COMMENTARY

Is it time for developing countries to adopt neonatal pulse oximetry screening for critical congenital heart disease?

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ABSTRACT

Critical congenital heart disease is often missed with resultant death or severe circulatory collapse and morbidity. Pulse oximetry screening has now been recommended for use in the United States of America and adopted in other developed world settings as part of the compulsory newborn screening programme. In this review we detail the rationale behind neonatal pulse oximetry screening, summarise the recent evidence and present data on method, cost-effectiveness and acceptance. However, differences in health systems in the developed world and developing countries are clearly reflected in the discrepancies in management and outcome of congenital heart disease. We discuss the importance of embedding a neonatal screening programme within local situations and suggest a method, using the infant mortality rate and other neonatal indicators, to position neonatal pulse oximetry screening into existing newborn screening programmes. SAHeart 2013;10:454-461

INTRODUCTION

A congenital heart defect (CHD) is the most common type of birth defect and the leading cause of infant deaths in the developed world.[1] The birth prevalence of a CHD is 1:100 - 1:150 while the figure of 8:1 000 is more widely reported from population based studies. A critical congenital heart defect (CCHD) refers to a potentially life-threatening cardiac abnormality; this is reported in 2 - 3/1 000 live births.[2]

Practitioners in developing countries have long bemoaned the fact that CHDs are either missed entirely, or detected at an advanced stage, too late for full repair.[3] The benefits of early detection of CHDs stretches beyond the survival of neonates and infants, and include improved long-term outcomes for those identified early in their disease.[4] This is particularly important in this era of vastly improved outcomes and survival for children with CHDs. It is thought that over 80% of babies born with a CHD will survive into their second decade. This estimate continues to increase in the developed world with current intensive care and surgical protocols.[5] However, infants with CCHDs are still being missed, often with dire consequences.

THE DIAGNOSTIC GAP

An undetected CCHD is a significant cause of sudden or unexpected early neonatal death, with over 50% of patients dying at home or in the hospital emergency department in a California review.[6] This paper reported that over 30 patients per year, with a median age of 2 weeks, died of a missed or delayed CHD diagnosis. The majority of lesions were left-sided obstructive lesions. These data are similar to United Kingdom (UK) data: in 1 study 15% of infants with a CHD, which died before 12 months, were undiagnosed prior to death.[7] Infants detected after post-natal discharge, who survived, are also more likely to present with cardiovascular collapse and organ dysfunction.[8]

Antenatal screening for birth defects has now become routine in many parts of the world with history taking, blood tests and antenatal ultrasound and advanced methods such as amniocentesis and chromosomal analysis becoming part of the prenatal assessment.[9,10] However, screening foetal echocardiography is not a universal test and in fact, routine antenatal ultrasound is limited to the developed world and to tertiary centres in low and middle-income countries.

Clinical assessment of infants in post-natal wards has been the routine method of screening for undiagnosed defects and to ensure that infants are healthy prior to discharge. Cardiovascular examina-

tion of the newborn should include auscultation, palpation of peripheral pulses and femoral pulses and noting the presence of central cyanosis. These clinical signs are difficult to detect in the newborn period. A UK study reported that over half of babies with a CHD detected in the first 12 months of life were discharged from hospital with a normal routine neonatal examination and that the 6 week examination missed one-third of affected babies.[11] Early post-natal discharge compounds this problem and increases the risk of missing a CCHD.[12] In many settings in low and middle-income countries, births are not attended and infants are discharged within hours of birth without examination from a health care practitioner.[13]

It is thus clear that in settings where antenatal ultrasound is not routine, where birth attendance is suboptimal and where early infant discharge is recommended practice, CCHDs will go undetected. Pulse oximetry screening has been suggested as a strategy to address the diagnostic gap.[14]

