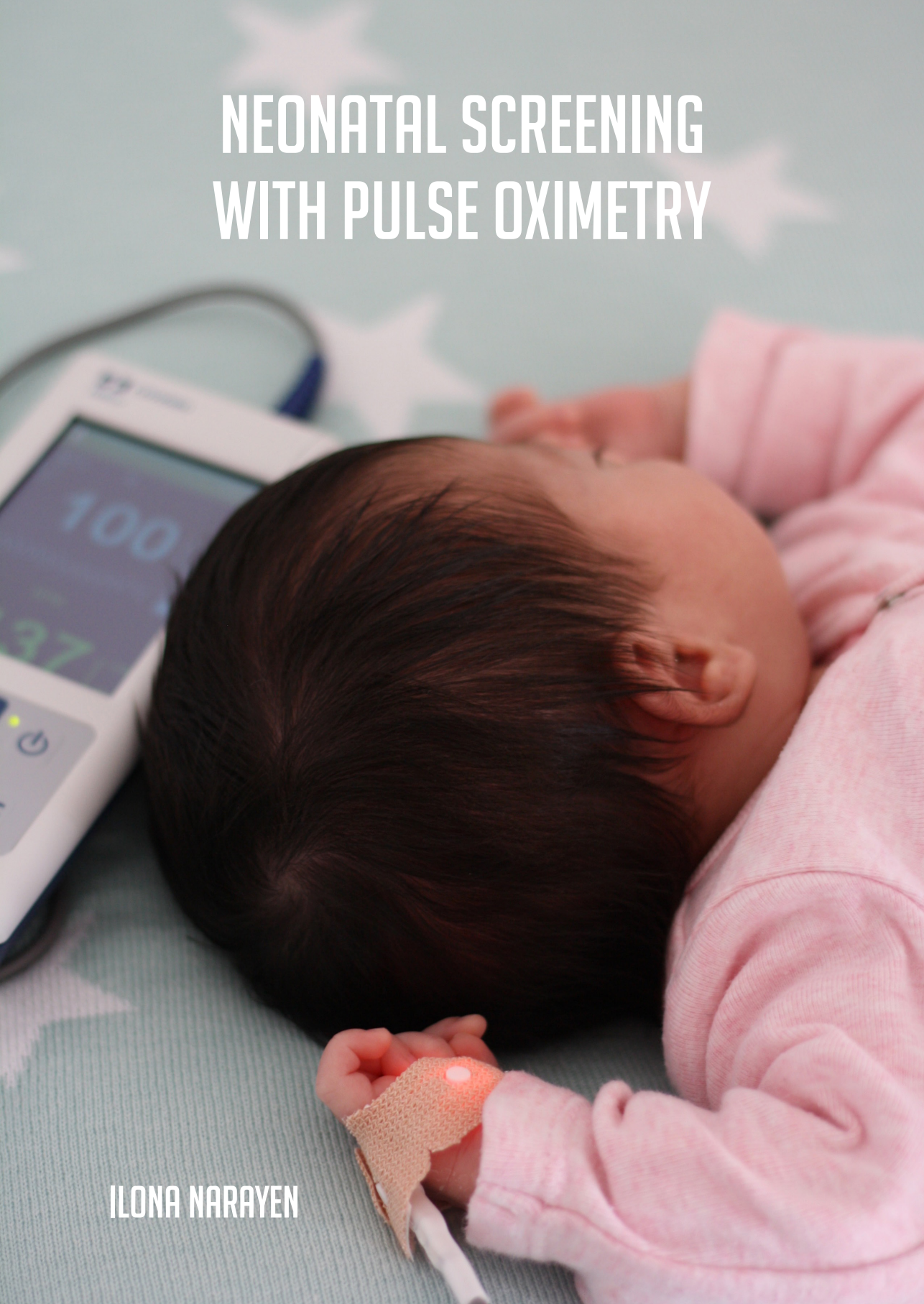
Neonatal screening with pulse oximetry

Narayen, I.C.

NEONATAL SCREENING WITH PULSE OXIMETRY



ILONA NARAYEN

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NEONATAL SCREENING WITH PULSE OXIMETRY

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VOOR JULIE

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PREFACE

PREFACE

“Timing is everything”

The heart is one of the most vital organs of our body; it functions as a pump and ensures that oxygenated blood reaches every part of our body. As the fetus (embryo) is growing in the uterus, the heart is developed from a tube that is first elongated, then folded several times, after which the different heart chambers are created. The heart is a genius design of mother nature, with its two atria and two ventricles: one pair to pump blood to the lungs, one to pump blood to the body. It is almost surprising that this organ most often develops without complications. However, sometimes mother nature makes constructional errors during the development of the heart, which results in a congenital heart defect. We speak of a *critical* congenital heart defect if a baby is born with a congenital heart defect that causes life-threatening problems shortly after birth. These babies cannot survive without an invasive medical intervention in their first weeks of life.

This thesis is about timing, specifically about increasing the amount of critical congenital heart defects that are timely diagnosed. During the years that we conducted the studies that now form my thesis, three babies were born with the same critical congenital heart defect. Their stories, with different courses, touch the essence of my thesis.

Detected before birth

Ellen and Bob* were expecting their first baby. At the ultrasound at 20 weeks of pregnancy a transposition of the great arteries was detected, which is a critical congenital heart defect. Ellen and Bob were counselled, which includes detailed information on the surgery that is needed, and the period that their baby will be in the hospital. They read about the condition and had the opportunity to speak with parents of children with a critical congenital heart defect. The obstetricians, neonatologists and paediatric cardiologists set up a treatment plan. The delivery would take place in an academic center, where an emergency intervention could be performed if necessary, and the parents were prepared that their baby might need interventions even directly after birth.

