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Cost-effectiveness analysis of neonatal screening of critical congenital heart defects in China

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Abstract

Background: Pulse oximetry screening is a highly accurate tool for the early detection of critical congenital heart disease (CCHD) in newborn infants. As the technique is simple, noninvasive, and inexpensive, it has potentially significant benefits for developing countries. The aim of this study is to provide information for future clinical and health policy decisions by assessing the cost-effectiveness of CCHD screening in China.

Methods and Findings: We developed a cohort model to evaluate the cost-effectiveness of screening all Chinese newborns annually using 3 possible screening options compared to no intervention: pulse oximetry alone, clinical assessment alone, and pulse oximetry as an adjunct to clinical assessment. We calculated the incremental cost per averted disability-adjusted life years (DALYs) in 2015 international dollars to measure cost-effectiveness. One-way sensitivity analysis and multivariate probabilistic sensitivity analysis were performed to test the robustness of the model. Of the three screening options, we found that clinical assessment is the most cost-effective strategy compared to no intervention with an incremental cost-effectiveness ratio (ICER) of Int$5,728/DALY, while pulse oximetry plus clinical assessment with the highest ICER yielded the best health outcomes. Sensitivity analysis showed that when the treatment rate increased up to 57.5%, pulse oximetry plus clinical assessment showed the best expected values among the three screening options.

Conclusion: In China, for neonatal screening for CCHD at the national level, clinical assessment was a very cost-effective preliminary choice and pulse oximetry plus clinical assessment was worth considering for the long term. Improvement in accessibility to treatment is crucial to expand the potential health benefits of screening.

Abbreviations: ACER = average cost-effectiveness ratio, CCHD = critical congenital heart disease, CHD = congenital heart disease, DALYs = disability adjusted life years, GDP = gross domestic product, ICER = incremental cost-effectiveness analysis, WHO = World Health Organization, WTP = willingness-to-pay.

Keywords: China, critical congenital heart disease, economic evaluation, neonatal screening, pulse oximetry

1. Introduction

Congenital heart defects (CHD) are the most common type of birth defect and a leading cause of infant mortality in China where approximately 216,000 infants with CHD are born every year[1]. The worldwide prevalence of CHD is estimated at 4 to 10 per 1000 neonates; of these, 1 to 2 neonates have critical CHD (CCHD), which can cause death or the need for surgical or catheter-based intervention in the neonatal period.[2] Population-based studies in Europe and America have shown the accuracy and value of adding pulse oximetry screening to the routine clinical assessment of neonates to aid in the detection of CCHD.[3–6] Early detection is critical to preventing infant morbidity and mortality. Combined with advances in therapeutic interventions, early detection can enable the majority of children born with CCHD to lead normal productive lives.[7]

In 2011, after being widely advocated by major medical societies, pulse oximetry screening of newborns for CCHD was included in the US-recommended uniform screening panel.[2,7,8] CCHD screening reportedly reduced the number of apparently healthy infants who might have died or suffered cardiovascular collapse without CCHD detection.[9–11] The impact of screening for CCHD in developing countries, however, is less certain. Owing to delays in timely diagnosis and case management, infant and child mortality related to CCHD remains high in developing countries.[12] As pulse oximetry screening provides an accurate, noninvasive approach that is simple, inexpensive, and less resource-intensive, it could be very beneficial for developing countries as long as access to treatment is available after detection.

A large-scale, multicenter, prospective screening study conducted in China confirmed the feasibility and accuracy of pulse oximetry screening for the detection of CCHD in neonates before discharge and recommended its widespread use in maternity

