

Mass Newborn Screening in Singapore—Position and Projections

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Abstract

Introduction: This paper describes the development, current position and projected development of mass newborn screening in Singapore. **Methods:** A search was conducted through the Medline and through the abstract books of conferences for papers on mass newborn screening in Singapore. This was complemented with the author's own records of the outcome of screening newborns at the National University Hospital. **Results:** Cord blood screening for glucose-6-phosphate dehydrogenase (G6PD) deficiency began in 1965; through patient isolation, prompt treatment of jaundice and parent education, kernicterus has been eliminated. Pilot screening for congenital hypothyroidism began in 1981 and has become nationwide since 1990. Screening rates are almost 100% and with early treatment, mental retardation has been eliminated in those affected. However, academic difficulties are present in about a third of patients. Screening for hearing impairment now covers 80% of newborns. The incidence of significant impairment is 1 in 1000 births and interventions have been in place before a year of age. Two strategies – measuring automated auditory brainstem responses (AABR) and otoacoustic emissions supplemented with AABR – are being evaluated. **Conclusions:** The programme requires refining of screening strategies, creation of a central registry of cases, provision of educational support and expansion to include screening with tandem mass spectrometry for multiple inborn errors of metabolism.

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Introduction

Mass newborn screening is an essential preventative public health programme which aims to diagnose, in the presymptomatic phase, diseases that have a better outcome with early intervention. The development in 1960 by the late Dr Robert Guthrie of a simple test, the GuthrieTest, that enabled the detection of phenylketonuria (PKU) on blood spots on filter paper paved the way for mass newborn screening to begin in the United States.¹ About a decade later, the ability with radioimmunoassay to determine thyroxine (T4) levels on a filter paper blood spot enabled newborn screening for congenital hypothyroidism to start.² Diseases screened for need to be well defined, occur with sufficient frequency and have a known natural history. The screening test should be able to discriminate between affected and unaffected individuals and the chance that those who have a positive result are affected should be known. In addition, the financial benefits to society, the facilities available to manage the patient identified by screening and the ethical issues that will arise will all need to be considered before a decision to screen is implemented.

These principles were first proposed by Wilson and Jugner in 1968.³ They have been dealt with in detail by Wald in 1984.⁴

Technological developments have enabled more chemicals to be measured on blood spots. The parallel development of automated specimen handling instruments, spectrophotometers, enzyme immunoassays and high pressure liquid chromatography enabled an array of diseases to be detected through screening. These include galactosemia, maple syrup urine disease, homocystinuria, sickle cell disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency, cystic fibrosis, congenital adrenal hyperplasia and neuroblastoma. More recently, the advent of gas chromatography and tandem mass spectrometry have enabled the screening of a host of inborn errors of metabolism including medium-chain acyl-coenzymeA dehydrogenase deficiency (MCAD) and other fatty acid oxidation defects.⁵ With the firm establishment of screening, the need for integration of screening programs into the basic health care delivery system and the requirements for proper follow-up of children, diagnosis, management and

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evaluation has been recognised. These were the subjects examined by the US Newborn Screening Task Force, 1999 and the Council of Regional Networks for Genetic Services, 2000.^{6,7} In this paper, the development and current position of mass newborn screening in Singapore will be described. This will be followed by a projection of the manner in which screening needs to or is likely to develop, in the immediate future.