PULSE OXIMETRY AND PRE- AND POST-DUCTAL SATURATIONS

Pulse oximetry has been used within clinical practice for some time and is a widely accepted method of assessing oxygen saturation.[15] Essentially a sensor is placed on an extremity such as a finger, toe or ear. Within the sensor, light emitting diodes shine red and infrared light through the tissue. The blood, tissue and bone at the application site absorb most of the light; however, some light passes through the extremity. A light-sensitive detector opposite the light source receives it, measures the amount of red and infrared light received by the detector and calculates the amount absorbed. The amount of light received by the detector indicates the amount of oxygen bound to the haemoglobin in the blood. Oxygenated haemoglobin (oxyhaemoglobinor HbO2) absorbs more infrared light than red light. Deoxygenatedhaemoglobin (Hb) absorbs more red light than infrared light. By comparing the amounts of red and infrared light received, the instrument can calculate the saturated oxygen (SpO2) reading. Pulse oximetry has been adopted as an essential element in the WHO surgical checklist and several organisations are committed to supplying each healthcare facility in the world with pulse oximeters.[16,17]

Critical congenital heart disease refers to a potentially life-threatening cardiac abnormality where either the systemic or pulmonary circulation is dependent on a patent ductus arteriosus (PDA) such as pulmonary atresia or interrupted aortic arch. Table 1 details other situations such as transposition of great vessels with poor inter-circulatory mixing due to a restrictive foramen ovale and the obstructed form of total anomalous pulmonary venous connections with severe pulmonary venous hypertension. In these situations, abnormally low pre- and post-ductal saturations or a differential of ≥3% between the 2 readings should alert the clinician to the possibility of cardiac anomalies.

TABLE 1: Critical congenital heart defects

Duct-dependent pulmonary blood flow
Tetralogy of Fallot
Tricuspid Atresia
All forms of anatomic pulmonary atresia with or without associated intracardiac anomalies.
Tricuspid Incompetence/Ebsteins (Functional pulmonary atresia)
Inter-circulatory mixing
Truncus Arteriosus
Transposition of the Great Arteries (TGA)
Total Anomalous Pulmonary Venous Drainage (TAPVD)
Systemic Hypoperfusion
Hypoplastic Left Ventricle/Critical aortic stenosis
Critical coarctation/Interrupted aortic arch

CURRENT EVIDENCE FOR NEONATAL PULSE OXIMETRY SCREENING

The first reports suggesting the use of pulse oximetry as a screening test for CCHD were published in 1995.[18] These were followed by single unit studies before several large cohort studies were undertaken. Firstly, a cohort study of 39 821 newborns in a single region in Sweden recorded a sensitivity of 82.9% and a specificity of 98%. Of interest is that no infant that underwent oximetry died of duct-dependent systemic or pulmonary circulation compared to 5 such deaths in regions without pulse oximetry.[19] This was followed by a German study of 3 364 term neonates who underwent pulse oximetry between 6 and 36 hours. Of the 18 neonates with abnormal results, 50% had critical congenital heart defects. Sensitivity was determined to be 82% and specificity 99.9%.[20] This was followed by a larger multi-centre study involving 34 units in Saxony and 42 240 infants born between 2006 and 2008. All participants with prenatal diagnoses were excluded. A variety of pulse oximeters were used and saturations of ≥96% taken on either foot were deemed normal. Measurements were taken at 24 - 72 hours. This study established that pulse oximetry screening had the potential to substantially reduce the postnatal diagnostic gap in primary, secondary and tertiary settings.[21-23]

In the UK, a study looking at cost-effectiveness of screening determined that pulse oximetry required testing within a UK setting in order to more accurately determine costs based on primary data.[5] A large multi-centre study was thus undertaken involving 20 555 newborn babies.[24] The study reported an incidence of major

congenital heart disease of 2.6:1 000 live births with 24 babies with a CCHD detected. The sensitivity reported was 75% (95% CI 53.29 - 90.23) for critical cases, 49.06% (95% CI 35.06 - 63.16) for a major CHD with a specificity 99.16% (95%CI 99.02 - 99.28) and false positive rate of 0.8%.[24]

When reviewed within a systematic review and meta-analysis,[25] some key observations were described:

- Pulse oximetry detected 30 additional cases of a CCHD per 100 000 live births.
- The false positive rate, if tested at >24 hours was 0.05 (0.02 - 0.12), which equates to a specificity of 99.95% and sensitivity of 77.5 (61.8 - 88.0).

