

## **New-born screening in large teaching hospital-six years of experience.**

**Su-Boon Yong<sup>1#</sup>, Yun-Tzu Chiou<sup>2#</sup>, Hao-Jan Yang<sup>3</sup>, Ming-Tsung Lee<sup>4</sup>, Tung-Ming Chang<sup>5</sup>, Hui-Chien Lai<sup>1</sup>, Tsung-Hua Wu<sup>1</sup>, Kuender D Yang<sup>6,7,8,9\*</sup>**

<sup>1</sup>Department of Pediatrics, Show Chwan Memorial Hospital, Changhua, Taiwan

<sup>2</sup>Department of Nursing, Chang Bing Show Chwan Memorial Hospital, Changhua, Taiwan

<sup>3</sup>Department of Public Health, Chung Shan Medical University, Taichung, Taiwan

<sup>4</sup>Research Assistant Center, Show Chwan Health Care System, Changhua, Taiwan

<sup>5</sup>Department of Pediatrics, Changhua Christian Children's Hospital, Changhua, Taiwan

<sup>6</sup>Institute of Clinical Medicine, National Yang-Ming University, Taiwan

<sup>7</sup>Department of Medical Research, MacKay Memorial Hospital, Taipei, Taiwan

<sup>8</sup>Department of Pediatrics, MacKay Memorial Hospital, Taipei, Taiwan

<sup>9</sup>Institute of Biomedical Sciences, MacKay Medical College, New Taipei, Taiwan

#These authors contributed equally to this work

### **Abstract**

**Introduction:** A nationwide new-born screening program was established in Taiwan in 1984, including screening for Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency. This study aimed to investigate the attendance rate and confirmation rate of G6PD deficiency screening, the rate of non-G6PD deficiency-related neonatal diseases, and to compare hospitalization and the length of hospital stay between G6PD-positive newborns and the matched controls.

**Material and methods:** Between January 2008 and December 2013, 3,517 neonates were screened at our hospital. We retrospectively analysed data on the attendance rate and confirmation rate of G6PD deficiency and non-G6PD deficiency-related neonatal diseases. We also compared the risk of hospitalization and length of stay of the newborns found to be positive for G6PD deficiency in the screening program and the matched controls.

**Results:** The most common disease in the 3,517 screened newborns was G6PD deficiency. The positive attendance rate of G6PD deficiency was 2.76%, and the positive confirmation rate was 1.45%. There were no significant differences in the risk of hospitalization between the newborns who were initially screened as being positive for G6PD deficiency (OR: 0.92, 95% CI 0.523-1.619) and those confirmed to have G6PD deficiency (OR: 1.172, 95% CI 0.537-2.558) over the matched controls.

**Conclusions:** Our results suggest the benefits of newborn screening programs, and the importance of establishing specific guidelines to regulate the parental consent process and education is crucial to relieve the stress and anxiety of the parents of newborns.

**Keywords:** Newborn screening, Glucose-6-phosphate dehydrogenase (G6PD) deficiency, Effectiveness, Hospitalization.

*Accepted on August 17, 2017*

### **Introduction**

A limited newborn screening program was launched in Taiwan in 1984, which had expanded to an attendance rate of 80% by 1990. As the program is covered by the National Health Insurance system, the screening program now covers more than 99% of the neonates in Taiwan [1,2]. The USA

successfully began a newborn screening program in the Asia Pacific region in the mid-1960s, however many developing countries are just beginning to implement mass screening programs [3,4]. Therefore, our experience may be helpful to countries planning to implement newborn screening programs.

Many challenges remain for newborn screening programs, including ethical, legal, and social concerns. Newborn screening is one of the key health care priorities of many governments, however parents play a vital role in deciding whether or not their child should receive screening, and this decision is usually based over concerns about the test results. Therefore, issues relating to obtaining parental consent for newborn screening and the delivery of health education to parents are becoming increasingly important [5,6].

A majority of the newborns in Taiwan receive neonatal screening within three days after birth. Blood specimens are collected from the sides of newborns' heels at the hospital or clinic where they are born, placed on filter paper, dried and then shipped to the Newborn Screening Center of the Department of Medical Genetics, National Taiwan University Hospital or other screening centers for screening tests [2].