When their baby Benthe* was born, she was immediately assessed by the neonatologist and paediatric cardiologist. Benthe was admitted to the neonatal intensive care unit, where all the necessary medication was given. She was intubated and ventilated and an emergency intervention was performed on the first day of life. Because of the proper counseling, Ellen and Bob were prepared that this could be the case. Benthe successfully underwent open heart surgery three weeks later and her recovery was uneventful (uncomplicated).

Diagnosed too late

Nora* was born at home after an uncomplicated pregnancy. When she was 5 days old, she was not drinking very well and her parents were alarmed by the fact that Nora did not respond when they stimulated her. The parents called the emergency hotline. Nora was in circulatory failure and was transported by ambulance to the emergency department of the nearest academic hospital by the ambulance after a resuscitation. At arrival at the hospital, a critical congenital heart defect was suspected and treatment was started to support the function of the heart and enable oxygenation of the blood. An ultrasound of the heart indeed revealed a transposition of the great arteries. The parents were deeply shocked by what had happened to their daughter in such a short time frame: a daughter who appeared completely healthy a few hours before. An emergency catheter intervention was needed and Nora was stabilised and admitted to the paediatric intensive care unit. She unfortunately developed end-organ failure and severe brain damage. Because of the poor prognosis the decision was made to not continue further treatment. Nora died in her parents' arms.

Diagnosed with PO screening on day of birth

Amara* was born at 40 weeks of pregnancy after an uncomplicated vaginal delivery. Pulse oximetry screening was performed just before discharge, two hours after birth, because she participated in the POLAR study. The screening result was not normal, and showed low oxygen saturations, so the nurse called the paediatrician for consultation. During the physical examination the paediatrician observed a pink alert baby without any signs of cardiac or respiratory abnormalities. However, the pulse oximeter remained showing low values of the oxygen saturation. For this reason, the paediatric cardiologist was consulted, who detected a transposition of the great arteries by performing an ultrasound of the heart.

A catheter intervention was performed on the same day, which prevented cardiovascular failure. Amara was admitted to the paediatric intensive care unit where she was kept stable until a successful arterial switch surgery was performed at the age of two weeks.

** These cases reflect true stories with fictive names.*

CHAPTER 1

General Introduction

GENERAL INTRODUCTION

Critical congenital heart defects

Congenital heart defects (CHD) form the most common group of congenital defects, occurring in 8/1,000 live born babies, and are the leading cause of infant death (3-7.5% of total infant death).[1-4] There is a range in severity of CHD; 20-25% are critical and usually lead to death or need medical intervention within the first month of life.[5] In the Netherlands, 1350 infants with CHD are born per year, of which around 300 are critical congenital heart defects (CCHD).

Cardiac surgery and catheter interventions have significantly improved the outcome of infants with CCHD in the last decades. However, if a CCHD is not diagnosed in an early stage it can cause severe hypoxemia, acidosis, shock and, without proper treatment, eventually lead to death. A timely diagnosis of CCHD, before cardiovascular collapse, is essential in order to reduce the risk of mortality and morbidity, including cerebral and organ damage, and neuropsychological impairment.[6,7] A timely diagnosis of CCHD can be made on several 'screening' moments: at the fetal standard anomaly scan, with postnatal physical examination, or by pulse oximetry screening.

Antenatal detection of critical congenital heart defects

All pregnant women in the Netherlands can be screened for fetal anomalies with a standard anomaly scan (ultrasound) at 20 weeks of gestation, which was implemented as a national screening programme in 2007. This screening programme is well organised in the Netherlands; the scan can only be performed by experienced and educated screeners who make at least 150 anomaly scans per year, and even 250 in the first two years of their career as ultrasonographer. Also, they are obliged to cooperate with a quality audit.

An analysis of the fetal standard anomaly scan in the Amsterdam-Leiden region from the period 2007-2012 demonstrated a 50% prenatal detection rate for CCHD.[8, 9] In case of a prenatal detection, a baby with CCHD is born in a congenital heart disease center with third level Neonatal Intensive Care Unit (NICU), so treatment can be started promptly. Unfortunately, not all CCHD can be detected prenatally and abnormal venous return and aortic arch obstructions are most difficult to detect.[8, 10, 11] Furthermore, the prenatal detection rate of CCHD varies among countries and regions.

Postnatal detection of critical congenital heart defects with physical examination

With postnatal physical examination, still 20-30% of CCHD are missed.[12] Common symptoms of CCHD, such as cyanosis, dyspnea, and feeding difficulties often occur some days later, when the ductus arteriosus closes. Early symptoms can be easily missed upon physical examination. Murmurs are not always present in newborns with CCHD and around 40% of newborns with

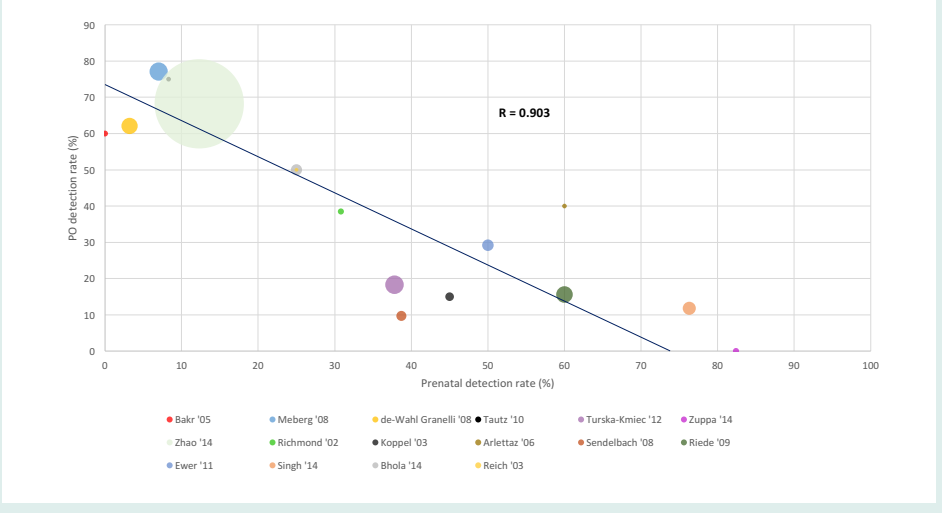
a murmur do not have CHD.[13, 14] Cyanosis is difficult to detect with the human eye and can be affected by factors in the environment (for example ambient light), making colour assessment unreliable.[15]