Position of Screening

In Singapore, mass newborn screening started at about the same time as in the United States, but for a different disease, namely G6PD deficiency. Neonates were presenting frequently with severe haemolytic jaundice and anaemia but without blood group incompatibility. Over a 10-month period starting in March 1955, 96 infants were admitted with very severe hyperbilirubinaemia (>20 mg/dL). Only two were due to iso-immunisation. Twenty-six (27%) of them were kernicteric and in addition, did not show evidence of iso-immunisation. Death occurred in 81% of the babies who had become kernicteric. As they were all mature infants, it was postulated that their hyperbilirubinaemia could have been due to the physiological haemolysis of red cells that occur in the newborn period aggravated by an inefficient liver secondary to protein malnutrition in the mother and precipitated by neonatal sepsis.⁸ Exchange transfusions were frequent and though able to control the rise in serum bilirubin in the majority of babies, the final outcome of death and or kernicterus in a large number of cases was of much concern. Further studies were carried out in the 237 cases admitted in 1960 and 1961 with bilirubin values exceeding 20 mg/dL. Kernicterus was present in 87 (37%). G6PD deficiency was identified in 44% of the kernicteric patients, whereas blood group incompatibility was the cause in only 13%.⁹

The ease with which the deficiency state could be detected and kernicterus prevented by the avoidance of triggers led to the establishment in 1965 of mass newborn screening for G6PD deficiency in Singapore by Wong.^{10,11} The primary objective since then of our mass newborn screening programme has been to prevent mental retardation arising from treatable conditions that can be identified by screening. Factors that have markedly influenced our screening strategy are: the almost universality of births in hospitals and secondly, the very short stay in hospital after delivery. Almost 30% and 60% of babies leave hospital within 24 hours and 48 hours of birth.

G6PD Deficiency

The strategy is to measure G6PD activity in cord blood using rapid, quantitative or semi quantitative techniques.¹² Babies identified are protected from haemolysis by keeping them in hospital. Initially it used to be for 3 weeks. The

parents were, in addition, counselled and educated on the nature of the disease, its heritability and the common triggers, namely naphthalene balls, Fava beans and herbal tonics taken in the puerperium. Since then, we have screened practically all 1.7 million of the babies born. G6PD deficiency was found in about 1.62% of all newborns, 3.15% of males and 0.11% of females. A distinct racial variation was observed in the males: Chinese, 3.94%; Malays, 2.95% and Indians 0.66%.^{13,14}

The molecular abnormality in our babies with G6PD deficiency has been studied.¹⁵ Here too, a racial variation is present. Among the Chinese the common variants are Canton (nt 1376 G→T), 24%; Kaiping (nt 1388 G→A), 21%; and Mediterranean, (nt 563 C→T) 10%. Two other mutants, Gaozhou (nt 95 A→G) and Chinese 5 (nt 1024 C→T) were identified, but in low frequencies. Among Malays, 6 different variants were identified, 3 not categorised previously and the others being the variants known commonly as Mahidol, Indonesian and Mediterranean. Studies done in Singapore in a cohort of 220 Chinese G6PD deficient babies revealed that they had bilirubin values on the first day of life that were significantly higher, 121.4 μ mol/L (SE 3.4) than that in a matched cohort of non-G6PD deficient babies, 2.8 μ mol/L (SE 1.7). In addition, the bilirubin levels in them remained significantly higher over the first 5 days of life.¹⁶ Hyperbilirubinaemia (>256 μ mol/L) developed in 22% of them in contrast to 10% in non-G6PD deficient babies. This difference was significant. None of the babies, however, developed hyperbilirubinaemia after the first week of life. Kaplan has shown that timed, predischARGE serum bilirubin screening can be used to identify affected neonates at low, intermediate or high risk of developing hyperbilirubinaemia.¹⁷ This offers the possibility of a selective approach to their discharge and follow-up surveillance.

As a result of preventive measures and parent education, the incidence of kernicterus dropped dramatically and there has been over the last 25 years, no reported cases of kernicterus secondary to G6PD deficiency.¹⁴ With greater awareness of the disease among the population, the risk of acute haemolysis in the neonatal period has reduced and the period of hospitalisation has been reduced in stages to 2 weeks and now 1 week. This reduction supported by the findings from Singapore that in G6PD newborns, bilirubin values are significantly higher only in the first 5 days of life¹⁶ and that in about 40% significant hyperbilirubinaemia does not develop.¹⁸ Another local study which has just been published has shown that G6PD deficient babies without significant jaundice in the first week of life are not at increase risk of its development in the second week of life. The negative predictive value was 100% (95% C.I., 86.7%-100%).¹⁹

Hospitalisations later in infancy or childhood for acute haemolysis are also very rare now. There is no report of the screening missing an affected child.