There is a well-organized newborn screening system in our hospital which includes four stages: specimen collection, screening, follow-up and re-examination, and confirmatory diagnosis. The staffs cooperate during each stage to identify high-risk cases, and then a confirmatory diagnosis is made as quickly as possible to identify cases. Upon confirmation, the Department of Medical Genetics and Pediatrics Department provide appropriate treatment and genetic counselling.

The most common manifestations of G6PD deficiency are neonatal jaundice, acute hemolysis, and kernicterus [3,5,7], which can result in hospitalization and even life-threatening conditions. Advanced screening tests make it possible to identify positive cases early, which allows clinicians to educate the patients and to implement appropriate preventative measures thereby avoiding complications and serious adverse effects. In this manner, subsequent treatment and hospitalizations can be reduced, lowering the cost of care.

The aim of this study was to retrospectively analyse the positive attendance rate and confirmation rate of G6PD deficiency as well as the rate of non-G6PD deficiency-related diseases in a large teaching hospital during a consecutive six-year period. We then compared the effectiveness of the newborn screening program at our hospital with national data with the goal of gaining an in-depth understanding of the positive rates of screened diseases to allow for the implementation of appropriate health education programs about screening based on these findings. In addition, we compared differences in the number of hospitalizations and length of hospital stay between newborns with G6PD and the general population.

## Material and Methods

### *Subjects and study design*

We retrospectively collected screening data and admission data from the baby room, sick baby room, and newborn intensive care unit at a large teaching hospital in central Taiwan from January 2008 to December 2013. All neonates with screening data during this period were included. The collected data

included results of the screening tests and results of the confirmatory tests for G6PD deficiency, and details of other non-G6PD deficiency-related neonatal diseases. For the admission data, each subject who was positive for G6PD in the initial screening program was matched to a general newborn born at our hospital on the same day with the same gender. This study has been approved by the Institutional Review Board of Show Chwan Memorial Hospital (No. 1030603).

### *Screening*

Collection of the blood specimens for screening was carried out 48 h after birth or 24 h after lactation, and the details of screening program were explained to the mothers at this time. The blood specimens were collected from the sides of the newborns' heels, placed on filter paper, dried and then sent to the newborn screening center [2]. The results of the primary screening tests were usually received within one month. If the first test result was positive, the parents were asked to bring their infant back for re-examination. If the result of the re-examination was positive, the parents were advised to take their infant to a referral hospital or clinic for further confirmation. In addition to the individual tests for some disorders, phenylketonuria, homocystinuria, maple syrup urine disease, methylmalonic acidemia, dehydrogenase deficiency, isovaleric acidemia, glutaric aciduria type 1, and other fatty acid oxidation defects were identified using tandem mass spectrometry [2,8]. G6PD activity was measured using the fluorescence spot test with dried blood samples on filter paper. The G6PD/6PGD rate of venous blood samples was further examined for confirmation [9-11].

### *Data analysis*

Data on the annual outcomes of the screened diseases were presented as the number of screened positive cases, positive attendance rate, number of confirmed cases, confirmation rate, and 95% confidence intervals. Odds ratios were estimated and paired T tests were performed to compare the rate of hospitalization and length of hospital stay between the newborns that were found to be positive for G6PD through the screening program and their matched general population using SPSS for Windows, Version 14.0 (Chicago, SPSS Inc.).

## Results

A total of 3,680 neonates were born in our hospital between January 2008 and December 2013, of whom 3,517 were screened. The attendance rates ranged from 92.1% in 2008 to 97.1% in 2013, with a steadily increasing trend. However, the coverage rates were lower than those of the national attendance rates which ranged from 98.7% in 2008 to 99.9% in 2013. The national attendance rate reached 99.9% in 2009, almost covering all of the neonates nationwide, and then varied very slightly from 2009 to 2013.

