | 17.50[c] |
| Korea (North) | 22 488 | 342 | 22 | 64 | – | – | ? | ? | ? |
| Laos | 5 924 | 205 | 35 | 55 | – | – | ? | ? | ? |
| Malaysia | 25 347 | 547 | 5 | 74 | 1980 | Singh (2003) | 95% | Govt/private | ? |
| Mongolia | 2 646 | 58 | 26 | 65 | 2000 | Erdenechimeg (2003) | <1% | Grant | ? |
| Myanmar | 50 519 | 976 | 40 | 61 | 2000 | A Thein, personal communication, 2006 | <1% | Govt | ? |
| Nepal | 27 133 | 787 | 40 | 62 | – | – | ? | ? | ? |
| New Zealand | 4 028 | 54 | 4 | 79 | 1966 | Veale and Houston (1976) | 100% | Govt | 15.00 |
| Palau | 20 | 0 | 14 | – | 2007 | – | 0 | Govt | No fee[g] |
| Pakistan | 157 935 | 4 773 | 57 | 64 | 2000 | IAEA Report (2002) | <1% | ? | ? |
| Philippines | 83 054 | 2 018 | 15 | 71 | 1996 | Padilla and Domingo (2002) | 16% | Family/ins. | 10.00[f] |
| Singapore | 4 326 | 39 | 1 | 79 | 1965 | Wong (1965) | >99% | Family 40% | 32.00[d] |
| Sri Lanka | 20 743 | 329 | 11 | 74 | 2005 | Wijekoon et al (2006) | <1% | Govt | ? |
| Taiwan | | | | | 1985 | Chen (1993) | >99% | Family | 26.00[e] |
| Thailand | 62 233 | 1 009 | 13 | 71 | 1992 | Charoensiriwatana et al (1995) | 97% | Govt | ? |
| Vietnam | 84 238 | 1 648 | 15 | 71 | 2000 | IAEA Report (2002) | <1% | Govt | ? |
| Totals | 3 544 580 | 66 561 | 25 | 69 | | | | | |
| World statistics | 6 449 371 | 133 449 | 30 | 68 | | | | | |

[a] M Fukushi, personal communication, 2006.
[b] Source: UNICEF (2007) *The State of the World's Children 2007*. New York: UNICEF, 102–105. (Available at: http://www.unicef.org/sowc/archive/ENGLISH/The%20State%20of%20the%20World%27s%20Children%202007.pdf).
[c] Government subsidy for 6 tests. Family pays for MS/MS (D. Lee, personal communication, 2006).
[d] Government subsidy of 60%. Screening for inborn errors plus hearing = US$120. Patient charges vary by hospital and patient class (R. Joseph, personal communication, 2006).
[e] Fee includes US$17 for test and US$9 handling. Government supplement to laboratory is US$3 per specimen (W. Hwu, personal communication, 2006).
[f] Insurance coverage is only for members of the national health insurance.
[g] Newborn screening expected to begin late in 2007.

(Mariana Islands) and Majuro (Marshall Islands) (Veale and Houston 1976; Guthrie 1992).

As a result of Dr Veale's training as a mathematician and his interest in computerizing the complex tracking of the large number of specimens from New Zealand and the islands, the New Zealand programme was an early leader in computerization and automation. The New Zealand programme was one of the first laboratories to experiment with the Phillips Punch Index Machine (Houston and Veale 1971). This quadratic punching machine allowed for the simultaneous punching of four samples from a single blood spot specimen. This procedure dramatically decreased sample preparation time for multiple screening tests and was one of the major contributors to facilitating programme expansion beyond PKU screening. Thus, following the development of a viable blood spot screening test for CH (Dussault and Laberge 1973) and its application to newborn screening in Canada (Dussault et al 1975), CH was added to the New Zealand NBS panel (Lyon 1983). New Zealand was also one of the early programmes researching cystic fibrosis screening. Their research with immunoreactive trypsinogen (IRT) screening in the late 1970s led to the first screening protocol utilizing a follow-up IRT for second tier screening (the so-called IRT–IRT screening protocol) (Crossley et al 1979; Lyon et al 1983).

Recognizing the importance of laboratory quality assurance (QA) as part of overall NBS system QA, the New Zealand programme initiated a blinded laboratory QA programme in 1986. Responding to the interests of the Joint Subcommittee of the Human Genetics Society of Australasia and the Australian College of Paediatrics, this programme provided dried blood spots enriched with abnormal concentrations of screening metabolites for internal programme QA. Programmes could provide their own collection cards for spotting and then randomly insert them into assays as a blinded check of laboratory proficiency. While initially intended for the programmes in New Zealand and Australia, the programme eventually expanded to include large numbers of laboratories around the world (Webster 1991).

The National Screening Unit assumed funding and governance responsibility for the Newborn Metabolic Screening Programme in July 2005. Screening policy is developed in conjunction with the Australasian Society of Human Genetics (see following section on Australia for details). The New Zealand screening programme has an advisory group (organized long before 2005) of people from various areas—parent support, Maori, children's groups and medical specialists. This group meets quarterly to provide advice to programme policy makers. NBS specimens are collected at 48 h of age (or as soon as possible thereafter) by the Lead Maternity Carer (LMC) and sent to the National Testing Centre at Auckland City Hospital for testing, analysis and result reporting. Screening reaches essentially 100% of New Zealand newborns (over 59 000 per year) and detects approximately 45 cases of screened conditions annually. The programme expanded in December 2006 to include testing by tandem mass spectrometry (MS/MS) and now lists 28 conditions on its NBS panel (http://www.moh.govt.nz/newbornscreening).

### *Australia*

Blood spot NBS for PKU began similarly throughout the six states of Australia during 1967–1968. At the time the number of births nationwide was approximately 225 000. Before this, in 1964, New South Wales had instituted a urine screening programme for PKU and other disorders, which achieved 80% coverage but was gradually phased out following the introduction of blood spot screening (Wilcken et al 1980). By 1968, Pitt reported that all Australian states and the Australian Capital Territory were offering NBS for PKU—New South Wales, Victoria (70% coverage), South Australia (95% coverage), Western Australia, Tasmania, Australia Capital Territory (100% coverage) and Queensland (Szeinberg 1971). Screening for CH started at different times in the various states between 1977 and 1982 (Wilcken 1999).

Some programmes in Australia have been particularly active in researching new technologies and testing protocols for newborn screening. As an example, NBS for cystic fibrosis (CF) began in July 1981 as part of the neonatal screening programme in New South Wales. Their studies showed significant reduction of CF morbidity in the first two years of life through CF NBS (Wilcken and Chalmers 1985 ; Wilcken and Brown 1987; Wilcken et al 1995). Research by this group continues to add to the knowledge about CF NBS (Wilcken and Gaskin 2007). In 1998, the NSW Newborn Screening Programme became one of the first NBS programmes to use electrospray tandem mass spectrometry (MS/MS). Their early reports added to the knowledge about value of MS/MS in NBS metabolic screening, and their reports provided a basis for others to begin this screening (Carpenter and Wilcken 1999; Wiley et al 1999; Wilcken et al 2003, 2007).