Congenital Hypothyroidism

Screening for congenital hypothyroidism started in 1980 as a pilot study using the primary T4, supplemental thyroid stimulating hormone (TSH) approach on the cord serum.²⁰ From 1985, it was part of the basic service to newborns at the National University Hospital and a T4 and TSH strategy was adopted to determine the relative merits of the following recall criteria: I) TSH >25 mIU/L (97th centile); II) T4 <90 nmol/L (10th centile) with a TSH >16.5 mIU/L (90th centile); and III) T4 <64 nmol/L (-2SD). In the 11,789 babies screened over the next 4 years, 3 babies with congenital hypothyroidism were detected. The recall criteria I, II and III identified all, one and none of the hypothyroids, respectively. All cases had TSH values of >50 mIU/L.²¹

Between 1985 and 1990, cord blood screening for congenital hypothyroidism began to be part of the service in some private hospitals. The coverage was, however, not universal and the strategies varied. In 1990, the Ministry of Health funded a 1-year study to further evaluate screening strategies. This involved extending the screening to babies born at the Singapore General Hospital and the Kangkar Kerbau Maternity Hospitals. The T4 and TSH strategy was again used. Congenital hypothyroidism was identified in 10 cases out of the 20,072 that were screened.²² The highest T4 in the screening specimen of any of the cases was 112 nmol/L (about 0.5 SD below the mean) and the lowest TSH was 40 mIU/L (>99th centile). None of those with a low T4 (-2SD) and TSH below <14 (90th centile) proved on follow-up to have hypothyroidism. The results strengthened our earlier finding of the poor sensitivity and specificity of a low T4 in the cord serum for identifying congenital hypothyroidism.

The beneficial effects revealed by the study led to screening for congenital hypothyroidism in the newborn period to be considered as part of basic health service in the country. Thus, nationwide screening was established in 1990 using the primary TSH strategy. We continue to use third generation semi-automated non-radioisotopic assay characterised by a high sensitivity, low interference rates and a short turn-around times. Thus the result of the screening is almost always known before the initial discharge (24 to 48 hours of age). Our experience has shown that hypothyroids have, by day 3 to 4, TSH values that are clearly different (higher) from that of normals. In a series of 130 healthy term infants we measured between 72 and 120 hours of age, the fT4 and TSH levels. The mean (1SD) was found to be 35.8 (11) pmol/L for fT4. For TSH, the 97th percentile value was 30 mIU/L of serum. In another analysis of TSH levels obtained from 65,761 babies screened

between days 2 and 3, only 0.2% had values that exceeded 15 mIU/L of blood (30 mIU/L of serum).²³

Hence, babies with TSH values greater than 25 mIU/L (97th centile) in the screening specimen are recalled between day 3 to 4 for evaluation and diagnostic tests. This enables treatment in affected babies to be initiated by the end of the first week of life.²⁴

Our screening rates are over 99.9% and recall rates just over 1%. The incidence of congenital hypothyroidism is about 1 in 3000 and two-thirds of the cases are due to dysgenesis. These prevalence rates are similar to those obtained by other screening programs that use a similar primary TSH strategy.²⁵⁻²⁸ Programmes that adopt the primary T4, supplemental TSH strategy report slightly lower prevalence rate of about 1 in 3500 to 1 in 4000 live births. Recall rates are determined by cut off values. With a cut off set at 40 mIU/L for cord serum, recall rates of less than 0.5% can be expected.