The cost-effectiveness analysis based on these data revealed a primary cost of £24 000 per case of timely diagnosis.[26] With a threshold £100 000, the probability of pulse oximetry being cost effective is greater than 90%. This is plausible if a newborn gained only 5 Quality Adjusted Life Years (QALYs).[27]

This assessment also reviewed acceptability of the intervention and was able to demonstrate that pulse oximetry screening was widely acceptable to parents. Careful communication of results needed to be conducted, both to minimise parental anxiety and to avoid false reassurance.[28] Parents may need information on heart defects in order to better understand both the screened conditions and the importance of testing. Participants from all groups felt that the test should be a routine part of standard care and felt pleased to have had the opportunity to take the test.[28] Of importance was the additional finding in those with false positive results. In 49/169 families with false positive results, pulse oximetry detected major congenital heart lesions or other critical conditions (infective, respiratory) which required intervention.[28]

Additional studies have now been performed in the US,[29-32] UK and Europe[33-35] while several studies have been performed outside of these large and well-resourced centres.[36] In Poland a prospective screening pulse oximetry test was conducted in 51 neonatal units in the Mazovia province between 2006 and 2008, screening over 52 993 newborns with a sensitivity of 78.9% and a specificity of 99.9%.[37] This protocol isolated asymptomatic from symptomatic infants. Only asymptomatic term newborns were screened and included in the analysis. In this asymptomatic group, pulse oximetry was performed between the second and 24th hour of life with test performed at a median fifth hour of life. Defects detected included transposition of the great arteries and hypoplastic left heart syndrome and increased the perinatal detection of CCHD from 76.8% to 95%.

In contrast, an earlier study from India[38] attempted to introduce pulse oximetry screening in a less resourced setting. Of interest was the use of different cadres of healthcare practitioners: the on-site paediatrician performed clinical evaluation while pulse oximetry was performed by a study nurse. Bedside echocardiography was performed by a research officer while only those babies with abnormal echoes were reviewed by a paediatric cardiologist. In this context the sensitivity of pulse oximetry with clinical examination was low with a sensitivity of <20%. This study expounded upon the limitations of technical and human factors as well as limited echo capacity. Only major lesions had a confirmatory echocardiogram immediately, minor lesions were echoed by 6 weeks.

PULSE OXIMETRY PROTOCOLS: HOW, WHERE AND WHEN?

How should pulse oximetry be performed?

It is critical to use a pulse oximeter licensed for use in neonates and infants and shown to produce stable, accurate recordings free from motion artefacts. It is important to standardise instruments, train staff in recognising normal plethysmogrpahic waveforms and to recognise pitfalls in measurements such as poor perfusion, severe haemolytic jaundice or tachyarrhythmias.[39]

Where should the probe be positioned?

Probe positioning is crucial as inaccurately low readings might occur when the probe is inappropriately placed on the small fingers of neonates and infants.[40] This pitfall can be avoided by using probes of appropriate size for neonates and infants. The threshold for an abnormal saturation is important in considering the sensitivity and specificity of the test; the higher the percentage saturation thresholds the greater the sensitivity but the lower the specificity, and the converse is true for a lower cut-off. The most frequently used upper threshold in the published studies is 95%.[41] Some have used post-ductal saturations as a single measurement,[42] while others used both pre- and post-ductal saturations and included a difference between the two in the definition of abnormality.[25] Use of a differential criterion may increase the likelihood of detecting those with obstructive left heart lesions, such as Coarctation of the Aorta, where the ductus supplies some of the systemic circulation and may result in a difference in saturation between the upper and lower limbs.

When should the reading be taken?

The increasing trend towards earlier discharge in North America, Scandinavia and the UK is well established and is likely to continue. This will result in an increasing number of babies being discharged from hospital before a CCHD is manifested.[12] This has influenced the outcomes of studies utilising different time periods for screening - in general those that screened between 24 - 72 hours had the lowest false positive rates[25] yet risked potential collapse within 12 - 24 hours in left sided obstructive lesions. It is thus important to take into consideration the policy of the unit and screen each infant prior to discharge regardless of the age – those

failing an early pulse oximetry screening test with a normal clinical evaluation could have a repeat pulse oximetry test performed at about 24 hours (Figure 1).