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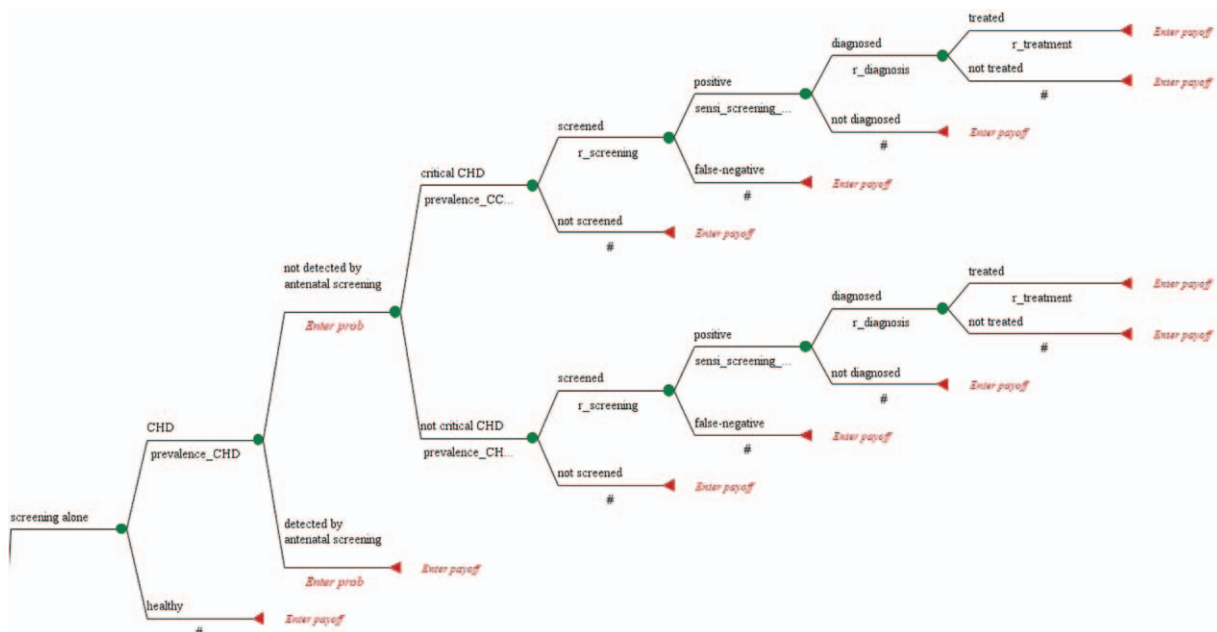
Figure 1. Decision model.

hospitals.[13] This screening method is considered feasible for the majority of Chinese neonates because the pulse oximeter is readily available in most secondary and tertiary hospitals, screening can also be provided by outreach services, and the proportion of neonates delivered at hospitals exceeds 90%. However, there are tremendous variations in socioeconomic status, access to antenatal screening and pediatric cardiological care, and performance and quality of healthcare across regions and facilities. Neonatal screening for CCHD is still at the pilot stage and has not yet been widely adopted in most Chinese hospitals. No study has yet evaluated the cost-effectiveness of CCHD screening in a developing country. Therefore, this study aimed to evaluate the cost-effectiveness of neonatal CCHD screening for neonates in China.

2. Methods

2.1. Decision model

A decision-analytic and cost-effectiveness analysis model was generated using TreeAge Pro.2015 (Fig. 1) and was programmed for a hypothetical annual birth cohort of 16 million neonates. The aim of the screening was to detect neonates with CCHD, whose condition had gone undiagnosed during antenatal care, before they were discharged from the birth hospital so that timely treatment could be administered before cardiac collapse. The primary outcomes were the number of lives saved during infancy and the Disability-Adjusted Life Years (DALYs) averted as a result. The time horizon was the lifetime.

Three screening options, namely, clinical assessment alone, pulse oximetry screening alone, and pulse oximetry screening as an adjunct to clinical assessment for early detection of CCHD, were compared to no intervention (status quo). Clinical assessment has always been fundamental to routine clinical practice in China where it encompasses 4 components: family history, particular facial features, heart murmurs, and extra cardiac malformation and is carried out before discharge (depending on the human and

technical capacities of the hospital).[13] Because neither clinical assessment nor pulse oximetry alone can detect all CCHD, a combination of the 2 is ideal.[14]

Infants in whom CCHD was diagnosed by fetal ultrasound during antenatal care were excluded from postnatal screening. Pulse oximetry measures the oxygen saturation of arterial blood 24 to 48 hours after birth. Whenever a positive result was identified by screening, the neonate underwent a diagnostic echocardiogram at the birth hospital or was referred to another hospital as needed. Furthermore, neonates with a CCHD diagnosis were expected to receive pediatric cardiological care including surgery or catheterization generally at the tertiary level before cardiovascular collapse.

