Pulse oximetry with clinical assessment to screen for congenital heart disease in neonates in China: a prospective study

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Summary

Background Several pioneering studies have provided evidence for the introduction of universal pulse oximetry screening for critical congenital heart disease. However, whether the benefits of screening reported in studies from high-income countries would translate with similar success to low-income countries is unknown. We assessed the feasibility and reliability of pulse oximetry plus clinical assessment for detection of major congenital heart disease, especially critical congenital heart disease, in China.

Methods We did a pilot study at three hospitals in Shanghai to assess the accuracy of pulse oximetry plus clinical assessment for detection of congenital heart disease. We made a data collection plan before recruitment. We then undertook a large, prospective, and multicentre screening study in which we screened all consecutive newborn babies (aged 6–72 h) born at 18 hospitals in China between Aug 1, 2011, and Nov 30, 2012. Newborn babies with positive screen results (either an abnormal pulse oximetry or abnormal clinical assessment) were referred for echocardiography within 24 h of screening. We identified false-negative results by clinical follow-up and parents' feedback. We calculated sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios for pulse oximetry alone, and in combination with clinical assessment, for detection of major and critical congenital heart disease.

Findings In the pilot study, 6785 consecutive newborn babies were screened; 46 of 49 (94%) cases of asymptomatic major congenital heart disease and eight of eight (100%) cases of asymptomatic critical disease were detected by pulse oximetry and clinical assessment. In the prospective multicentre study, we screened 122 738 consecutive newborn babies (120 707 asymptomatic and 2031 symptomatic), and detected congenital heart disease in 1071 (157 critical and 330 major). In asymptomatic newborn babies, the sensitivity of pulse oximetry plus clinical assessment was 93·2% (95% CI 87·9–96·2) for critical congenital heart disease and 90·2% (86·4–93·0) for major disease. The addition of pulse oximetry to clinical assessment improved sensitivity for detection of critical congenital heart disease from 77·4% (95% CI 70·0–83·4) to 93·2% (87·9–96·2). The false-positive rate for detection of critical disease was 2·7% (3298 of 120 392) for clinical assessment alone and 0·3% (394 of 120 561) for pulse oximetry alone.

Interpretation Pulse oximetry plus clinical assessment is feasible and reliable for the detection of major congenital heart disease in newborn babies in China. This simple and accurate combined method should be used in maternity hospitals to screen for congenital heart disease.

Funding Key Clinical Research Project sponsored by Ministry of Health, Shanghai Public Health Three-Year Action Plan sponsored by Shanghai Municipal Government, and National Basic Research Project of China.

Published **Online** April 23, 2014 http://dx.doi.org/10.1016/S0140-6736(14)60198-7

See **Online/Comment** http://dx.doi.org/10.1016/S0140-6736(14)60575-4

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Introduction

Congenital heart defects are a leading cause of infant death in high-income countries, and affect eight of 1000 livebirths.[1] About one to two per 1000 newborn babies have critical congenital heart disease, which is defined as disease that causes death or needs invasive intervention in the neonatal period, and neonates with this disease benefit most from early detection.[2] During the past few years, several pioneering studies have provided compelling evidence for the addition of pulse oximetry to fetal ultrasound screening and routine clinical assessment as a complementary method for detection of critical congenital heart disease.[3–8] In view of strong supporting evidence, this method was considered in several high-income countries to detect critical disease.[9–12] However, many children born with simple but serious congenital heart disease (such as large ventricular septal defects) in low-income countries cannot be recognised early enough to avoid irreversible pulmonary vascular disease.[13,14] Therefore, all major congenital heart diseases (those causing death or requiring invasive intervention during infancy) should be regarded as main targets of neonatal screening in low-income countries.

Although favourable outcomes of studies of pulse oximetry in high-income countries might not predict similar success in low-income countries, we believed that lower prenatal and postnatal detection rates in low-income countries would increase the benefit of screening. However, pulse oximetry should not preclude routine clinical assessment, which can sometimes detect a

serious congenital heart disease before the development of hypoxia. China is the largest developing country in the world, with an annual birth rate of roughly 16 million.[15] Nearly 5·6% of newborn babies have a birth defect, 27% of which is congenital heart disease.[15] Because of a paucity of large-scale screening for neonatal congenital heart disease in low-income countries, whether pulse oximetry plus clinical assessment could lead to major progress in timely detection of serious disease in these countries might be difficult to establish. We aimed to assess the feasibility and reliability of pulse oximetry plus clinical assessment for detection of major congenital heart disease, especially critical congenital heart disease, in newborn babies in China.

