To assess the accuracy of pulse oximetry screening as a tool to detect critical congenital heart disease in asymptomatic newborns at altitude

Dr Michael Platten

Student Number 1176556
MMed Paediatrics
University of the Witwatersrand

Supervisors
Professor A.M. Cilliers
Dr H. Ntsinjana

Abstract

Introduction: Pulse oximetry screening (POS) in the newborn period has been shown to improve early detection of critical congenital heart disease (CCHD) before significant morbidity and/or mortality develop. Acceptable sea-level saturation thresholds range from 90-95% in newborns whereas at altitudes >1500m this decreases to 88-93% due to lower partial pressures of oxygen. Objective: To determine whether lower oxygen saturation thresholds would be better suited to direct POS in neonates born at altitude (>1500m), and to compare the revised cut-offs to those recommended by the American Academy of Pediatrics (AAP) guidelines for POS for CCHD. Methods: We performed a prospective descriptive study of well newborn patients born during a period of two months (October and November 2015) at Chris Hani Baragwanath Academic Hospital (CHBAH). POS was conducted in term newborns at >12 hours of age measuring saturations in the right hand (pre-ductal) and either foot (post-ductal). Using a modified version of the AAP POS guidelines (Pre-ductal saturations 93% and post-ductal 88% for CHBAH versus 95%/90% for AAP), all patients underwent echocardiogram to confirm the results of screening. Results were analysed assessing the effects of altitude on screening. Results: Three-hundred and forty eight infants were included in the study. No patients with CCHD were identified. Mean saturations were 94% for right hand and foot. Adjusted cut-offs of 93-88% result in 15.2% of patients requiring repeat screening and 41.3% using AAP guidelines (95-90%). Failed screens were attributed to physiological right-to-left or bi-directional shunting in 3/348 (0.8%). Accuracy is comparable internationally (sensitivity (100%), specificity (99.4%) and false positive rate (0.64%)). Conclusions: Altitude does not affect the accuracy of POS. If screening is to be implemented above 1700m, adjusted POS cut-offs of 93-88% should be considered at altitudes above 1700m.

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24 May 2018

Dr Michael Platten

Dedication

To Welma

For all your support and encouragement

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Abbreviations

AAP	American Academy of Pediatrics
CHD	Congenital Heart Disease
CCHD	Critical Congenital Heart Disease
CHBAH	Chris Hani Baragwanath Academic Hospital
ECHO	Echocardiogram
FT	Foot – Left or Right
MOU	Midwife Obstetric Units
MR	Mitral Regurgitation
PDA	Patent Ductus Arteriosus
PFO	Patent Foramen Ovale
PO	Pulse Oximetry
POS	Pulse Oximetry Screening
RH	Right Hand
SD	Standard Deviation

Introduction

The use of pulse oximetry screening (POS) in South Africa for the detection of critical congenital heart disease is still gaining momentum. With interest increasing in the field of POS in South Africa, this research was designed to answer two main questions, namely, should hospitals in Gauteng be using lower saturation cut-offs for POS due to its elevation above sea-level and secondly, does altitude affect the accuracy of pulse oximetry screening? I hypothesised that altitude would not affect the accuracy of POS but given Johannesburg's elevation above sea-level (1700m), lower oxygen saturation cut-offs would need to be used.

Congenital heart disease (CHD) is the most common form of congenital malformation in newborns, affecting 7-9/1000 live births worldwide[1, 2]. CHD accounts for 3% of all infant mortality, while comprising 46% of deaths attributed to congenital malformations[1]. The term Critical Congenital Heart Disease (CCHD) refers to the presence of a cardiac lesion requiring surgery or cardiac catheterisation within the first year of life[3].

Clinical context

With advances in medical diagnostic technology, the diagnosis of CCHD can be made through multiple methods. Primary screening can be done at the bedside using clinical examination. However, antenatal diagnosis is possible nowadays, through the use of foetal ultrasound or echocardiography. However, in South Africa, there is limited access to experienced obstetricians and foetal echocardiographers who can perform routine foetal ultrasound screening for pregnant mothers. Anecdotally these experts are mainly found in tertiary and quaternary government institutions and private hospitals. Screening antenatal ultrasound alone has been used in the past, but it has been shown to increase the chance of missing CCHD. When compared with Pulse

Oximetry (PO), the sensitivity of isolated antenatal ultrasound screening was 50% versus 75% for PO[4]. Echocardiography (ECHO) is regarded as the definitive test to confirm the presence of CCHD[5]. The 'gold standard' for arterial blood oxygen saturation analysis as a way of screening for CCHD is invasive capillary arterial blood gas, which is not ideal for well neonates. Known physical manifestations suggestive of CCHD include the presence of heart murmurs, tachypnoea and cyanosis, but can also present with severe hypoxaemia, shock and acidosis[5]. Unfortunately, these signs may only be present after discharge when there is alteration in pulmonary and systemic vascular changes due to the closure of the patent ductus arteriosus. This can result in acute clinical deterioration as the patent ductus is essential in maintaining adequate blood flow, depending on the lesion involved (Table 1)[5]. The lesions that are considered part of CCHD can be seen in Table 1.

Outflow tract defects	Transposition of the great arteries Double outlet right ventricle Truncus arteriosus Tetralogy of Fallot
Right obstructive defects	Pulmonary atresia Tricuspid atresia
Left obstructive defects	Aortic stenosis Hypoplastic left heart syndrome Coarctation of the aorta (including interrupted aortic arch)
Other defects	Ebstein anomaly Total anomalous pulmonary venous drainage Single ventricle

Table 1: CCHD Malformations [5]

Morbidity and Mortality

As the above clinical context suggests, thirty percent (30%) of newborns with CCHD are missed during routine clinical examination[6]. Moreover, population-based studies have shown that one-quarter of the newborns with critical cardiac problems were detected late. Consequently, there was prolonged hospitalisation with exuberant hospital costs[7]. Morbidity in these patients is related to the effects of prolonged

hypoxaemia and ischaemia caused by the CCHD lesion where tissues most profoundly affected are those with high oxygen requirements, such as neuronal tissue. This is particularly important in the neonate as the neonatal brain is very sensitive to changes in blood flow, pressure and oxygen content due to impaired autoregulation. Alteration in cerebral blood flow control as well as reduced or absent reactivity to carbon dioxide and mean arterial blood pressure have shown to contribute to cerebral damage[8]. As a result, the neonatal brain can be significantly injured prior to diagnosis, but also pre-, intra- and post-operatively which could have an impact on long term quality of life[8].

Current mortality associated with the above lesions varies, but multiple studies have shown that mortality is high in those with missed diagnoses. Kuehl, *et al*, published a study looking at CCHD related deaths between 1981 and 1989, and reported a mortality rate of 1.7% (76 of 4360 children) in those dying prior to a diagnosis being made[9]. More recent studies reveal that CCHD related deaths are now in the region of 0.4-2.0/10000[10]. The improved survival is due to increased use of prostaglandin therapy for duct dependent lesions and improved surgical techniques[5].

Cyanosis and Pulse Oximetry

Cyanosis is described as a blue discolouration of the skin and mucous membranes due to an increased quantity of deoxygenated haemoglobin in the body. In the majority of CCHD lesions, cyanosis and hypoxia are caused by the presence of deoxygenated haemoglobin. This occurs when deoxygenated pulmonary blood mixes with oxygenated aortic blood through a shunt resulting in higher oxygen saturations pre-ductal and lower saturations post-ductal. This shunt could be intracardiac (e.g. VSD) or extracardiac (e.g. PDA). In a very early 1920's study, it was shown that 4-5g of deoxygenated haemoglobin was required to cause clinically evident cyanosis[11]. Therefore, as cited by Mahle, *et al*[5], cyanosis will only be present in an infant (who

has a haemoglobin concentration of 20g/dL) when the arterial oxygen saturation is <80%. Therefore, many infants with arterial oxygen saturation between 80-95% will not have overt cyanosis present. This is further made challenging in patients with darker skin pigmentation[5]. Extensive work and progress was made in the 1970's when PO was identified as a valuable non-invasive patient monitoring adjunct[12]. Pulse oximetry employs principles of spectrophotometry, and it works on the basis of differential absorption spectra of arterial blood and its pulsatile nature to determine the oxygen saturation of the blood. With increasing oxygen saturation, the haemoglobin absorbs more infrared light (940nm) but more red light (660nm) when deoxygenated. The ratio between these key measurements is used to extrapolate the oxygen saturation of blood[13].

Differentiating respiratory from cardiac causes of cyanosis can be challenging in a clinical setting. The use of the 'Hyperoxia Test' has been proffered as a tool to assist in this diagnosis. During this test, the neonate is exposed to more than 95% inspired oxygen for 30 minutes and in the presence of a cyanotic heart lesion, the PaO_2 will not rise above 100mmHg[14].

Current Screening Practice

At present, there is no uniform screening protocol legislated in South Africa, nor any hospital-based protocol outlining the routine screening of newborns for CCHD in Chris Hani Baragwanath Academic Hospital (CHBAH). This is in stark contrast to the United States of America, Nordic countries, Switzerland and the United Arab Emirates. These countries have variable uptake of screening but are heading toward universal screening. The USA is the most progressive with an estimated 90% screening by the end of 2014[15]. In South Africa, the POPSICLE feasibility study was done in the Western Cape looking at implementing routine pulse oximetry screening (POS)[16]. The study findings were in keeping with those overseas (incidence of CCHD,

diagnostic accuracy of POS) when using the same oxygen saturation cut-offs as the AAP guidelines (Appendix 1).

Evidence Supporting Use of Pulse Oximetry Screening in Newborns

There are multiple studies validating the use of PO monitoring in clinical practice. There are also studies outlining normal reference ranges of oxygen saturations in healthy, term newborns. The median baseline oxygen saturation for term neonates in their first 24 hours of life was shown to be 98.3%[17]. Oxygen saturations in the same range have been found to exist throughout the remainder of the first month of life[18-20]. This shows that oxygen saturations remain above 95% throughout the first month of life in healthy term newborns; consequently, a saturation reading less than 95% can indicate the presence of pathology, even during the first day of life.

Several studies have been published looking at the screening of CCHD in the neonatal period using PO[18, 21-24]. While these studies have varying guidelines when screening for the presence of CCHD using PO, they have contributed to the body of knowledge that assists in creating screening protocols. The American Academy of Paediatrics (AAP) guidelines[5] stopped short of recommending a universal screening protocol in their 2009 paper so in a later *Paediatrics* publication, an approach was put forward when screening newborns (Appendix 1)[25] . While the guidelines are compiled using best available evidence, concerns were raised by the study about the risk of false-positive results in newborn screened at higher altitudes, especially >5000ft (>1524m). This is of consideration in the proposed study at CHBAH as Johannesburg is located at an altitude of approximately 1700m. Studies looking at normal oxygen saturation levels at high altitudes revealed that normal values range from 88%-93% at elevation above 1500m[26-28].

Screening at altitude

Currently there are no guidelines available for the screening of patients at high altitude, though some work is being done in the area to ascertain improved normal values[25]. Preliminary work by Bakr in 2005 examining the effects of altitude on newborn screening shows that those at higher altitude should be using lower oxygen saturation cut-offs when screening newborns[26]. In their study, mean PO levels at 24 hours in newborns was 94.3% and 95.4% at 1 hour and 24 hours, respectively. This was done at an altitude of 1640m above sea level. A more recent study looking at the effects of altitude on POS in newborns shows that oxygen saturations at 1500-1600m above sea-level are expected to fall between 93-95% which is in keeping with the findings of Bakr, *et al[26, 29]*.