2.2. Costs

Cost estimates were based on the societal perspective and discounted at 3%.[15] Data were first collected in Chinese yuan in 2015 and then converted to international dollars using purchasing power parities and gross domestic product (GDP) deflators.[16] The estimates included 3 items: cost of screening by either clinical assessment or pulse oximetry, the cost of diagnostic echocardiography, and the cost of treatment.

The cost of pulse oximetry screening was estimated based on the salaries of doctors and nurses and the average screening time, reported as 1.6 minutes.[13] We also considered equipment and maintenance costs and program costs for implementing screening. The figures for the salary of the medical staff and the direct medical costs for clinical assessment, echocardiography tests, surgery, and catheterization were obtained from tertiary hospitals and local health services, as infants with, or suspected of having, CCHD in rural areas are referred to tertiary hospitals in urban centers for diagnosis and treatment (pediatric cardiac surgery or catheterization). Considering the diversity in the cost of screening and diagnosis across health facilities at different levels, an up-and-down level of 50% was used in the sensitivity analysis to examine these uncertainties (Table 1).

Cost estimates of neonatal screening for CHD.

Screening options	Unit costs per infant (international dollars)	Ranges for sensitivity analysis (international dollars)
Clinical assessment	0.5	0.2–0.8
Pulse oximetry	2	1–3
Diagnosis	35.0	30–40
Pediatric cardiological care	31,098	95% CI: 25,912–42,064

CHD = congenital heart disease.

2.3. Screening performance and diagnostic follow-up

Data on screening accuracy were obtained from the largest multifacility investigation in the developing world, which was conducted by Zhao et al.[13] As screening performance was likely to vary across different health facility levels, sensitivity and specificity were reduced by 50% in the sensitivity analysis, taking into account the probability that lower level and remote hospitals would perform more poorly than major urban hospitals. Generally, newborns can receive a diagnostic echocardiogram either at the birth hospital or a nearby tertiary hospital, and confirmed cases receive pediatric cardiological care at a tertiary hospital. Table 2 shows the base-case values and plausible ranges used for the sensitivity analysis.

2.4. Estimates of health impacts

The model assessed the number of additional neonates with CCHD detected at the birth hospital before discharge, the number of lives saved, and the number of disability adjusted life years (DALYs) averted. The willingness-to-pay (WTP) threshold was calculated at 34,857 international dollars (Int$) per DALY

averted, or 3 times the GDP per capita based on the WHO guidelines for cost-effectiveness analysis of interventions.[16]

In China, access to healthcare, especially advanced-level pediatric cardiological care, varies widely across the country. Unlike in developed countries, a significant proportion of infants with CCHD are unable to receive any treatment before cardiovascular collapse. Given the lack of data on infant mortality without treatment, the adverse outcomes owing to poor access to pediatric cardiological care were estimated by using a proxy of the natural history derived from a study conducted in the 1950s when cardiac surgery was not commonly available worldwide. We also used recent reports on infant mortality oowing to CCHD in China to reflect health outcomes with treatment, under the assumption that the probability of death would be reduced if CCHD was detected before discharge and the neonate received advanced-level pediatric cardiological care. The average and incremental costs per DALYs averted were calculated.

2.5. Sensitivity analysis

For the base-case, univariate sensitivity analyses were conducted to explore the impact of the parameters listed in Table 2 on the cost, health outcomes, and cost-effectiveness of the 3 screening options. Monte Carlo simulations were then applied to the multivariate sensitivity analyses to test the robustness of the model while taking into account simultaneous changes in key parameters whose variations had the greatest impact on cost-effectiveness.

2.6. Ethical consideration

As our study was a modeling-based approach and data for cost estimates did not include individual information, no ethical approval was necessary.

Baseline values and ranges used for sensitivity analysis.