Almost all proven cases had cord TSH values that were clearly high (>40 mIU/L). The majority required only one visit for the diagnosis to be established. A preliminary audit of screening at National University Hospital revealed 212 babies (1.56%) with a cord TSH >25 mIU/L in 13,584 babies who were screened at National University Hospital between June 1994 and December 1998. Statistical evaluation of these results revealed a positive predictive value (PPV) of 0.04 (9/212). The likelihood ratio was 67 (13575/203). Assuming a pre-test probability of 1 in 3000, the post-test probability was 1 in 46 {67/(2999 + 67)} (Joseph R, unpublished observation). We have studied methods to lower the recall rate. One is to measure a supplemental free thyroxine (fT4) concentrations in the screening specimen of babies with a high cord TSH and recall only if the fT4 level is below 1 SD above the mean. This was shown to reduce the recall rates to about 0.7% with increase in the PPV but no loss of sensitivity.²⁹ The numbers in this study are small and need to be verified with a larger cohort of babies with elevated cord TSH levels.

The 5 cases that were identified in the pilot study 20 years ago have all completed the regular 12 years of formal schooling, are now working or undergoing post-secondary education and remain physically and emotionally healthy. Among the cohort of 10 babies that were diagnosed in National University Hospital from 1985 and who are in school now, only 1 is in the monolingual stream. Another 2 are experiencing difficulties in meeting academic requirements.

Hearing Impairment

At the National University Hospital, we have been screening newborns for hearing impairment from 1995, using initially the distraction method and from 1999, the

transient evoked otoacoustic emissions (TEOAE). The screening is conducted at the bedside, usually on the first day of life and normal response is assigned when the TEOAEs meet predetermined criteria. Babies with TEOAEs that do not meet predetermined criteria are rescreened using the same technique about 2 weeks later and once more at 6 weeks. Those failing at 6 weeks are considered to be tested positive on screening and referred to the Otolaryngology Department for formal diagnostic tests. Our screening rates have risen from an initial 97% to 99% currently and normal screening results are obtained in 95%. A 1 in 1036 incidence of severe hearing impairment was found in our newborn population of 6219 that were screened.³⁰ In all but 1 the diagnosis was made by 7 months of age and interventions set in place within 2 months of diagnosis. A specificity of 95% and PPV of 29% were obtained. A similar strategy was used at the Singapore General Hospital from 1998.³¹ Similar outcomes were obtained in the 4000 babies screened. The OAE screening is simple and cheap but has a high false positive rate (about 15% at the first screen on day 1 and then reducing by about 50 % with each retest). In contrast, screening using the automated auditory brain stem responses (AABR) technique is associated with a much lower false positive rate (about 5% on day 1 and reducing to about 1% by the 2nd retest). The instrument and the consumables are, however, are about 6 to 10 times the costs of the OAE screener and its consumables, respectively. In addition, the test takes longer to complete and the screener needs to be more experienced. An OAE with a supplemental AABR strategy may help to garner the benefits of both tools.

We have, since 2002, complemented the TEOAE screen with an early, automated auditory brainstem response (AABR) evaluation. This has reduced our referral rate for diagnostic evaluation to less than 1%. The outcome of the pilot programmes at National University Hospital and Singapore General Hospital has resulted in the initiation in 2002 of a pilot national study of screening for hearing impairment at the National University Hospital, Singapore General Hospital and the KK Women's and Children's Hospital. This study is supported by a central database that tracks every baby that has been screened, through recall, diagnosis and intervention, measuring outcomes at each of the stages.

Phenylketonuria (PKU)

Screening for PKU requires that the baby needs to have been sufficiently challenged with proteins. The standard phenylalanine assay is able to reliably discriminate between affected and healthy newborns only by about 72 to 96 hours of age. We have thus not initiated mass screening of newborns for PKU because the majority of the newborns go home within 48 hours of birth. Our screening for PKU

has been confined to babies of parents coming from countries where the disorder is screened for.