Pulse oximetry screening to detect critical congenital heart defects in newborns

Pulse oximetry (PO) is a safe and reliable method to measure the peripheral oxygen saturation (SpO_2) and detect (subclinical) cyanosis in newborns. PO measures the SpO_2 by the use of red and infrared light. The difference in light absorption in saturated and desaturated haemoglobin is used to calculate the SpO_2.[16] The use of a sensor and light makes it a non-invasive painless method that is able to measure the SpO_2 continuously.

Since 2000 many studies have been performed assessing PO as a screening tool for CCHD in asymptomatic newborns. Studies performed with delivery in hospital have shown that PO screening for CCHD is accurate, safe, acceptable, cost-effective, and easy to perform.[17-22] The sensitivity of the screening varies, and is also correlated with the fetal detection rate of CCHD. The sensitivity of PO screening was lower in settings with a higher prenatal detection of CCHD, as shown in Figure 1.

Figure 1. Bubble chart of pulse oximetry (PO) and prenatal detection rates for individual studies with regression line weighted by study cohort size (y=74.21-1.007x).



Detecting other pathology with PO

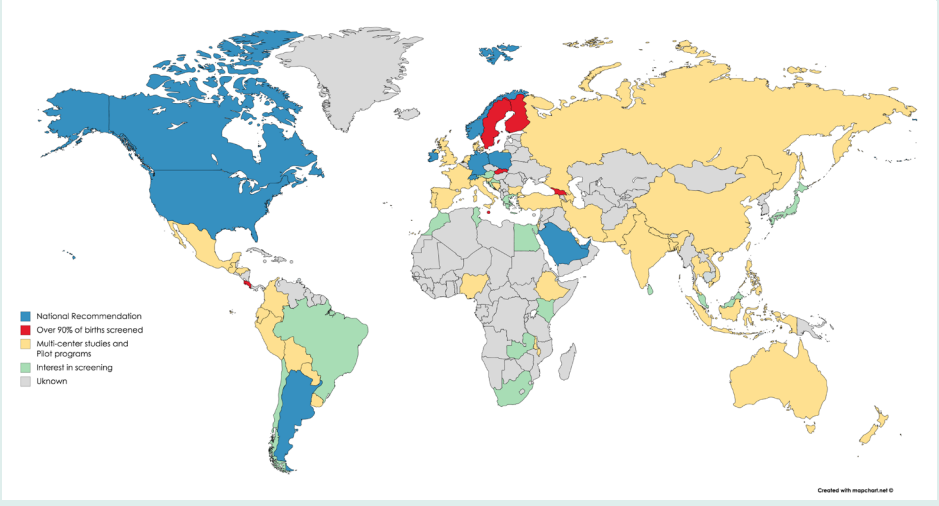
Since cyanosis (low SpO_2) occurs also in other, non-cardiac, pathology, PO screening has the advantage of detecting infections, pulmonary pathology, and haematological disorders in an early stage in newborns as well.[22, 23] These potentially life-threatening diseases are present in up to 80% of newborns with false positive screenings.[22-25] Early detection of infections and respiratory pathology enable prompt treatment and can prevent deterioration to severe conditions such as sepsis and persistent pulmonary hypertension of the newborn (PPHN).

The current status of implementing PO screening

PO screening to detect CCHD in newborns is gaining ground in countries spread over all continents.[26] The United States have a legislation for universal PO screening since 2011, while the Nordic European countries were the first to reach >90% of newborns screened. The screening is recommended by the UK National screening committee, and has been implemented in Costa Rica, Georgia, Germany, Malta, Slovakia, Switzerland, Poland and the United Arab Emirates.[26]

However, the accuracy and cost-effectiveness is still unknown in settings with home births, early discharge after hospital deliveries, high altitude and on Neonatal Intensive Care Units.

Figure 2. Status of implementation of PO screening for CCHD.



Created with data from Children's National. Updated May 2017

Dutch neonatal care setting

The Dutch perinatal care setting is unique with the highest rate of home births (18%) among developed countries.[27, 28] In the Netherlands, 33% of all deliveries are supervised by a community midwife, either at home or in a birthing facility. A community midwife stays for approximately three hours after birth and returns for a follow-up visit for mother and newborn on day two or three of the newborn's life (day of birth is day one) and is responsible for the care of mother and newborn within the first ten days of life. Also, mother and newborn are discharged from hospital within five hours after an uncomplicated clinical vaginal delivery, with postnatal follow-up visits by a community midwife at home starting on day two or three. In order to perform PO screening for CCHD in the Dutch perinatal care setting community midwives should be involved, and timing of the screening should be adjusted to fit their working scheme. Also, there should be a referral system for abnormal screenings obtained at home. Adjustment in the previously assessed protocols might affect the feasibility, accuracy and cost-effectiveness of PO screening for CCHD.