Parameters	Baseline	Ranges for sensitivity analysis	References
Annual birth cohort of newborns	16,000,000	(—)	[22]
Life expectancy in Chinese population	75	(—)	[22]
Prevalence of CHD	0.8%	0.6%–1.3%	[1,23–25]
Prevalence of critical CHD	0.2%	0.1%–0.3%	[1,23–25]
Sensitivity of pulse oximetry for CHD	58.7%	53.2%–64.0%	[13]
Sensitivity of clinical assessment for CHD	81.3%	76.6%–85.2%	[13]
Sensitivity of pulse oximetry plus clinical assessment for CHD	90.2%	86.4%–93.0%	[13]
Sensitivity of pulse oximetry for critical CHD	83.6%	76.7%–88.7%	[13]
Sensitivity of clinical assessment for critical CHD	77.4%	70.0%–83.4%	[13]
Sensitivity of pulse oximetry plus clinical assessment for critical CHD	93.2%	87.9%–96.2%	[13]
Specificity of pulse oximetry for CHD	99.7%	99.7%–99.8%	[13]
Specificity of clinical assessment for CHD	97.4%	97.3%–97.5%	[13]
Specificity of pulse oximetry plus clinical assessment for CHD	97.3%	97.2%–97.4%	[13]
Specificity of pulse oximetry for critical CHD	99.7%	99.6%–99.7%	[13]
Specificity of clinical assessment for critical CHD	97.3%	97.2%–97.4%	[13]
Specificity of pulse oximetry plus clinical assessment for critical CHD	97.1%	97.1%–97.2%	[13]
Neonatal screening coverage	90%	80%–100%	Expert's opinion based on facility-based delivery from the 5th National Health Service Survey[26]
Proportion of infants with critical CHD access to pediatric cardiological care	30%	10%–50%	Expert opinion
Infant mortality due to critical CHD (without treatment)	75%	60%–90%	[27,28]
Infant mortality due to critical CHD (with treatment)	25%	20%–30%	[29,30]
Discounting rate	3%	1.5%–6%	[16]

CHD = congenital heart disease.

Table 3

Estimates of expected values of costs and health impacts.

Screening strategies	Estimated costs, Int$ (95% CI)	DALYs averted (95% CI)	ICER (95% CI)
No intervention	0	0	(—)
Clinical assessment	2,798,053 (2,775,895–2,814,737)	371.67 (242.56–521.57)	7,528 (5322–11,604)
Pulse oximetry	3,172,834 (3,162,109–3,184,932)	322.65 (213.48–487.43)	Dominated
Pulse oximetry plus clinical assessment	5,918,728 (5,887,615–5,938,153)	426.63 (256.18–576.15)	56,778 (48,020–65,482)

CI = confidence interval, DALYs = disability adjusted life years, ICER = incremental cost-effectiveness analysis.

3. Results

3.1. Base case

Table 3 showed the expected values and cost-effectiveness of the 3 options. Of the 3 screening strategies, clinical assessment alone was very cost-effective, with an incremental cost-effectiveness ratio (ICER) of Int$7528/DALY averted from no intervention (95% CI: 5322–11,604). Pulse oximetry screening alone was dominated. As for the combined strategy, the average cost-effectiveness ratio (ACER) pulse oximetry as an adjunct to clinical assessment is under the threshold of WTP, Int$34,857/DALY, whereas its ICER compared to clinical assessment alone was Int$56,778/DALY averted (95% CI: 48,020–65,482) (Fig. 2).
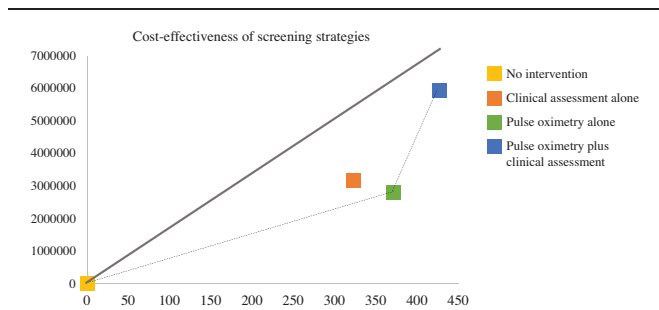

Figure 2. Cost-effectiveness of screening options.

3.2. Sensitivity analysis

The results of the 1-way sensitivity analysis by parameter for the cost-effectiveness of the 3 screening options are shown in a Tornado diagram (Fig. 3). The parameter with the greatest range was the proportion of patients receiving pediatric cardiological care, followed by infant mortality averted by timely treatment, unit cost of pulse oximetry screening, the prevalence of CCHD, and the proportion of suspected cases, which were diagnosed. Because treatment rate was found to be the most influential parameter and equal in importance to the proportion of patients receiving pediatric cardiological care, its impact on cost-effectiveness and the expected value of different screening options was explored, as shown in Figure 4. When the treatment rate was increased to 57.5%, the ICER of pulse oximetry plus clinical assessment acquired the best expected values among the 3 options at the threshold of Int$34,857/DALY.