Summation

Screening of newborns for CCHD has been around for just over 20 years, but has only gained momentum clinically in the last 10 years. Significant progress is being made abroad in establishing routine screening, but the progress in South Africa has been particularly slow. As can be seen, the benefits of establishing routine screening are many, especially in reducing morbidity and mortality associated with CCHD. As such, the establishment of a standardised screening protocol in South African hospitals would be of great benefit.

This study therefore aims primarily to assess the accuracy of POS at altitude and, secondarily, the need for an adjusted screening algorithm with lower pulse oximetry cut-offs compared to sea-level (Appendix 2). It too seeks to assess the feasibility of screening at Chris Hani Baragwanath Academic Hospital given the current resources.

Methods

Setting/Location

Chris Hani Baragwanath Academic Hospital (CHBAH) manages and treats a vast majority of patients in the greater Gauteng region, servicing nearby Soweto and acting as a tertiary referral hospital for the surrounding clinics and district hospitals. This drainage area results in approximately 20000 to 25000 deliveries per annum at the hospital (Premature and Term deliveries). The CHBAH Obstetrics and Gynaecology Department comprises five postnatal wards which are divided into two normal vertex delivery wards, two post-Caesar wards and one ward that admits patients with post-partum complications. The normal vertex wards admit patients on alternate days and the Caesar wards admit new patients on a daily basis. Of these wards, both vertex delivery wards and one Caesar ward were selected to be included in the study.

Participants

Patients eligible for inclusion were those who had a normal birthweight of 2500g to 4000g, were 12 hours or more of life at time of screening and were otherwise healthy patients. Both Caesarean section and Normal Vertex Delivery newborns were included.

Study Design and Sample Size

I undertook a prospective descriptive study assessing the accuracy of newborn pulse oximetry screening in patients delivered at Chris Hani Baragwanath Academic Hospital (CHBAH) between 1 October 2015 and 6 November 2015. The objectives were to evaluate the accuracy of POS at altitude, to determine whether adjusted saturation cut-offs should be used at altitude and to assess the feasibility of implementing POS in a resource limited setting.

The hospital sees between 20000 and 25000 deliveries per annum and therefore initially the study aimed to enrol 1000 patients, with the expectation of detecting 8 CCHD lesions (Incidence of CHD is 8/1000). Due to personnel limitations, this had to be reduced and a final total of 350 patients were included. This number was chosen based on an estimate of how many patients would be screened in the time available. No formal calculation of power for the sample size was undertaken.

Interventions/Exposures

The primary investigator enrolled patients daily. All patients that were identified as eligible were approached for enrolment in the study based on the inclusion and exclusion criteria. After this list was populated, each of the mothers was addressed detailing the purpose of the study and if the mothers showed interest in taking part, the consent form was explained, and any questions raised were answered. Once completed, relevant information was collected from the maternal bed-letter, details of which can be found in Outcomes/Variables below.

Following this, a measurement of oxygen saturations was taken on the neonate using the Masimo SET® Rad 8 Signal Extraction Pulse Oximeter (Masimo Corporation, Irvine, California). This was placed on the right hand then either foot. The same pulse oximeter and neonatal probe attachment was used for the entire study. A reading was considered favourable if the machine returned a regular pulse with an accompanying perfusion index of 2% (Two percent) or more. The highest sustained saturation level was recorded. The screening values for right hand and foot pulse oximetry were recorded and compared with a standardised screening protocol (Appendix 2) adapted from the AAP guidelines (Appendix 1). The adaptation was accomplished by reducing the AAP guideline cut-offs from 95%/90% to 93%/88%. Therefore, a measurement of ≥93% in either hand or foot was considered a Pass. If there was a difference of >3% between the hand and foot, the patient was flagged for a Repeat screen. Where

patients had either hand or foot saturations between 88% and 92%, they were flagged for a Repeat though if the hand saturations were between 88% and 92% and the foot was ≥93% then the patient was flagged as a Pass as it was deemed that the pre-ductal saturations were under-reading or due to a delay in screening the foot, the saturations had increased sufficiently. Any reading <88% in hand or foot was flagged as a Fail. Every single patient who underwent screening had an echocardiogram performed.

Hereafter, each patient who completed screening were taken to the Echocardiogram room where the Echocardiogram was performed using a portable Vivid ultrasound machine (MV13-0034 Rev2: GE Healthcare Vivid e Compact Digital Ultrasound Console BT12). If patients required repeat screening and the Echocardiogram room was free, they were first taken through for the Echocardiogram and the repeat screen was done once the echo was completed. The Echocardiograms were performed by one of two qualified Paediatric Cardiologists or an Echocardiographic Technologist. If the screening failed at any point, the patient was examined by a Paediatric Registrar to assess for a non-cardiac cause for the failure. In the event of a patient requiring a second or third saturation screen, repeat oxygen saturations were taken as close to one hour after the initial screen as possible for the first, and if required, second repeat an hour later. Once the cardiac echocardiogram was completed, and the patients required no further screening, they were discharged.

Outcomes / Variables

Data collected included basic demographics namely, sex, race, gestational age, birthweight, APGARS at 1 and 5 minutes, delivery by Caesarean or normal vertex delivery, family history of congenital heart disease and province or country of origin. Age in hours was calculated at the time of screening. Preductal and Postductal saturations were recorded for each individual screen undertaken and the CHBAH

adjusted protocol (Appendix 2) applied to assess Passes, Failures and need for Repeats.

The results of the screening Echocardiogram were also recorded including any findings of significance such as a Patent Foramen Ovale (PFO), Atrial Septal Defect (ASD), Ventricular Septal Defect (VSD), Patent Ductus Arteriosus (PDA) or Mitral Regurgitation (MR). Critical congenital heart lesions were also screened for. Patients with a PDA ≥1.5mm were flagged for repeat echo between one and four months later to assess resolution, those <1.5mm were not followed up. Other patients given a follow-up echo date were those with ASD, VSD, MR and patients with a PFO exhibiting right to left shunting (PFO R>L) or bi-directional shunting (PFO BD). As no critical congenital heart lesions were identified, surrogate lesions (PFO R>L and PFO BD) were used in the statistical calculations. While this is not optimal, these lesions were used in the study as significant lesions as they were deemed to have a measurable impact on the outcome of POS. This shunting is expected to be a transient abnormality but important to identify as it is a possible cause for failed PO screening in an otherwise well newborn.

Statistical methods

Collected data was captured using Microsoft Excel 2010 (Microsoft Corporation, Bellevue, Washington, United States of America). Categorical variables were analysed as percentages and bar graphs while parametric continuous variables were analysed as means and standard deviations. Non-parametric variables were reported as medians and interquartile ranges. Student's t-test was used to compare two independent groups while Pearson χ^2 or the Fisher exact test was used to test differences between categorical variables. Sensitivity and specificity along with positive and negative predictor values and false positive rates were calculated comparing pulse oximetry screening outcomes against the gold standard of

echocardiography. A p-value of <0.05 was used throughout the data analysis. IBM SPSS Statistics Version 16.0 (Statistical Package for the Social Sciences) was used for statistical analysis.

Ethical Issues/Consent

No significant ethical issues were encountered during the study. All patients gave voluntary informed consent and strict control of the collected identifying data and contact information was ensured throughout the collection process. Study numbers were given to all those who participated to facilitate anonymity. Pulse oximetry and Echocardiography pose no immediate risk of injury, or any other, to the patient. Consent from the Hospital Chief Executive Officer and approval from the Human Research Ethics Committee (Medical) was obtained.

Results

Basic Demographics

During the study period, a total of 353 newborns were identified as potentially enrolable. Of these, three refused consent and two absconded after enrolment totalling 350 patients enrolled in the study, 348 completing all requirements of the study.

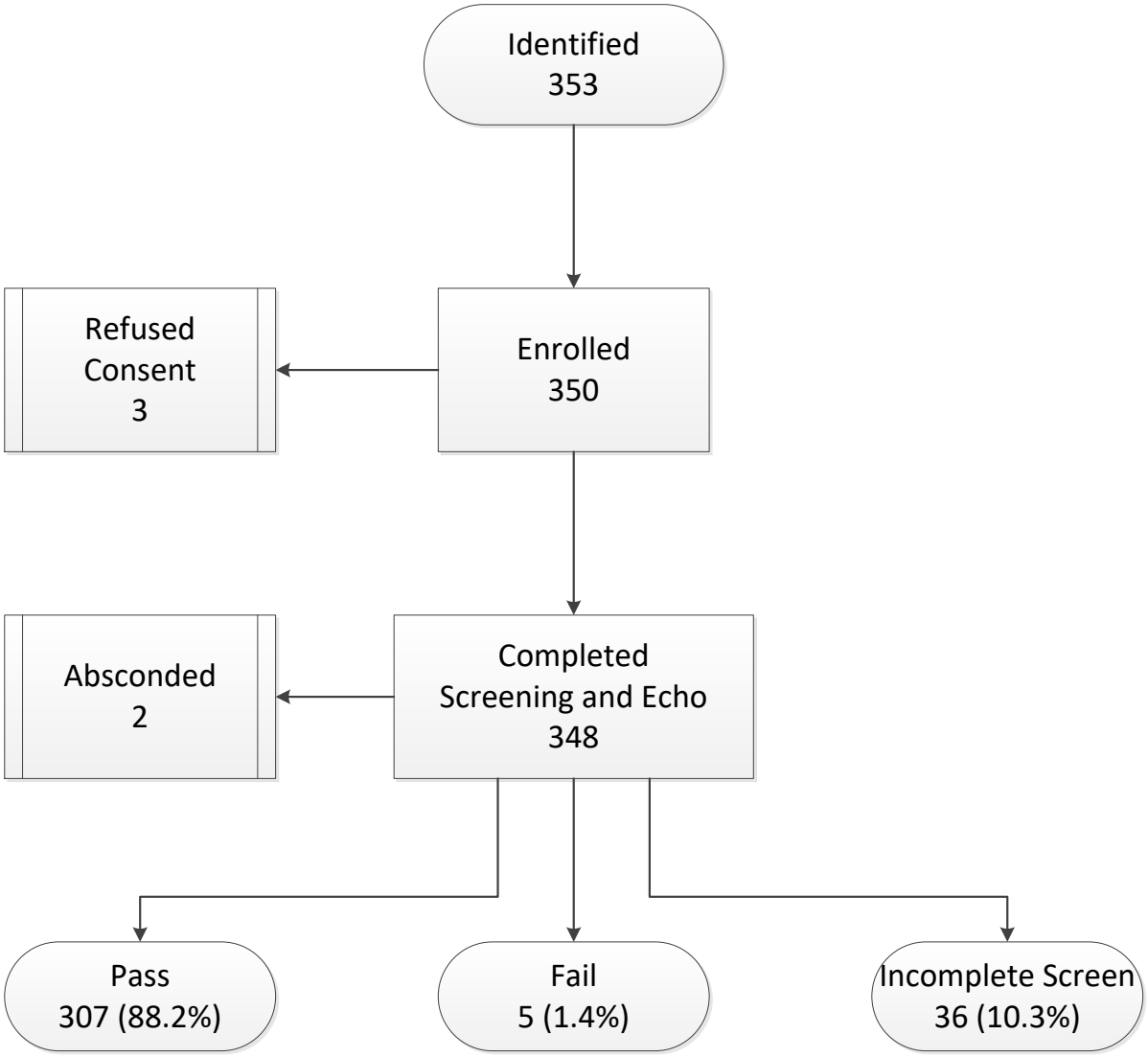

Figure 1: Flow of Patients

Table 2 shows the demographic breakdown and descriptive statistics of the study population. Points to note from the table are that the mean birthweight was 3162g (SD–363g) and mean gestational age was 38.7 weeks (SD–1.8 weeks). Patient lengths revealed a mean of 50.2cm (SD–3.1cm) and of 346 patients the mean age at screening was 29.71 hours of life (SD–11.65 hours). Most patients were from Gauteng (237, 67.9%), while patients from outside Gauteng but still from South Africa numbered 63 (18%). Those from outside South Africa numbered 49 (14.1%). One patient did not have the Area of Origin recorded.