Methods

Study design and participants

We did a pilot study in three hospitals in Shanghai (Songjiang Maternity Hospital, Minhang Maternity Hospital, and Songjiang District Central Hospital) between Feb 1, 2011, and July 31, 2011, to assess the practicability and accuracy of pulse oximetry plus clinical assessment screening for the detection of congenital heart disease in newborn babies. The three hospitals were selected as being representative of most birthing facilities in China. Findings of the pilot study showed that pulse oximetry used in conjunction with clinical assessment could be successfully implemented in common hospital settings with few barriers, and resulted in a high detection rate of major and critical congenital heart disease.

To verify the pilot study, we did a multicentre prospective screening study between Aug 31, 2011, and Nov 30, 2012, in 18 hospitals in China. Of the 18 hospitals, 12 were located in the east (two in Shanghai, three in Jiangsu Province, three in Zhejiang Province, two in Shandong Province, and two in Fujian Province), six in the west (one in Shanxi Province, one in Gansu Province, two in Guizhou Province, one in Sichuan Province, and one in Guangxi Province). 16 hospitals (89%) had echocardiography on site and the two without echocardiography stated that referral for cardiology consultation in a nearby facility could be immediately available. All consecutive newborn babies were eligible (irrespective of gestational age or neonatal intensive care unit status), but newborn babies with prenatally diagnosed congenital heart disease were excluded before screening with a postnatal echocardiogram.

This study was approved by ethics committee of Children's Hospital of Fudan University. Oral informed consent was obtained from the participating babies' parents.

Panel 1: **Indicators of clinical assessment**

Family history of congenital heart disease

- First degree relatives with congenital heart disease

Particular facial features

- Babies with the following distinct facial features should be assessed for possible cardiac abnormalities: a flattened facial profile, wide-set and down-slanting eyes, a protruding tongue, a deep groove and wide peaks in the upper lip, a short neck, and a low hairline on the back of the head

Heart murmur

- Loud or faint but immediately audible after the first day of life

Extracardiac malformation

- Malformations of craniofacial, genitourinary, musculoskeletal, respiratory, gastrointestinal, CNS, and spleen anomalies

Procedures

For the screening study, in the asymptomatic neonate cohort (without tachypnoea or cyanosis), a trained clinician did universal pulse oximetry screening with a new generation RAD-5v pulse oximeter (Masimo, Irvine, CA, USA) with a multisite reusable sensor (LNOP YI, Masimo). In the neonatal intensive care unit setting, disposable sensors (LNOP Inf-L, Masimo) were used. Testing was done in babies aged between 6 h and 72 h. We used measurement criteria proposed by the US Secretary of Health and Human Services to implement screening.[9] The clinician repeated pulse oximetry testing 4 h later if the first pulse oximeter oxygen saturation (SpO_2) measurement was between 90% and 95%. Screening was deemed positive if an SpO_2 of less than 95% was obtained both on the right hand and on either foot on two measures, separated by 4 h; a difference between the two extremities was more than 3% on two measures, separated by 4 h; or any measure was less than 90%.

The same clinician did clinical assessment just before pulse oximetry measurement, to ensure that the clinical assessment result would not be affected by knowledge of pulse oximetry test. If the SpO_2 was very low (<90%), the clinician would immediately know the result after clinical assessment and pulse oximetry test had been done. Four well defined components to the clinical assessment were recorded (panel 1), which were introduced as part of the study but not included in previous routine practice. We regarded any newborn baby with one of these abnormal findings to be positively screened.

In the symptomatic neonate cohort (with tachypnoea or cyanosis), all newborn babies were referred for echocardiography, irrespective of whether pulse oximetry or clinical assessment had been done (although clinicians were still requested to do these procedures). However, newborn babies who needed oxygen supplementation had to be weaned to room air for at least 12 h before pulse oximetry measurement. Pulse oximetry screening was not applicable for babies receiving a prostaglandin infusion.

In the pilot study, the reference standard was echocardiography. All screened newborn babies

underwent echocardiography within 1 h of the index test by a doctor who was masked to the results of the index test. In the multicentre screening study, the reference standard was echocardiography, clinical follow-up, and parents' feedback. Newborn babies who screened positive for congenital heart disease were referred for echocardiography within 24 h of screening. Late-presenting cases of congenital heart disease were identified through re-assessment by clinical examination at 6 weeks of age at the hospital where the newborn baby had been born; if the baby had congenital heart disease after 6 weeks of age, parents were recommended to contact the hospital. The Children's Hospital of Fudan University provided help with further confirmation of diagnosis for all affected babies from the participating hospitals. All cases of congenital heart disease were followed up by telephone review at atleast 1 year of age.