Organisation of Screening

Mass newborn screening in Singapore has certain unique features. The screenings have always been physician-initiated, physician-driven and hospital-based. There is no central screening laboratory and personnel have not been specifically hired to administer or manage the screening programme. The national policy is that screening for G6PD deficiency and congenital hypothyroidism will be considered as part of basic health care. However, the State does not, through legislation, mandate screening. The State meets a major proportion of the screening charges incurred by a subsidised patient. The primary role of the State was and continues to be the encouragement of the establishment of effective and efficient screening programmes. This is mainly through the provision of research grants at the stage when screening for a particular disease is being considered. The charge for screening varies slightly between the hospitals.

Projections for Screening

Our experience with screening has helped us identify certain principles. These include aiming for 100% coverage, ensuring affordability of the screening, the benefit of using sensitive and rapid assays, daily receipt of the screening results, initiation of the recall process before discharge, and personalised and customised counselling for parents of babies who tested positive.

For G6PD deficiency, studies are underway to ascertain the risks if any of an earlier discharge (<1 week) from hospital.

In the case of newborn screening for congenital hypothyroidism, we are exploring the likelihood of further reduction in recall rates by performing a second TSH assay in babies with a cord TSH >25 mIU/L at about 24 to 48 hours of age (i.e. just before hospital discharge). We were able to obtain an early sample (<48 hours and before hospital discharge) in 45 of the 66 that met recall criteria over a 17-month period of screening 4706 babies. In 39 babies, the TSH had already fallen to below 20 mIU/L (90th centile) and did not warrant further evaluation. Thus, only 6 babies needed a formal recall. The effective recall rate was 0.2%, a more than 80% reduction from the original 1.5% recall rate.³² We have continued with the use of a 2-stage screening, and recall rates have remained low. It is envisaged that with increasing numbers screened in this manner formal statistical analysis will prove the benefits of this strategy and facilitate a refinement in our national screening strategy for congenital hypothyroidism.

One often stated weakness of a primary TSH screening

strategy for congenital hypothyroidism is the inability to identify newborns with secondary or primary hypothyroidism manifesting with only a low T4 value. A number of programmes have reported on the nature and frequency of this situation. From the United States, the North West Regional Newborn Screening Programme, which uses a primary T4 and supplemental TSH strategy, reported an incidence of such abnormalities in less than 1 in 50,000 of the approximately 1.74 million babies they screened over a 20-year period.³³ The French audit of their primary TSH screening strategy revealed an incidence of 1 in 299,736 of hypothyroids with delayed rise in TSH levels.³⁴ More recently, researchers from Ontario used a receiver operating characteristic (ROC) plot to evaluate the diagnostic accuracy of a primary TSH screening strategy and the primary T₄ and supplemental TSH strategy. The ROC areas of the respective strategies were 0.9841 and 0.9557, respectively.³⁵ Nine out of 117 cases would have been misclassified as normal by the T4/TSH strategy while the TSH strategy correctly classified all 9 as being abnormal. Thus, the evidence for the superiority of the TSH strategy is very strong. Detecting the odd case of secondary hypothyroidism or primary hypothyroidism with a “delayed” TSH rise through the introduction of a parallel T4 screen will not only double the cost but also require follow-up of a very large number of patients, resulting in an increase in the number of parents who have been disturbed by the knowledge of a positive screening test, a substantial increase in the burden of those managing the follow-up and even reducing the credibility of the programme. As establishing a diagnosis of hypothyroidism in the absence of an abnormal TSH is very difficult and tedious, there may even be a tendency for an expedient diagnosis to be made and treatment inappropriately and unnecessarily introduced. The best way to deal with this group may be to accept that screening can never pick up every case and by having a high index of suspicion when symptoms are present.

The long-term outcome of hypothyroids detected by newborn screening, who in addition had an early onset (<3 months of age) of treatment, is far superior than that of the patient treated later. They function well within the normal range. Nevertheless, even in patients with early onset of treatment, abilities and academic performance are below that of age-matched controls or siblings.³⁶ They thus require surveillance and special attention during their school years.