The positive screening and confirmation rates of the newborn screening program at our hospital from 2008 to 2013 are shown in Table 1. The most common disease identified by the

screening program was G6PD deficiency, and 97 neonates had a positive test result for G6PD deficiency during initial screening, for a positive attendance rate of 2.76% (95% Confidence Interval (CI) 2.27-3.36%). Among these 97 newborns, 51 were confirmed to have G6PD deficiency, for a confirmation rate of 1.45% (95% CI 1.10-1.90%). A total of 184 neonates had positive attendance results for non-G6PD deficiency-related diseases (positive attendance rate, 5.23%, 95% CI 4.54-6.02%), of whom 12 received a confirmatory diagnosis for a confirmation rate of 0.34% (95% CI 0.19-0.059%). The most common non-G6PD deficiency-related disorder was congenital hypothyroidism (58 newborns, positive attendance rate 1.65% (95% CI 1.28-2.13%)), of whom only four (0.11%, 95% CI 0.04-0.29%) received a confirmatory diagnosis. Thirty-four newborns initially tested positive for Fabry disease (positive attendance rate 0.97% (95% CI 0.70-1.35%)), of whom only two had a confirmatory diagnosis (0.06% (95% CI 0.02-0.21%)). Thirty neonates were initially positive for galactosemia (positive attendance rate 0.85% (95% CI 0.60-1.21%)), none of whom received a confirmatory diagnosis. The fourth most common non-G6PD deficiency-related disease was Pompe disease, followed by congenital adrenal hyperplasia with positive attendance rates of 0.82% (95% CI 0.57-1.18%) and 0.31% (95% CI 0.17-0.56%), respectively. Of these cases, four were confirmed to have Pompe disease (0.11% (95% CI 0.04-0.29%)). Fewer than 10 other non-G6PD deficiency-related disorders were identified during initial screening, including severe combined immunodeficiency, C3, and Gaucher's disease.

We also analysed the annual positive attendance and confirmation rates of G6PD deficiency in our hospital as shown in Table 1. The primary positive attendance rate was high in 2008 at 3.94% (95% CI 2.44-6.30%), however the rate dropped sharply to 1.2% (95% CI 0.55-2.60%) in 2009, and then varied from 1.99% to 4.03% during the rest of the six-year study period. The confirmation rate was the second highest in 2008 at 1.97% (95% CI 1.00-3.84%), however it dropped dramatically to 0.60% (95% CI 0.20-1.75%) in 2009, and then varied from 1.17% to 1.99% from 2010 to 2013. According to the nationwide data from 2008 to 2013, 1:54 neonates (1.85%) had positive attendance results for G6PD deficiency compared to 1:36 neonates (2.78%) in our study. The positive attendance rate of G6PD deficiency was therefore higher in our hospital than nationally. With regards to the confirmatory diagnosis of G6PD deficiency using the G6PD ratio test, only national data from 2012 were retrieved, with 1:51 confirmed cases (1.96%) compared to 1:85 (1.17%) in our study. The confirmation rate of G6PD deficiency nationally in 2012 was therefore higher than in our hospital but similar to the rates in our hospital in 2008, 2010, and 2013.

We further analysed the confirmation rates of G6PD deficiency between 2008 and 2013. Positive predictive values were calculated as the number of true positive cases divided by the number of positive screening cases, which indicated the probability of being a confirmed case after an initially positive attendance result. It was impractical to recall the newborns with negative attendance results for re-examinations, resulting

in the calculation of sensitivity and negative predictive value were less meaningful. Specificity ranged from 0.951 to 0.999. The overall positive predictive value of G6PD screening was 0.526 between 2008 and 2013, and ranged from 0.304 in 2011 to 0.692 in 2010. The positive predictive value of screening for other non-G6PD deficiency-related diseases ranged from 0.065 to 0.222 over the six years. The specificity for G6PD deficiency was 0.987 with a positive predictive value of 0.526, and the specificity for non-G6PD deficiency-related diseases was 0.951 with a positive predictive value of 0.065. During this period, 51 (51/97) true positive results and 17 (17/97) false positive results were noted in screening for G6PD deficiency. The number of false positive cases was relatively high in 2011 (11 neonates), with four and two false positive cases in 2013 and 2008, respectively. No false positive cases were noted in 2009, 2010, or 2012. The parents of the other 29 neonates refused further evaluations.