ADVOCACY, POLICY AND LAW

In 2012, following a series of pulse oximetry screening studies, the American Academy of Paediatrics (AAP) released a policy statement endorsing the recommendation of pulse oximetry screening for critical congenital heart disease.[42] This initiated the process of legislating for pulse oximetry in many states in the United States of America (USA). This recommendation has not been replicated in other countries and mixed feelings still exist regarding the routine use of pulse oximetry screening.[43,44]

The debate has, however, succeeded in raising awareness of congenital heart disease and the importance of early detection and the policy of neonatal screening programmes. In order to introduce and run an effective newborn screening programme, some critical elements need to be addressed namely:

- An innovative and sustainable financial strategy.
- Strong leadership in developing and working towards national programme implementation.
- Strategic advocacy programmes to ensure programme sustainability.
- Strong multi-sectoral collaboration in planning and implementation.
- A comprehensive public health system.

Introducing a newborn screening programme has clear benefits, yet implementation has been less than ideal. A survey undertaken in the South African private health care sector of hearing screening showed that newborn hearing screening was only available in 53% of private units in which only 14% provided universal screening.[45] Neonatal screening for congenital hypothyroidism however has been well established with coverage of over 75% reported in less resourced nations.[46,47] A strongly committed team, together with governmental support, financial costs related to cover and treatment and adequate teaching and training are essential in establishing comprehensive newborn screening programmes.[48] All of these elements are crucial in developing a pulse oximetry screening programme, even if underpinned by the recent evidence of sensitive, specific and cost-effective protocols in studies.