On the basis of the severity classification of congenital heart disease recommended by Ewer and colleagues,[3] we divided cases of the disease into four groups: critical (defects causing death or needing intervention before 28 days of age), serious (defects needing intervention before 1 year of age), significant (defects persisting longer than 6 months of age, but not classified as critical or serious), and non-significant (defects not physically appreciable and not persisting after 6 months of age). We classified critical and serious cases of congenital heart disease as major congenital heart disease; the other two groups were classified as minor congenital heart disease. Critical congenital heart disease was the main screening target, and serious congenital heart disease was the secondary. We made a data collection plan before we started to recruit study participants at all sites.

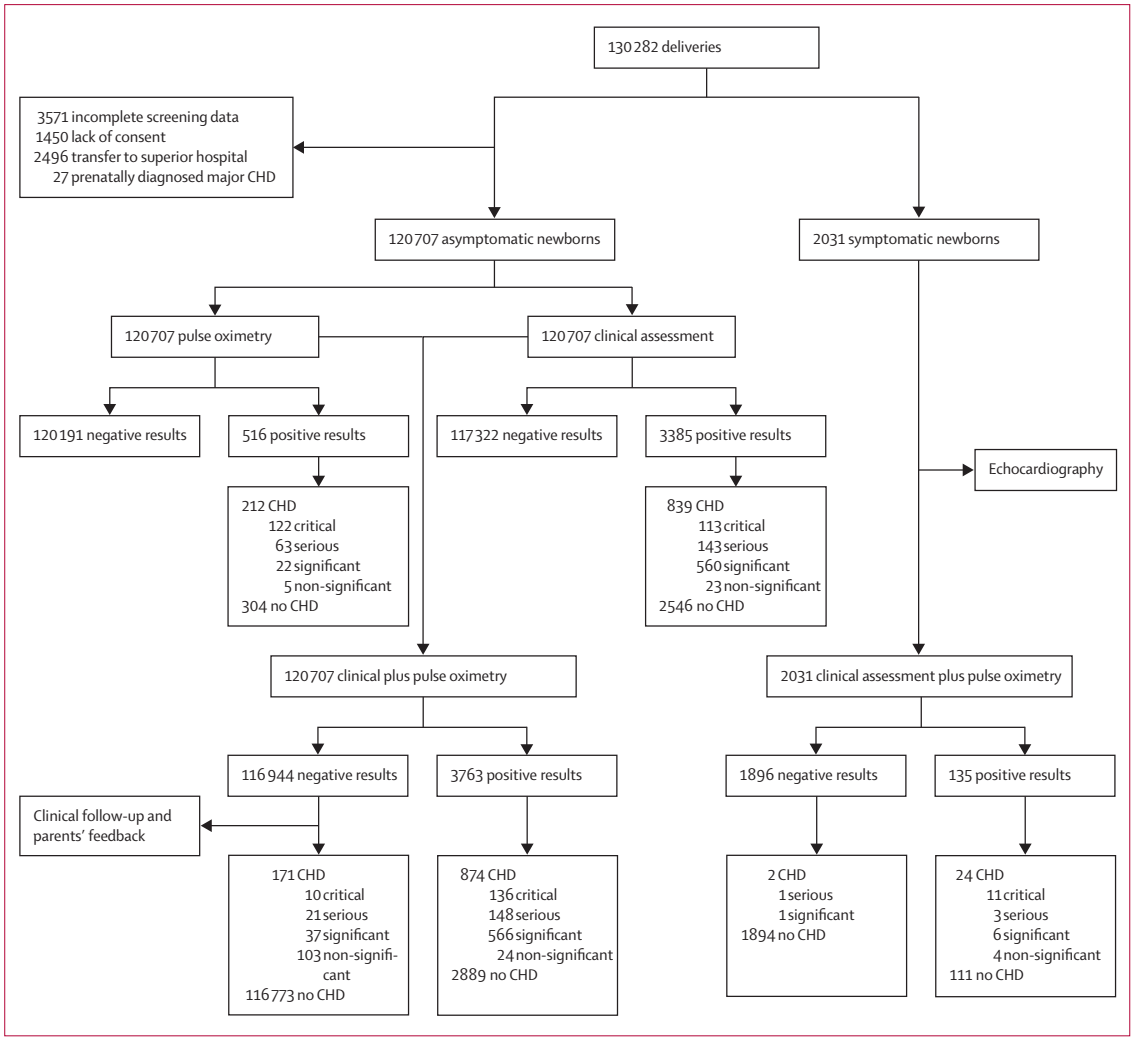

Figure: **Study profile**
CHD=congenital heart disease.