We need to establish a central registry to enhance the gathering of comprehensive epidemiologic data that will help in understanding the aetiology, diagnostic features and outcome of patients identified by screening. This, in turn, will help to refine screening strategy, recall criteria and goals of therapy.

In the area of newborn hearing screening, we anticipate that by 2004, all newborns in Singapore will have access to

hearing screening. The task is to ensure that the screening programmes at the different hospitals achieve the quality indicators of screening rates of >95%, diagnostic referral rates of <4%, diagnosis by 3 months of age and interventions within 6 months of age as recommended by the Joint Committee on Infant Hearing (United States).³⁷

In a society with a norm of only 1 to 2 children per family, the value of a screening for other inborn errors of metabolism rises tremendously. We have observed that informed parents are willing to pay for efficient and effective screening services. The inborn errors of metabolism, though rare individually, are quite common when seen as a single group. The South Australian Neonatal Screening Centre has recently reported a 1 in 3862 (95% C.I., 3312 to 4450) incidence rate of inborn errors in a population of 54,079 newborn screening specimens.³⁸ All these illnesses are characterised by the likelihood of creating mental retardation, being detectable before the onset of damage by neonatal screening and the retardation being preventable by dietary modification.

As such, mass newborn screening for inborn errors of metabolism should be readily accepted and eagerly requested for by parents. Paediatricians are thus obliged to make this service available. Screening for a single disorder, such as PKU, may not be the best strategy, now that with tandem mass spectrometry, many metabolic disorders can be screened from a single spot of blood and at minimal cost increments.³⁹ The sensitivity of the measurements are such that babies with most metabolic disorders can be picked up as early as 24 to 48 hours of birth. It used to be taught that PKU is rare in the Chinese when compared to the Caucasian incidence of 1 in 16,000. Screening results from China have shown that this is not true (1:14,767 out of a screened population of 1.1 million) and the disease is just as common in the Chinese.⁴⁰ Thus, the setting up in Singapore of a screening service for inborn errors using tandem mass spectrometry will be the next step in the expansion of newborn screening. This will require investment in state-of-the-art equipment, appointing dedicated technologists, developing access to reference laboratories for confirmation of diagnosis and training clinicians for the comprehensive management of the affected child and its family. Our current cord screening programme for G6PD deficiency and congenital hypothyroidism will also need to be integrated into a day-2 screening. Since our annual births would use up only about 50% of the capacity of such a screening tool, we will be able to offer the services to patients in the region.

Amidst the burden of meeting basic health care of Singaporean children, the time has come for advances to be made. Expanded mass newborn screening and comprehensive treatment and follow-up of cases will be one of the fronts of the advance.