Similarly to screening in New Zealand, all Australian screening programmes are voluntary and fully publicly funded. Newborn screening services are coordinated from the five centralized screening

laboratories (Western Australia, South Australia (also covering Tasmania and part of the Northern Territory), Victoria, New South Wales (also covering the Australian Capital Territory) and Queensland (also covering part of the Northern Territory)). Policy governing the Australian and New Zealand programmes is developed by a joint Subcommittee of the Genetics Society of Australasia and the Division of Paediatrics of the Royal Australasian College of Physicians. Screening is recommended if four conditions are met: (1) there is benefit to the individual from early diagnosis; (2) the benefit is reasonably balanced against financial and other costs; (3) there is a reliable test suitable for newborn screening; and (4) there is a satisfactory system in operation to deal with diagnostic testing, counselling, treatment and follow-up of patients identified by the test. At present, the recommended panel includes PKU, CH, CF and over 20 additional disorders of amino acid, organic acid and fatty acid metabolism detectable by MS/MS screening. Additionally, galactosaemia is included in the screening panel of all states except Victoria (http://hgsa.com.au).

*Japan*

Building on a urine screening programme that had existed in Japan since 1963, the Ministry of Health and Welfare in Japan organized a 'working party' in 1967 that recommended adoption of the Guthrie method as the screening method for PKU. In 1972, the Japan Association for Maternal Welfare (JAMW), the professional society for obstetricians and gynaecologists, began to work with the government to adopt this testing procedure (Nozue et al 1983). Following special government training courses in 1976 and 1977 for the technicians responsible for screening, nationwide screening for five inborn errors of metabolism in October 1977. In addition to PKU, NBS also included MSUD, HIS, HCY and GAL. There were initially 52 screening laboratories covering 47 prefectures and 9 big cities. Screening coverage quickly increased from about 15% before nationwide screening to 50% during the first 6 months, with almost full population coverage by the end of 1978. The working party also recognized the importance of possibly including screening for CH and organized a national study committee (Naruse 1980a). The Japanese Society for Mass Screening (JSMS) also played an important role in the development of newborn screening in Japan. Organized in 1973, the membership grew to about 380 by the end of 1977 and today the membership is around 550. The JSMS was instrumental in getting the federal government to implement a national QA system for NBS (Naruse et al 2003).

Research on NBS CH detection by Irie in the mid-1970s (Irie et al 1975, 1987) using thyrotropin (TSH) led to a project to investigate the incidence of CH in Japan. Newborns were screened using TSH and limited thyroxine ($T_4$) screening on blood spots collected at 5–7 days of life (Irie and Naruse 1980). Acknowledging the importance of NBS for CH, the Ministry of Finance approved a budget for adding CH to the ongoing Japanese NBS programme in late 1979. Because of government restrictions on the use of radioisotopes, a non-isotopic screening approach was preferred (Naruse 1980b). CAH was subsequently added in 1988 (Fujieda et al 1987; Suwa et al 1987). Various researches were undertaken to explore the feasibility and cost-benefit of screening of other disorders, i.e. urea cycle disorders (Fujimoto et al 1987; Suzuki et al 1983), MSUD (Matsuda et al 1987), galactosaemia (Kawamura 1987) and biotinidase deficiency (Yamaguchi et al 1987). Currently, there is full population screening for PKU, MSUD, HCY, GAL, CH and CAH (Aoki, 2003) in 47 prefectures and 15 designated big cities. Local governments each have their screening programmes. Screening is free of charge and samples are sent to 48 screening laboratories (M. Fukushi, personal communication, 2007).

When the Japanese government started NBS, a quality assurance programme for laboratories was also introduced. This was the first national multi-laboratory QA programme for NBS in the world. Responsibility for the programme was given to the Japanese Public Health Association. The programme began in October 1978 with proficiency testing (PT) cards prepared and submitted to the 52 screening laboratories weekly. The initial programme included 10 specimens randomly enhanced with varying amounts of different metabolites. The number of elevated samples was varied irregularly from 4 to 8, and laboratories were asked to report qualitatively the samples outside the normal range. In this way, laboratories with unsatisfactory performance were identified and counselled in an effort to improve their overall quality (Naruse 1980a). The QA programme continued to evolve and was reported to be expanded with additional analytes by 1986. Filter paper cards continued to be submitted to each testing laboratory, but on a bi-weekly schedule. Centralized coordination was an essential part of the programme and assistance to laboratories with difficulty in analysing the specimens was a responsibility of the central laboratory (Amino 1987). The QA system has continued to evolve until now monthly PT specimens are distributed from an officially designated

Quality Control (QC) Center for Mass Screening in Japan. The duties of the Center include: (1) inter-laboratory QA survey; (2) QC of calibrators, filter paper, and other critical reagents that are part of testing; (3) distribution of 'control materials' for laboratory internal QC; (4) analysis of 'cut-off levels' and 'rate second screening samples requested' in all screening laboratories; (5) training, instruction and consultation for laboratory technical staff members; and (6) distribution of 'primary standards' for use in the screening laboratories. Guidelines for computerized reporting systems are also in place and monitored by the QC Center (Naruse et al 2003).

*Singapore*

In the early 1960s it was recognized that erythrocytic glucose-6-phosphate dehydrogenase (G6PD) deficiency led to kernicterus, a significant contributor to newborn mortality and morbidity. The hyperbilirubinaemia seen in some G6PD-deficient infants was shown to be due to mild haemolysis as a result of the G6PD-deficient state and inherent transient hepatic dysfunction in bilirubin conjugation occurring in the first two weeks of life. About 70% of cases of hyperbilirubinaemia were due to G6PD deficiency or liver immaturity or a combination of both. Nearly half of all cases of severe neonatal jaundice needing exchange transfusion or terminating in kernicterus were due to erythrocytic G6PD deficiency with haemolytic triggers resulting from mothballed clothes and various herbs (Wong 1965, 1975).

The strategy for early diagnosis of G6PD deficiency in the mid-1960s was to measure the enzyme activity in cord blood (Joseph et al 1999a,b; Wong 1965, 1975). Thus, newborn screening for G6PD deficiency (incidence of approximately 2%) to combat the very high incidence of neurological morbidity and mortality due to kernicterus in Singapore began in 1965. In December 1981, a pilot screening programme for CH was started at the Kandang Kerbau Maternity Hospital, where approximately half of all Singapore births occur. The 18-month pilot provided support data for CH screening, and in 1990, the G6PD screening programme was expanded nationwide to include CH (Joseph et al 1999a,b; Yeo et al 1983).

The current NBS programme continues to utilize cord blood to detect G6PD deficiency and CH. MS/MS screening from blood spot specimens is available by parent request, and a centralized screening laboratory is used (R. Joseph, personal communication, 2007). Births number approximately 45 000, with one-third leaving the hospital by 24 h of birth and about 40% staying longer than 48 h. All screening is performed in hospitals without a centralized laboratory facility. The government subsidizes 40–60% of the cost of screening within the public hospitals, where approximately half of the births occur. Newborn screening has essentially eradicated kernicterus secondary to G6PD deficiency, with no newborn deaths reported in the last two decades. The strategy has been to keep identified G6PD-deficient babies in the hospital for a variable time up to 2 weeks to prevent exposure to environmental triggers. There is pressure to discontinue this practice and allow G6PD-deficient patients to be discharged much earlier, in line with other newborns, and it is a challenge to prevent adverse events related to G6PD deficiency. For CH, the recall rate is now about 0.5% using a TSH screen followed by $T_4$ in cases of elevated TSH (Joseph 2003).

## Second Asia Pacific screening era

The second NBS era in the Asia Pacific emerged about 20 years later (Table 1). During this period, screening activity began with limited programmes in Malaysia in 1980 (cord blood for G6PD deficiency), India in 1980, China in 1981, Taiwan in 1984 and Hong Kong (then a UK Crown Colony) in 1984 (cord blood for G6PD deficiency and CH).