AIM AND OUTLINE OF THIS THESIS

After publication of the meta-analysis regarding PO screening in the Lancet in 2012, there were concerns regarding performance of the screening in the Dutch perinatal care setting. These concerns were based on the high rate of home births, early postnatal discharge after delivery and the newborns with false positive screenings referred from home to hospital.(29)

The aim of this thesis was to assess the feasibility, accuracy, acceptability and costs of PO screening for CCHD with a protocol that is adapted to the Dutch perinatal care system with home births and early discharge after in-hospital delivery. Also, the detection of non-cardiac significant pathology by PO, such as infectious and respiratory pathology, might be of extra importance in the Netherlands where newborns are at home without monitoring or medical attendance within the first day of life. **For this reason, we also aimed to assess the rate of detection of these pathologies.**

In **Chapter 2** we provide an overview of all aspects that need to be considered by caregivers when choosing an optimal protocol for PO screening for CCHD in their specific setting. In this review, an update and overview is given of the available research regarding PO screening, including an update of the worldwide implementation.

In **Chapter 3** we describe a protocol for PO screening that is adapted to the Dutch perinatal care setting with home births and early discharge after delivery in hospital.

In **Chapter 4** we demonstrate the feasibility of performing PO screening using the adapted protocol for home births and early discharge after delivery in hospital in the Leiden region.

Chapter 5 reports the accuracy, expressed in the sensitivity and specificity, of PO screening in the Dutch perinatal care setting in a prospective study of 23.996 newborns. Also, the detection of secondary pathology, such as infections and pulmonary pathology is described.

The costs of PO screening in the Dutch setting are analysed in **Chapter 6**, based on the results of the implementation study described in Chapter 5.

In **Chapter 7** the maternal acceptability of PO screening at home is assessed, while **Chapter 8** provides more details on reliability of low signal quality measurements of pulse oximetry.

The general discussion and summary in **Chapter 9 and 10** outline the most important findings of this thesis and the future perspectives for research.

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CHAPTER 2

Aspects of pulse oximetry screening for critical congenital heart defects: when, how and why?

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ABSTRACT

Pulse oximetry (PO) screening for critical congenital heart defects (CCHD) has been studied extensively and is being increasingly implemented worldwide. This review provides an overview of all aspects of PO screening that need to be considered when introducing this methodology. PO screening for CCHD is effective, simple, quick, reliable, cost-effective, and does not lead to extra burden for parents and caregivers. Test accuracy can be influenced by targets definition, gestational age, timing of screening, and antenatal detection of CCHD. Early screening can lead to more false positive screenings, but has the potential to detect significant pathology earlier. There is no apparent difference in accuracy between screening with post-ductal measurements only, compared with screening using pre- and post-ductal measurements. However, adding pre-ductal measurements identifies cases of CCHD which would have been missed by post-ductal screening. Screening at higher altitudes leads to more false positives. Important non-cardiac pathology is found in 35-74% of false positives in large studies. Screening is feasible in Neonatal Intensive Care Units and out-of-hospital births. Training caregivers, simplifying the algorithm, and using computer-based interpretation tools, can improve quality of the screening. Caregivers need to consider all aspects of screening to enable them to choose an optimal protocol for implementation of CCHD screening in their specific setting.

INTRODUCTION

Introduction

Critical congenital heart defects (CCHD) occur in 2-3 per 1,000 live births, usually require invasive medical intervention within the first month of life, and can lead to death or significant morbidity if not diagnosed in a timely manner.[1] Early detection is important for reducing the mortality and improving the postoperative outcome.[2-6]

Routine fetal ultrasound screening has led to increased antenatal detection of around 50-70% of all CCHD.[7] Postnatally, 20-30% of CCHD are still missed by physical examination, as symptoms often occur later, when the ductus arteriosus closes.[8, 9] Murmurs are not always present with CCHD, and may occur in up to 60% of healthy newborns.[10] Also, it has been shown that assessment of cyanosis is unreliable for detecting hypoxemia.[4, 11] Pulse oximetry (PO) is a widely available, accurate method to objectively quantify oxygen saturations (SpO_2), and thereby identify the clinically undetectable hypoxemia that occurs in the majority of neonates with CCHD.[11, 12]

Early studies assessing neonatal PO screening for CCHD demonstrated proof of concept,[13-15] followed by large accuracy studies.[16-20] This led to a recommendation in 2011 by the US Secretary of Health and Human Services to add CCHD screening to the recommended uniform screening panel, which was also endorsed by the American Academy of Pediatrics.[21] A meta-analysis of 13 screening studies, including almost 230,000 infants, reported a sensitivity of 76.5%, specificity of 99.9%, and false positive rate of 0.16%.[22] The authors concluded that PO screening met the universal screening criteria. Since then further studies focusing on feasibility, implementation, and logistical aspects of CCHD screening have been performed.[23-38]

This review provides an overview of all aspects that need to be considered when performing PO screening. We also provide an update of the current status of PO screening worldwide. Caregivers can use this information to implement an optimal screening protocol in their local care system.

Aspects influencing the accuracy of pulse oximetry screening

Sensitivity ranged from 60-100%, whereas specificity was ³94%, and in most studies >99% (Table 1). This high specificity is accompanied with a false positive rate varying between 0% and 1.8% (Table 1). So far, no difference has been shown in accuracy when pre- and post-ductal PO measurements are performed versus only post-ductal measurements.[18, 20, 22] Screening performed >24 hours after birth decreases the false positive rate, but increases the risk of late detection of infants with CCHD who may decompensate prior to screening.[18-20] Furthermore, non-critical cardiac defects and other significant pathology may be found in up to 80% of the false positive cases (Table 2).[18, 20, 25, 28]

Table 1. Overview of accuracy studies.