The cost-effectiveness acceptability curve indicated the robustness of the cost-effectiveness of different options at different WTP thresholds. At a threshold of Int$34,857/DALY, clinical assessment alone was very cost-effective with a probability of 100%. The probability of cost-effectiveness of pulse oximetry plus clinical assessment gradually increased with the WTP threshold and exceeded that of clinical assessment when the threshold reached Int$57,000/DALY (Fig. 5).

4. Discussion

To the best of our knowledge, this study provides the first cost-effectiveness evaluation of the universal application of CCHD
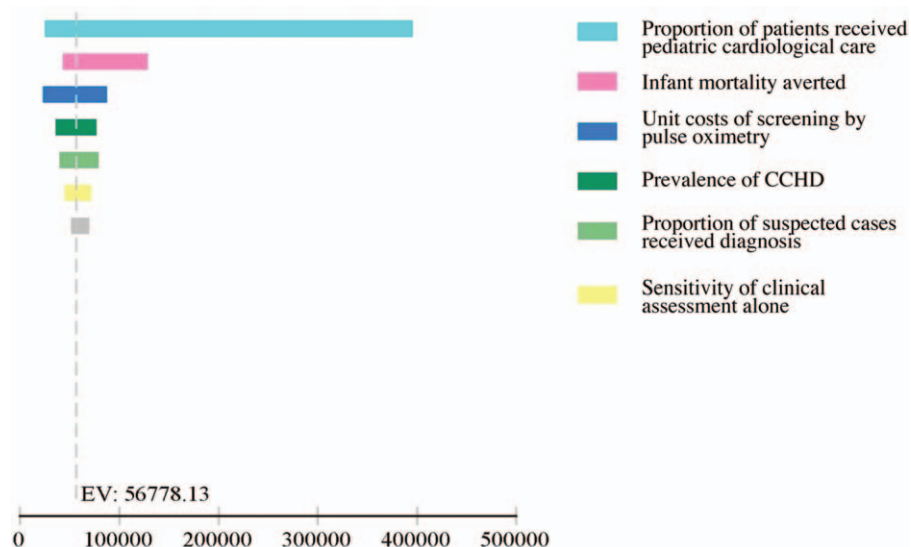

Figure 3. Tornado diagram (1 sensitivity analysis of ICER of the combined strategy vs. clinical assessment alone).
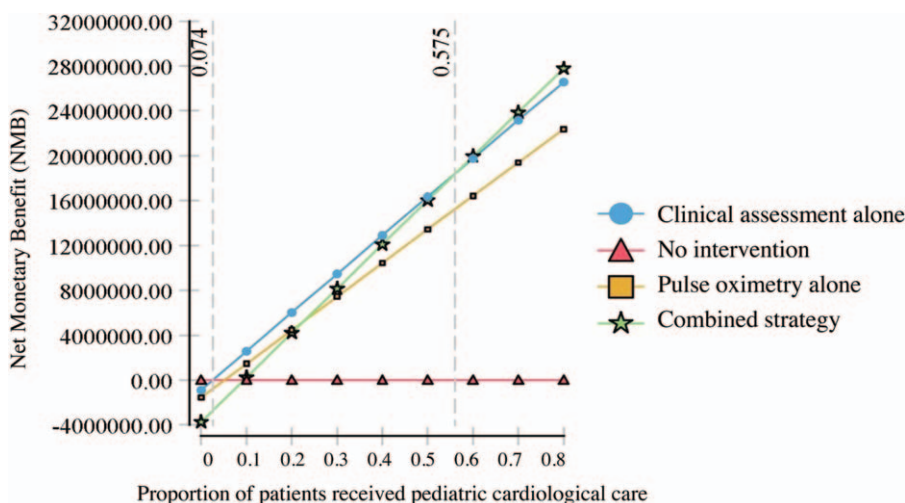
Figure 4. Impact of treatment rate on cost-effectiveness and expected value of different screening options.

screening in maternity hospitals in China as well as in the developing world. Screening makes it possible to detect CCHD before discharge, potentially reducing infant deaths because of late case management. Our analysis found that under base-case assumptions, clinical assessment was a very cost-effective preliminary choice. Pulse oximetry plus clinical assessment, however, yielded the best health outcomes on DALYs averted and became the dominant option as the WTP threshold and the proportion of patients receiving pediatric cardiological care increased.