The analysis of the risk of hospitalization for the newborns with G6PD deficiency compared to the matched general population is demonstrated in Table 2. Ninety-seven newborns with positive attendance results for G6PD deficiency were matched to general newborns born at our hospital, and the 51 neonates with confirmed G6PD deficiency were also matched 1:1 with general infants born at our hospital. Overall, 52.6% of the newborns with positive attendance results for G6PD deficiency were hospitalized, compared to 54.6% of the matched general population from 2008 to 2013 (odds ratio 0.92 (95% CI 0.523-1.619)). For the confirmed cases with G6PD deficiency, 56.9% were hospitalized compared to 52.9% of the matched general population over the six-year period (odds ratio 1.172 (95% CI 0.537-2.558)). There were no significant differences in the risk of hospitalization for any disease between the newborns with a positive attendance result of G6PD deficiency and those with confirmed G6PD deficiency over their corresponding matched general population.

We also analysed differences in hospitalization for jaundice, and found that 11.3% of the newborns with positive attendance results for G6PD deficiency were admitted for jaundice compared to 7.2% of the matched general population (odds ratio 1.645 (95% CI 0.609-4.438)). Of the confirmed cases of G6PD deficiency, 17.6% were hospitalized for jaundice, compared to 9.8% of the matched general population (odds ratio 1.971 (95% CI 0.612-6.355)). There were no significant differences in the risk of hospitalization for jaundice between the newborns with a positive attendance result of G6PD deficiency and those with confirmed G6PD deficiency over their corresponding matched general population.

We further compared the total length of hospital stay in 2008-2013 for the newborns with a positive attendance result of G6PD deficiency and those with confirmed G6PD deficiency to their corresponding matched general population (Table 2). The mean length of stay for the newborns with a positive attendance result of G6PD deficiency was 11.12 d (SD=13.80), comparing to 10.93 d (SD=10.47) for the matched general population. There was no significant difference between the two groups ( $t=0.107$ ,  $p=0.915$ ). For the confirmed

cases of G6PD deficiency, the average length of hospital stay was 13.39 d (SD=17.62), compared to 10.43 d (SD=9.42) for the matched general population. There was no significant difference between the confirmed cases and their matched general population ( $t=0.997$ ,  $p=0.324$ ). There were no

significant differences in the average length of hospital stay between the newborns with a positive attendance result of G6PD deficiency and those with confirmed G6PD deficiency over their corresponding matched general population.

**Table 1.** Positive attendance and confirmation rates of the newborn screening program in a teaching hospital from 2008 to 2013.

Disease	No. of positive attendance cases	Positive attendance rate	95% CI	No. of confirmed cases	Confirmation rate	95% CI	Positive predictive value
G6PD Deficiency	97	2.76%	2.27-3.36%	51	1.45%	1.10-1.90%	0.526
Year							
2008	16	3.94%	2.44-6.30%	8	1.97%	1.00-3.84%	0.5
2009	6	1.20%	0.55-2.60%	3	0.60%	0.20-1.75%	0.5
2010	13	2.69%	1.58-4.55%	9	1.86%	0.98-3.50%	0.693
2011	23	4.03%	2.70-5.97%	7	1.23%	0.60-2.51%	0.304
2012	17	1.99%	1.25-3.16%	10	1.17%	0.64-2.14%	0.588
2013	22	3.13%	2.08-4.69%	14	1.99%	1.19-3.31%	0.636
Non-G6PD Deficiency-Related Diseases							
CHT	58	1.65%	1.28-2.13%	4	0.11%	0.04-0.29%	0.069
Fabry	34	0.97%	0.70-1.35%	2	0.06%	0.02-0.21%	0.059
GAL	30	0.85%	0.60-1.21%	0			0
GAA	29	0.82%	0.57-1.18%	4	0.11%	0.04-0.29%	0.138
CAH	11	0.31%	0.17-0.56%	0			0
SCID	6	0.17%	0.08-0.37%	0			0
C3	5	0.14%	0.06-0.33%	0			0
ABG	2	0.06%	0.02-0.21%	0			0
Others	9	0.26%	0.14-0.49%	2	0.06%	0.02-0.21%	0.222
Subtotal	184	5.23%	4.54-6.02%	12	0.34%	0.19-0.59%	0.065

No. of screened neonates=3517. Positive predictive value=True positive/No. of positive screened cases. G6PD Deficiency: Glucose-6-Phosphate Dehydrogenase Deficiency; CHT: Congenital Hypothyroidism; GAL: Galactosemia; GAA: Pompe Disease; CAH: Congenital Adrenal Hyperplasia; SCID: Severe Combined Immunodeficiency; C3: Propionic Acidemia; ABG: Gaucher's Disease.