		NVD (n)	Percentage	C/S (n)	Percentage	Total (n)
Sex	*Male*	*101*	*64,74%*	*55*	*35,26%*	*156*
	Female	*138*	*71,13%*	*56*	*28,87%*	*194*
	Total	*239*	*68,29%*	*111*	*31,71%*	*350*
Race	*African*	*229*	*68,15%*	*107*	*31,85%*	*336*
	Coloured	*9*	*75,00%*	*3*	*25,00%*	*12*
	Indian	*1*	*100,00%*	*0*	*0,00%*	*1*
	Other	*0*	*0,00%*	*1*	*100,00%*	*1*
	Total	*239*	*68,29%*	*111*	*31,71%*	*350*
Age in hours	*<= 23*	*92*	*84,40%*	*17*	*15,60%*	*109*
	> 24	*144*	*60,76%*	*93*	*39,24%*	*237*
	Total	*236*	*68,21%*	*110*	*31,79%*	*346*
Birthweight	*2500 - 2750*	*39*	*73,58%*	*14*	*26,42%*	*53*
	2751 - 3000	*46*	*63,01%*	*27*	*36,99%*	*73*
	3001 - 3250	*54*	*72,97%*	*20*	*27,03%*	*74*
	3251 - 3500	*61*	*70,93%*	*25*	*29,07%*	*86*
	3501 - 3750	*28*	*63,64%*	*16*	*36,36%*	*44*
	3751 - 4000	*11*	*55,00%*	*9*	*45,00%*	*20*
	Total	*239*	*68,29%*	*111*	*31,71%*	*350*

Table 2: Descriptive Statistics

Pulse Oximetry Screening Results

Of the 350 patients, 348 were screened before discharge. For the initial screen the mean oxygen saturation for the right hand (RH) was 94.44% (SD–2.454%) and 94.41% (SD–2.434%) for the foot (FT); 95% confidence intervals were 94.18% –

94.7% and 94.15% – 94.66% respectively. The second screen revealed mean oxygen saturations of 92.54% (SD–2.377%) and 92.67% (SD–2.426) for the RH and FT, respectively. Only one patient underwent a third screen who subsequently failed the screening with RH and FT saturations of 92% in both. This resulted in an overall failure rate of 1.4% and a pass rate of 88.2%.

When evaluating the outcome of the screening using the CHBAH protocol, the results of the first and second screens show that most (83.1%) of the patients passed on their first screen, but 53 required repeat screening. Just under half of patients (24 of 53) who required repeat screening were screened for a second time and of the seven who required a third repeat, only one was screened. This attrition is due to the patients being discharged before screening could be completed in 36 (9.77%) of patients.

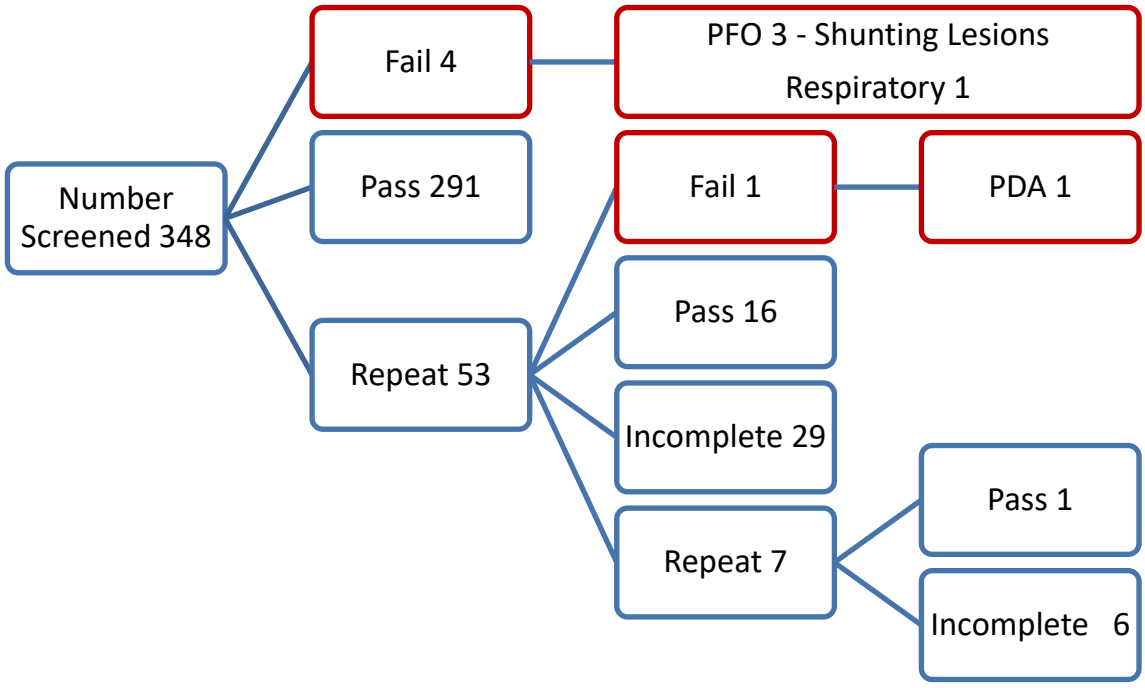

Figure 2: Outcome of Screening

[Pass – patient required no further screening; Fail – patient underwent no further screening and referred for echo; Repeat – patient required a further screen; Incomplete – Patients lost to follow up]

The American Academy of Paediatrics screening protocol stipulates higher cut-off values to determine screening outcome[5]. This protocol was used post-hoc to analyse

its effect on the screening outcome and showed a statistically significant proportion of patients to not have passed their first screen (189 vs 291) and therefore required more repeat screens (Chi^2 $p<0.001$, Cramer's V 0.640 [large effect]) and a likelihood ratio of 330 ($p<0.001$). If the higher AAP guideline cut-offs were to be used for screening, it would result in 31.7% more patients requiring at least one repeat screen and 3.2% more failing outright. This equates to a fail rate of 4.6% when using higher saturation cut-offs.

When looking at the accuracy of screening before 24 hours of age, the percentage of those passing their first screen for <24 hours and ≥24 hours was 89.91% and 80.59%, respectively. None failed their first screen at less than 24 hours of age but 11 required repeat screening. A similar percent required repeat screens between the two groups; <24 hours 10.09% and 17.7% for ≥24 hours. A total of 109 (31%) of patients were screened before 24 hours of life. An independent-samples t-test to compare the effect of screening at age <24 hours and ≥24 hours on pulse oximetry results showed there was a statistically significant difference between saturations at <24 hours (mean = 94.47%, SD 2.49) and ≥24 hours (mean = 94.33%, SD 2.594; t (411) = 2.143, p=0.033, two-tailed). The magnitude of the differences in the means (mean difference = 0.613, 95% CI 0.051 to 1.176) was very small (eta squared = 0.011). The clinical significance of this is of limited value. What is important to note is that the mean saturations are below 95%.

Accuracy of Screening

A product of the Pivot Table below (Table 5) shows the sensitivity and specificity of the screening at altitude are 100% and 99.4%, respectively. A positive predictor value is evident at 60.0% with a high negative predictor value of 100%. The false positive rate is 0.64%.

		Echo Results		
		Echo with shunting	Normal Echo	Total
Screening Test	Screen Failed	3	2	5
	Screen Passed	0	307	307
	Total	3	309	312

Table 3: Pivot Table – Echo and Pulse Oximetry Results

Independent Predictors of Screening Failure

	Pass	Fail	*P* value
Gender, Male	134	4	0.412
Gestational Age, Mean	38.67	38.40	0.636
Birthweight, Mean (g)	3146.78	3334.40	0.083
Mode of Delivery, NVD	210	1	0.111
Ethnicity, African	295	5	0.800
Time of Screen, Hours	29.02	31.00	0.008
Time Taken to Screen, Seconds	205.18	234.5	0.610
Apgar at 5 Minutes, Apgar 10	258	5	0.978
Area of Origin, Gauteng	212	4	0.870
Family History of CHD, Yes	10	0	0.447

Table 4: Independent Predictors of Screening Failure

Evaluating independent predictors of failure revealed that gender, gestational age, birthweight, mode of delivery, ethnicity, Apgar score at 5 minutes, area of origin and any history of congenital heart disease in the family had no effect on screening failure. The only factor that proved to significantly affect screening failure was the age at which screening was performed (p=0.008). There was no significant relationship between mode of delivery and incomplete screens (p=0.111) showing that a patient who was born by C/S was not more likely to have completed screening, but there was a statistically significant relationship between being screened after 24 hours and incomplete screening (p=0.045) showing that patients screened after 24 hours were less likely to complete screening. These results must be treated with reserve as the

number of failures were very small and therefore lacks statistical power to draw meaningful conclusions.

Overall Saturation Results for Age

	Pass	Fail	Incomplete	Total
Age <24 hours	103	1	5	109
Age ≥24 hours	202	4	31	237
Total	305	5	36	346

Table 5: Overall Saturation Results for Age

[Pass – patient required no further screening; Fail – patient underwent no further screening and referred for echo; Incomplete – screening not completed]

Echocardiogram Results

The screening echo findings can be seen in Table 8. The total number is larger than the sample size as some patients had multiple diagnoses. A very large number of patients, 236 (63.8%) had a PDA while no critical congenital heart disease was picked up during the study.

	Frequency	Percent
Nil	95	25.7
PDA <1.5mm	229	61.9
PDA ≥1.5mm	7	1.9
ASD	12	3.5
VSD	7	1.9
MR	9	2.4
PFO R>L	3	0.8
PFO BD	5	1.4
Total	370	100.0

Table 6: Screening Echo Results

[PDA – patent ductus arteriosus; ASD – atrial septal defect; VSD – ventricular septal defect; MR – mitral regurgitation; PFO R>L – patent foramen ovale with right to left shunt; PFO BD – patent foramen ovale with bi-directional shunting]

The total number of patients with normal echocardiograms, considering normal variations for age, was 324. This total included PDAs that measured less than 1.5mm. This was an arbitrary cut-off for normal versus abnormal echocardiograms. No official

assessment was made regarding the haemodynamic significance of any lesion found on echo. Patients with an ASD were labelled as such if their ASD was more than 3mm in size and all the patients who had a VSD only had tiny, mid-muscular VSDs. The mild mitral regurgitation found during the study was attributed to factors such as the sudden increase in systemic vascular resistance after delivery once the low vascular resistance placenta is separated from the circulation when the cord is cut. The significance of this result was not investigated as it fell outside the scope of this study.