Statistical analysis

We calculated the sample size for the pilot study with the detection rate of routine clinical assessment (50%) used by Wren and colleagues.[16] On the basis of a prevalence of congenital heart disease of eight per 1000 livebirths (and assuming a 50% sensitivity and 90% specificity of routine clinical assessment), and with a sample size of 6700 (including 54 cases of congenital heart disease), the study had 99% power to prove the sensitivity was at least 80% with a two-sided test with type I error of 5%. The sample size needed to detect a 5% increase in specificity from 90% was 552 on the basis of a two-sided test with type I error of 5% (99% power).

For the asymptomatic cohort, we calculated sensitivity, specificity, positive and negative predictive value, and positive and negative likelihood ratios for pulse oximetry alone and in combination with clinical assessment. 95% CI of sensitivity and specificity was computed by the Wilson method. We used McNemar's test to compare differences in sensitivity and specificity between pulse oximetry alone and in combination with clinical assessment. We used a logistic regression model to calculate the accuracy of pulse oximetry and clinical assessment according to the timing of screening, with time from birth to the first stage of pulse oximetry as a continuous variable.

Role of the funding source

The Key Clinical Research Project sponsored by Ministry of Health, Shanghai Public Health Three-Year Action Plan sponsored by Shanghai Municipal Government, and National Basic Research Project of China monitored study progress but had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

	Asymptomatic newborn babies (n=120 707)	Symptomatic newborn babies (n=2031)
Gestational age (weeks)		
<35	5535 (5%)	122 (6%)
35–36	8160 (7%)	171 (8%)
37–38	36 458 (30%)	754 (37%)
39–40	70 020 (58%)	978 (48%)
>40	534 (<1%)	6 (<1%)
Gestational age (weeks)	38·9 (1·9)	38·2 (1·9)
Sex (male)	66 147 (55%)	1104 (54%)
Weight (kg)	3·23 (0·54)	3·19 (0·52)
Age at screening (h)	43 (6–72)	12 (0–24)
Test-positive cases		
Clinical assessment alone	3385 (3%)	112 (6%)
Pulse oximetry alone	516 (<1%)	38 (2%)
Either clinical assessment or pulse oximetry	3763 (3%)	135 (7%)
Both clinical assessment and pulse oximetry	138 (<1%)	15 (1%)

Data are number (%), mean (SD), or median (range).

Table 1: **Characteristics of newborn babies**

Results

During the pilot study, 6785 livebirths were recorded in the three hospitals. Of these, 35 newborn babies presented with tachypnoea or cyanosis before screening; the symptoms were caused by a lung problem, and no congenital heart disease was detected. The remaining 6750 newborn babies were asymptomatic at the time of screening. The median age of screening was 43 h (range 2–97). Pulse oximetry test was done for a mean of 1·6 min (range 0·8–4·0). Pulse oximetry plus clinical assessment detected 46 of 49 cases (94% sensitivity) of asymptomatic major congenital heart disease and eight of eight cases (100% sensitivity) of critical congenital heart disease. The corresponding specificity was 93% (6226 of 6701) and 92% (6228 of 6742). Pulse oximetry plus cardiac murmur had the same sensitivity (46 of 49 [94%]) but a higher specificity for detection of major congenital heart disease than pulse oximetry plus clinical assessment (6267 of 6701 [94%] vs 6226 of 6701 [93%]). However, if the pulse oximetry test had not been introduced, one critical congenital heart disease (single ventricle with pulmonary atresia) and one major congenital heart disease (double outlet right ventricle) would have been missed. The false-positive rate of the pulse oximetry test was 0·3% (16 of 6701) for major congenital heart disease and 0·3% (17 of 6742) for critical congenital heart disease.

Findings of the pilot study showed that pulse oximetry used in conjunction with clinical assessment could be successfully implemented in common hospital settings with few barriers because of short screening time, little additional workload, and easy performance, and resulted in a high detection rate of major and critical congenital heart disease. Data suggested that a prospective multicentre study in a larger population was feasible in China.

In the prospective study, of 130 282 deliveries, we screened 122 738 newborn babies (94%) in China (figure), including 120 707 asymptomatic newborn babies and 2031 symptomatic newborn babies (table 1). 27 newborn babies with major congenital heart disease (22 critical and five serious) were prenatally diagnosed and verified by immediate postnatal echocardiography; these newborn babies were excluded from the study analysis.

In the asymptomatic neonate cohort, the median age at pulse oximetry plus clinical assessment screening was 43 h (range 6–72). Table 1 shows the percentage of positive results based on different methods. 874 patients with congenital heart disease (including 136 critical and 148 serious) were identified before discharge. An additional 171 patients with congenital heart disease (including ten critical and 21 serious) were diagnosed later by clinical follow-up and parents' feedback (figure).