**Table 2.** Comparisons of hospitalization and length of hospital stay of newborns with positive attendance results for G6PD deficiency and confirmed cases with their matched controls.

		Positive cases	Control	Total N (%)	Odds ratio	95% confidence interval	
		N (%)	N (%)			Lower	Upper
G6PD screen test							
		51	53	104	0.92	0.523	1.619
	Yes	52.60%	54.60%	53.60%			
		46	44	90			
Hospitalization for any diseases	No	47.40%	45.40%	46.40%			
Total		97	97	194			

		100.00%	100.00%	100.00%			
LoS* (mean ± SD)		11.1 ± 13.80	10.9 ± 10.47	(t=0.107, p=0.915)			
		11	7	18	1.645	0.609	4.438
	Yes	11.30%	7.20%	9.30%			
		86	90	176			
Hospitalization for jaundice	No	88.70%	92.80%	90.70%			
		97	97	194			
Total		100.00%	100.00%	100.00%			
G6PD confirmed							
		29	27	56	1.172	0.537	2.558
	Yes	56.90%	52.90%	54.90%			
		22	24	46			
Hospitalization for any diseases	No	43.10%	47.10%	45.10%			
		51	51	102			
Total		100.00%	100.00%	100.00%			
LoS* (mean ± SD)		13.4 ± 17.62	10.4 ± 9.42	(t=0.997, p=0.324)			
		9	5	14	1.971	0.612	6.355
	Yes	17.60%	9.80%	13.70%			
		42	46	88			
Hospitalization for jaundice	No	82.40%	90.20%	86.30%			
		51	51	102			
Total		100.00%	100.00%	100.00%			

\*LoS: Length of Hospital Stay.

## Discussion

A total of 3,680 neonates were born in our hospital between January 2008 and December 2013, of whom 3,517 were screened. The attendance rate was 97.1% in 2013, with a steadily increasing trend. The most common disease detected by the neonatal screening program was G6PD deficiency, with a positive attendance rate of 2.76%. Over the six-year period, there were 51 true positive cases and 17 false positive cases of G6PD deficiency. There were no significant differences in the number of hospitalizations and length of hospital stay between those with G6PD deficiency and their matched general population.

G6PD deficiency is the most common congenital metabolic disease in Taiwan. It is characterized by neonatal jaundice and acute hemolytic anemia, and if not managed adequately can result in death and poor neurological outcomes [5,7,8,12]. A mass neonatal screening program for G6PD deficiency using the fluorometric spot test was launched with a pilot program in Taiwan in 1984, with nationwide screening being implemented in July 1987. A follow-up network was also established, comprising of 18 referral hospitals throughout Taiwan for

confirmatory testing, medical care and genetic counselling. G6PD deficiency is diagnosed with active enzyme G6PD reaction semi-quantitative fluorescence analysis of neonatal blood spots, with weak fluorescence indicating a positive result [2,8]. If the initial attendance result is positive, the parents are asked to return to the hospital for a confirmatory test.

The attendance rates in our hospital were lower than the national data, which covered almost all of the neonates in Taiwan [13]. A possible reason is that the educational level of the residents near our hospital could be lower than average. For our hospital is located in a coastal area, the parents of newborns may be unwilling to undergo or be unaware of the screening program due to the lack of appropriate knowledge. A previous study suggested that promoting screening programs and educating the parents are important [3]. Another possible reason is that accessibility to health care services in Taiwan is high. Therefore, some of the parents may have chosen a hospital or clinic closer to their place of residence to undergo further examinations. The steady trend of an increase in the attendance rate over the study period in our hospital indicates that our staff worked hard to contact the parents and advise them of the screening program. Around half of the newborns

with a positive attendance result for G6PD deficiency were later confirmed to have the disease (51 of 97), indicating a high positive predictive value and specificity of the screening test. However, only 12 of 184 neonates with a positive attendance result for non-G6PD deficiency-related diseases subsequently received a confirmatory diagnosis, a rate far below that of G6PD deficiency. It seemed that there was a gap of the efficiencies between the screening tests of G6PD deficiency and non-G6PD deficiency disorders, which may be due to the longer experience and higher accuracy of the screening tests of G6PD deficiency.

