

Impact of clinical research on public health policy of neonatal screening for congenital heart disease in China

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Congenital heart disease (CHD) is one of the most common congenital malformations, with a prevalence of approximately 1% in live births.^[1,2] Among them, 1/4 to 1/3 are major CHD, including critical CHD (CCHD) and serious CHD, which require surgical or catheter intervention before 1 year of age.^[3] Major CHD, if left untreated, may cause serious outcomes, such as heart failure, cardiogenic shock, acidosis, and hypoxic-ischemic brain damage, and is one of the leading causes of infant death and childhood disability.^[4] The missed diagnosis rate of CCHD in four nurseries ranges from 13% to 48% in developed countries,^[4,5] but in China, is >71% before serious symptoms occur after birth.^[6] Therefore, screening for CHD is useful for early detection, diagnosis, and treatment and helps to improve prognosis and reduces the medical, economic, and mental burden to both the family and the society.^[5,7]

The monitoring and treatment of CHD are gaining increasing attention in China. According to a 2018 survey, 17 provinces in China had issued provincial policies or projects related to the monitoring or treatment of CHD. From 2015 to 2017, the coverage of CHD monitoring gradually expanded, with a significant increase in the number of participating counties and medical institutions [Supplementary Table 1, <http://links.lww.com/CM9/A963>]. The survey showed that screening methods for CHD, including physical examination, pulse oximetry (POX), and fetal echocardiography, varied among provinces. Screening targets were mostly children, some newborns, and pregnant women. For example, cardiac auscultation combined with neonatal visits and children's routine physical examination were used for CHD screening among children of 0–6 years old in Beijing, while fetal echocardiography was among pregnant women

in Hebei. These screening programs were not targeted at newborns; there was a lack of accurate and convenient methods and a unified public health policy for CHD screening. Although fetal echocardiography has a moderate sensitivity of 68.1% and a favorable specificity of 99.9% in the detection of CHD,^[8] it is time-consuming, requires prolonged expertise training, and is expensive. Hence, screening ability to detect major CHD in the early newborn period using these methods is very limited. It is, therefore, necessary to establish an acceptable screening method for neonatal CHD (NCHD) in China, which will benefit newborn babies with severe cardiac defects.

POX has been confirmed as an effective screening modality for CCHD, with moderate sensitivity and high specificity.^[9] However, POX only detects lesions with hypoxia.^[10] Simple but serious CHDs such as severe left heart obstructive lesions and large left-to-right shunts cannot be recognized early enough by POX to avoid heart failure or irreversible pulmonary vascular disease.

Since 2011, two large, prospective, multicenter studies have been conducted to develop an effective, feasible, and reliable screening method for NCHD in China.^[11,12] The first study ($n=122,738$) evaluated the effectiveness of POX combined with cardiac auscultation (dual-index method) in screening for major CHD in newborns between 6 h and 72 h of life. It was found that the sensitivity rates of screening for CCHD and serious CHD in newborns were 93.2% and 90.2%, respectively. It was also likewise discovered that POX with cardiac auscultation could achieve similarly high specificity (97.1% for CCHD, 97.3% for serious CHD), with a significantly reduced false positivity rate.^[11] These results were further verified in a

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subsequent study ($n = 168,575$), which proposed that the dual-index method may be used as a CHD screening strategy in the early neonatal stage, detecting over 92.1% of major CHDs with a reasonable false positivity rate (1.1%).^[12] This strategy has been applied and confirmed in Shanghai, one of the most developed regions in China.