Pulse oximetry alone as a screening method detected 122 of 146 (84%) cases of asymptomatic critical congenital

	Major congenital heart disease			Critical congenital heart disease		
	Pulse oximetry alone	Clinical assessment alone	Pulse oximetry plus clinical assessment	Pulse oximetry alone	Clinical assessment alone	Pulse oximetry plus clinical assessment
True positives	185	256	284	122	113	136
False negatives	130	59	31	24	33	10
False positives	331	3129	3298	394	3272	3446
True negatives	120 061	117 263	117 094	120 167	117 289	117 115
False-positive rate	0·3%	2·6%	2·7%	0·3%	2·7%	2·9%
Sensitivity (95% CI)	58·7% (53·2–64·0)	81·3% (76·6–85·2)	90·2% (86·4–93·0)*	83·6% (76·7–88·7)	77·4% (70·0–83·4)	93·2% (87·9–96·2)*
Specificity (95% CI)	99·7% (99·7–99·8)	97·4% (97·3–97·5)	97·3% (97·2–97·4)	99·7% (99·6–99·7)	97·3% (97·2–97·4)	97·1% (97·1–97·2)
Positive predictive value (95% CI)	35·9% (31·8–40·1)	7·6% (6·7–8·5)	7·9% (7·1–8·9)	23·6% (20·2–27·5)	3·3% (2·8–4·0)	3·8% (3·2–4·5)
Negative predictive value (95% CI)	99·89% (99·87–99·91)	99·95% (99·94–99·96)	99·97% (99·96–99·98)	99·98% (99·97–99·99)	99·97% (99·96–99·98)	99·99% (99·98–100)
Positive likelihood ratio (95% CI)	213·6% (210·8–216·5)	31·3% (31·2–31·3)	32·9% (32·9–33·0)	255·7% (253·6–257·8)	28·5% (28·4–28·7)	32·6% (32·5–32·6)
Negative likelihood ratio (95% CI)	0·41% (0·41–0·42)	0·19% (0·19–0·20)	0·10% (0·10–0·11)	0·17% (0·15–0·18)	0·23% (0·22–0·25)	0·07% (0·06–0·09)
Odds ratio (95% CI)	516·2 (402·4–662·1)	162·6 (122·3–216·3)	325·3 (224·1–472·0)	1550·0 (989·8–2428·0)	122·7 (83·2–181·2)	462·2 (243·0–879·3)

*Addition of pulse oximetry to clinical assessment significantly improved sensitivity for critical congenital heart disease (p<0·0001).

Table 2: **Accuracy of screening methods for detection of major and critical congenital heart disease in asymptomatic newborn babies**

heart disease, but only 185 of 315 (59%) cases of asymptomatic major congenital heart disease (table 2). Table 3 shows sensitivities of pulse oximetry for individual critical congenital heart disease. Compared with clinical assessment, pulse oximetry had higher detection rate of total anomalous pulmonary venous connection, transposition of the great arteries, pulmonary atresia, and double outlet right ventricle, whereas clinical assessment detected more critical left heart obstructive defects including hypoplastic left heart syndrome, critical coarctation of the aorta, interrupted aortic arch, and critical aortic stenosis (11 of 22 [50%] *vs* nine of 22 [41%]).

The overall false-positive rate for detection of critical congenital heart disease was 0·3% (394 of 120 561) for pulse oximetry alone (table 1). However, 180 (46%) false positives by pulse oximetry needed medical intervention or further monitoring (90 with other congenital heart disease, 41 persistent pulmonary hypertension of the newborn, 23 lung problem, 16 preterm birth, and ten infection). Thus, the true false-positive rate for pulse oximetry alone was 0·2% (214 of 120 561). We recorded a significant decrease in the false-positive rate for pulse oximetry with age of newborn baby at screening (odds ratio [OR] 0·67, 95% CI 0·57–0·78, p<0·0001), and for clinical assessment (OR 0·81, 0·77–0·86, p<0·0001; table 4). However, we recorded no significant difference in false-positive rate for pulse oximetry and clinical assessment after 24 h of age compared with at 6–24 h of age (pulse oximetry: OR 0·90, 0·69–1·18, p=0·46; clinical assessment: 0·95, 0·87–1·04, p=0·30). Sensitivity for both pulse oximetry and clinical assessment did not change over time (pulse oximetry OR 0·66, 0·37–1·20, p=0·17; clinical assessment 0·74, 0·44–1·27, p=0·28).