Clinical assessment is a basic practice for detecting CCHD and can be implemented immediately after delivery. It is not yet a routine practice in China owing to varying human and technical capacities across regions and institutions. Training is necessary for physicians at lower level and remote hospitals to recognize typical symptoms such as heart murmurs, tachypnea, and overt cyanosis. Compared with pulse oximetry, clinical assessment demonstrated a higher detection rate for critical left heart syndrome, critical coarctation of the aorta, interrupted aortic arch, and critical aortic stenosis, whereas pulse oximetry was more likely to detect total anomalous pulmonary venous connection, transposition of the great arteries, pulmonary atresia,

and double outlet right ventricle.[13] Therefore, the combination of pulse oximetry with clinical assessment is likely to improve performance significantly and is an ideal option for achieving the best screening results. Once the treatment rate, that is, the proportion of children with CCHD who are able to access pediatric cardiological care increases to 57.5%, this combined approach will become cost-effective and practicable for use in hospitals universally in the long term.

The findings of our study highlighted the impact of accessibility to pediatric cardiological care on the health and economic effects of screening strategies. It is reasonable to predict that the timely treatment of infants with positive screening results for CCHD will improve significantly if screening were to be universally introduced. However, in light of China's low "ceiling" levels, post-payments, and various restrictions on reimbursements, the current medical insurance system is failing to fulfill its protective function against catastrophic payments and impoverishment owing to serious illness including CHDs, particularly for rural and rural-to-urban migrant children. Medical expenditures for pediatric cardiological care principally relies on out-of-pocket payments and charities, with an actual reimbursement rate of 20% to 45% or even <20% for payments exceeding 200,000
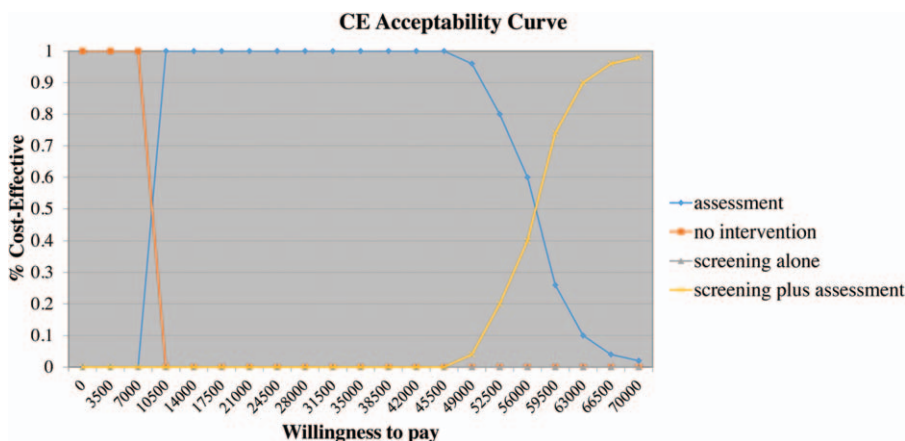

Figure 5. Acceptability curve.

Chinese yuan, a figure far removed from the Ministry of Health's ambitious target of 90%.[17] Questions also remain regarding the highly concentrated distribution of advanced medical technology for diagnosis and treatment in urban hospitals. This situation leads to difficulties not only in access but also reimbursement because healthcare obtained outside of one's area of residence is subject to much lower reimbursement and complicated procedures. Furthermore, significant geographical gaps remain in facilities' technical capacity for pediatric cardiological care across the country. Timely treatment after early detection is often hindered by catastrophic payments because of out-of-pocket expenses and the lack of advanced medical technology in lower level and remote facilities, which negatively affect the potential benefits of screening strategies, especially those of pulse oximetry as an adjunct to clinical assessment.