Chien et al. reported that the annual incidence of G6PD deficiency decreased from 1.94% in 1996 to 1.61% in 2005, but that the incidence was significantly higher in male neonates than in female neonates (2.81% (2.57-3.07%) vs. 0.7% (0.45-0.95%), respectively) [10]. Another study reported the results of G6PD screening using the fluorescence spot test in China, with positive rates of G6PD deficiency of 4.2% and 5.2% for all neonates and male newborns, respectively, and confirmation rates using the G6PD/6PGD ratio of 86.8% and 100% [14]. Another study reported that the overall positive predictive values of screening for G6PD deficiency were 0.53 between 2008 and 2013, and 0.30 in 2011 to 0.69 in 2010, compared to 0.07 to 0.22 over the six-year study period for non-G6PD deficiency-related diseases. The positive predictive values for screening for non-G6PD deficiency-related diseases were therefore lower than for G6PD deficiency, but still higher than those reported in a nationwide survey, but similar to programs in other countries [2].

The most common clinical presentations of G6PD deficiency are neonatal jaundice, acute hemolysis, and kernicterus [3,5,7], which may lead to critical conditions requiring costly treatment and hospitalization. Effective newborn screening programs should be able to detect affected individuals to help prevent the need for treatment and hospitalization *via* methods such as avoiding specific food, drugs, and infections. In addition, some medications may trigger severe complications in patients with G6PD deficiency, and this in itself may require treatment and hospitalization thereby incurring healthcare resources and costs and thus increasing the public health burden [15].

A previous study investigated the relationships between G6PD deficiency and bacterial infections, and concluded that a compromised host defense mechanism in patients with G6PD deficiency may be related to serious infections, and that this may increase the rate of hospitalization in such patients [16]. Another study compared the rates of hospitalization for acute hemolysis in patients with G6PD deficiency before and after the implementation of a screening program, and found that a G6PD screening program effectively reduced the rate of hospitalization for acute hemolysis [17]. Munyanganizi et al. [18] also suggested that newborn screening programs including those for G6PD deficiency could reduce the incidence of severe episodes of hemolysis and hospitalization rates.

Our results indicated no significant difference in the risk of hospitalization between the neonates with G6PD deficiency and their matched general population. In addition, there was no

significant difference in the length of hospital stay between the two groups. These findings are likely due to the newborn screening program, in that the neonates who received positive attendance results for G6PD deficiency received suitable interventions to prevent acute hemolysis and kernicterus and thus the need for hospitalization.

The fluorescence spot test is widely used in neonatal screening programs for G6PD deficiency because of its high accuracy, applicability, and simplicity. Moreover, dried blood samples on filter paper can be tested quickly [9-11]. The early diagnosis and treatment of G6PD deficiency is an important issue which may significantly reduce morbidity and mortality of the affected individuals [4].

Many challenges remain to be overcome before newborn screening programs can be expanded. Some of the disorders included in newborn screening programs may be mild or even asymptomatic, and some rare disorders cannot currently be treated. Moreover, some current treatments have harmful effects, and the expense of treatment may be difficult to manage over the long term. In addition, positive attendance results, whether false or true, increase the stress and anxiety of parents.

There are several limitations to this study. We retrospectively collected the screening and admissions data from 2008 to 2013, and the accuracy of these data was subject to the completeness of the medical records. Owing to the high accessibility of health care services in Taiwan, the parents may have taken their newborns to other hospitals or clinics for newborn screening, which may have led to the underestimation of the attendance rate of the newborn screening program and the frequency and length of hospitalization. In addition, we were unable to ask negative screening cases to return for a confirmatory diagnosis. This resulted in zero false negative cases and may have resulted in the high sensitivity and high negative predictive values for the screening. Furthermore, this study was conducted at a large teaching hospital in Taiwan, and the results may not be applicable to hospitals in other countries. We collected the admissions data of the infants born between 2008 and 2013, however, the number of admissions of the infants born late this period may have been underestimated because the observation period was too short.

## Conclusions

This study demonstrated the results of the primary screen test and final confirmatory diagnosis of a newborn screening program designed for G6PD deficiency. There were no significant differences in the risk of hospitalization between G6PD deficient newborns and the matched general population. Our results suggest that the implementation of the screening program was comprehensive and effective. Establishing guidelines to regulate parental consent and to educate medical personnel and the parents of newborns is crucial to relieve the stress and anxiety of the parents.