	N	Detection rate		
		Pulse oximetry alone	Clinical assessment alone	Pulse oximetry plus clinical assessment
Critical pulmonary stenosis	10	10 (100%)	10 (100%)	10 (100%)
Tetralogy of Fallot	9	9 (100%)	9 (100%)	9 (100%)
Truncus arteriosus	5	2 (40%)	3 (60%)	4 (80%)
Single ventricle	11	8 (73%)	9 (82%)	10 (91%)
Pulmonary atresia	30	30 (100%)	28 (93%)	30 (100%)
Transposition of great arteries	33	32 (97%)	29 (88%)	32 (97%)
Double outlet of right ventricle	9	8 (89%)	6 (67%)	9 (100%)
Hypoplastic left heart syndrome	7	3 (43%)	2 (29%)	4 (57%)
Critical coarctation of the aorta	7	3 (43%)	4 (57%)	5 (71%)
Interrupted aortic arch	5	2 (40%)	2 (40%)	4 (80%)
Critical aortic stenosis	3	1 (33%)	3 (100%)	3 (100%)
Total anomalous pulmonary venous connection	17	14 (82%)	8 (47%)	16 (94%)
Total	146	84% (122 of 146)	77% (113 of 146)	93% (136 of146)

Table 3: **Detection rate for individual critical congenital heart disease in asymptomatic newborn babies**

Pulse oximetry plus clinical assessment detected 136 of 146 (93%) cases of asymptomatic critical congenital heart disease and 284 of 315 (90%) cases of asymptomatic major congenital heart disease. Combination of pulse oximetry and clinical assessment significantly improved sensitivity of screening for both critical congenital heart disease and major congenital heart disease (p<0·0001; tables 2 and 3). Because 20 of 22 (91%) newborn babies with prenatally diagnosed critical congenital heart disease did not present clinically soon after birth, if combined with prenatal screening, the real-world detection rate of asymptomatic critical congenital heart disease before

	Age 6–24 h (n=20 055)	Age 25–48 h (n=74 326)	Age 49–72 h (n=26 326)
Pulse oximetry test			
True positives	67	40	15
False negatives	9	11	4
False positives	109	216	69
True negatives	19 870	74 059	26 238
False-positive rate (%)	0·55%	0·29%	0·26%
Sensitivity (95% CI)	88·2% (79·0–93·6)	78·4% (65·4–87·5)	79·0% (56·7–91·4)
Specificity (95% CI)	99·4% (99·3–99·6)	99·7% (99·7–99·8)	99·7% (99·7–99·8)
Clinical assessment			
True positives	62	37	14
False negatives	14	14	5
False positives	723	1905	644
True negatives	19 256	72 370	25 663
False-positive rate (%)	3·62%	2·56%	2·45%
Sensitivity (%, 95% CI)	81·6% (71·4–88·7)	72·6% (59·1–82·9)	73·7% (51·2–88·2)
Specificity (%, 95% CI)	96·3% (96·1–96·6)	97·4% (97·3–97·5)	97·6% (97·4–97·7)

Table 4: **Accuracy of screening methods for detection of critical congenital heart disease by age in asymptomatic newborn babies (n=120 707)**

discharge would have been increased to 94% (156 of 166). In the ten missed cases of critical congenital heart disease before discharge, left-heart obstructive defects constituted six cases (with five readmitted in the collapsed status) and cyanotic heart defects four (all identified by physician during clinical follow-up at 6 weeks of age).

Pulse oximetry plus cardiac murmur had the same accuracy as did pulse oximetry plus clinical assessment (four aspects) in the detection of major congenital heart disease (90% sensitivity) and critical congenital heart disease (93% sensitivity), whereas the false-positive rate was significantly lower (2876 of 120 392 [2·4%]) *vs* 3298 of 120 392 [2·7%]) for major congenital heart disease (p<0·0001), and (3024 of 20 561 [2·5%] *vs* 3446 of 120 561 [2·9%]) for critical congenital heart disease (p<0·0001). Pulse oximetry and cardiac murmur were measured in a post-hoc analysis.

The symptomatic neonate cohort consisted of 2031 newborn babies with clinical presentations frequently associated with congenital heart disease (926 with tachypnoea, 501 with cyanosis, and 604 with tachypnoea combined with cyanosis). Of these, only 135 newborn babies had abnormal clinical assessment or pulse oximetry results, including 11 with critical congenital heart disease (five had transposition of great arteries, three had pulmonary atresia, two had total anomalous pulmonary venous connection, and one had interrupted aortic arch). Of 1896 newborn babies with normal clinical assessment and pulse oximetry results, we recorded no critical, but one serious and one significant case of congenital heart disease. Most cases of cyanosis judged by clinicians were not related to critical congenital heart disease. Furthermore, in newborn babies with tachypnoea, only one had interrupted aortic arch. Thus, 11 of 157 (7%) newborn babies with critical congenital heart disease developed symptoms before the onset of screening. We recorded no adverse events from reference and index tests.