In April 2016, the Shanghai Municipal Health Commission established a neonatal screening program for CHD using the dual-index method in all 87 delivery hospitals in Shanghai.^[13] A systematic network was established to cover the entire city with partition management for NCHD screening, diagnosis, and treatment. The municipal diagnosis and treatment centers were established in four children's medical centers for further diagnosis, treatment, and management of screened positive babies from delivery hospitals. The Shanghai Maternal and Child Health Center was responsible for the management of the design and frame construction of the NCHD screening and referral system. Meanwhile, the Shanghai Quality Control Center of Neonatal Screening Program for CHD was established at the Children's Hospital of Fudan University for data collection and quality improvement purposes. Training is conducted at least twice each year for medical staff involved in the program to ensure the quality of NCHD screening and diagnosis. The quality control center will confirm possible errors in the data reported by the screening unit, and a team of experts will be sent to the screening units for on-site supervision if there are frequent data errors. In this way, timely measures can be taken to ensure the quality of screening in response to identified problems. In 2017, a total of 197,400 (screening rate 99.16%) newborns were screened in Shanghai, 691 of whom were diagnosed with CHD; of these, >100 babies with CCHD and serious CHD were treated promptly and effectively.

Given the encouraging evidence of the benefits of CCHD screening conducted in the United States and other countries,^[9] together with the successful experience of the NCHD screening program in Shanghai, the National Health Commission of China planned to incorporate CHD screening into the universal neonatal disease screening spectrum, becoming the third-largest project of neonatal disease screening along with screening for inborn errors of metabolism and hearing disorders. However, it is a huge challenge to use a unified and low-cost method for NCHD screening in China, with such a vast territory and large population. In 2017, the Division of Maternal and Child Health Care Services organized an expert group to investigate the necessity and feasibility of promoting a nationwide program. Four representative regions were selected for investigation: Guangxi Zhuang Autonomous Region (Southwest China), Hainan Province (South China), Gansu Province (West China), and Henan Province (Central China). Based on the investigation, three documents for NCHD screening were developed: "Neonatal Congenital Heart Disease Screening Management Requirements," "Neonatal Congenital Heart Disease Screening Technical Standard," and "Neonatal Congenital Heart Disease Screening, Diagnosis and Treatment Organization Criteria." Meanwhile, several seminars and workshops were organized by the Children's

Hospital of Fudan University in collaboration with the Newborn Foundation (USA) and CHAMPS Foundation at New York, to discuss the importance and difficulties of CHD screening in newborns in China; government officials responsible for child health care were invited to attend the meeting. In March 2018, experts from around the country in the field of neonatal screening, neonatology, cardiology and cardiac surgery, child health care, public health, and policymaking were invited to review the documents. Almost all experts recommended that NCHD screening should be performed throughout the country. Importantly, they agreed that using the dual-index method for NCHD screening in China is feasible, low-cost, accurate, and convenient. It was time to establish a nationwide neonatal screening program for CHD.

On July 30, 2018, the National Health Commission of China issued "The Work Scheme of Neonatal Congenital Heart Disease Screening Program" as a public health policy in China, and encouraged provinces to actively participate in this program voluntarily.^[14] At first, 24 provincial-level administrative regions declared that they would implement NCHD screening in 2018, which marked the inclusion of NCHD screening in the spectrum of universal neonatal disease screening in China. Meanwhile, the National Management Office of Neonatal Screening Project for CHD was established at the Children's Hospital of Fudan University with the responsibilities for project implementation, routine management, standardized training, technical support, information system management, quality control and supervision, data collection, analysis, and reporting. For this nationwide project, screening training and quality control practices were similar to those in Shanghai. In addition, an information management system has been established, and the screening, diagnosis, and treatment data for CHD are reported directly from each unit. By the end of 2019, 28 provincial-level administrative regions have participated in the NCHD screening project in China, and most provinces had set up the steering and provincial management offices, formulated work plans, and held provincial-level kick-off and training meetings. From January 2019 to December 2020, >6 million newborns were screened for CHD using the dual-index method in China, 25,649 newborn babies were diagnosed with CHD, and thousands of major CHD babies were treated.

Although sporadic, evidence-based public health policy-making has increased in China in recent years.^[15] The success of neonatal screening for CHD has become a model of the transformation of clinical research results into national public health policy, and it may be of benefit to international proponents of neonatal screening and countries that are working to overcome implementation challenges.

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Conflicts of interest

None.

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