Previous economic evaluations of neonatal CCHD screening have been published, but all were conducted in the developed world.[18–21] Although these studies suggested that screening by pulse oximetry plus clinical assessment was cost-effective in light of the accepted thresholds in high-income countries, in China and other developing countries, the health system and socioeconomic environment influencing clinical and policy decision-making differ from those of developed countries. First, access to pediatric cardiological care is limited by technical, geographical, and financial factors, whereas an access rate >10% was reported for the developing world.[12] Second, China has huge gaps in socioeconomic status as well as in the quality, capacity, and accessibility of medical care. Last but most importantly, the WTP threshold varies significantly across regions in China, causing correspondingly greater variations in cost-effectiveness analysis results than in developed countries.

This study has some limitations. A major limitation is the lack of precise population-based information on the outcomes of childhood mortality and morbidities during the long term in cases of timely treatment, delayed treatment, and no treatment, and the impact of early detection by neonatal or prenatal screening on the improvement of those outcomes. We primarily considered DALYs because of infant mortality averted based on currently available information. However, the potential health benefits are not limited to infant mortality, but also include morbidities avoided in the long term and facilitating and informing pediatric cardiological care. Additionally, we did not investigate the impact of secondary life-threatening neonatal conditions that may be detected by pulse oximetry, such as pneumonia and sepsis. In the developing world, the detection of these conditions may be of more benefit than the detection of CCHD. Therefore, the potential benefits of neonatal CCHD screening may be largely underestimated. Moreover, data on screening performance derived from urban tertiary hospitals and real-world accuracy in lower-level hospitals are likely to be poorer and largely dependent on physicians' clinical experience and facility capacity. To adjust for this uncertainty, we reduced sensitivity by 50% in the sensitivity analysis. Finally, owing to the lack of information, the proportion of infants with CCHD receiving pediatric cardiological care was based on the opinion of an expert panel. To adjust for this uncertainty, we set a wide range in the sensitivity analysis to accommodate the huge geographical and socioeconomic diversity within the country.

5. Conclusion

In China, for neonatal screening of CCHD at the national level, clinical assessment is a very cost-effective preliminary choice and pulse oximetry plus clinical assessment is worth considering for the long term as accessibility to timely treatment improves and the WTP threshold increases with socioeconomic development. Public investment and insurance coverage for children with CCHD are crucial for exploiting the health benefits of the screening.

References

[1] Ministry of Health of People's Republic of China. National birth defects control and prevention report 2012. Available: http://www.gov.cn/gzdt/att/att/site1/20120912/1c6f6506c7f811bacf9301.pdf.

[2] Mahle WT, Newburger JW, Matherne GP, et al. Role of pulse oximetry in examining newborns for congenital heart disease: a scientific statement from the American Heart Association and American Academy of Pediatrics. Circulation 2009;120:447–58.

[3] Ewer AK, Middleton LJ, Furmston AT, et al. the PulseOx Study GroupPulse oximetry screening for congenital heart defects in newborn infants (PulseOx): a test accuracy study. Lancet 2011;378:785–94.

[4] De-Wahl Granelli A, Wennergren M, Sandberg K, et al. Impact of pulse oximetry screening on the detection of duct dependent congenital heart disease: a Swedish prospective screening study in 39,821 newborns. BMJ 2009;338:a3037.

[5] Riede FT, Worner C, Dahnert I, et al. Effectiveness of neonatal pulse oximetry screening for detection of critical congenital heart disease in daily clinical rountine – results from a prospective multicenter study. Eur J Pediatr 2010;169:975–81.

[6] Liske MR, Greeley CS, Law DJ, et al. Report of the Tennessee task force on screening newborn infants for critical congenital heart disease. Pediatrics 2006;118:e1250–1256.

[7] Mahle WT, Martin GR, Beekman RH3rd, et al. Section on Cardiology and Cardiac Surgery Executive CommitteeEndorsement of health and human services recommendation for pulse oximetry screening for critical congenital heart disease. Pediatrics 2012;129:190–2.

[8] Centers for Disease Control and PreventionNewborn screening for critical congenital heart disease: potential roles of birth defects surveillance programs—United States, 2010–2011. MMWR Morb Mortal Wkly Rep 2012;61:849–53.

[9] Ailes EC, Gilboa SM, Honein MA, et al. Estimated number of infants detected and missed by critical congenital heart defect screening. Pediatrics 2015;135:1000–8.