Discussion

In high-income countries about 13–48% of newborn babies with critical congenital heart disease leave hospital undiagnosed;[17] however, no population-based data have been reported in low-income countries. In our study, if pulse oximetry had not been incorporated into the routine care, 33 of 179 (18%) newborn babies with critical congenital heart disease would have left the hospital undiagnosed. However, this figure is likely to be higher in birthing hospitals in which clinicians are not well trained in how to do cardiac auscultation. Advances in paediatric cardiology and cardiac surgery during the past 30 years in China have made possible the diagnosis and treatment of most cases of critical congenital heart disease. Echocardiography is available in most hospitals for about US$30 per case. Futhermore, so-called green channels for surgical treatment of neonatal critical congenital heart disease have been established in major paediatric cardiac centres.[18] With increasing availability of treatment opportunities for critical disease, early detection and timely intervention are crucial. Our data suggest that neonatal screening for major congenital heart disease could reduce infant mortality and the social and medical burden of long-term morbidities associated with critical congenital heart disease.

Although the target of screening is identification of critical congenital heart disease in high-income countries, major congenital heart disease often remains undiagnosed in most children in low-income countries.[14] This undiagnosis further compromises the outcome of surgery because most physicians in less privileged areas are less able to clinically diagnose congenital heart disease, mainly because of limited exposure to paediatric cardiology during their training. In view of these caveats, we suggest that clinical assessment, added to pulse oximetry screening should be used in maternity hospitals as a screening method for major congenital heart disease.

Our findings showed that pulse oximetry alone had enough sensitivity and high specificity for detection of critical congenital heart disease, which is in accordance with other studies (panel 2).[3–8] Without pulse oximetry, discharge of asymptomatic newborn babies with undiagnosed congenital heart disease was three times more likely in babies with critical disease and almost twice as likely in babies with major disease. With combined pulse oximetry and clinical assessment, we detected 284 of 315 (90%) cases of critical congenital heart disease and 136 of 146 (93%) cases of major congenital heart disease. Typically, newborn babies with abnormal clinical findings suggestive of congenital heart

disease will need an echocardiogram. But the results of clinical assessment are probably affected by the physician's clinical experience, especially in low-income countries where physician training varies from university graduate training in provincial to 3 months after secondary school in villages. To reduce interobserver variability in clinical assessment, we standardised the definition of a presumptively positive clinical assessment result. Findings of our study showed that pulse oximetry plus cardiac murmur and pulse oximetry plus all four aspects of clinical assessment had the same sensitivity in detection of asymptomatic major congenital heart disease, making screening quick and simple.

Several well designed studies of pulse oximetry screening have been published,[3–8] but the absence of agreed definitions makes direct comparisons between them difficult. In a meta-analysis[19] of 13 studies that focused on pulse oximetry alone as a screening method for detection of asymptomatic critical congenital heart disease, Thangaratinam and colleagues reported that overall estimate of sensitivity was 76·5% (95% CI 67·7–83·5). Compared with other studies,[3–5,7] even if the same inclusion criteria of critical congenital heart disease were used, our data still suggested a higher sensitivity of pulse oximetry than in the meta-analysis (>80%; appendix). The higher sensitivity in our study was probably related to the lower proportion of left-heart obstructive defects in newborn babies with critical congenital heart disease, because detection of aortic obstruction with pulse oximetry alone remains difficult (appendix).[20,21] Furthermore, the prevalence of all left-heart obstructive defects in our study (0·40 per 1000 livebirths) was also lower than in previously reported estimates from studies done in high-income countries (eg, 0·81 per 1000 livebirths in Germany,[22] 0·82 per 1000 in Atlanta, USA[23]), whereas we recorded more right-heart obstructive defects (1·06 per 1000 livebirths *vs* 0·76 per 1000 in Germany,[22] 0·59 per 1000 in Atlanta[23]).

In 2011, the Advisory Committee on Heritable Disorders in Newborns and Children of the US Health and Human Services Secretary investigated seven specific lesions as primary targets for screening on the basis of advice from a technical expert panel:[9] hypoplastic left heart syndrome, pulmonary atresia, tetralogy of Fallot, total anomalous pulmonary venous connection, transposition of great arteries, tricuspid atresia, and truncus arteriosus. However, the panel also recommended that, "Comparing the accuracy of pulse oximetry monitoring for the seven defects to that of other studies was challenging because of differences in the lesions that were targeted for detection by the screening".[9] In our study, pulse oximetry detected 138 of 164 cases with the seven asymptomatic critical congenital heart diseases (sensitivity 84·1%), which included hypoplastic left heart syndrome (four of seven), pulmonary atresia (34 of 34), tetralogy of Fallot (42 of 55), total anomalous pulmonary venous connection (15 of 20), transposition of great arteries (32 of 33), tricuspid atresia (six of seven) and truncus arteriosus (five of eight).