First Author, year	N	Prenatal detection of CCHD	GA	Sensor probe location
Hoke, 2002[29]	2,876	17%	≥34 wk	Pre and post
Richmond, 2002[13]	5,626	10%¥	All, not neonatal unit	Post
Koppel, 2003[14]	11,281	45%	All, well infant nursery	Post
Reich, 2003[36]	2,114	33%	All, not NICU	Pre and post
Rosati, 2005[31]	5,292	Not mentioned	Healthy term	Post
Bakr, 2005[32]	5,211	0%	All healthy	Pre and post
Arlettaz, 2006[33]	3,262	28%¥	≥35wk	Post
Ruangritnamchai, 2007[34]	1,847	Not mentioned	All healthy	Pre and post
Meberg, 2008[16]	50,008	7%	Healthy at nursery	Post
Sendelbach, 2008[17]	15,233	80%	≥35wk	Post
De-Wahl Granelli, 2009[18]	39,821	3.3%		Pre and post
Riede, 2010[19]	41,445	63%	Healthy term	Post
Tautz, 2010[35]	3,364	10%	≥35wk	Post
Ewer, 2011[20]	20,055	50%	>34 wk	Pre and post
Turska-Kmiec, 2012[23]	51,698	38%	All at neonatal unit	Post
Kochilas, 2013[24]	7,549	Not mentioned	Healthy newborns	Pre and post
Singh, 2014[25]	25,859	76%	Postnatal ward	Pre and post
Zuppa, 2014[26]	5,750	82%	Healthy at nursery	Post
Bhola, 2014[27]	18,801	11%	>36 wk	Post
Zhao, 2014[28]	120,707	8%†	all	Pre and post

FP= false positive; GA=gestational age; PE=physical examination; pre=pre-ductal; post=post-ductal; ¥for all CHD; ^group too small to assess sensitivity; †for major CHD; &for CCHD; *mean

Cut-off values	Time screening, h (median)	Sensitivity	Specificity	FP rate
<92%; Pre-post>7%	24 or discharge	69%[¥]	99.0%	1.8%
2x <95% or 1x<95% and abnormal PE	>2, <discharge (11.7*)	25%[¥]	99.0%[¥]	1.0%
≤95%	>24	60.0%	99.95%	0.009%
3x <95% or Δ>3%	<discharge	---^	99.8%	0.04%
≤95%	>24 (72)	66.7%	100%	0.019%
1x <90%, 3x 90-94%	<discharge (31.7*)	77%	99.7%	0.02%
1x <90%, 2x 90-94%	6-12 (8)	100%	99.6%	0.4%
1x <95%	24-48	98.5%	96.0%	0.05%
2x <95% or 1x <95% and symptoms	First day (6)	77.1%	99.4%	0.6%
<96%	4	75%	94%	5.6%
	<discharge (38)	82.7%	97.9%	0.17%
2x <96%	24-72 (-)	77.8%	99.9%	0.1%
<90%, 2x <90-94%	6-36 (12)	82.0%	99.9%	0.3%
1x <95% or Δ>2% + symptoms OR 2x <95% or Δ2%	<24 (12.4)	75.0%[&]	99.1%[&]	0.9%[&]
2x <95%	2-24(7)	78.9%	99.9%	0.026%
1x <90 3x 90-94% or Δ>3%	≥24 (30*)	100%	99.9%	0.07%
<95% or Δ>2%	<24 (7.5)	60%	99.2%	0.8%
2x <95%	48-72 (64)	--	99.9%	0.05%
1x <90% or 3x 90-95%	24-72 (-)	80%	99.8%	0.13%
1x <90% or 2x 90-95% or Δ>3%	6-72 (43)	83.6%	99.7%	0.3%

Table 2. detection of pathology other than CCHD.

Author, year	N	TP	FP (%)	PPHN	Other lung pathology	Infection/ sepsis	Non-critical CHD	Other	Healthy (%)
Hoke, 2002[29]	2,876	4	53 (1.8)	1	-	-	-	-	39 (74)[#]
Richmond, 2002[13]	5,626	4	47 (0.8)	1	2	-	-	4	40 (90)
Koppel, 2003[14]	11,281	2	1 (0.009)	1					0 (0)
Reich, 2003[36]	2,114	2	2 (0.1)	-	-	-	-	-	2* (100)
Rosati, 2005[31]	5,292	2	2	-	-	-	-	1	1 (50)
Bakr, 2005[32]	5,211	3	2 (0.04)	-	-	-	1	1	0 (0)
Arlettaz, 2005[33]	3,262	14	10 (0.3)	5			4		1 (10)
Ruangritnamchai, 2007[34]	1,847	2	1	-	-	-		-	Not mentioned
Meberg, 2008[16]	50,008	27	297 (0.6)	6	68	55	17	4	147 (49)
Sendelbach, 2008[17]	15,233	3	856 (5.6)	-	-	-	2	12	841 (98)
De-Wahl Granelli, 2009[18]	39,821		69 (0.2)	6	7	10	14	8	24 (35)
Riede, 2010[19]	41,445	14	40 (0.1)	15	-	13	-	-	12 (30)
Tautz, 2010[35]	3,364	8	10 (0.3)	2	-	7	1	-	- (0)
Ewer, 2010[20]	20,055	18	177 (0.9)	40			14		123 (69)
Turska, 2012[23]	51,698	15	14 (0.026)	-	-	5	1	-	8 (57)
Kochilas, 2013[§24]	7,549	1	5 (0.07)	3	-	-	-		1 (20)
Singh, 2014[25]	25,859	9	199 (0.8)	12	-	85	8	44	43 (22)
Zuppa, 2014[26]	5,750	0	3 (0.05)	3					
Bhola, 2014[27]	18,801	4	11 (0.13)	3	2	1	-		5 (45)
Zhao, 2014[28]	120,707	122	394 (0.3)	41	23	10	106		214 (54)

FP= false positive; TP= true positive. [#]unknown in 13 infants; * these two infants had a large patent ductus arteriosus; [§]test of 1 infant was misinterpreted.

Targets

To interpret the observed accuracy in PO screening studies, the specified target should be taken into account as they vary between studies (all CHD,[13, 29, 32] significant CHD,[30, 33] major CHD,[20, 28] all duct dependent CHD,[18, 20] and CCHD[17, 26, 28, 31, 34]).