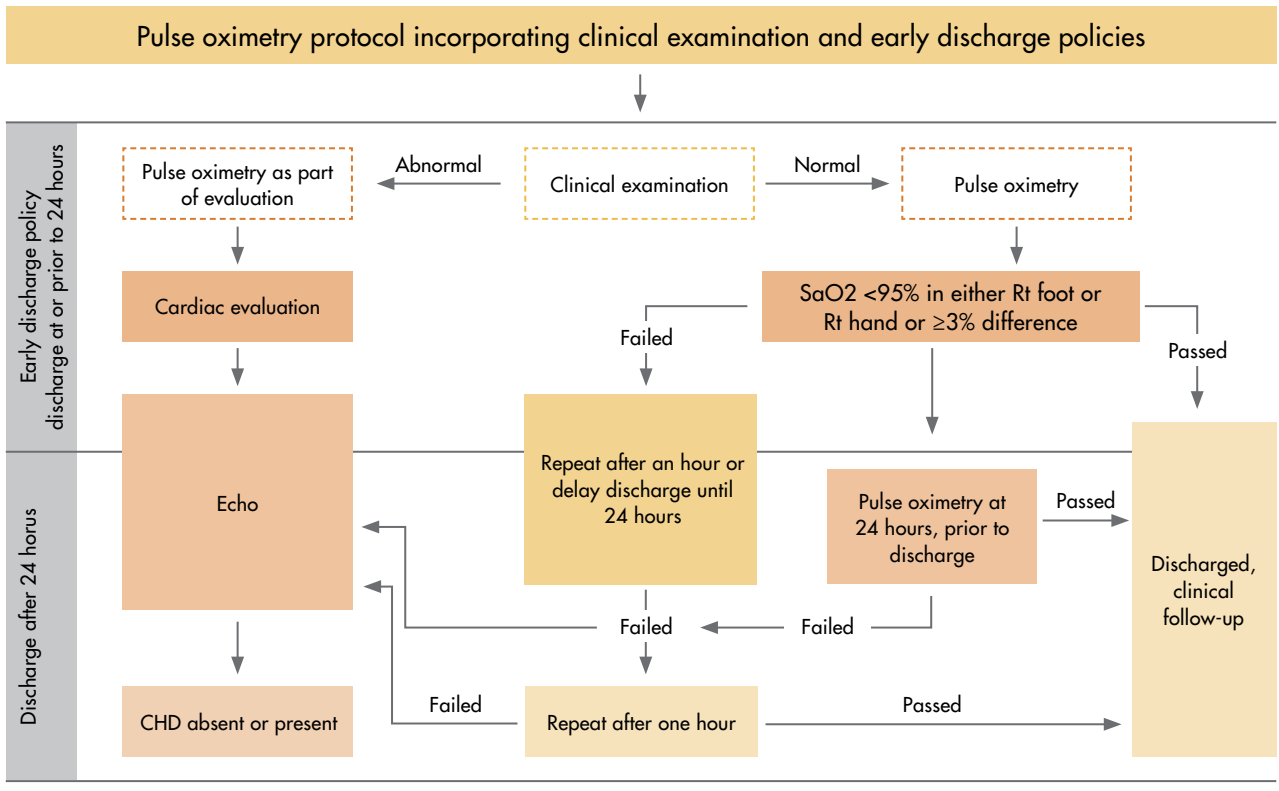

FIGURE 1: Pulse oximetry protocol

After the endorsement by the AAP, efforts were co-ordinated by several advocacy groups to introduce pulse oximetry as law. As a result, several states in the USA have adopted laws requiring newborn screening for CCHD as depicted on the CCHD screening map in Figure 2. It is unprecedented for a health intervention to be adopted as law in the United States at this scale and within such a relatively short period of time, with the major lobbyists being parent and advocacy groups rather than medical professionals.

IS THIS REALLY AN OPTION FOR DEVELOPING COUNTRIES?

The healthcare systems in the developing world are vastly different from those in the industrialised nations. Within large developing countries, significant differences exist in health care indices such as infant mortality rate (IMR) and priorities for health care. In India the national IMR value is 44;48 for rural India and 29 for urban areas.[50] There is a very wide gap in IMR between states with good human development indices (Kerala IMR 12) and those with less well developed health care systems (Odisa IMR 57). This gap is also present in emerging economies such as South Africa, China and Brazil. The causes of childhood mortality is remarkably different in areas with low IMR vis-à-vis those with high IMR. Typically, in the high IMR areas, most of the infant and childhood deaths are attributed to preventable causes like malnutrition, diarrheal illness, pneumonia and birth asphyxia.[51] However, once the IMR values start declining, the proportion of childhood deaths due to congenital malformations like CCHD becomes more important.

The overall data about the utility of pulse oximetry in the developed world seems to favour its introduction as a screening tool for neonatal CCHD screening. Following these studies and the active campaigning by advocacy groups, several countries have introduced mandatory pulse oximetry screening as a part of routine newborn screening. However, the major public health concerns about mandatory screening centres around the issue of false positives.[52] Assuming sensitivity and specificity values based on data from the