Those who had an echo showing a VSD, ASD, PDA ≥1.5mm or right to left shunting or bi-directional shunting across any lesion numbered 34 (9.7%) and has been reported as the incidence of congenital heart disease shortly after birth (<48 hours). The persistence of these lesions at follow-up echo after discharge brings this number down to 4 (1.14%), which includes one VSD (tiny mid-muscular) and three ASDs ≥3mm. Of the seven large PDA's detected at the initial echocardiogram, only one had a residual PDA at follow-up after three months. There were eight patients (2.3%) who had potentially cyanotic heart lesions that could have affected the outcome of the PO screening results, namely right to left shunting or bi-directional shunting across a PFO. There was one patient who failed screening in the presence of a PFO with bi-directional shunting and two with right to left shunting. The rest of the patients with a bi-directional shunt or right to left shunt failed to complete screening and therefore could not be included in the analysis. Table 9 shows the details of the three patients who failed screening and in addition also had an echo diagnosis of a lesion that could be attributable to the failed screening. It compares the initial RH and FT saturations and the screening outcome.

Patient Number	RH Saturations	FT Saturations	Screening Outcome	Echo Findings
1	85	86	Fail	PFO R>L
2	84	89	Fail	PFO Bi-Directional Shunt
3	89	87	Fail	PFO R>L

Table 7: Potentially Cyanotic Congenital Heart Disease

[RH – right hand; FT – either foot; PFO R>L – patent foramen ovale with right to left shunt]

Feasibility of Screening

Time taken to screen

The time taken to perform the first screen was recorded for the RH and FT in 49 patients. For the RH the mean time to obtaining a valid reading was 88.90 seconds (SD–69.09s) while the FT required an average of 113s (SD–117.6s). The minimum time for both hand and FT screening was 20s, while the maximum time was 410s (6.8 minutes) and 620s (10.3 minutes) for the RH and FT, respectively. The table below shows the time taken to screen.

	Right Hand Screening Time		Foot Screening Time		Total Time to Screen	
Time (s)	Number	Percent	Number	Percent	Number	Percent
<= 60	16	32.7	17	34.7	1	2.0
61 - 120	22	44.9	19	38.8	12	24.5
121 - 180	7	14.3	8	16.3	19	38.8
181 - 240	2	4.1	1	2.0	6	12.2
241 - 300	1	2.0	0	0.0	1	2.0
301+	1	2.0	4	8.2	10	20.4
Total	49	100.0	49	100.0	49	100

Table 8: Time Taken to Screen

Fall-out Rates

The fall-out rate for second and third screens is attributable to two aspects of the study and setting. All the consenting, screening and patient transport was performed by myself, including all the second and third screens. While it was possible to ensure everyone was screened at appropriate times as indicated in the protocol, the setting where the study took place was the major limiting factor. Patients post NVD could be

discharged within six hours of delivery, but at CHBAH the majority of patients are discharged by midday (12h00) the day after delivery. Screening started around 08h30 every day. Those requiring second and third screens were discharged by 12h00. During the normal course of the day (between 08h00 and midday), the mothers needed to be seen by the obstetricians, some of the newborns required paediatric review, mothers were required to walk to the kit room to collect their belongings if discharged as well as have lunch. Once patients were screened, I escorted the patients to and from the echo room without the assistance of the nursing staff as there was continually a nursing staff shortage. These factors all impacted on the ability to complete the screening adequately.

Discussion

Lower Oxygen Saturation Cut-offs

The primary outcome of this study shows that it is imperative that lower POS saturation cut-offs are used when screening at altitudes above 1500m. The mean POS saturations of 94.44% (RH) and 94.41% (FT) (with a range of 84% to 100%) of the first screen results in 83.1% of patients passing and therefore completing their screening. If the AAP guidelines (Appendix 1) were to be implemented, it can clearly be seen that the mean saturations for the hand and foot already lie below 95%. In theory, the real-world impact is that out of 2000 deliveries per month at CHBAH using adjusted cut-offs will result in 304 (15.2%) patients requiring repeat screens compared to 828 (41.3%) patients if the AAP guidelines are to be used. The mean saturations during the second screen were 92.54% (SD–2.377%) and 92.67% (SD–2.426) for the RH and FT. This lower mean could be due to the persistence of lower oxygen saturations in patients who required repeat screening due to low oxygen saturations following their first screen. Only one patient of seven received a third and final screen. The reason

for the high drop-out rate is described in detail presently as significant logistical issues were encountered during the course of screening.

The mean saturations found in this study are in keeping with those found internationally. Thilo, *et al* found that at an altitude of 1610m in Denver, expected post-ductal saturations would fall between 92-93% with a range of 80-98%[28], while at an altitude of 1640m one study reported pre-ductal (right hand) saturations to be 95.4% with a 2 standard deviation range of 88.7-100%[26]. Furthermore, Ravert[30] compared two altitudes of 1371m and 2073m and resultant effect on saturations showed that at 1372m, pre-ductal and post-ductal saturations were 96.67% and 96.29%, respectively (range 88-100%); at 2073m elevation, pre- and post-ductal saturations fell to means of 93.39% and 94.38%, respectively (range 76-100%)[30]. At lower altitudes of 780m in a study by Samuel[31] pre-ductal saturations fell between 97.86-98.49% (range 94.7-100%). This shows that there is a significant difference in saturations at increasing altitude. Hoffman described the effects of altitude particularly well by explaining the scientific basis of lower oxygen saturations at high altitude in their study[29]. Using partial pressures of oxygen and oxygen saturation curves in the newborn soon after delivery, they reported that in newborn babies at altitudes of around 1500m (altitude of Johannesburg) expected oxygen saturations are between 92-95%[29].

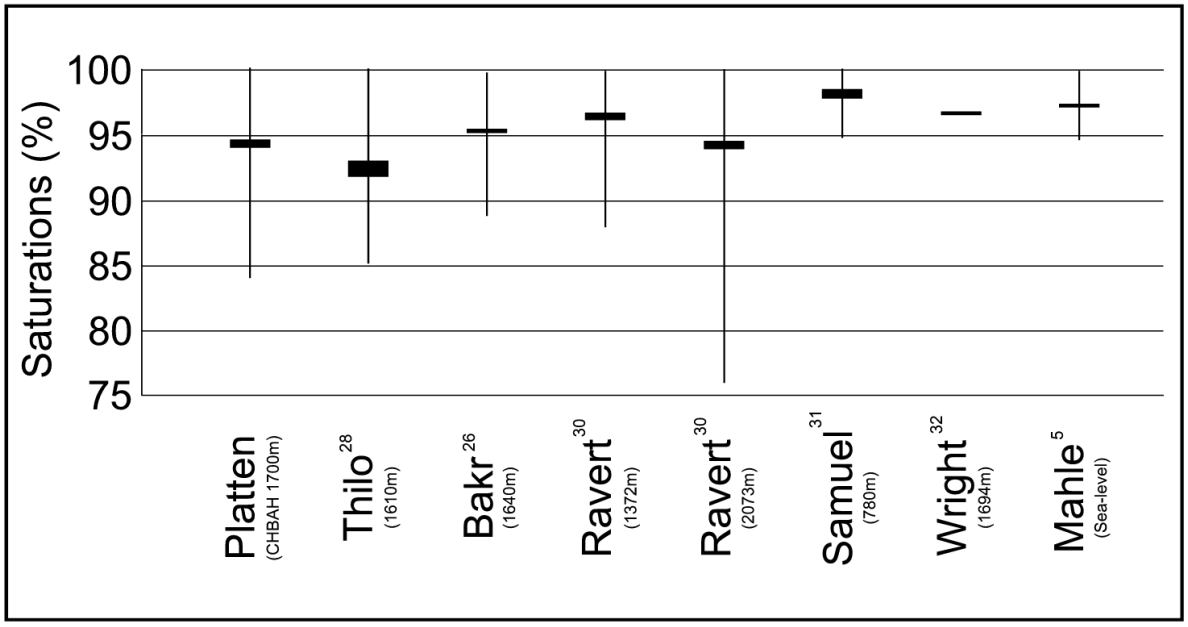

Figure 3: Mean and Range of Saturations for Altitude per Study; Adapted from Wright [32]

This supports the findings of the mean saturations in the 93-95% range reported during this study and even though the power of this study is limited due to few patient numbers, the effect of altitude is still evident. How this will translate into a real-world context remains to be elucidated completely with further larger population-based studies at altitude in our setting. A large study by Wright[32], in contrast, reported saturations of 97.2% pre- and post-ductal at an elevation of 1694m in Colorado, yet the article explains that the saturations are in keeping with the research by Bakr, Samuel and Ravert which does not appear to be the case. Their saturation level of 97.2% is above the cut-off for the AAP guidelines (95%), and therefore it would be expected that a larger number of patients would pass screening than expected by the other studies, mine included. What this shows is that more research and larger region-specific studies are required to accurately establish normal saturation guidelines at altitude.

Due to lower partial pressures of oxygen at altitude that reduce the oxygen content of blood in newborns delivered at altitude compared to sea-level, it is postulated that the reduced oxygen content in the blood retards the physiologic pulmonary vasodilation that occurs in the presence of oxygen[33]. This results in higher pulmonary pressures (due to a smaller decrease in pulmonary pressures) and results in a shunt across the ductus arteriosus, and therefore deoxygenated blood shunting systemically and causing post-ductal saturations to be low; The second mechanism involved is a certain amount of intra-atrial shunting (right to left atrium) which also contributes to deoxygenated systemic blood[33].

Effect of Altitude on Accuracy of Pulse Oximetry Screening

It is important to note that no patients with CCHD were picked up during the five-week duration of my study. The low incidence of critical congenital heart disease and challenging study circumstances were partly responsible for this outcome, as were the restrictive inclusion criteria for this study. Therefore, I chose to focus on those patients who failed screening having had an echocardiographic diagnosis that would correlate with the propensity to fail screening due to abnormal shunting of deoxygenated blood. As such, the three patients who have been allocated a diagnosis of cyanotic congenital heart disease had lesions causing intracardiac right to left shunting – but not a CCHD lesion. The pivot chart in Table 3 reflects only those patients who had a complete screen. These values are likely to have changed if all the screenings had been completed.

Looking at the accuracy of POS at altitude, the 100% sensitivity reported in my study is above what is reported internationally. Thangaratinam reviewed studies assessing the accuracy of pulse oximetry in newborn screening and found that there was a wide variation in sensitivity (between 25% and 98.5%) and that the low sensitivity could be

attributed to the low incidence of CCHD[24]. Specificity ranged between 98% and 100% which remains standard across many studies [18, 22, 23, 26, 34], including my study (99.4%). In terms of sensitivity and specificity, my study shows that there is no significant difference between the accuracy of POS at sea-level and at altitude. The expectation prior to the commencement of the study was that altitude would not have a discernible effect on the accuracy of POS, which is consistent with other research. It is important to clarify that an adjusted algorithm (Appendix 2) is used to account for the effect of altitude on oxygen saturations, not to attempt to mitigate the effects of altitude on the accuracy.