*Malaysia*

In Malaysia, G6PD deficiency screening using cord blood was planned in the 1970s. In 1975, cord blood specimens were collected from hospitals in Kuala Lumpur and Petabling Jaya and showed an incidence similar to that in Singapore (Robinson et al 1976). Another pilot study in Malacca showed that the incidence was higher among Chinese and Malays but low among Indians (Singh 1986) and higher among Malay males (8%) compared to females (1.1%) (Choo et al 1994). In 1980, G6PD deficiency screening became part of routine newborn care in Malaysia.

In June 1991, a national meeting of government paediatricians at Ipoh Hospital commissioned a report on a national screening programme for CH and discussions continued the next year as part of the Malaysian Paediatricians Conference. Between 1991 and 1997, there were five separate pilot studies in different parts of the country. The incidence figures varied from 1:2400 to 1:3666, with an average CH incidence of 1:3026. In 1997, the Ministry of Health organized a national committee to consider CH screening implementation. The Ministry of Health commissioned a health technology assessment

(systemic review) of the benefits of CH screening and the report was accepted. The national CH screening programme began in October 1998 with three government hospitals and one district hospital participating. During the first year, slightly fewer than 6000 newborns were screening (approximately 1.8% of the newborn population). The programme has steadily increased ever since with approximately 45% of newborns screened in 2003 (Singh 2003).

*Taiwan*

The population of Taiwan is approximately 98% Chinese, mostly immigrants from the southern provinces of China, particularly Fujien and Guangdong provinces. In the early 1980s when NBS began, approximately 85% of births occurred in hospitals. By the early 1990s, the number of hospital births had risen to more than 98%. NBS in Taiwan began in the late 1970s in two institutes through the aid of the National Science Council (Chen 1993). An official pilot study to initiate NBS began in 1981. The socioeconomic situation at the time was not good and health education was inadequate. For that reason, NBS started very slowly with PKU and CH (Hwu et al 2003). In 1983, the Department of Health (DOH) of the Federal Government took over the studies and since then has provided funds to two NBS screening laboratories. In 1984, two medical genetic counselling centres were established to act as clinical networks for inborn errors—National Taiwan University Hospital and V.A. General Hospital. The national neonatal mass screening programme officially started in 1985. In addition to heel-stick blood, cord blood was accepted from 1987–1991, but was discontinued when the results were not found to be satisfactory. City and country health bureaus are responsible for specimen collection, recalling positive screening cases and referring detected cases to referral hospitals (Chen 1993).

Because G6PD deficiency is the most common enzymatic disease in Taiwan and 20–40% of patients with neonatal hyperbilirubinaemia have G6PD deficiency, it was included in the NBS programme from the beginning. All positive screening results were referred for confirmatory testing and the incidence was found to be about 2%. Kernicterus and exchange transfusions due to neonatal hyperbilirubinaemia decreased dramatically after screening for G6PD deficiency was begun. Some deaths continued to occur after screening was started, emphasizing the need for better education of parents (Hsiao et al 1991).

There is no mandatory screening law in Taiwan and all of the screening centres are coordinated by the DOH. There are currently five conditions included in the NBS package: PKU, CH, HCY, GAL and G6PD deficiency. The cost for NBS is USD 17, with another USD 9 charged for shipping and handling. The government provides a USD 3 supplement for each screen. A monitoring system has been in place since the beginning and information is collected through annual records review or electronic submission. Data are maintained on all cases including if medications are stopped and if deaths occur. One of the screening centres has included screening for CAH since 2000 for almost half of their newborn population. This centre also began expanded metabolic screening using MS/MS in 2001 on approximately 30% of their births (Huang et al 2006). A second centre began CAH screening in 2001 and MS/MS screening in 2002. In cases where tests beyond the government recognized programme occur, parents must pay and give informed consent. Current screening coverage in the country is approximately 97% (Hwu et al 2003).

The current Taiwan screening system includes three screening centres (one public and two private hospitals) and 18 referral hospitals, including outlying islands. The referral hospitals are geographically distributed and provide confirmatory tests, medical care and genetic counselling as follow-up to positive screens. An external QA programme has been in place since January 1988 to assess the reliability of confirmatory testing for G6PD deficiency. In 1999, an external QA programme to assess the reliability of the G6PD screening testing was implemented. At 1–2-month intervals, 10 PT samples are sent to participant screening laboratories and their results are compared to a quantitative reference value from the sending laboratory. Results from the participant laboratories are assessed against the reference value and the mean of the participating laboratories. Those needing assistance to improve their testing quality are identified and offered technical assistance. This programme represents the only international programme for G6PD QA and, in addition to Taiwan, currently includes participants from the Philippines, Thailand, Lebanon, Vietnam, Macau (via Shanghai), Germany (Hamburg) and China (Chiang et al 2003; K-J Hsiao, personal communication, 2007).

*Hong Kong*

Hong Kong is one of the most densely populated areas on earth. The population in 1990 was approximately 6 million, growing to approximately 7 million by 2000. For decades, G6PD deficiency has been known to be rampant in Hong Kong, accounting for mortality and

morbidity from acute haemolysis and neonatal hyperbilirubinaemia triggered by viral infections and exposure to noxious agents (e.g. Chinese herbs, mothballs and fava beans). In 1984, the Central Genetic Neonatal Screening Unit was established as part of the Clinical Genetic Service in Hong Kong and screening officially began in March 1984. The unit screened for G6PD deficiency and congenital hypothyroidism in babies born at government hospitals and maternal and child health clinics, covering about 90% of the newborns (Lam 1994; Lo et al 1995).

By 1995, screening covered 10 hospitals administered under the Hospital Authority of Hong Kong and six government maternity homes, which represented the majority of all newborns delivered in the public sector. Coverage today is almost 100%. For screening, umbilical cord blood is collected on the placental side immediately after delivery. Screening for CH includes TSH testing and over the years the procedure has been shown to detect relatively high numbers of transient CH. For G6PD deficiency, newborns with enzyme activity below a statistically determined cut-off level are recalled for assessment and their families are counselled by community nurses, obstetric nurses, nurses at the Central Genetic Neonatal Screening Unit and nurses at the maternal and child health centres. Both mortality and morbidity from neonatal hyperbilirubinaemia greatly decreased through the decades from over 300 cases annually to about 1 per year at present. (Lam 1994; Lam and Cheng 2003; Lo and Lam 1995; Lo et al 1995). A universal automated otoacoustic emission (AOAE) hearing screening programme was implemented in August 2003, with approximately 95% of registered births screened during the first year (Hau and Lam 2004).

*China*

With assistance from Guthrie (USA) and Naruse (Japan), a collaborating integrated screening programme was started in Shanghai in October 1981 with 14 maternity hospitals participating. The NBS test panel included CH, PKU and GAL (Chen and Guo 1983). Eight years later in 1989, NBS was begun in Beijing (Xi 1994). From 1992 to 1993, the World Health Organization (WHO) and the Ministry of Public Health sponsored a cooperative project to pilot NBS in seven major cities. In 1994, a survey of 17 cities in China showed that about 1% of babies born in the country were being screened. However, in Shanghai, Beijing, Tianjin and Guangzhou, screening was started systematically and coverage of 80–90% was being achieved (Ying et al 1996).