[10] Peterson C, Ailes E, Riehle-Colarusso T, et al. Late detection of critical congenital heart disease among US infants: estimation of the potential impact of proposed universal screening using pulse oximetry. JAMA Pediatr 2014;168:361–70.

[11] Brown KL, Ridout DA, Hoskote A, et al. Delayed diagnosis of congenital heart disease worsens preoperative condition and outcome of surgery in neonates. Heart 2006;92:1298–302.

[12] Saxena A. Congenital cardiac surgery in the less privileged regions of the world. Expert Rev Cardiovasc Ther 2009;7:1621–9.

[13] Zhao Q, Ma X, Ge X, et al. Pulse oximetry with clinical assessment to screen for congenital heart disease in neonates in China: a prospective study. Lancet 2014;384:747–54.

[14] Knowles R, Griebsch I, Dezteux C, et al. Newborn screening for congenital heart defects: a systematic review and cost-effectiveness analysis. Health Technol Assess 2005;9:1–52.

[15] Tan-Torres Edejer T, Baltussen R, Adam T, et al. Making Choices in Health: WHO Guide to Cost-effectiveness Analysis. World Health Organization, Geneva:2003.

[16] International Monetary Fund. GDP deflator and purchasing power parity exchange rate, China. Available at: http://www.imf.org/external/pubs/ft/weo/2014/02/weodata/weoselco.aspx?g=2505&sg=All+countries+%2f+Emerging+market+and+developing+economies+%2f+Emerging+and+developing+Asia.

[17] China Philanthropy Research Institute, China Red Cross Foundation. Analysis report of medical insurance and social aid for serious diseases among Chinese children. 2013. Available: http://new.crcf.org.cn/html/2014-11/24906.html (in Chinese).

[18] Peterson C, Grosse SD, Oster ME, et al. Cost-effectiveness of routine screening for critical congenital heart disease in US newborns. Pediatrics 2013;132:e595–603.

[19] Roberts TE, Barton PM, Auguste PE, et al. Pulse oximetry as a screening test for congenital heart defects in newborn infants: a cost-effectiveness analysis. Arch Dis Child 2012;97:221–6.

[20] Griebsch I, Knowles RL, Brown J, et al. Comparing the clinical and economic effects of clinical examination, pulse oximetry, and echocardiography in newborn screening for congenital heart defects: a probabilistic cost-effectiveness model and value of information analysis. Int J Technol Assess Health Care 2007;23:192–204.

[21] Ewer AK, Furmston AT, Middleton LJ, et al. Pulse oximetry as a screening test for congenital heart defects in newborn infants: a test accuracy study with evaluation of acceptability and cost-effectiveness. Health Technol Assess 2012;16:1–84.

[22] National Bureau of Statistics of the People's Republic of China. China Statistical Yearbook 2014. Available: http://www.stats.gov.cn/tjsj/ndsj/.

[23] Yeh SJ, Chen HC, Lu CW, et al. Prevalence, mortality, and the disease burden of pediatric congenital heart disease in Taiwan. Pediatr Neonatol 2013;54:113–8.

[24] Reller MD, Strickland MJ, Riehle-Colarusso T, et al. Prevalence of congenital heart defects in metropolitan Atlanta, 1998–2005. J Pediatr 2008;153:807–13.

[25] Khoshnood B, Lelong N, Houyel L, et al. Prevalence, timing of diagnosis and mortality of newborns with congenital heart defects: a population-based study. Heart 2012;98:1667.

[26] The Ministry of Health. The 4th National Health Service Survey. 2009. Available at: http://www.moh.gov.cn/mohwsbwstjxxzx/s8211/list.shtml (in Chinese).

[27] Warnes CA, Liberthson R, Danielson GK, et al. Task force 1: the changing profile of congenital heart disease in adult life. J Am Coll Cardiol 2001;37:1170–5.

[28] Macmohan B, Mckeown T, Record RG, et al. The incidence and life expectation of children with congenital heart disease. Br Heart J 1953;15:121–9.

[29] Yan S, Zhu X. Epidemiological study on the trend of accidental deaths among children under five in Beijing, during 2003–2012. Zhonghua Liu Xing Bing Xue Za Zhi 2014;35:562–5.

[30] Oster ME, Lee KA, Honein MA, et al. Temporal trends in survival among infants with critical congenital heart defects. Pediatrics 2013;131: e1502–8.