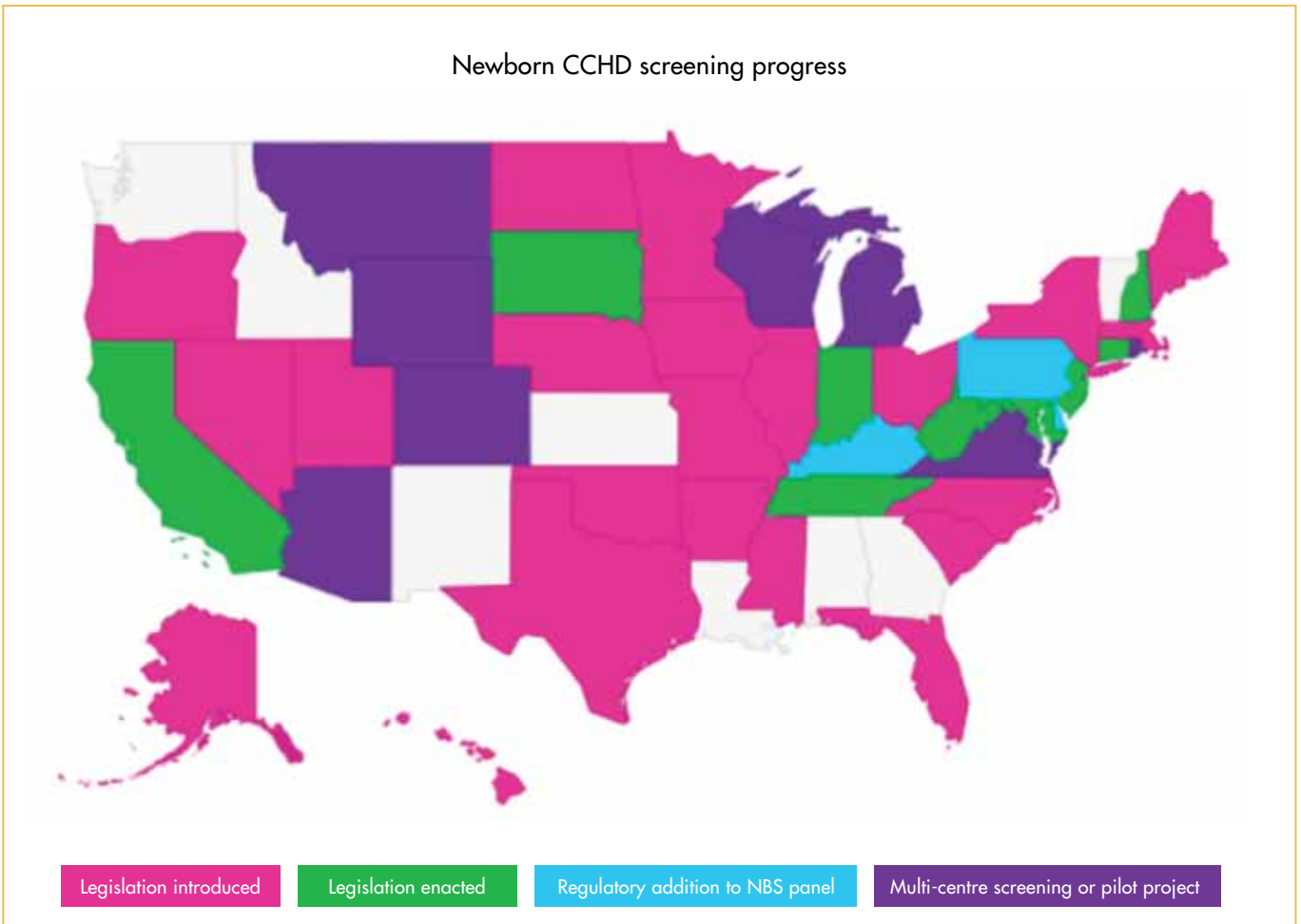

FIGURE 2: Newborn screening for CCHD. With kind permission from the Newborn Foundation Coalition.[49]

developed world and applying the Bayes Theorem, the post-test probability of CCHD following a positive pulse oximetry screen would be 16%. If we take the data from the developing world and re-apply the Bayes theorem, this probability would further decrease to 3%. Considering the fact that the overall accuracy of pulse oximetry in mass community settings is much lower than in trial settings, the overall prevalence of false alarms is likely to be much higher in community based screening programmes. Consequently, if we routinely practice pulse oximetry screening for all asymptomatic newborns in a community, the absolute number of referrals for further testing (principally paediatric echocardiography) is going to be very high. This may simply overwhelm the already delicate health care facilities in developing countries. To add to the problem, many developing countries do not have clear health policies or infrastructure to treat children with a CCHD, especially in public sector, government funded hospitals.

Hence, introduction of newer neonatal screening tests should complement the local child health care priorities and should be dictated principally by the local needs rather than based on data from a completely different healthcare system. Ideally, this should be based on local prevalence data, currently available infrastructure for treatment once a diagnosis is made and local health economics and priorities. Essentially, as Winston Churchill famously said, "It is not enough that we do our best, sometimes we have to do what is required". The following discussion will examine the role of pulse oximetry in the context of developing economies with this background in mind.

PULSE OXIMETRY IN AREAS WITH LOW IMR

A typical situation where this scenario exists within India is the state of Kerala from where a prospective study on clinical utility of pulse oximetry for newborn CCHD screening was published.[38] The current IMR in Kerala is 12 and this is a very clear reflection of reduction in mortality due to preventable causes. The Millennium development goal (MDG) target for IMR in Kerala by 2015 is 5.5. It is very clear that in order to achieve this we need to focus on other causes of childhood mortality of which major congenital malformations, especially CCHDs, contribute significantly. The feasibility of performing neonatal heart surgeries with in-hospital mortality almost comparable to developed nations has been already reported from Kerala.[53] Hence, the focus has to shift towards early detection of critical CHD, more efficient transport of neonates with a CCHD to a tertiary centre before clinical deterioration and reducing the pre-operative morbidity. Hence, routine screening of all newborns with pulse oximetry seems to be an attractive concept in these health care systems. In addition, pulse oximetry screening may facilitate early diagnosis and management of severe non-cardiac problems like respiratory illnesses, thereby contributing further to reduction in neonatal mortality. In tandem with pulse oximetry screening, the following additional measures may also facilitate early detection and safe transport of infants with a CCHD.