Presidential Order 33 was promulgated in October 1994 and the Law of the People's Republic of China on Maternal and Infant Health Care became enforceable on 1 June 1995. Article 24 of the law stated that "Medical and health institutions shall gradually develop medical and healthcare service such as the screening of the newborn babies". This has been interpreted by most provincial health departments to authorize newborn screening (Ying et al 1996). In addition to PKU and CH, in some areas there is optional screening for GAL and HIS (Gu et al 1999). Recently the US Centers for Disease Control and Prevention (CDC) has assisted in developing a quality assurance programme for newborn screening laboratory testing in Shandong Province similar to one already developed in Thailand. In this model, a central authority is sent sufficient PT materials to supply the necessary laboratories in a given region, in this case Shandong Province. The materials are then distributed to the screening laboratories and testing results are reported to the central authority. Results are then transmitted to the CDC and included in their PT analysis. In time, the intent is to have the central authority prepare their own PT materials in consultation with CDC and to develop a provincial QA programme (Wang et al 2003).

*India*

The first pilot newborn screening project in India occurred in 1980 in Bangalore, Karnataka (South India), with particular interest in the high rate of consanguinity in the population. Using toe sticks, 98 256 samples were collected and analysed for various aminoacidopathies. HCY, hyperglycinaemia, MSUD and PKU were found to be common, with transient tyrosinaemia most common (Devi et al 1983; Rao et al 1988). A second pilot was conducted beginning in Hyderabad in 2000 looking at other conditions in addition to amino acids. This study found that CH was most common, followed by CAH and G6PD deficiency (Devi and Naushad 2004). A smaller study in North India also looked at referred cases and found the most prevalent conditions to be HCY, alcaptonuria, MSUD and nonketotic hyperglycinaemia (Kaur et al 1994). Various other studies have confirmed high prevalences of CAH, CH in sub-Himalayan areas and sickle cell disease in various tribal populations and at least one non-tribal population in Chattisgarh State. A review of the case for newborn screening in developing countries used India as its example and reviewed in depth the CH studies over time (Bhatara et al 2002). In 2005, the Indian Council for Medical Research

(ICMR) created a task force comprising clinicians, paediatricians, geneticists and laboratory scientists. This task force is coordinating a pilot study covering over 1 million newborns from Mumbai, New Delhi, Cochin and Hyderabad. The ICMR pilot project is the first coordinated nationwide screening effort and is expected to be completed in 2 years. This project will form the basis for national implementation of NBS (http://www.expresshealthcaremgmt.com/20050915/coverstory01.shtml; accessed May 1, 2007).

## Third Asia Pacific screening era

A third era of NBS in the Asia Pacific appears to have occurred during the 1990s after the initiation of CH screening in much of the economically developed world (Table 1). Because of the improved cost-benefits realized through CH screening, and an increased CH incidence in iodine-deficient areas, screening emphasis was increased for CH. NBS projects were begun in South Korea and iodine-deficient areas of Thailand as pilots in 1991 and 1992, respectively. The Thailand pilot project became a national project in 1996, and the South Korean pilot became a national programme in 1997. Screening began in the Philippines as a pilot project in 1996 and became a national programme in 2004.

### *South Korea*

In South Korea, the Ministry of Health and Social Affairs adopted newborn screening for low-income families in 1991, with payment from the Social Welfare fund. Six conditions were initially included in the screening panel: CH, PKU, GAL, MSUD, HCY and HIS. In 1992, three screening centres were established and there was an increase in cost. Central government subsidy helped to support the programme. In 1993, the number of screening centres increased to five including one university hospital, three Planned Parenthood Federation laboratories, and one Health Center Association laboratory, and in 1994 it expanded to 21 laboratories. Local governments also began to assist in programme funding (Han et al 2003; Lee 1994).

In 1995, the screening panel was reduced from six conditions to two—PKU and CH—because the others were rarely detected and screening was not cost-effective. Funding in 1995 included only the central and local governments, and in 1997 the programme was expanded to include all newborns regardless of financial position. From 1998, the cost was shared 40% by the central government and 60% by the local government. Follow-up support from the government for treatment items such as formula applied only to low-income families. Screening for GAL, MSUD, HCY and HIS was optional if the parents agreed to an additional cost. Programme participation over the years grew from about 35% in 1994 to about 90% in 2000 (Han et al 2003; Lee 1994).

While the programme has progressed steadily over the years in terms of coverage, programme management challenges still exist. There is no organization responsible for programme coordination or control of national screening services. The number of screening laboratories progressed to 76 in 2000, and this number of laboratories means that many are processing very small numbers of specimens. The amount of government support limits the tests to PKU and CH unless parents choose to pay for others. Likewise, the follow-up support services are inadequate. Recovery of funds from the government is complicated and necessitates completion of a number of administrative processes (Han et al 2003). Nonetheless, screening continues to expand and coverage is now reported to be 94.2% (D. Lee, personal communication, 2006).

### *Thailand*

In 1992, a pilot project to establish the preliminary incidence of CH and PKU was conducted in 13 provinces in rural Northern Thailand. The survey showed a high incidence of CH, especially in iodine deficient areas. Additionally, one case of PKU was detected during the pilot period. These data provided the basis for phased implementation of nationwide neonatal screening services. In 1995, a public health policy was issued emphasizing the importance of neonatal screening for CH and PKU. In 1996, it was declared a national project. The country was divided into four regions—North, East, Central and South. Regional laboratories were established along with a central oversight/QA laboratory—one central screening laboratory at NIH and three Regional Medical Sciences Centres. Besides routine operation, dedicated personnel at the NIH laboratory are also responsible for reagents for affiliated laboratories and NBS QA. The Neonatal Screening Program is now a well established national programme and is integrated into the national public health service infrastructure throughout the country. Extensive public relations materials in the Thai language exist along with a comprehensive data reporting system and a programme website. The QA programme was developed with the assistance of the CDC and serves as a model for other Asian programmes. Approximately 97% of the country now has screening available for

CH and PKU (Charoensiriwatana et al 1995, 2003; http://www.neoscreen.in.th).

*Philippines*

In 1996, a pilot project was initiated by a Newborn Screening Study Group (the Group) of interested paediatricians and obstetricians in 24 hospitals in Metro Manila. The pilot programme was to establish preliminary incidence data for five conditions (CH, CAH, GAL, PKU, HCY) for recommendation to government for policy adoption. The programme proceeded in four phases: (1) 1996, screening for CH, CAH, GAL, PKU, HCY; (2) 1998, pilot screening for G6PD deficiency; (3) 2000, the programme was evaluated for cost effectiveness and policy changes; and (4) 2004, legislation introduced and passed mandating the offering of NBS (Padilla 2003). The net result was a recommendation for nationwide screening for five conditions (excluding HCY, adding G6PD deficiency), with samples collected after 24 h of age (Padilla 2003).

In April 1999, the Group opened the programme to hospitals outside of Manila and by September 2001, there were over 200 hospitals in the programme. The DOH recognized the importance of newborn screening and adopted it as a priority project. An Administrative Order directed regional health officials to assist in implementing screening and a multidisciplinary Technical Working Group was established to develop a national NBS implementation plan (Padilla 2003; Padilla and Domingo 2002).