Most studies report a false positive rate between 0 and 2% [24], but in a study by Hoke[21], the false positive rate was 12%. The false positive rate in my study is 0.64% which is similar to those found internationally. Wright, *et al* expected to see a false positive rate of 3.3% in their moderate altitude based study but this was reported to be only 1.1%[32]. Initially there was a concern about the effects of ethnicity and dark skin pigmentation on the accuracy of POS. This was not substantiated in our study. A recent study by Foglia showed that there was no effect on accuracy of PO regarding dark- versus light-skinned neonates[35], but it remains to be seen if the effect of altitude combined with dark-skinned individuals may affect accuracy. Research also suggests that saturations in the neonate can decrease while asleep[36], and anecdotally in our unit during feeding. No record was made to identify which patients were crying, asleep or feeding during this study and as far as possible, motion disturbance was minimised by allowing a restless infant to settle first before POS was performed.

These results show that screening at altitude in Johannesburg is comparable internationally regarding accuracy of POS. The detection rate of cyanotic heart lesions

(other than CCHD) is equivalent to international findings and the institution of POS in our setting has a sound scientific background. It is important to note the many benefits of screening an at-risk population who struggle with accessing reliable transport required to present to hospital in an emergency. Therefore, early detection and intervention for patients with possible CCHD is invaluable in our setting as patients are likely to experience delays in presentation, which could be detrimental to the health of the children.

Independent Predictors of Failure

It is important to note that very small numbers of failures were recorded, so the following results needs to be treated with reserve. Multiple factors were assessed to identify their impact on screening failure. Most of the factors assessed showed no predilection to failure. These included basic demographics such as gender, gestational age, birthweight, mode of delivery, family history of congenital heart disease and ethnicity. This is in keeping with findings by Wright[32]. Area of origin (Gauteng, Free State, Zimbabwe, etc.) did not have an impact on propensity to failure; neither did the 5 minute Apgar score.

Surprisingly, there is a statistically significant association between screening after 24 hours and failures (p=0.008). This is an unexpected finding. It is well documented that screening after 24 hours improved the accuracy of screening and reduces the false positive rate [24, 32]. Closer examination reveals that other than the one patient who failed due to a respiratory cause, the four remaining patients had no evidence of respiratory disease or features of sepsis after a clinical examination. Three of the four patients had lesions with right to left or bidirectional shunting and were screened after 24 hours. This finding can therefore be explained by the presence of high pulmonary pressures in the newborn period which results in right to left shunting and propensity

to fail screening, and also explains the statistically significant result of screening at more than 24 hours [33]. The fifth patient was screened at 22 hours and on echo had a PDA <1.5mm and is likely to be a true false positive. Regarding the failures, it is unlikely that the failures were related to variations in technique or in incorrect technique being used to perform the screens as all the screens were performed by the same individual. Many of the patients who were screened after 24 hours were patients delivered by Caesarean section but this did not show a statistically significant tendency to fail screening (p=0.111).

Wright found that gestational diabetes and increased birthweight were associated with failed screens[32]. My study did not look at gestational diabetes so this finding cannot be commented on, but there appeared to be no correlation between birthweight and screening failures (p=0.083). This is likely a result of my inclusion criteria for birthweight being 2500 to 4000g whereby it is possible that the patients in Wrights' study were above my inclusion cut-off levels, but this data is not reported in the study.

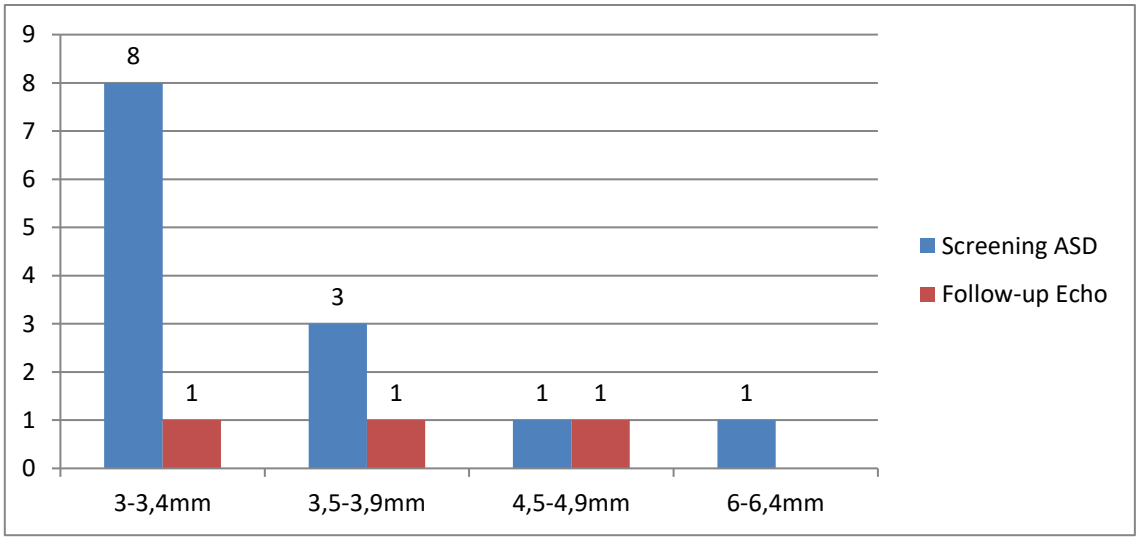

Figure 4: Initial Atrial Septal Defect (ASD) Findings and Persistence of ASD at Follow-Up

Echocardiographic Findings

Congenital heart disease prevalence is between 7-9/1000 patients worldwide[1,2]. The prevalence detected in my study population at follow-up is 11.4/1000 which is marginally higher than international reports. A significant proportion of patients had normal echocardiograms with no abnormality whatsoever and a large number had a PDA <1.5mm (229, 61.9%) that were considered to be normal in the first few days of life. Unfortunately, this study failed to detect any CCHD lesions and while this is likely due to the short duration of the study and the small sample size, certain inferences can still be made regarding the results.

The patients who have an echo consistent with a possible cyanotic lesion (ASD BD, PFO R>L and PFO BD) did not consistently fail screening. This inconsistency cannot be related to technique as the same investigator performed all the POS using the same technique throughout the study. Those with an ASD ≥3mm numbered 12 and a fair number of the patients were found to have a PFO shortly after delivery, the exact numbers were not recorded as the presence of a PFO in a newborn is of no known clinical significance. The patients who demonstrated a PFO with bi-directional shunting or right to left shunt either had low saturations on their first screen or failed their screening altogether. Those who had a PFO with right to left and bi-directional shunt totalled seven. Of these, two of the three with PFO R>L failed screening which suggests that a right to left shunt is an important contributor to failed screens. The other patients who had a PFO with bi-directional shunting failed to complete their screening, so it is unsure if these patients would have continued to fail or pass their screening. What can be seen is that all the patients with bi-directional shunting across their PFO had low saturations (between 90-94%) which may be a reason for many patients requiring a repeat screen. This suggests that bi-directional or right to left shunting may be a possible cause for failing screening which could be explained by a

delayed neonatal transition from foetal to extra-uterine physiology[37]. Unfortunately, this study failed to elucidate a connection between the two (PFO BD and repeat screen requirements) due to incomplete screening. Further, a significant number of patients had a PFO with no shunting but this was considered normal for age and therefore not recorded for the purposes of this study.

Current management practice at CHBAH for any patient with low oxygen saturations is that the patient be placed on oxygen, undergo a thorough clinical examination and if required are admitted and treated for suspected neonatal sepsis. While this is prudent practice, especially in a teaching hospital, if a causative lesion could be identified that is attributable to the low oxygen saturations (in the presence of a normal clinical examination) it raises the question as to whether these patients need admission for low oxygen saturations. In the absence of screening echocardiograms to prove the presence of such a lesion, current clinical practice must continue. While it is safer for the newborn in the acute setting, it prolongs neonatal stay, exposes the patient to hospital acquired infections and adds to the burden of the neonatal service. It is unlikely that the current practice will change in the foreseeable future, though this may be a consideration in reducing the risk to the patient and the patient load on the health system.

For those patients found to have a PDA of any size, few had false positive screens. Patients with a PDA <1.5mm only failed screening 0.29% of the time; one patient failed due to a respiratory cause (0.29%). No patient failed their screening in the presence of a PDA ≥1.5mm. In the absence of a functional assessment of the significance of the PDA it is difficult to ascertain the clinical impact this has on patients and therefore the effect on screening. There were seven patients with large PDA's who were followed up between two to four months after delivery. Of these seven, only one patient was

found to have a tiny PDA and was discharged from follow-up. No further residual PDA's were detected.

No patient diagnosed with a VSD failed screening, though all the VSDs detected were mini-muscular VSDs. No functional assessment was performed in these patients but it is expected that these lesions would not have an impact on the outcome of the screening. Out of the seven VSDs detected, only one patient had a persistent VSD at follow-up three months after delivery and was called back for repeat echo.

Screening Duration

A subset of patients was selected to record the time taken to screen. Only 49 patients had times recorded. There was a definite delay in obtaining foot saturations compared with hand saturations. The average time of FT screening was 113 seconds, 24 seconds more than the RH. This could be because the hand had less subcutaneous tissue and was therefore easier to obtain a saturation reading, or that there was less movement interference with the hand than foot or the hand was warmer and therefore perfusion was better. The patients who took the longest had cool peripheries and consequently decreased perfusion. This is confirmed in the review by Nitzan, *et al* who report on the effects of poor perfusion on the accuracy and difficulty in obtaining accurate PO values[38].

Challenges and Outcomes

Incomplete Screening

My study suffered from a significant number of patients who failed to complete screening. Of 53 patients who required repeat screening after the first screen, only 24 received a screen, and of the seven who required a third screen, only one managed to undergo the screen. The loss of patient screening occurred when patients required screening after midday as they would be discharged before repeat screening could be performed. As such, if routine screening was to be implemented, the additional burden

of work would not be easily bourn by the nursing staff given the current staffing complement. It is can therefore only be concluded that the implementation of routine screening at CHBAH is not a viable option at present unless there is an institutional change to support the routine screening of neonates.

Mode of Delivery

Two-thirds of the patients were delivered by NVD compared to Caesarean section. This discrepancy is due to the logistics of how the respective NVD and post Caesarean wards work. The NVD ward allows the mothers to stay in the same ward from admission to discharge, and the mothers are able to walk with their child to the ward in which the echocardiograms were being performed. This allowed a smooth flow of patients between screening and echo. In stark contrast, the logistics of screening and performing an echo on a baby in the post Caesarean ward posed a significant challenge. A mother post Caesarean can be moved to three different wards in the course of three days post-delivery. In addition, the mothers are not as mobile after the operation and are therefore less likely to accompany their child to the echo room. Due to staff shortage, the sisters in the post Caesar ward were unwilling to assist in transporting patients to the adjacent ward to receive their echo and were also unwilling that the newborn leave the ward unaccompanied by a mother or sister, for safety and security reasons. The result was that screening was more efficient in the post NVD wards than the Caesarean wards.