- Improving the efficiency of antenatal screening for serious CHDs in early mid trimester scans by educating obstetric sonographers on foetal heart screening protocols.
- In-utero transport of foetuses with critical but repairable CHDs like TGA and Coarctation for planned delivery in a tertiary cardiac care facility.
- Training of healthcare personnel in primary health centres and district level hospitals to facilitate more efficient neonatal cardiac evaluation, including pulse oximetry. The importance of repeat testing in case of an initial abnormal screen needs to be highlighted.
- Training of neonatologists in bedside echocardiography as a screening tool for major CHDs in the event of a positive pulse oximetry screen. This can avoid a lot of referrals due to false positive screens, thus saving time and costs and reducing the risk associated with transport.
- Improving networking and transfer of data between peripheral centres and tertiary hospitals through newer strategies like Telemedicine.
- Improving facilities for the transport of sick neonates to a tertiary centre using monitored systems of transport.

The situation in urban South Africa is remarkably similar to that in India with low infant mortality rates within cities with largely privately insured patients and excellent cardiac surgical centres. Based on evidence presented in 2010,[54] it is clear that there is a significant diagnostic gap with far less patients being diagnosed with critical congenital heart disease than expected, even in private units. It is thus an appropriate consideration to investigate the feasibility of launching pulse oximetry programmes within pilot South African sites.

PULSE OXIMETRY IN AREAS WITH HIGH IMR

These are areas where the basic child health care systems need to be energised and deaths, due to preventable causes, prevented. Management of critical and complex CHDs may not be a very major public level child health priority in these areas at present. In these areas, the current focus should be on raising awareness about CHDs, especially those with good outcomes, amongst the health care professionals and ensuring that the available resources are channelled more efficiently towards treatment of such lesions. Pulse oximetry may aid early detection of correctable non-cardiac problems like respiratory illnesses. We need to ensure that the healthcare providers who practice pulse oximetry are adequately trained in the technique[14] which will have an impact on the entire health system. We need more data from these contexts about the utility of newborn screening using newer techniques, like pulse

oximetry, before recommending this strategy as standard of care for a community level practice. Furthermore, we need more data about the cost effectiveness of newer screening strategies to ensure that the cost of case finding is in tandem with the infrastructure available to ensure effective follow-up action and aftercare including tertiary cardiac care. This requires an integration of medical personnel, research bodies, local academic organisations and the government agencies keeping the needs of the average citizen of the community in the centre of the algorithm. Areas of South Africa that are severely under-resourced, such as the provinces without any paediatric cardiac services,[55] will need significant infrastructure and health system development prior to the implementation of a new screening programme.

CONCLUSION

Pulse oximetry is a safe, feasible, easy test which is also cost-effective. It has been shown to be acceptable to parents and medical staff alike and is unprecedented as a screening test to detect CCHD. However, implementation necessitates integration into existing newborn screening programmes with commitment to training, sustainability and strengthening of collaborating healthcare infrastructure. The optimal programme for early detection, follow-up and data management in existing programmes must be developed while CCHD screening must be integrated with current birthing services, ideally with centralised data management and quality control. Contextualising the local situation is key, as is consideration of primary mortality indicators. Until infants born in developing countries have access to comprehensive primary healthcare services (including antenatal assessment, qualified birth attendance and post-natal examination) and only if cardiac services have improved concurrently in many of the regions under discussion, pulse oximetry screening will not change the undeniable fact that infants with critical congenital heart disease will continue to be missed and die, many undiagnosed.

"No mother should find out about her child's heart defect from the coroner" - Kristine Brite McCormick, Indiana.[56]

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