Despite DOH support, implementation proceeded slowly with some resistance from hospitals, primarily over laboratory services, which were to be limited in number and regionally located. A newborn screening bill was introduced and was signed into law in 2004 as Republic Act 9288 or Newborn Screening Act of 2004 (www.nsrc-nih.org.ph). This law requires NBS to be offered to parents of newborns. The programme continues to grow, with more than 1000 hospitals offering screening. Newborn population coverage is about 16%. The primary challenges centre around financing, which may be partially solved with the recent inclusion of NBS in the national newborn insurance package, and home births which number about 75%. Significant public relations and education efforts have provided examples for other developing countries in the region.

Fourth Asia Pacific screening era

Late in the 1990s, a push to expand screening to other countries in the Asia Pacific received a boost from the International Atomic Energy Agency (IAEA) and the fourth era of screening in the region began. This expansion continues today. It was during this period that the IAEA expanded its support to the countries of the region through a regional (East Asia) technical cooperation project RAS 6/032 'Regional Screening Network for Neonatal Hypothyroidism.' The project began in May 1999 and included both developed and developing programmes within the region. Thus, representatives from Bangladesh, China (Tianjin), Indonesia, Malaysia, Mongolia, Pakistan, Philippines, South Korea, Thailand, and Vietnam became a project team to expand CH screening in the region, building on the experience of developed programmes in the region and elsewhere. Since 1999, the IAEA has provided assistance (both financial and technical) to begin pilot NBS programmes for CH in Bangladesh (Hasan et al 2003; Moslem et al 2003), Vietnam and Indonesia (Rustama et al 2003) in 1999, Mongolia (Erdenechimeg 2003) and Myanmar in 2000, Sri Lanka in 2005 and Pakistan in 2006 (Table 1). A guidance book for developing countries beginning CH screening also resulted from this project (Therrell and Padilla 2005). The project is continuing for an undetermined time and has now expanded to include countries from West Asia (Middle East). There continues to be little or no newborn screening activity in Nepal, Cambodia, Laos and North Korea.

*Pacific Islands*

The Asia Pacific region includes a large number of island countries with small populations and low numbers of births. However, taken together, they represent a significant number of babies that should be included in screening. During the mid-1960s, the New Zealand screening laboratory was active in receiving newborn screening specimens from many of these areas as noted previously. Specimens were received from at least 10 island nations and occasionally others (Houston and Veale 1971). Over time, the information from these programmes has been limited, with only small numbers of specimens reported received by the New Zealand screening laboratory. Countries with island territories generally include screening for those babies in their national or regional programme(s). So, for example, Australia receives samples from Norfolk Island and Lord Howe Island. (B. Wilcken, personal communication, 2007), Taiwan provides services for nearby islands (Chiang et al 2003), and Guam and Saipan send samples to the Oregon and Colorado programmes in the USA Recently, Palau has entered into an arrangement to

utilize the screening programme in the Philippines and will soon begin to screen its 3000 newborns using the Philippine screening panel with the exception of G6PD deficiency screening. However, for the vast majority of the smaller island nations and territories in the Asia Pacific (see Fig. 1) there is no available information about newborn screening services.

## Conclusions

Eighty per cent of the births in the Asia Pacific region occur in five countries—China, Indonesia, Bangladesh, India and Pakistan (see Table 1). All countries with an infant mortality rate (IMR) of less than 10/1000 live births have achieved better than 90% screening coverage of their newborn population. Most are approaching full coverage, although the number of conditions screened varies widely. Of the remaining countries with higher IMRs, Thailand (IMR 13/1000) is the only one that has achieved a high rate of newborn coverage (~97%). Among the countries that lack total coverage, the obstacles most often cited are poor economies, insufficient health education, lack of government support, early hospital discharge, and large numbers of out-of-hospital births.

The following items were identified as integral to the success of full population newborn screening: (1) government prioritization; (2) full or partial government financing; (3) public education and acceptance; (4) health practitioner cooperation/involvement; and (5) government participation in institutionalizing a newborn screening system. Integration into the national health care delivery system was cited as the single most critical element. While most of the developed programmes in the region have successfully accomplished health care integration without requiring legislation, at least two of the developing programmes (China and the Philippines) have found national legislation to be necessary. While the Chinese law is permissive in gradually developing a screening system, the Philippine law is more aggressive in requiring that every newborn be given access to newborn screening by the health practitioner who delivers or assists in the delivery of a newborn. The government's and physicians' responsibilities are also clearly outlined in the Philippine law.

Many of the developed programmes of the Asia Pacific Region have been active in advancing newborn screening. New Zealand was one of the first to have a national newborn screening programme; Japan initiated the first national multilaboratory QA programme; Australia was one of the first to utilize MS/MS as a newborn screening tool; and both New Zealand and Australia have been leaders in research on CF screening. Based on the information available from the programmes, Table 2 was constructed to provide an overview of current activities within the region. In several of the developing countries, screening for CH is in its infancy and has been indicated as pilot testing. In the developed programmes, MS/MS is now in varying stages of use. When asked to indicate the status of MS/MS screening, almost all users indicated that there were caveats to their result interpretation (see Table 2) and these are indicated as 'restricted interpretation.' While MS/MS testing is routine in Australia and New Zealand, there is still not complete consensus on the conditions to be investigated. In Singapore, MS/MS screening is routine in the government hospitals, with the goal of detecting over 25 metabolic conditions. The method of recruitment (opt in or opt out) varies from hospital to hospital. In Malaysia and Thailand, there is MS/MS pilot testing in some hospitals. In Japan, while the core group of conditions is the same in all prefectures and big cities, the pilot testing varies. A pilot of MS/MS testing is currently ongoing with support from the Ministry of Health, Labor and Welfare. While MS/MS equipment is available for diagnostic testing in some facilities in Hong Kong, there is not yet acceptance for newborn screening, and there are some MS/MS pilot screening activities in a few centres in the rest of China.

The genetic nature of most of the screened conditions provides an interesting mix of screening conditions across the region. The universally important condition is CH, which has a similar incidence across all countries in the region, with the exception of pockets of iodine deficiency, where it is much higher. These pockets most often occur in the developing countries and so CH is usually the first condition considered for screening. The exception is G6PD deficiency, which is known to be of high incidence in the Asian population, in some countries approaching 5% in males (Lo et al 1995). Therefore, several countries in the region began screening for G6PD before considering other conditions. Because cord blood samples were readily available, several programmes began their G6PD or CH screening using cord blood. There continue to be mixed reactions concerning the specimen of choice in these countries and in others who do not fully embrace the idea of expanded screening to other less frequent metabolic conditions. It is likely that this debate will not end soon.