Demographics

The area that CHBAH services comprises a large majority of Gauteng province and extends its services out to the neighbouring North West province as there is no tertiary hospital located in the North West. Direct questioning of patients allowed more accurate details of patient origin, which shows that the majority of patients are from Gauteng (237, 67.9%), and of the expected referrals from North West, only 8 patients

(2.29%) delivered at CHBAH. The largest number of patients from South Africa came from Kwa-Zulu Natal (KZN) totalling 21 (6.0%). Of significant interest, or concern, is that an equal number of patients (21, 6.0%) originated from Zimbabwe. This was followed closely by Limpopo (15, 4.29%), Mozambique (13, 3.71%) then Lesotho (11, 3.2%). This shows that of the top 5 areas of origin (outside Gauteng), there are two from South Africa and three from the South African Development Community (SADC) countries. South Africa is therefore, in part, bearing the healthcare burden for these countries regarding their Obstetric as well as the Surgery, General Medicine and Paediatric services.

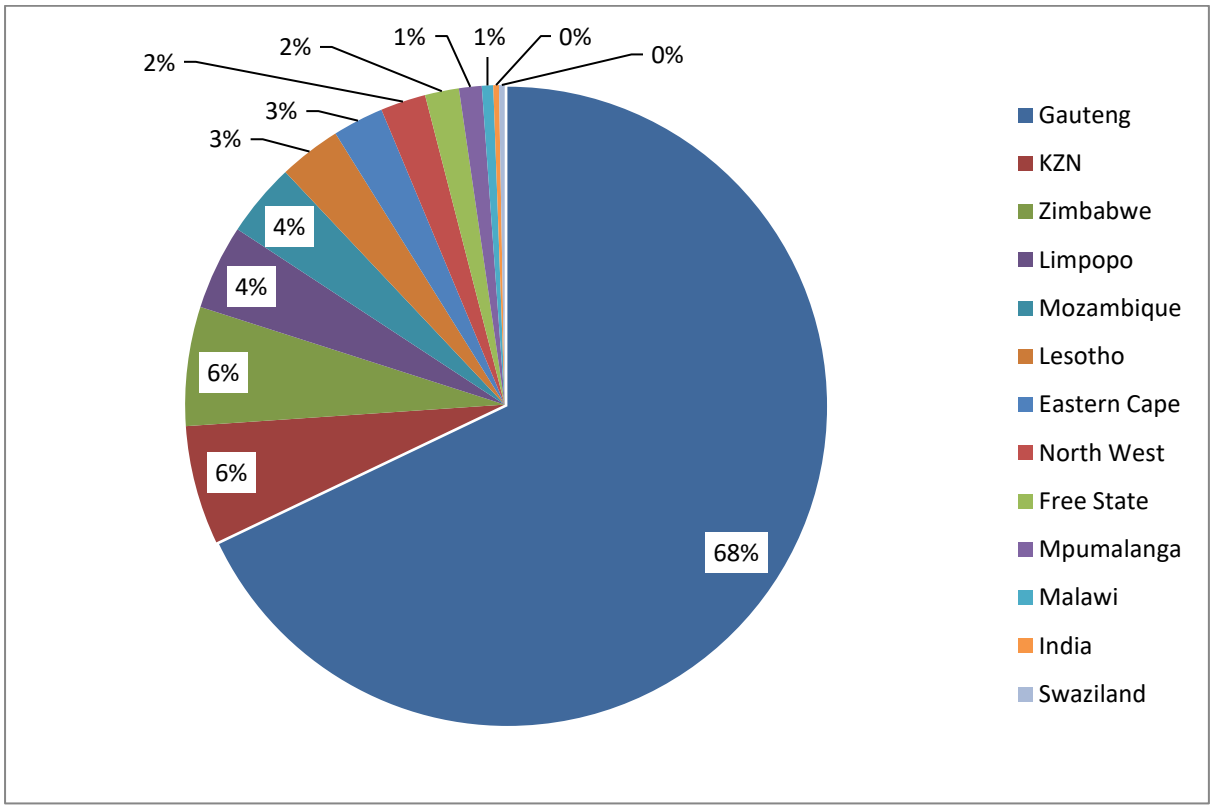

Figure 5: Area of Origin

Strengths

The zenith of this study is that every patient who was screened had an echocardiogram performed the same day to confirm the findings. While the burden of work is significant during the study, the robustness of the data collected outweighs the difficulties experienced in ensuring all patients received an echo. Most of the studies that have been done internationally have relied on echocardiograms being performed only if the patient fails screening which could lead to patients being missed or dying before a diagnosis has been made especially in those who had false negative screens.

This is also the first study assessing screening at altitude in South Africa. Internationally there has only been a handful of studies looking at the effects of altitude on screening accuracy and most of those only in the last five years[29-32, 37]. In a country where a large proportion of the population are living at an altitude above 1150m[39], it is imperative that accurate POS protocols are developed for use in these areas.

The same investigator performed all the POS therefore the inter-observer bias has been minimised significantly, the same methods were undertaken in screening for each patient and accurate adherence to the protocol was followed at all times with no procedural errors caused when following the CHBAH protocol.

While limited, this studies' comparison between the CHBAH and AAP guidelines assists in identifying the effect of not adjusting the cut-offs for POS at altitude. The fact that the false positive rate in this study is in keeping with international studies and is in reality lower than the largest moderate altitude based study to date[32], indicates that this studies' findings are significant.

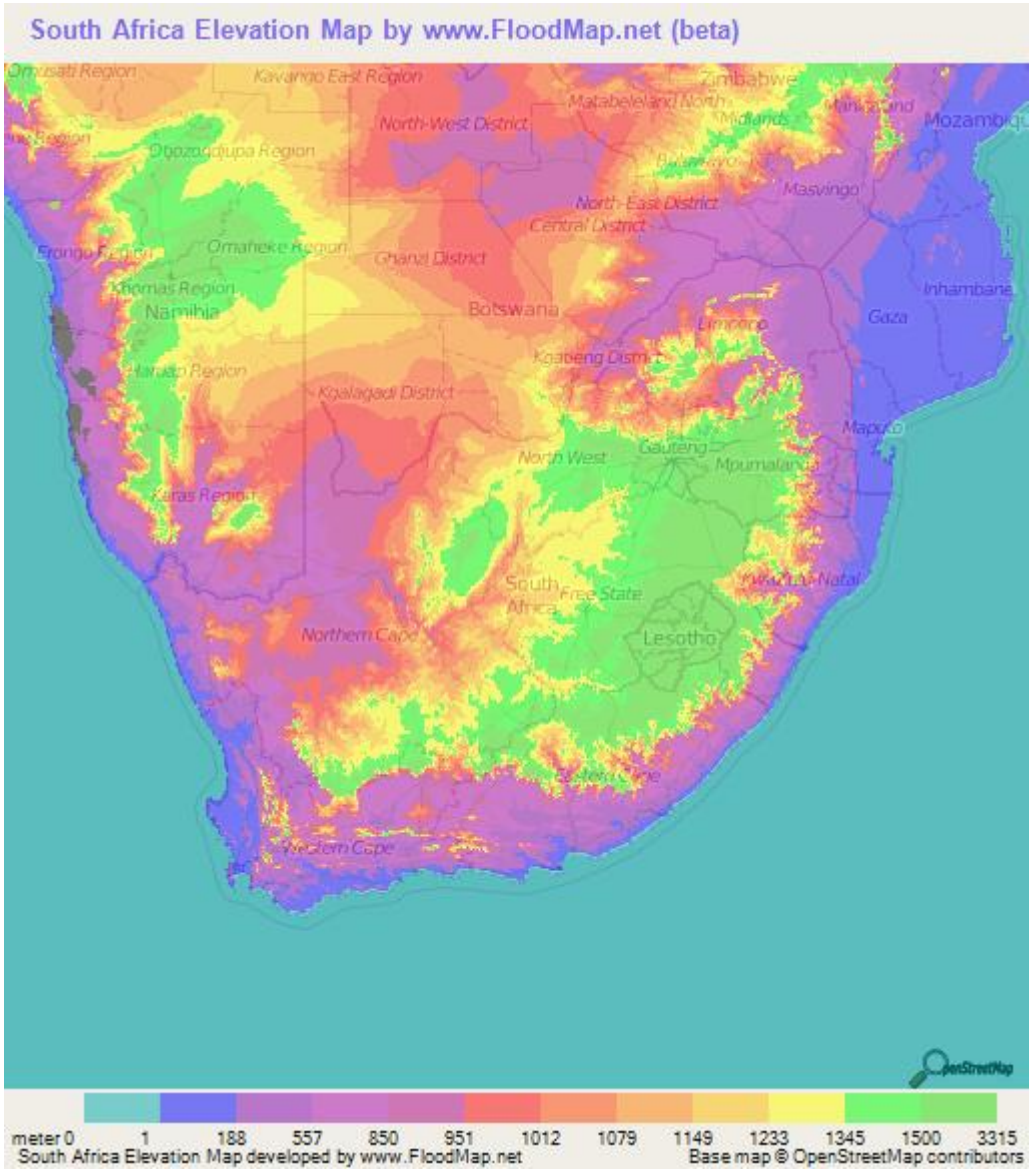

Figure 6: South Africa Elevation Map [39]

Weaknesses

The main weakness of this study is the sample size. It was physically impossible due to limited human resources to increase the number of patients included in the study given the time available for the study to be completed. The inferences made by this study are therefore of limited value but with the results aligning with international findings it may find some traction in the South African setting.

Incomplete screenings are the next major weakness. A good amount of useful data could not be discussed due to the incomplete data set. As explained prior, this is a

systemic issue and speaks of the challenges present and the changes that would need to be embraced to see neonatal screening realised in public practice in South Africa.

The randomisation in this study could not be optimised as there were not enough human resources available to make this possible. The random selection of patients based on inclusion criteria and time of delivery was not optimal.

The lack of physical examination of the infants in the study could also be a contributing factor, especially if the infants did not display overt signs of respiratory distress that was not picked up by any of the clinicians involved in the study. The lack of clinical examination would not affect the false positive rate directly, but could result in failures secondary to other clinical causes being missed. Studies describe improved sensitivity if clinical examination accompanies POS[5].

Conclusions

Critical Congenital Heart Disease is widely recognised as a significant cause of neonatal mortality in those with congenital heart disease. While the incidence remains low, the clinical presentation and often catastrophic deterioration in condition in a previously well child is profound. Much research has focused on the screening of newborns to identify CCHD in the early stages of life to ensure appropriate and timeous interventions, medical and surgical, to provide the patient the best chance at survival. Early detection and intervention is critical. Currently, routine pulse oximetry is the best way to detect these lesions and this has been proven world-wide yet South Africa is only beginning to show interest in newborn POS.

When the screening rate in South Africa for newborn CCHD starts to improve, it is essential that lower oxygen saturation cut-offs be used when screening at altitude. This finding is congruent across multiple studies[26-32]. While the AAP guidelines suggest the use of 95%/90% POS values[5], it is evident that this recommendation is not sufficiently generalisable to moderate or high-altitude areas. Therefore, the use of adjusted cut-offs for POS in this study (Appendix 2) is of utmost importance, namely 93/88%.