Panel 2: Research in context

Systematic review

We searched Medline (from Jan 1, 1951, to Dec 31, 2013), Embase (from Jan 1, 1974, to Dec 31, 2013), and the Cochrane Library (from inception to Dec 31, 2013) for systematic reviews and primary studies of screening for congenital heart disease in neonates. Language restrictions were not applied. A combination of MeSH and text words was used as "congenital heart disease AND screen AND (neonate OR newborn)" to generate a subset of citations relevant to our research question. We identified three closely related systematic reviews and 14 primary studies.

Interpretation

This study is the largest test accuracy study of congenital heart disease screening with more than twice as many babies screened than in the previous largest study.[7] We showed for the first time the performance of pulse oximetry and clinical assessment in a low-income country. Because most physicians in less-privileged areas in China are less able to clinically diagnose congenital heart disease than are those in more privileged areas, mainly because of little exposure to paediatric cardiology during their training period, we predict that clinical assessment added to pulse oximetry screening would help to diagnose cases of major congenital heart disease. The results of this study add to the strong evidence that suggests potential benefits of congenital heart disease screening in early neonatal stage.[3–8,12,19,20] The screening strategy with pulse oximetry plus abnormal cardiac murmur proved to be an effective and convenient method for detection of asymptomatic major and critical congenital heart disease, which provided a strong argument for implementation of routine congenital heart disease screening in low-income countries.

With regard to the false-positive rate of pulse oximetry, our results were nearly identical with those in the recent meta-analysis; false-positive rate was affected by timing of the test and was significantly lower when the screening was done after 24 h of birth than when it was done before 24 h (table 4). We also noted this trend for clinical assessment. However, sensitivity for both pulse oximetry and clinical assessment did not differ significantly during the study.

In practice, diagnostic echocardiography would also follow an abnormal clinical assessment, which identified most cases of asymptomatic congenital heart disease (839 of 1045 [80%] in our study; figure 1). We could not disregard the information about less critical disease. In view of this association, we presented all cases of congenital heart disease identified through our screening programme, clinical follow-up, and parents' feedback in this study. The appendix shows the prevalence and severity of individual congenital heart disease lesions.

In China, no congenital anomaly registry or autopsy data are available to verify the cause of infant death that might be related to congenital heart disease. Additionally, identification of the missed cases by study of all hospital admissions for congenital heart disease is difficult because of the great population mobility. Nonetheless, data from the pilot study suggested that all cases of critical congenital heart disease and 94% of cases of major disease cases could have been detected by pulse oximetry plus clinical assessment before discharge. Therefore, very few cases of critical or major congenital heart disease are likely to have been missed through screening, clinical examination at 6 weeks of age, and parents' feedback in the main study.

See Online for appendix

Findings of our study showed that the benefits of pulse oximetry recorded in high-income countries could be translated with great success to China. However, all newborn babies with major congenital heart disease should be targeted for screening in low-income countries. Pulse oximetry plus abnormal cardiac murmur proved to be an accurate and quick method for detection of asymptomatic major congenital heart disease and critical congenital heart disease. The results of this study provide a strong argument for implementation of screening for congenital heart disease as a basic routine in Chinese maternity hospitals.

Contributors

G-yH and BJ contributed to the study design and the establishment of the screening system. All authors discussed, critically revised, and approved the final study protocol. G-yH, BJ, X-jM, Q-mZ, and X-lG organised and conducted the project. Q-mZ, X-jM, X-lG, and W-lY undertook data management and data analysis. All authors discussed and approved the final strategy for analysis. Q-mZ and X-jM drafted the first version of the report. All authors discussed, revised, and approved the final version of the report for publication.

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Declaration of interests

We declare that we have no competing interests.

Acknowledgments

Our study was funded by the Key Clinical Research Project Sponsored by Ministry of Health (BJ and G-yH, number 2010–239), Shanghai Public Health Three-Year Action Plan Sponsored by Shanghai Municipal Government (G-yH, number 2011–55), and National Basic Research Project of China (G-yH, number2010CB529504). We thank all professionals involved in the Neonatal Congenital Heart Disease Screening Project; Wyman W Lai (Morgan Stanley Children's Hospital of New York Presbyterian, NY, USA) and Yiu-fai Cheung (University of Hong Kong, Hong Kong, China) for their comments and review of the report; Jian-feng Xu (Wake Forest School of Medicine, Winston-Salem, NC, USA) and Duo-lao Wang (University of London, London, UK) for their valuable comments on the revision of the report; and Anne de-Wahl Granelli from Queen Silvia Children's Hospital (Gothenburg, Sweden) for serving as our advisory board.

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