The developed programmes within the region are continuing to refine and expand their NBS pro-

**Table 2** Screened conditions in Asia Pacific newborn screening programmes

| Jurisdiction | Screened conditions | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Congenital hypothyroidism | Phenylketonuria | Galactosaemia | Maple syrup urine disease | Congenital adrenal hyperplasia | Homocystinuria | Cystic fibrosis | G6PD deficiency | MS/MS Detectable | | | Others: lysozomal storage disorders |
| | | | | | | | | | Other amino acid disorders | Fatty acid oxidation disorders | Organic acid disorders | |
| Australia | • | • | • | • | | • | • | | • | • | • | ‡ |
| Bangladesh | • | | | | | | | | | | | |
| Cambodia | | | | | | No data | | | | | | |
| China | • | • | | | | | | | ‡ | ‡ | ‡ | |
| Hong Kong (China) | † | | | | | | | † | | | | |
| India | ‡ | ‡ | ‡ | ‡ | ‡ | ‡ | ‡ | ‡ | ‡ | ‡ | | |
| Indonesia | ‡ | | | | | | | | | | | |
| Japan | • | • | • | • | • | | | | ‡ | ‡ | ‡ | |
| Korea (South) | • | • | • | | | | | | ‡ | ‡ | ‡ | |
| Korea (North) | | | | | | No data | | | | | | |
| Laos | | | | | | No data | | | | | | |
| Malaysia | • | | | | | | | • | ‡ | ‡ | ‡ | |
| Mongolia | ‡ | | | | | | | | | | | |
| Myanmar | ‡ | | | | | | | | | | | |
| Nepal | | | | | | No data | | | | | | |
| New Zealand | • | • | • | • | • | • | • | | • | • | • | |
| Palau | (•) | (•) | (•) | (•) | | | | | | | | |
| Pakistan | ‡ | | | | | | | | | | | |
| Philippines | • | • | • | | • | | | • | | | | |
| Singapore | † | | | | | | | † | • | • | • | |
| Sri Lanka | ‡ | | | | | | | | | | | |
| Taiwan | • | • | • | | • | • | | • | • | • | • | ‡ |
| Thailand | • | • | | | ‡ | | | | ‡ | ‡ | ‡ | |
| Vietnam | ‡ | | | | | | | ‡ | | | | |

• Offered to full population being screened—for MS/MS indicates screening and interpretations available for all detectable conditions.
(•) Contracted with Philippines to begin same screening panel.
† Cord blood screening.
‡ Pilot testing or select population screening—not full population screening.

grammes, and there are many research projects ongoing. Of particular interest is a pilot screening programme for Pompe disease in Taiwan and other lysosomal storage disease screening in Australia (Meikle et al 2006). Hearing screening is also expanding throughout the region, with a number of national projects underway. The developing CH programmes are continuing to show progress and there are indications of screening interest in some of the countries with no known programmes. Recent inquiries to the US National Newborn Screening and Genetics Resource Center from Nepal and India are of particular interest since both inquiries appeared to indicate serious interest in developing pilot projects that could lead to expanded programmes. The challenges to developing screening in some parts of the region are formidable, but they can be overcome with dedication, ingenuity and support from developed programmes and health advocacy organizations.

**Acknowledgements** We are grateful to the following individuals for providing country data: Veronica Wiley and Bridget Wilcken (Australia,) Mizanul Hasan (Bangladesh), Xue Fan Gu (China), Stephen Lam (Hong Kong ) Ishwar Verma (India), Diet Rustama (Indonesia), Masaru Fukushi (Japan), Dong Hwan Lee (Korea), Thong Meow Keong (Malaysia), Aye Aye Thien (Myanmar), Dianne Webster (New Zealand), Roy Joseph (Singapore), Damayanthi Nanayakkara (Sri Lanka), Wuh-Liang Hwu (Taiwan), Wiyada Charoensiriwatana and Pornswan Wasant (Thailand), and Hoan Thi Nguyen (Vietnam). Special appreciation is extended to Bridget Wilcken, Dianne Webster and Masaru Fukushi for their review and suggestions in the final manuscript.

## References

American Academy of Pediatrics, Newborn Screening Task Force (2000) Serving the family from birth to the medical home—Newborn screening: a blueprint for the future. *Pediatrics* **106**(supplement): 383–427.

Amino Y (1987) Quality control system in Japan. In: Therrell BL, ed. *Advances in Neonatal Screening*. Amsterdam: Elsevier Science Publishers, 531–535.

Aoki K (2003) Newborn screening in Japan. *Southeast Asia J Trop Med Pub Health* **34**(Supplement 3): 80.

Bhatara V, Sankar R, Jurgen U, Peabody J (2002) A review of the case for neonatal thytropin screening in developing countries: the example of India. *Thyroid* **12**: 591–598.

Charoensiriwatana W, Janejai N, Boonwanich W, Krasao P, Nakpresit S (1995) Establishment of national neonatal screening programme in Thailand. In: Therrell B, Aldis B, eds. *Proceedings of 11th national Neonatal Screening Symposium*, September 12–16, 1995, Corpus Christi, Texas. Washington, D.C.: Association of State and Territorial Public Health Laboratory Directors, 1–4.

Charoensiriwatana W, Janejai N, Boonwanich W, Krasao P, Chaisomechit S, Waiyasilp S (2003) Neonatal screening program in Thailand. *Southeast Asia J Trop Med Pub Health* **34**(Supplement 3): 94–100.

Carpenter KH, Wilcken B (1999) Neonatal diagnosis of long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency and implications for newborn screening by tandem mass spectrometry. *J Inherit Metab Dis* **22**: 840–841.

Chen JS (1993) The organization of neonatal screening programs and international cooperation systems in Taiwan. In: Takasugi N, Naruse H, eds. *New Trends in Neonatal Screening.* Sapporo: Hokkaido University Press, 33–35.

Chen R, Guo Di (1983) The initiation of neonatal programmed in Shanghai, China. In: Naruse H, Irie M, eds. *Neonatal Screening*. Amsterdam: Excerpta Medica, 483–484.

Chiang S-H, Wu K-F, Liu T-T, Wu, S-J, Hsiao K-J (2003) Quality assurance program for neonatal screening of glucose-6-phosphate dehydrogenase deficiency. *Southeast Asia J Trop Med Pub Health* **34**(Supplement 3): 130–134.

Choo KE, Ariffin WA, Normah J, Oppenheimer SF, Selamah G (1994) Cord blood G6PD activity in Malay neonates. In: Takasugi N, Naruse H, eds. *New Trends in Neonatal Screening.* Sapporo: Hokkaido University Press, 7–10.

Crossley JR, Elliott RB, Smith PA (1979) Dried-blood spot screening for cystic fibrosis in the newborn. *Lancet* **1**: 472–474.

Devi AR, Rao NA, Bittles AH (1983) Newborn screening for aminoacidopathies in South India. In: Naruse H, Irie H, eds. *Neonatal Screening*. Amsterdam: Elsevier Science Publishers, 493–494.

Devi AR, Naushad SM (2004) Newborn screening in India. *Indian Journal of Pediatrics* **71**: 157–160.

Dussault JH, Laberge C (1973) Thyroxine (T4) determination in dried blood by radioimmunoassay: a screening method for neonatal hypothyroidism. *Union Med Can* **102**: 2062–2064.

Dussault JH, Coulomb P, Laberge C, Letarte J, Guyda H, Khoury K (1975) Preliminary report on a mass screening program for neonatal hypothyroidism. *J Pediatr* **86**: 670–674.

Erdenechimeg S (2003) National newborn hypothyroid screening program in Mongolia. *Southeast Asia J Trop Med Pub Health* **34**(Supplement 3): 85–86.

Fujieda K, Matsuura N, Takasugi N, Fukushi M, Arai O, Mizushima Y (1987) Five years experience of newborn screening program for congenital adrenal hyperplasia in Sapporo. In: Therrell BL, ed. *Advances in Neonatal Screening*. Amsterdam: Elsevier Science Publishers, 281–286.

Fujimoto A, Ohtake H, Miyagi T, et al (1987) Blood spot enzyme multiple auxotroph screening for urea-cycle disorders in Osaka. In: Therrell BL, ed. *Advances in Neonatal Screening*. Amsterdam: Elsevier Science Publishers, 215–216.

Gu XF, Jun Y, Chen R-G (1999) Neonatal screening of phenylketonuria and congenital hypothyroidism in China. *Southeast Asia J Trop Med Pub Health* **30**(Supplement 2): 17–19.