Lower POS cut-offs does not appear to affect the accuracy of screening. A false positive rate of 0.64% found in this study as well as the sensitivity of 100% and specificity of 99.4% is equivalent to other studies investigating similar outcomes [18, 21-24, 26, 34]. Noting that no specific CCHD lesions were found in this study, the fact that every patient who was screened subsequently had an echo performed added to the strength and allowed more accurate comparisons to be drawn, specifically regarding sensitivity and specificity. Even though this study lacks power due to the small sample size, it can be used as a basis on which to build larger studies to investigate the utility of POS at altitudes >1500m. It must be noted that while not an outcome of this study, the effect of skin pigmentation does not appear affect the accuracy of POS at altitude as most patients included in this study are of African descent. This could provide an opportunity for further research.

The high number of incomplete screens reported sheds light on the sheer number of patients CHBAH manages daily and the high turnover of newborns through the unit. If screening is to be implemented, the Neonatal unit will need to provision sufficient staff and equipment to ensure comprehensive screening is facilitated. Beside the increased failure rate in those patients screened after 24 hours, there were no statistically significant factors that contributed to failure. Further research may be warranted investigating the effect of large for gestational age patients (birthweights >4000g) and

patients with gestational diabetes on screening outcomes as this is a factor Wright reported in their study [32].

The effect of a lesion with bi-directional shunting, be it and ASD or PDA, has been shown to affect the outcome of screening. While the lesion is not expected to cause a clinically significant deterioration, it may be attributed to failed screens and subsequent referral for further assessment. CCHD has a low incidence and due to the short duration of this study none were detected. A study over a longer period may be of significant benefit, especially in a facility such as CHBAH where a substantial proportion of deliveries take place.

Until South Africa can improve basic service delivery and staffing shortages, this very accessible and feasible opportunity to detect significant heart disease is going to be missed unless institutional and programmatic adjustments are made mandating the routine screening of newborns in the public sector.

Recommendations

Lower Oxygen Saturation Cut-Offs

In the areas of South Africa that are at moderate altitude, especially above 1700m, my study shows that it is imperative that lower oxygen saturation cut-offs be used to decrease the number of false positive screens and the number of repeat screenings required. An average saturation of 94% in patients at our altitude shows that the AAP guidelines are not adequately suited for implementation above 1700m.

If new guidelines are to be promulgated I recommend that adjusted pulse oximetry saturation cut-offs are used in areas with elevations above 1700m to the effect of approximately 2% below the AAP recommendations (Appendices 1 and 2) as this adjustment has shown to not increase the false positive rate or impact on the accuracy

of screening. Further research is recommended assessing appropriate cut-off saturations for altitudes between 1300-1700m.

Feasibility

At present, the main obstacle in providing a reliable POS at CHBAH is staffing shortages. If the task of screening were to befall the nursing staff it will likely be very difficult to obtain reliable screening results due to the increased time required to screen newborns. The provisioning of doctors tasked to see and screen the well newborns before discharge may alleviate some of the pressure on the nursing staff, but also place more pressure on the already understaffed doctor-based services.

Screening of newborns can definitely not be performed by one individual on a daily basis at CHBAH. It has been shown in this study that the patient load is just too great to expect one individual to screen all patients and perform repeat screenings as required. Given there are four post-natal wards at CHBAH, at *minimum* there should be 2 dedicated individuals trained in screening newborns according to the protocol; even with two people screening, it will still be a challenge to adequately and accurately screen all the patients. I would therefore suggest that between three to four people are required daily to deliver an accurate and reliable POS service at CHBAH.

Local Clinics

Due to the decentralised newborn delivery system in use in South Africa where patients are mainly delivering in their communities in Midwife Obstetric Units (MOUs), it is imperative that POS is taught and promoted in these units. It will likely be easier and more cost-effective to screen in the MOU's due to smaller patient volumes where it is hoped that the coverage rate of POS will be enhanced compared to that of a tertiary level facility.

A functional referral procedure would need to be set up where patients failing screening can be referred to the required services for further assessment. This may not necessarily be a Cardiology service initially, but the general Paediatric service may be able to assess and refer further to Cardiology services after an initial assessment, if required. The process of referring to a Paediatric service will likely result in less of a delay in assessment, improving appropriate referral to the necessary Cardiology service for those requiring it.

Demographics

The effect of demographics on human resources and staffing is significant. This study revealed that an unexpectedly substantial proportion of the patients served by CHBAH are from areas outside the legislated drainage area. The result is that the patient load is much larger than reported by census data. Migrants are often not included in census data and are therefore not considered when provisioning human resources to various areas of need. While beyond the scope of this study, it may be prudent to investigate the effects of migrants on the health system so that corrected provisioning of services can be undertaken to assist in staffing shortages.

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- The Neonatal Department at CHBAH for allowing me to use their patients and facilities required to complete the study
- The mothers who agreed to being involved in the study

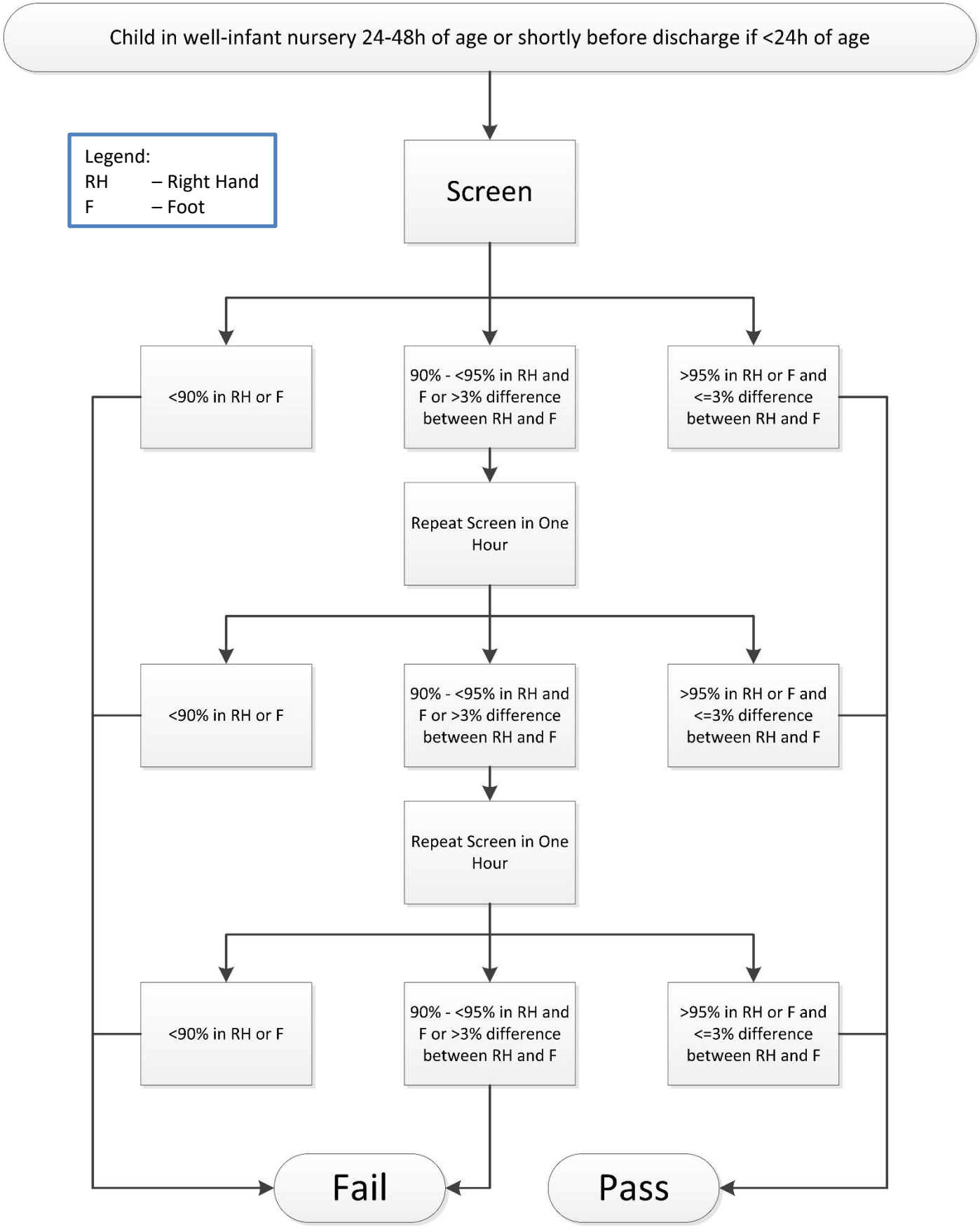
References

1. Botto, L.D., A. Correa, and J.D. Erickson, *Racial and temporal variations in the prevalence of heart defects.* Pediatrics, 2001. **107**(3): p. E32.
2. Knowles, R., et al., *Newborn screening for congenital heart defects: a systematic review and cost-effectiveness analysis.* Health Technol Assess, 2005. **9**(44): p. 1-152, iii-iv.
3. Talner, C.N., *Report of the New England Regional Infant Cardiac Program, by Donald C. Fyler, MD, Pediatrics, 1980;65(suppl):375-461.* Pediatrics, 1998. **102**(1 Pt 2): p. 258-9.
4. Martin, G.R. and E.A. Bradshaw, *Sensitivity of pulse oximetry for detection of critical congenital heart defects in newborn infants higher than that of antenatal ultrasound with few false positives.* Evid Based Med, 2012. **17**(2): p. 57-8.
5. Mahle, W.T., et al., *Role of pulse oximetry in examining newborns for congenital heart disease: a scientific statement from the AHA and AAP.* Pediatrics, 2009. **124**(2): p. 823-36.
6. Ailes, E.C., et al., *Estimated number of infants detected and missed by critical congenital heart defect screening.* Pediatrics, 2015. **135**(6): p. 1000-8.
7. Peterson, C., et al., *Hospitalizations, costs, and mortality among infants with critical congenital heart disease: how important is timely detection?* Birth Defects Res A Clin Mol Teratol, 2013. **97**(10): p. 664-72.
8. Pryds, O., et al., *Vasoparalysis associated with brain damage in asphyxiated term infants.* J Pediatr, 1990. **117**(1 Pt 1): p. 119-25.
9. Kuehl, K.S., C.A. Loffredo, and C. Ferencz, *Failure to diagnose congenital heart disease in infancy.* Pediatrics, 1999. **103**(4 Pt 1): p. 743-7.
10. Wren, C., Z. Reinhardt, and K. Khawaja, *Twenty-year trends in diagnosis of life-threatening neonatal cardiovascular malformations.* Arch Dis Child Fetal Neonatal Ed, 2008. **93**(1): p. F33-5.
11. Lundsgaard, C., D. Van Slyke, and M.E. Abbott, *Cyanosis.* Can Med Assoc J, 1923. **13**(8): p. 601-4.
12. Aoyagi, T., *Pulse oximetry: its invention, theory, and future.* J Anesth, 2003. **17**(4): p. 259-66.
13. Salyer, J.W., *Neonatal and pediatric pulse oximetry.* Respir Care, 2003. **48**(4): p. 386-96; discussion 397-8.
14. Hashim, M.J. and R. Guillet, *Common issues in the care of sick neonates.* Am Fam Physician, 2002. **66**(9): p. 1685-92.
15. Hom, L.A. and G.R. Martin, *U.S. international efforts on critical congenital heart disease screening: can we have a uniform recommendation for Europe?* Early Hum Dev, 2014. **90 Suppl 2**: p. S11-4.
16. Van Niekerk, A.M., et al., *Feasibility of Pulse Oximetry Pre-discharge Screening Implementation for detecting Critical Congenital heart Lesions in newborns in a secondary level maternity hospital in the Western Cape, South Africa: The 'POPSICLe' study.* S Afr Med J, 2016. **106**(8): p. 817-21.
17. O'Brien, L.M., et al., *Oxygen saturation during the first 24 hours of life.* Arch Dis Child Fetal Neonatal Ed, 2000. **83**(1): p. F35-8.
18. Arlettaz, R., et al., *The contribution of pulse oximetry to the early detection of congenital heart disease in newborns.* Eur J Pediatr, 2006. **165**(2): p. 94-8.
19. Levesque, B.M., et al., *Pulse oximetry: what's normal in the newborn nursery?* Pediatr Pulmonol, 2000. **30**(5): p. 406-12.
20. Poets, C.F., et al., *Arterial oxygen saturation in healthy term neonates.* Eur J Pediatr, 1996. **155**(3): p. 219-23.
21. Hoke, T.R., et al., *Oxygen saturation as a screening test for critical congenital heart disease: a preliminary study.* Pediatr Cardiol, 2002. **23**(4): p. 403-9.
22. Koppel, R.I., et al., *Effectiveness of pulse oximetry screening for congenital heart disease in asymptomatic newborns.* Pediatrics, 2003. **111**(3): p. 451-5.
23. Richmond, S., G. Reay, and M. Abu Harb, *Routine pulse oximetry in the asymptomatic newborn.* Arch Dis Child Fetal Neonatal Ed, 2002. **87**(2): p. F83-8.