REFERENCES

- Guthrie R, Susi A. A simple phenylalanine method for detecting phenylketonuria in large populations of newborn infants. *Pediatrics* 1963; 32:338-43.
- Dussault J H, Laberge C. Thyroxine (T4) determination in dried blood by radioimmunoassay: A screening method for neonatal hypothyroidism. *Union Med Can* 1973; 102:2062-4.
- Wilson J M G, Jugner G. Principles and practice of screening for disease. Public Health Paper WHO 1968:34.
- Wald N J. Antenatal and neonatal screening. Oxford: Oxford University Press, 1984.
- Chace D H, Kalas T A, Naylor E W. The application of tandem mass spectrometry to neonatal screening for inherited disorders of intermediary metabolism. *Annu Rev Genom Hum Genet* 2002; 3:17-45.
- Newborn Screening Task Force. Serving the family from birth to the medical home. *Pediatrics* 2000; 106:S383-427.
- Statement of the Council of Regional Networks for Genetic Services (CORN). *J Pediatr* 2000; 137:S1-46.
- Wong H B. Kernicterus not associated with haemolytic disease. *Arch Dis Child* 1957; 32:85-9.
- Wong H B. Hyperbilirubinaemia and kernicterus in Singapore. *J Singapore Paediatr Soc* 1964; 6:1-6.
- Wong H B. Singapore kernicterus—the position in 1965. *J Singapore Paediatr Soc* 1965; 7:35-43.
- Wong H B. A surveillance system to prevent kernicterus in Singapore infants. *J Singapore Paediatr Soc* 1975; 17:1-9.
- Brown W R, Wong H B. Hyperbilirubinemia and kernicterus in glucose-6-phosphate-dehydrogenase deficient infants in Singapore. *Pediatrics* 1968; 41:1055-62.
- Wong H B. Erythrocytic glucose-6-phosphate dehydrogenase deficiency. *J Singapore Paediatr Soc* 1983; 25:6-13.
- Joseph R, Ho L Y, Gomez J M, Rajadurai V S, Sivasankaran S, Yip Y Y. Mass newborn screening for glucose-6-phosphate dehydrogenase deficiency in Singapore. *Southeast Asian J Trop Med Pub Health* 1999; 30:70-1.
- Quak S H, Saha N, Tay J S. Glucose-6-phosphate dehydrogenase deficiency in Singapore. *Ann Acad Med Singapore* 1996; 25:45-8.
- Tan K L. Glucose-6-phosphate dehydrogenase deficiency status and neonatal jaundice. *Arch Dis Child* 1981; 56:874-7.
- Kaplan M, Hammerman C, Feldman R, Brisk R. PredischARGE bilirubin screening in glucose-6-phosphate dehydrogenase deficient neonates. *Pediatrics* 2000; 105:533-7.
- Ho N K. Neonatal jaundice—a second 4-year experience in Toa Payoh Hospital (1986-1990). *J Singapore Paediatr Soc* 1999; 33:149-55.
- Lim H H, Daniel M, Lee J, Tan M C. Predicting significant hyperbilirubinemia and early discharge for glucose-6-phosphate dehydrogenase deficient newborns. *Ann Acad Med Singapore* 2003; 32:257-61.
- Yeo P P B, Joseph R, Chng K P, Chua D, Thai A C, Ng C S N, et al. Screening programme for congenital hypothyroidism in Singapore. In: Naruse H, Irie M, editors. *Neonatal Screening*. Amsterdam: Elsevier Science Publishers, 1993:113-4.
- Joseph R, Aw T C, Koay S C, Tan K L. Congenital hypothyroidism—screening strategies. Book of Abstracts of the 5th Congress of the Asean Federation of Endocrine Societies; 1989 Nov 30-Dec 3; Singapore. Singapore: Endocrine and Metabolic Society of Singapore and Academy of Medicine, Singapore, 1989:65.
- Joseph R, Ho L Y, Gomez J M, Ikshuvanam M, Aw T C, Aw S E, et al. Non isotopic cord serum screening for congenital hypothyroidism in Singapore—the TSH and T4 Strategy. In: Wilcken B, Webster S, editors. *Screening in the Nineties. Proceedings of the 8th International Neonatal Screening Symposium*; 1991 Nov 12-15; Leura, NSW. Australia: 8th International Screening Symposium, 1991:69-70.
- Dussault J H, Morissette J. Analysis of the TSH levels measured by a screening program in regard to the day of screening. Book of Abstracts of the 9th International Neonatal Symposium and Second Meeting of the International Society for Neonatal Screening. 1993 September 13-17; Lille, France. Lille: International Neonatal Symposium and International Society for Neonatal Screening, 1993:73.