Guthrie R (1962) Screening for 'inborn errors of metabolism' in the newborn infant—a multiple test program. *Birth Defects Original Article Series* **IV**: 92–98.

Guthrie R (1992) The origin of newborn screening. *Screening* **1**: 5–15.

Guthrie R, Susi A (1963) A simple phenylalanine method for detecting phenylketonuria in large populations of newborn infants. *Pediatrics* **32**: 338–343.

Han YJ, Lee D-H, Jong WK (2003) Newborn screening in Korea. *Southeast Asia J Trop Med Pub Health* **34**(Supplement 3): 81–84.

Hasan M, Nahar N, Ahmed A, Moslem F (2003) Screening for congenital hypothyroidism—a new era in Bangladesh.

*Southeast Asia J Trop Med Pub Health* **34**(Supplement 3): 162–164.

Hau W, Lam TS (2004) 20 years experience in neonatal screening in Hong Kong. *Abstracts 5th Asia Pacific Regional Meeting of the International Society for Neonatal Screening*, 14–17 September 2004, Shanghai, China, 31.

Houston IB, Veale AMO (1971) Screening for inborn errors of metabolism. *Lab Manag* **9**: 30–32, 53.

Hsiao K-J, Chiang SH, Chang TT, Liew DG, Chao YY (1991) Experience of neonatal G6PD deficiency screening in Taiwan. In: Wilcken B, Webster D eds. *Neonatal Screening in the Nineties*. Leura, NSW: The Kelvin Press, 217–218.

Huang HP, Chu KL, Chien YH, et al (2006) Tandem mass neonatal screening in Taiwan—report from one center. *J Formos Med Assoc* **105**: 882–886.

Hwu WL, Huang AC, Chen JS, Hsiao KJ, Tsai W-Y (2003) Neonatal screening and monitoring system in Taiwan. *Southeast Asia J Trop Med Pub Health* **34**(Supplement 3): 91–3.

IAEA Report of East Asia Project Coordination and Planning Management Meeting (2002) *Workshop on Congenital Hypothyroidism: Quality Assurance and Validation (RAS6032)*, Tianjin, China. Vienna: International Atomic Energy Agency, 10–12.

Irie M, Naruse H (1980) Mass screening for neonatal hypothyroidism in Japan. In: Bickle H, Guthrie R, Hammersen G, eds. *Neonatal Screening for Inborn Errors of Metabolism*. Berlin: Springer-Verlag, 247–251.

Irie M, Enomoto K, Naruse H (1975) Measurement of thyroid-stimulating hormone in dried blood spot. *Lancet* **2**: 1233–1234.

Irie M, Nakajima H, Inomata H, Naruse H, Suwa S, Takasugi N (1987) Screening of neonatal hypothyroidism in Japan. In: Therrell BL, ed. *Advances in Neonatal Screening*. Amsterdam: Elsevier Science Publishers, 41–47.

Joseph R (2003) Mass newborn screening in Singapore. *Southeast Asia J Trop Med Pub Health* **34**(Supplement 3): 89–90.

Joseph R, Ho LY, Gomez JM, Rajdurai VS, Sivasankaran S, Yip YY (1999a) Mass newborn screening for glucose-6-phosphate dehydrogenase deficiency in Singapore. *Southeast Asia J Trop Med Pub Health* **30**(Supplement 2): 70–71.

Joseph R, Ho LY, Gomez JM, Rajdurai VS, Sivasankaran S, Yip YY (1999b) Newborn screening in Singapore. *Southeast Asia J Trop Med Pub Health* **30**(Supplement 2): 23–24.

Kaur M, Das GP, Verma IC (1994) Inborn errors of aminoacid metabolism in North India. *J Inherit Metab Dis* **17**: 230–233.

Kawamura M (1987) Neonatal screening for galactosemia. In: Therrell BL ed. *Advances in Neonatal Screening*. Amsterdam: Elsevier Science Publishers, 227–230.

Koch JH (1997) *Robert Guthrie: The PKU Story*. Pasadena: Holt Publishing House.

Lam STS (1994) The organization of genetic screening programmes in Hong Kong — An overview. In: Takasugi N, Naruse H, eds. *New Trends in Neonatal Screening*. Sapporo: Hokkaido University Press, 29–31.

Lam STS, Cheng ML (2003) Neonatal screening in Hong Kong and Macau. *Southeast Asia J Trop Med Pub Health* **34**(Supplement 3): 73–75.

Lee DH (1994) Neonatal screening in Korea. In: Takasugi N, Naruse H eds. *New Trends in Neonatal Screening*. Sapporo: Hokkaido University Press, 3–5.

Lo KK, Lam TS (1995) Neonatal screening programme for congenital hypothyroidism in Hong Kong. In: Lam TS, Pang CP, eds. *Neonatal and Perinatal Screening: the Asian Pacific Perspectives.* Hong Kong: The Chinese University Press, 145–148.

Lo KK, Chan ML, Lo IFM, et al (1995) Neonatal screening for glucose-6-phosphate dehydrogenase deficiency in Hong Kong In: Lam TS, Pang CP, eds. *Neonatal and Perinatal Screening: the Asian Pacific Perspectives.* Hong Kong: The Chinese University Press, 33–35.

Lyon I (1983) Screening for hypothyroidism: the New Zealand experience. In: Naruse H, Irie M, eds. *Neonatal Screening*. Amsterdam: Elsevier Science Publishers, 111–112.

Lyon IC, Crossley JR, Smith PA (1983) Screening for cystic fibrosis. *New Zealand Med J* **96**: 673–675.

Matsuda I, Endo Y, Edo F, Akaboshi I (1987) Clinical and biochemical observation of maple syrup urine disease patients found by neonatal screening. In: Therrell BL, ed. *Advances in Neonatal Screening*. Amsterdam: Elsevier Science Publishers, 217–218.

McCabe LL, Therrell BL, McCabe ERB (2002) Newborn screening: rationale for a comprehensive, fully integrated public health system. *Mol Genet Metabol* **77**: 267–273.

Meikle PJ, Grasby DJ, Dean CJ, et al (2006) Newborn screening for lysosomal storage disorders. *Mol Genet Metabol* **88**: 307–314.

Moslem F, Yasmeen S, Hasan M, Karim MA, Nahar N, Ahmed A (2003) Newborn screening in Bangladesh. *Southeast Asia J Trop Med Pub Health* **34**(Supplement 3): 71–72.

Naruse H (1980a) System of neonatal screening for inborn errors of metabolism in Japan. In: Bickle H, Guthrie R, Hammersen G, eds. *Neonatal Screening for Inborn Errors of Metabolism*. Berlin: Springer, 299–305.

Naruse H (1980b) Neonatal thyroid screening as part of a multiple genetic screening program in Japan. In: Burrow GN, Dussault JH, eds. *Neonatal Thyroid Screening*. New York: Raven Press, 133–137.

Naruse H, Tsuji A, Suzuku E, et al (2003) Quality control system for mass screening in Japan. *Southeast Asia J Trop Med Pub Health* **34**(Supplement 3): 30–35.

Nozue G, Moriyama Y, Gomibuchi M, et al (1983) Propagation and results of a neonatal screening program concerning inborn errors of metabolism in Japan In: Naruse H, Irie M, eds. *Neonatal Screening*. Amsterdam: Elsevier Science Publishers, 477–480.