## References

1. Chiang SH, Fan ML, Hsiao KJ. External quality assurance programme for newborn screening of glucose-6-phosphate dehydrogenase deficiency. *Ann Acad Med Singapore* 2008; 37: 84-87.
2. Niu DM, Chien YH, Chiang CC, Ho HC, Hwu WL, Kao SM. Nationwide survey of extended newborn screening by tandem mass spectrometry in Taiwan. *J Inherit Metab Dis* 2010; 33: 295-305.
3. Arain Y, Bhutani V. Prevention of kernicterus in South Asia: role of neonatal G6PD deficiency and its identification. *Indian J Pediatr* 2014; 81: 599-607.
4. Padilla CD, Therrell BL. Newborn screening in the Asia Pacific region. *J Inherit Metab Dis* 2007; 30: 490-506.
5. Watchko JF, Kaplan M, Stark AR, Stevenson DK, Bhutani VK. Should we screen newborns for glucose-6-phosphate dehydrogenase deficiency in the United States. *J Perinatol* 2013; 33: 499-504.
6. Wilcken B. Expanded newborn screening: reducing harm, assessing benefit. *J Inherit Metab Dis* 2010; 33: 205-210.
7. Cappellini MD, Fiorelli G. Glucose-6-phosphate dehydrogenase deficiency. *Lancet* 2008; 371: 64-74.
8. Huang HP, Chu KL, Chien YH, Wei ML, Wu ST, Wang SF. Tandem Mass Neonatal Screening in Taiwan-Report from One Center. *J Formosan Med Assoc* 2006; 105: 882-886.
9. Chiang SH, Wu KF, Liu TT, Wu SJ, Hsiao KJ. Quality assurance program for neonatal screening of glucose-6-phosphate dehydrogenase deficiency. *Southeast Asian J Trop Med Publ Health* 2003; 34: 130-134.
10. Chien YH, Lee NC, Wu ST, Liou JJ, Chen HC, Hwu WL. Changes in incidence and sex ratio of glucose-6-phosphate dehydrogenase deficiency by population drift in Taiwan. *Southeast Asian J Trop Med Publ Health* 2008; 39: 154-161.
11. Chiang SH, Wu SJ, Wu KF, Hsiao KJ. Neonatal screening for glucose-6-phosphate dehydrogenase deficiency in Taiwan. *Southeast Asian J Trop Med Publ Health* 1999; 30: 72-74.
12. Cheng SW, Chiu YW, Weng YH. Etiological analyses of marked neonatal hyperbilirubinemia in a single institution in Taiwan. *Chang Gung Med J* 2012; 35: 148-154.
13. Health Promotion Administration, Ministry of Health and Welfare, Taiwan. The statistics of neonatal screening for metabolic disorders in recent years (in Chinese) 2015.
14. Jiang J, Ma X, Song C, Lin B, Cao W, Wu S. Using the fluorescence spot test for neonatal screening of G6PD deficiency. *Southeast Asian J Trop Med Publ Health* 2003; 34: 140-142.
15. Peixoto HM, Brito MAM, Romero GAS, Monteiro WM, de Lacerda MVG, de Oliveira MRF. G6PD deficiency in male individuals infected by *Plasmodium vivax* malaria in the Brazilian Amazon: a cost study. *Malaria J* 2015; 14: 126.
16. Clark M, Root RK. Glucose-6-phosphate dehydrogenase deficiency and infection: a study of hospitalized patients in Iran. *Yale J Biol Med* 1979; 52: 169-179.
17. Cohan N, Karimi M, Khalili AH, Falahzadeh MH, Samadi B, Mahdavi MR. The efficacy of a neonatal screening programme in decreasing the hospitalization rate of patients with G6PD deficiency in southern Iran. *J Med Screening* 2010; 17: 66-67.
18. Munyanganizi R, Cotton F, Vertongen F, Gulbis B. Red blood cell disorders in Rwandese neonates: screening for sickle cell disease and glucose-6-phosphate dehydrogenase deficiency. *J Med Screening* 2006; 13: 129-131.

### \*Correspondence to

Kuender D Yang  
Department of Pediatrics  
Mackay Memorial Hospital  
Taiwan