24. Thangaratinam, S., et al., *Accuracy of pulse oximetry in screening for congenital heart disease in asymptomatic newborns: a systematic review.* Arch Dis Child Fetal Neonatal Ed, 2007. **92**(3): p. F176-80.
25. Kemper, A.R., et al., *Strategies for implementing screening for critical congenital heart disease.* Pediatrics, 2011. **128**(5): p. e1259-67.
26. Bakr, A.F. and H.S. Habib, *Normal values of pulse oximetry in newborns at high altitude.* J Trop Pediatr, 2005. **51**(3): p. 170-3.
27. Salas, A.A., *Pulse oximetry values in healthy term newborns at high altitude.* Ann Trop Paediatr, 2008. **28**(4): p. 275-8.
28. Thilo, E.H., et al., *Oxygen saturation by pulse oximetry in healthy infants at an altitude of 1610 m (5280 ft). What is normal?* Am J Dis Child, 1991. **145**(10): p. 1137-40.
29. Hoffman, J.I., *Is Pulse Oximetry Useful for Screening Neonates for Critical Congenital Heart Disease at High Altitudes?* Pediatr Cardiol, 2016. **37**(5): p. 812-7.
30. Ravert, P., T.L. Detwiler, and J.K. Dickinson, *Mean oxygen saturation in well neonates at altitudes between 4498 and 8150 feet.* Adv Neonatal Care, 2011. **11**(6): p. 412-7.
31. Samuel, T.Y., et al., *Newborn oxygen saturation at mild altitude versus sea level: implications for neonatal screening for critical congenital heart disease.* Acta Paediatr, 2013. **102**(4): p. 379-84.
32. Wright, J., et al., *Feasibility of critical congenital heart disease newborn screening at moderate altitude.* Pediatrics, 2014. **133**(3): p. e561-9.
33. Miao, C.Y., J.S. Zuberbuhler, and J.R. Zuberbuhler, *Prevalence of congenital cardiac anomalies at high altitude.* J Am Coll Cardiol, 1988. **12**(1): p. 224-8.
34. Saxena, A., et al., *Pulse oximetry as a screening tool for detecting major congenital heart defects in Indian newborns.* Arch Dis Child Fetal Neonatal Ed, 2015. **100**(5): p. F416-21.
35. Foglia, E.E., et al., *The Effect of Skin Pigmentation on the Accuracy of Pulse Oximetry in Infants with Hypoxemia.* J Pediatr, 2017. **182**: p. 375-377 e2.
36. Gamponia, M.J., et al., *Reference values for pulse oximetry at high altitude.* Arch Dis Child, 1998. **78**(5): p. 461-5.
37. Han, L.M., et al., *Feasibility of pulse oximetry screening for critical congenital heart disease at 2643-foot elevation.* Pediatr Cardiol, 2013. **34**(8): p. 1803-7.
38. Nitzan, M., A. Romem, and R. Koppel, *Pulse oximetry: fundamentals and technology update.* Med Devices (Auckl), 2014. **7**: p. 231-9.
39. Burle, S. *Elevation and Elevation Maps of Cities/Towns/Villages in South Africa*. 2014 [cited 2017 21 March]; Available from: http://www.floodmap.net/Elevation/CountryElevationMap/?ct=ZA.

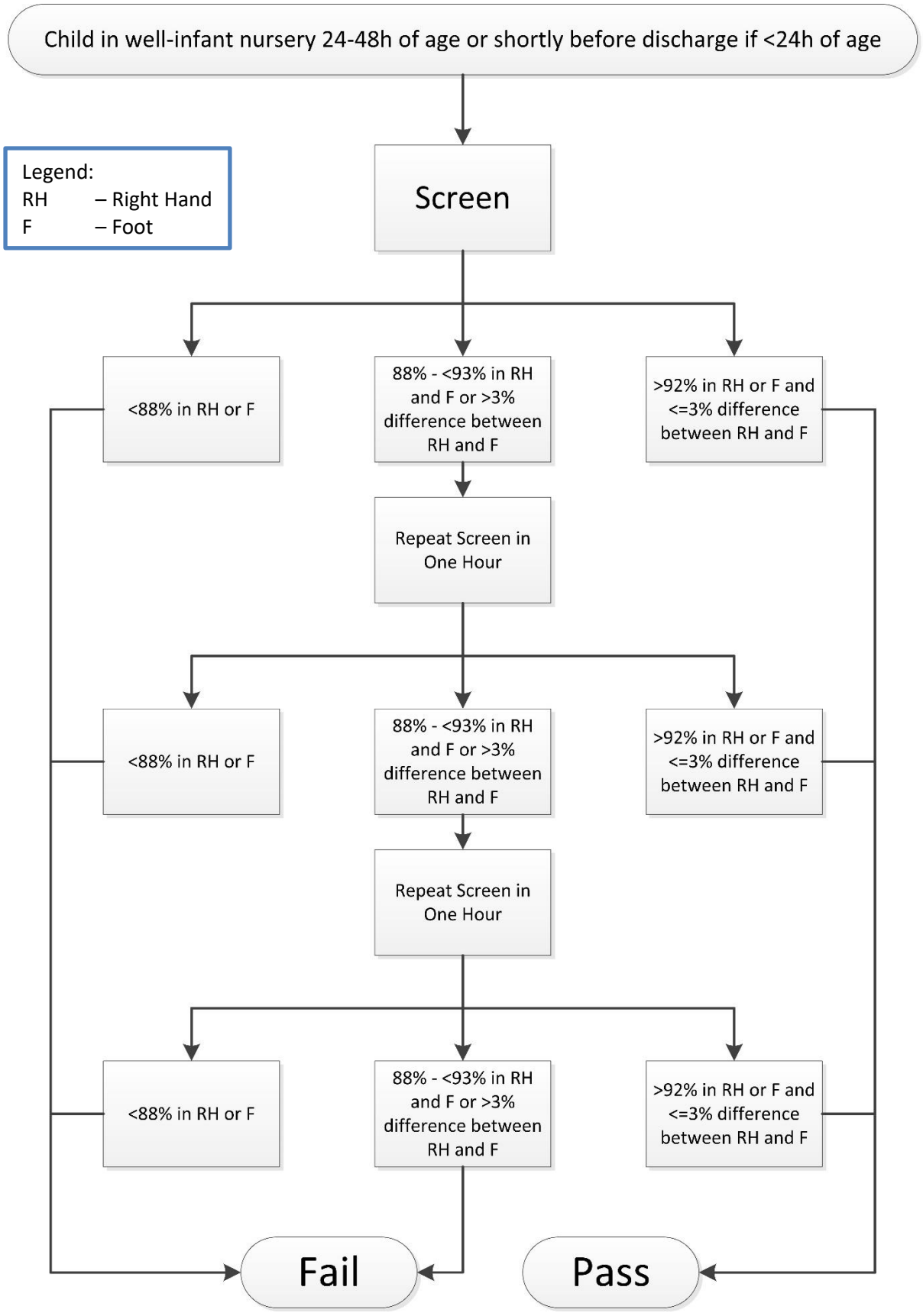
Appendix 1

American Academy of Pediatrics Proposed Algorithm[25]



Appendix 2

Proposed algorithm for screening in high altitude centres, adapted[25]



Appendix 3

Screening Failures

Patient Number	Mode of Delivery	Birthweight (g)	Apgar at 5 minutes	Age at Screening (hours)	RH Saturations (%)	Foot Saturations (%)	Echo Findings
4	NVD	3987	10	30	88	86	No Lesion
11	C/S	3435	10	27	85	86	PFO R>L Shunt
12	C/S	3440	10	22	87	89	PDA <1.5mm
13	C/S	2515	10	35	84	89	PFO Bi-Directional Shunt
14	C/S	3295	10	41	89	87	PFO R>L Shunt

[RH – right hand; PDA – patent ductus arteriosus; PFO R>L – patent foramen ovale with right to left shunt; PFO R>L – patent foramen ovale with right to left shunt]

Appendix 4

Masimo Set Pulse Oximeter

Appendix 5

Data Collection Sheet

Study No.			**Sex**	M	F	**Race**	B	W	C	I	O
Date of Birth	/ /15	**Date of Screening**	/ /15			**Age in hours**					
Birth History	Gestational Age		Birthweight		Apgar	1		5		10	
Family History of CHD			**Area of origin Province/Country**								

Pulse Oximetry	**Hand**	**Foot**		
1st screen			Pass	Fail
2nd screen				
3rd screen				

Appendix 6

Echo Data Collection Sheet

Study Number											
Levocardia	Dextrocardia		Mesocardia		Situs Solitus		Situs Inversus		Situs Ambiguous		
TGV	Truncus		Pulmonary Atresia		Single Ventricle		AVSD		DORV		
SVC	Normal				PV	Normal					
RA	Normal				AV	Normal					
TV	Normal				LVOT	Normal					
RV	Normal				PV	Normal					
IVC	Normal				MV	Normal					
IAS	Normal				Coronaries	Normal					
IVS	Normal				PDA	Absent	Present:	Size:			
LA			Ao				Ratio				
Ao + Arch	Left		Right		Override		CoArct				
LV	Function		LVIDd		LVIDs		SF		EF		
Diagnosis											

Appendix 7

Human Research Ethics Committee Clearance Certificate

R14/49 Dr Micheal Platten

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150721

NAME: (Principal Investigator)	Dr Micheal Platten
DEPARTMENT:	Paediatrics Chris Hani Baragwanath Academic Hospital, Post-natal Maternity Wards
PROJECT TITLE:	To Assess the Accuracy of Pulse Oximetry Screening as a tool to Detect Critical Congenital Heart Disease in Asymptomatic Newborns at Altitude.
DATE CONSIDERED:	31/07/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Antoinette Cilliers
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	9/9/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 8

Turn-It-In Report