Padilla C (2003) Newborn screening in the Philippines. *Southeast Asia J Trop Med Pub Health* **34**(Supplement 3): 87–88.

Padilla C, Domingo C for the Newborn Screening Study Group (2002) Implementation of newborn screening in the Philippines. *Philippine J Pediatr* **51**: 2–10.

Pass KA, Lane PA, Fernhoff PM, et al (2000) U.S. Newborn Screening system guidelines II: follow-up of children, diagnosis, management and evaluation—statement of the Council of Regional Networks for Genetics Services (CORN). *J Pediatr* **137**: S1–S46.

Rao NA, Devi AR, Savithri HS, Rao SV, Bittles AH (1988) Neonatal screening for amino acidaemias in Karnataka, South India. *Clin Genet* **34**: 60–63.

Robinson MJ, Lau KS, Lin HP, Chan GL (1976) Screening for G6PD Deficiency. *Med J Malaysia* **30**: 287–290.

Rustama DS, Fadil MR, Harahap ER, Primadi A (2003) Newborn screening in Indonesia. *Southeast Asia J Trop Med Pub Health* **34**(Supplement 3): 76–79.

Singh A (2003) Malaysia country report—newborn screening. IAEA 2003 RAS 6/32 Project Report, Hanoi, Vietnam.

Singh H (1986) Glucose-6-phosphate dehydrogenase deficiency: a preventable cause of mental retardation. *Br Med J* **292**: 397–398.

Suzuki K, Tochizawa K, Suzuki R, Owada M, Sakayam T, Kitagawa T (1983). A trial of the screening for urea cycle disorders. In: Naruse H, Irie M, eds *Neonatal Screening*. Amsterdam: Elsevier Science Publishers, 372–373.

Suwa S, Shimozawa K, Kitagawa T, et al (1987) Collaborative study on regional neonatal screening for congenital adrenal

hyperplasia in Japan. In: Therrell BL, ed. *Advances in Neonatal Screening*. Amsterdam: Elsevier Science Publishers, 279–280.

Szeinberg A (1971) Neonatal screening for phenylketonuria and some other metabolic disorders. In: Cohen BE, Rubin MI, Szeinberg A, eds. *Proceedings of the International Symposium on Phenylketonuria and Allied Disorders*, Tel Aviv, 15–22 June 1969. Tel Aviv: Translators' Pool, 47–52.

Therrell BL (2001) U.S. newborn screening policy dilemmas for the twenty-first century. *Mol Genet Metab* **74**: 64–74.

Therrell BL, Hannon WH (2006) National evaluation of U.S. newborn screening system components. *Ment Retard Dev Disabil Res Rev* **12**: 236–245.

Therrell BL, Padilla CD (2005) *Screening of Newborns for Congenital Hypothyroidism Guidance for Developing Programmes*. Vienna: International Atomic Energy Agency, 15.

Therrell BL, Panny SR, Davidson A, et al (1992) U.S. newborn screening system guidelines: statement of the Council of Regional Networks for Genetic Services (CORN). *Screening* **1**: 135–147.

UNICEF (2007) State of the world's children 2007. New York: Gist and Herlin Press. (Available at: http://www.unicef.org/sowc07/docs/sowc07.pdf).

Veale AMO, Houston IB (1976) Administration and organization of the New Zealand screening program. In: Rubin MI, Jeljaszewicz J, Cabalska B, eds. *Proceedings of the International Symposium on Laboratory Screening Techniques for Inborn Errors of metabolism in Newborn and Selected High-Risk Infants*, Warsaw, Poland, 3–6 September 1972. Warsaw: National Center for Scientific, Technical and Economic Information, 221–224.

Veale AMO, Houston IB (1978) Mass screening for inborn errors of metabolism. *Patient Manag* 20–24.

Wang W, Chen X, Zang J, He Y Zhang P, Shen F (2003) Development of a newborn screening laboratory quality assurance system in Shandong, China. *Southeast Asia J Trop Med Pub Health* **34**(Supplement 3): 36–38.

Webster D (1991) Why blind quality assurance—the HGSA QAP. In: Wilcken B, Webster D, eds. *Neonatal Screening in the Nineties*. Leura, NSW: The Kelvin Press, 278–279.

Wijekoon A, Nanayakkara D, Jiffry N, et al (2006) Towards neonatal screening for congenital hypothyroidsm in Sri Lanka: a pilot project. In: *Book of Abstracts, International Society for Neonatal Screening Convention*, Awaji, Japan, 16–18 September 2006, 108.

Wilcken B (1999) Neonatal screening in Australia. *Southeast Asia J Trop Med Pub Health* **30**(Supplement 2): 41–42.

Wilcken B, Brown A (1987) Screening for cystic fibrosis in the New South Wales, Australia: evaluation of the results of screening 400 000 babies. In: Therrell BL, ed. *Advances in Neonatal Screening*. Amsterdam: Elsevier Science Publishers, 385–390.

Wilcken B, Chalmers G (1985) Reduced morbidity in patients with cystic fibrosis detected by neonatal screening. *Lancet* **2**: 1319–1321.

Wilcken B, Gaskin K (2007) More evidence to favour newborn screening for cystic fibrosis. *Lancet* **369**: 1146–1147.

Wilcken B, Smith A, Brown DA (1980) Urine screening for aminoacidopathies: is it beneficial? Results of a long-term follow-up of cases detected by screening one millon babies. *J Pediatr* **97**: 492–497.

Wilcken B, Wiley V, Sherry G, Bayliss U (1995) Neonatal screening for cystic fibrosis: a comparison of two strategies for case detection in 1.2 million babies. *J Pediatr* **127**: 965–970.

Wilcken B, Wiley V, Hammond J, Carpenter K (2003) Screening newborns for inborn errors of metabolism by tandem mass spectrometry. *N Engl J Med* **348**: 2304–2312.

Wilcken B, Haas M, Joy P, et al (2007) Outcome of neonatal screening for medium-chain acyl-CoA dehydrogenase deficiency in Australia: a cohort study. *Lancet* **369**: 37–42.

Wiley V, Carpenter K, Wilcken B (1999) Newborn screening with tandem mass spectrometry: 12 months' experience in NSW Australia. *Acta Pædiatr Suppl* **432**: 48–51.

Wong HB (1965) Singapore kernicterus—the position in 1965. *J Singapore Paediatr Soc* **7**: 35–43.

Wong HB (1975) A surveillance system to prevent kernicterus in Singapore infants. *J Singapore Paediatr Soc* **17**: 1–9.

Xi YS (1994) Newborn screening in Beijing China. In: Takasugi N, Naruse H, eds. *New Trends in Neonatal Screening*. Hokkaido University Press, Sapporo 19–21.

Yamaguchi A, Fukushi M, Mizushima Y, Sato Y, Takasugi N (1987) A simple method for quantification of biotinidase activity in dried blood spot and its application to screening for biotinidase deficiency. In: Therrell BL, ed. *Advances in Neonatal Screening*. Amsterdam: Elsevier Science Publishers, 319–321.

Yeo PP, Joseph R, Chng KP, et al (1983). Screening programme for congenital hypothyroidism in Singapore. In: Naruse H, Irie M, eds. *Neonatal Screening*. Amsterdam: Elsevier Science Publishers, 113–114.

Ying D, Chen R, Shen Y, et al (1996). Neonatal screening in mainland China: current status and future plans and proposals. In: Lam S, Pang C, eds. *Neonatal and Perinatal Screening*. Hong Kong: The Chinese University Press, 21–23.