Targeting all CHD instead of only CCHD could decrease the sensitivity, as not all CHD lead to hypoxemia in the first days of life. In contrast, when considering only CCHD as a target for PO screening, the false positive rate will be higher. However, the false positive screens will include other, non-critical CHD, which are also important to detect. Non-critical CHD could therefore be classified as secondary target for the screening.

Gestational age

While most PO screening studies included only asymptomatic infants, not admitted to a Neonatal Intensive Care Unit (NICU),[13, 16, 19, 24-26, 31, 32, 34, 36] a few studies also included late preterm infants (≥34 weeks of gestational age).[20,29] Although the extra value of PO screening in monitored preterm infants is uncertain, concomitant pre- and post-ductal PO measurements may detect CHD earlier when these infants are also included in the screening (Table 3).

Timing

The meta-analysis demonstrated a significantly lower false positive rate when the screening was performed ≥24 hours after birth.[22] In several countries, there is a tendency for early discharge, <24 hours of life.[37] Moreover, up to half of all infants with CCHD presented with symptoms prior to the screening, with circulatory collapse in up to 9% of these infants when screening > 24 hours was performed.[18,38]

Ewer *et al.* showed the highest sensitivity if screening took place 6-12 hours after birth, but specificity was the highest at 0-6 hours after birth.[20] In a large Chinese study, the false positive rate was higher when screening was performed at 6-24 hours after birth (0.55%) as compared to 25-48 (0.29%) and 9-72 (0.26%) hours after birth. but sensitivity was 10% higher at 6-24 hours.[28]

Performing PO screening in the first hours of life is likely to lead to more false positive screenings, but this must be weighed against the potential benefit to detect significant pathology, including non-critical CHDs, infections and pulmonary disorders, at an early stage of the disease, preventing deterioration (Table 3).

When determining the timing of screening, the logistics of perinatal care should be taken into account as the duration of hospitalization after birth and the rate of home births vary between hospitals and countries. An international group of experts on CCHD screening recommended pilot studies in individual European countries to test feasibility, accuracy and cost-effectiveness in the local care systems.[37]

Post-ductal or pre-and post-ductal measurement

All studies performed post-ductal measurements, as there is a possibility of missing CCHD associated with predominant right to left shunting at the ductus arteriosus and stenosis of the aortic isthmus when only pre-ductal measurements are obtained (Table 1). However, in half of the studies, pre- and post-ductal measurements were obtained (Table 1). The meta-analysis showed no difference in accuracy between only post-ductal versus combined measurements, but certain left outflow tract obstructions might be missed with post-ductal measurements alone.[20, 22] However, Ewer *et al.* and Granelli *et al.* observed that adding a pre-ductal measurement also increased the false positive rate.[18, 20]

Cut-off values

The definition of threshold values will determine the sensitivity and specificity of the screening tool. When choosing the cut-off value, the false positive rate must be balanced against the risk of missing CCHD. Ewer *et al.* defined SpO_2 <95% in either limb or a difference of >2% between the limbs as abnormal.[20] In their study, the false positive rate would have been reduced from 0.8 to 0.5% if they had used a difference of >3% in both limbs; however, 13 respiratory disorders and 3 CHDs would have been missed.[18, 20] Cost-effectiveness and accuracy analyses should be performed for different thresholds and probe placement approaches to determine the optimal threshold values.

Altitude

At moderate or high altitudes, a delay in the decrease in pulmonary vascular resistance will lead to lower SpO_2 after birth when compared to infants born at sea level.[39-41] At mild elevation Han *et al.* concluded that the screening is feasible with a low false positive rate.[42] Wright *et al.* observed more positive screenings (1.1%) in infants at moderate altitude with the recommended screening protocol.[43] Infants with SpO_2 ≥95% and ≤3% difference in SpO_2 passed the screening, while infants with SpO_2 <85% at any screening were assigned fail screen status. More studies need to be performed to define optimal cut-off levels for PO screening at moderate and high altitudes and the sensitivity must be balanced against the high false positive rate

The influence of the antenatal detection rate

The sensitivity and cost-effectiveness of the screening will also be influenced by the antenatal detection rate of CCHD (Table 1), which is strongly influenced by the training, experience and equipment of the sonographer, and by the quality and organization of the antenatal health services.[7, 44] Fetal echocardiography was not routinely available in two large PO screening studies.[18, 32] In case of low antenatal CCHD detection, the value by PO will be higher compared to settings with high fetal detection rates. Furthermore, infants with prenatally detected CHD were excluded for PO screening in the majority of studies.[13, 20, 29, 33, 35]

Devices

It is recommended to use pulse oximeters that are cleared for use in newborns, are usable in low perfusion states, report functional oxygen saturation, and are motion tolerant.[45, 46] Dawson *et al.* demonstrated a good agreement between measurements obtained with Masimo and Nellcor PO when SpO_2≥70%, but a low agreement when SpO_2 <70%.[47] This is unlikely to affect screening sensitivity.

Table 3 provides an overview of the described aspects of the screening and their advantages and disadvantages.

Table 3. advantages and disadavantages of aspects in protocol for pulse oximetry screening.