- Joseph R, Ho L Y, Gomez J M, Rajadurai V S, Sivasankaran S, Yip Y Y. Newborn screening in Singapore. *Southeast Asian J Trop Med Pub Health* 1999; 30:23-4.
- Naruse H. Establishment of screening systems in East Asia. *Southeast Asian J Trop Med Pub Health* 1999; 30:17-9.
- Wilcken B. Neonatal screening in Australia. *Southeast Asian J Trop Med Pub Health* 1999; 30:41-2.
- Fagela-Domingo C, Padilla C D, Cutiongco E M for the Philippine Newborn Screening Study Group. Screening for congenital hypothyroidism (CH) among Filipino newborn infants. *Southeast Asian J Trop Med Pub Health* 1999; 30:20-2.
- Thaithumyanon P, Srivuthana S, Poshychinda M. Neonatal screening for hypothyroidism at a university hospital in Thailand. *Southeast Asian J Trop Med Pub Health* 1999; 30:25-7.
- Joseph R, Aw T C, Tan K L. Free thyroxine as a supplement to thyrotrophin in cord screening for hypothyroidism. *Ann Acad Med Singapore* 1993; 22:549-52.
- Joseph R, Low K T, Tan K K, Ng P, Tunnel J, Mathew S. Mass newborn screening for hearing impairment in Singapore. Book of Abstracts of the 2nd International Conference on Newborn Hearing Screening, Diagnosis and Intervention; 2002 May 30-June 1; Villa Erba (Como), Italy. Milan: Institute of Biomedical Engineering CNR, 2002:51.
- Ho S K Y, Lian W B, Yeo C L, Ho L Y, Burgess R, Low W K. Universal newborn hearing screening: A Singapore experience. Book of Abstracts of the 2nd International Conference on Newborn Hearing Screening, Diagnosis and Intervention; 2002 May 30-June 1; Villa Erba (Como), Italy. Milan: Institute of Biomedical Engineering CNR, 2002:124.
- Joseph R, Tan K L. Value of early repeat TSH determination in newborns with elevated cord serum TSH levels. In: Lam S T S, Pang C C P, editors. *Neonatal and perinatal screening—the Asian Pacific perspective*. Hong Kong: The Chinese University Press, 1996:133-6.
- Hunter M K, Mandel S H, Sesser D E, Miyabira R S, Rien L, Skeels M R, et al. Follow up of newborns with low thyroxine and non elevated thyroid-stimulating hormone - screening concentrations: results of the 20 year experience in the Northwest Regional Newborn Screening Program. *J Pediatr* 1998; 132:70-4.
- Leger J. Screening for congenital hypothyroidism in France. Misdiagnosed cases: collaborative study of screening centres in France. *Eur J Pediatr* 1990; 149:605-7.
- Wang S T, Pizzolato S, Demshar H P. Diagnostic effectiveness of TSH screening and of T₄ with secondary TSH screening for newborn congenital hypothyroidism. *Clin Chim Acta* 1998; 274:151-8.
- Rovet J F. Long term neurophysiological sequelae of early-treated congenital hypothyroidism: effect in adolescence. *Acta Paediatr Suppl* 1999; 432:88-95.
- Year 2000 position statement: principles and guidelines for early hearing detection and intervention programs. Joint Committee on Infant Hearing, American Academy of Audiology, American Academy of Pediatrics, American Speech-Language-Hearing Association, and Directors of Speech and Hearing Programs in State Health and Welfare Agencies. *Pediatrics* 2000; 106:798-817.
- Ranieri E, Geracce R L, Metz M, Bartlett B, Barnard K, Harrison J R, et al. Performance of the South Australian expanded neonatal screening programme using tandem mass spectrometry: results from the first 2.5 years. Abstract Book of the 4th Asia Pacific Regional Meeting of the International Society for Neonatal Screening and the 1st Annual Convention of the Newborn Screening Society of the Philippines; 2001 Oct 17-19; Mandaluyong City, Philippines. Manila: International Society for Neonatal Screening and Newborn Screening Society of the Philippines, 2001:PS-III A-1.
- Insinga R P, Laessig R H, Hoffman G L. Newborn screening with tandem mass spectrometry: examining its cost-effectiveness in the Wisconsin Newborn Screening Panel. *J Pediatr* 2002; 141:524-31.
- Fan G X, Jun Y, Rui-guan C. Neonatal screening of phenylketonuria and congenital hypothyroidism in China. *Southeast Asian J Trop Med Pub Health* 1999; 30:17-9.