Aspect in protocol	Advantage	Disadvantage
Targeting all CHD instead of only CCHD	Increased specificity Decreased false positive rate	Decreased sensitivity
Including preterm infants	Earlier detection of CCHD and other pathologies	Possible increase in false positive rate
Early screening (<24 h)	Detect significant pathology in an early stage Possible higher specificity Fits in setting with early discharge	Possible increase in false positive rate
Adding pre-ductal measurement to post-ductal PO measurement	Possible improved detection of left outflow tract obstructions	More time consuming
Screening at moderate-high altitude	Early detection of significant pathology	Possible increase in false positive rate
Including infants with antenatal CHD detection	Increase in sensitivity and specificity	No clinical consequences for CHD
Reusable sensors	Decrease costs	Must be disinfected between uses to minimize risk of infection

CCHD: critical congenital heart defect; CHD: congenital heart defect; PO: pulse oximetry

Detection of other pathologies

PO can also detect other causes of hypoxemia, including infections and pulmonary/respiratory disorders. In Table 2 we calculated the detection of important pathology other than CCHD. Although detection of these conditions is currently considered as false positives, it is important to detect them early, so treatment can be started before deterioration occurs with increased risk of death, morbidity and longer hospitalization. There is large variation in detection of other pathology in the reported studies (0-90%; Table 2). Since different screening targets were used in the studies, the false positive rates are difficult to compare. According to the power analysis of Ewer *et al.* 20,000 neonates were required to accurately assess accuracy of

PO screening. There are 7 studies with inclusion of >20,000 neonates, in which the detection of other important pathology amongst the false positive screening was 27-74%.[16, 18-20, 23, 25, 28]

Setting

In most countries where it has been implemented, the screening takes place in hospitals. Screening has been performed in major centers and regional hospitals.[24, 48]

PO screening in the NICU has been less well investigated. However, a recent study showed similar discharge SpO_2 values in late preterm and term infants at a NICU with a 100% screening rate and, therefore, the current screening protocol is feasible for these groups upon discharge from a NICU.[49] Although screening in the NICU is feasible, underlying illnesses and timing of the screening increased the false positive rate.[50]

Studies have also investigated PO screening out-of-hospital and after early discharge from hospital.[19, 25, 27, 51] In Australia, the screening was performed 24-72 hours after birth or, in case of early discharge, prior to discharge with a repeated measurement at home within the first 3-5 days after birth.[27] All four detected cases of CHD were found prior to discharge from the maternity service. Also, in Wisconsin, with a home birth rate of 1.67%, screening could be obtained in only 1/3 of all home births.[51] In the Netherlands 33% of births are supervised by community midwives, in birthing facilities or at home, and an adjusted screening protocol has been developed to fit in the working scheme of the midwives.[52, 53]

Acceptability

Two studies reported that parents widely accepted the test and the false positive results did not lead to more anxiety.[23, 54] Furthermore, the medical staff considered the test as highly important and easy to carry out.[20] Tautz *et al.* reported a feeling of security and confidence of the nursery staff by using the PO measurements.[35] Most of the physicians involved in newborn medicine endorsed it as an effective tool.[55]

Cost-effectiveness

Several studies on cost-effectiveness of pulse oximetry screening have been performed.[18, 24, 56-58] Roberts *et al.* calculated incremental costs of £24,900 per timely diagnosis, with a 90% chance of being cost-effective with a Willingness To Pay threshold of £100,000.[56] Peterson *et al.* also demonstrated that the screening was cost-effective. The PO screening costs $3.83 per newborn, or $4,693 for each life saved by screening. With an estimation of 248 cases of CCHD detected early by the screening and 110 deaths averted annually, they conclude that the screening is cost effective.[57] Kochilas *et al.* reported the costs of $5.10 per screening and, con-

sidering the numbers needed to screen, $46,300 per patient diagnosed with CCHD.[24] Griebsch *et al.* and De-Wahl Granelli *et al.* concluded that the screening is at least cost neutral, since in the Swedish study the costs per timely diagnosis made due to screening were £3,430 while the costs per infant with circulatory collapse due to CCHD were £3,453.[18, 58] All these studies imply that PO screening for CCHD is cost-effective.

Quality improvement

Experience has been gathered in ways to improve the use of the PO for CCHD screening.[15, 24, 59-62] Training could lead to more adequate use of PO and the algorithm.[15, 24, 59, 60] Also, the use of a computer-based tool for interpretation of the results could improve the accuracy, since human interpretation is susceptible to errors.[61, 62]

Barriers for implementation

Impact on echocardiography service

The concern of a possible increased workload for echocardiography services and paediatric cardiologists could not be confirmed. Bhola *et al.* reported only 5 extra echocardiograms during a 42 months screening period of 18,801 infants.[27] Also, studies showed that only a few infants had structurally normal hearts on performed echocardiograms.[24, 30]

Furthermore, the introduction of PO screening reduced the number of emergency and "unnecessary" echocardiograms.[14, 30, 35]

In addition, when PO screening is routinely implemented, it is reasonable to perform echocardiography only in infants with persistent abnormal SpO_2 without evidence for another, non-cardiac diagnosis.[25] All infants with positive screens should be carefully assessed by well-trained paediatric staff. Next to CHD the differential diagnosis includes respiratory pathology (inter alia pneumonia, aspiration, pneumothorax), infections and sepsis, and transitory problems, such as persistent pulmonary hypertension of the neonate (PPHN).

Staff/working time

All studies reported a maximum of 5.5 minutes per screening, with a mean of even 1.6 minutes in Zhao's study.[18, 24, 27, 28, 33, 48] No extra staff members were needed to perform the screening.[26, 47]

Current Implementation

There is an increased interest in CCHD screening all over the world. It was estimated that ≥90% of infants born in the United States were screened for CCHD screening by the end of 2014.[63] Finland has the highest screening rate after implementation (97%), followed by Sweden (91%) and Norway (90%).[64] In 2009 Switzerland screened 85% of infants.[65] PO screening has been

recommended in Abu Dhabi, Ireland, Sri Lanka, and Poland.[66] Furthermore, pilot studies are or have been performed in many countries, including UK, Germany, Spain, Italy, Australia, China, and the Netherlands.[23, 27, 28, 38, 53] A group of international CCHD screening experts encourage European societies to formulate statements regarding CCHD screening to enhance implementation of the screening across Europe.[37]

Limitations

It is important to emphasize that PO screening does reduce the diagnostic gap but will not lead to 100% detection of CCHD. Defects with aortic obstruction are most commonly missed with PO, and these are also more difficult to diagnose with prenatal ultrasound.[14, 28, 67, 68]

Although CCHD screening has been thoroughly investigated and implemented in settings with delivery in hospitals, more studies are needed testing the accuracy and (cost)effectiveness of the screening in special settings, such as home births, very early discharge, moderate-high altitude, and NICUs.

CONCLUSION

PO is an effective method to detect CCHD, as an adjunct to prenatal ultrasound and physical examination. The tool is simple and reliable, has low costs, is not time consuming, and there is no extra burden for the parents and infants. Furthermore, it is widely available and detects other potential life-threatening pathology such as infections, and persistent pulmonary hypertension of the newborn. Early detection of CCHD reduces the mortality and morbidity. Studies on protocols at NICUs, out-of-hospital births, and early discharge are still subject to investigation.

PO screening is introduced increasingly in countries all over the world and in different settings, with different timing of the screening. Before implementing the screening in a specific setting, it is important to know the experience and evidence for CCHD screening in that setting. In this review we have given an overview of the different aspects of the screening, which can be used for developing an optimal screening protocol for a specific local setting.

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CHAPTER 3

Adapted protocol for pulse oximetry screening for congenital heart defects in a country with home births

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ABSTRACT

Pulse oximetry has been recommended for neonatal screening for critical congenital heart defects (CCHD) and is now performed in several countries where most births take place in hospital. However, there is a wide variation in perinatal care in European countries and studies are now recommended to determine the cost-effectiveness CCHD screening in individual countries. In the Netherlands, a large part of births is supervised by a community based midwife, at home or policlinical. A screening protocol has been developed to fit into the Dutch perinatal setting, and also has the potential to increase safety in home birth deliveries.

Conclusion*:* the provided protocol might be useful for other countries that are planning to implement CCHD screening after home births or early discharge from hospital.

What is known: pulse oximetry screening is a recommended tool to screen newborns for critical congenital heart defect and is implemented increasingly. So far, the screening only takes place in hospital.

What is new: The presented screening protocol is adapted to fit into a perinatal setting with home births and early discharge after delivery in hospital.

INTRODUCTION

Congenital heart defects (CHD) are the most common birth defects, occurring in 0.8% of live births and are a leading cause of infant death in the developed world. Approximately 20-30% of the CHD are critical (CCHD) and require surgical or catheter intervention in the first month of life.[1] Early detection of CCHD in both pre- and postnatal period is vital for the prognosis.[2] However, recent unpublished data from the Amsterdam-Leiden region, in the Netherlands, have shown that still around 50% of CCHD cases remain undetected in the prenatal stage. Also, after birth around 30% of CCHD are missed since physical examination alone is not sensitive enough for screening.[3] It is expected that early detection can decrease the incidence and severity of brain injury and increase chances of survival.[3]

Pulse oximetry (PO) is a simple and non-invasive method for screening for CCHD in low risk infants.[4] A systematic review of 13 studies has shown a sensitivity of 76.5%, a specificity of 99.9% and a false positive rate of 0.14%.[2] Moreover, studies imply that 27-70% of infants with false positive tests were diagnosed with other significant pathology, such as non-critical CHD, persistent pulmonary hypertension of the newborn (PPHN), infection and sepsis.[1, 4] In 2011 PO screening was recommended by The Health and Human services, and it is now introduced in the United States, Switzerland and regionally in Abu Dhabi, recommended in Poland, and piloted in several countries, including the United Kingdom, Nordic European countries and China.[1,5] In these countries the screening normally takes place in hospital, prior to discharge, at least two hours and mostly 24-48 hours after birth.[6] Thangaratinam *et al.* showed that the false positive rate is lower when the screening is obtained >24 hours after birth.[2] However, a recent study of Singh *et al.* with screening <12 hours after birth showed a false positive rate of 0.16% of which 79% suffered from other significant pathology and a Polish study with screening at median age of 7 hours showed a false positive rate of only 0.026% with other significant pathology found in 43% of these false positive screening tests.[4, 12] Early screening can have the potential of detecting CCHD and other significant pathology in an early stage leading to a lower morbidity and mortality. So far, CCHD screening has only been performed in countries where almost all mothers give birth in hospitals. Recently, experts on PO screening published their awareness of variable settings in international perinatal health care systems. For this reason, they recommend the performance of individual pilot studies.[6]

In the Netherlands, the perinatal health care of low-risk infants is unique compared to other countries. Community based midwives supervise 33% of all deliveries, either at home, at a birth clinic or in hospitals. In case of a home birth, the midwife stays for approximately three hours after birth, to return for follow-up on the second or third day. After an uncomplicated birth in hospital mother and child are discharged within a few hours. The baby will be checked

upon at home by the midwife one or two days later. Although studies have shown the benefits of implementing PO for CCHD screening, the question remains if it is possible to fit the PO screening in the Dutch setting of perinatal care and to reach the same benefits. To perform an adequate PO screening in the Netherlands would implicate that all 1854 midwives from home practices would need a pulse oximeter at their disposal. Although recent cost-effectiveness studies have shown that PO as an additional screening tool for CCHD is likely to be cost-effective[8], it remains to be determined whether the benefit of CCHD screening in the Netherlands weighs against the costs of providing all midwives with a pulse oximeter. In addition, infants with positive screenings at home should be transported to hospitals by ambulance, possibly causing more distress in parents and midwives supervising the births than previously described in mothers of infants with false positive screenings.[9] Also, logistics would be a challenge; in very few regional hospitals echocardiography is possible and all infants with persistent unexplained abnormal SpO_2 readings would need to be referred to the academic hospitals.

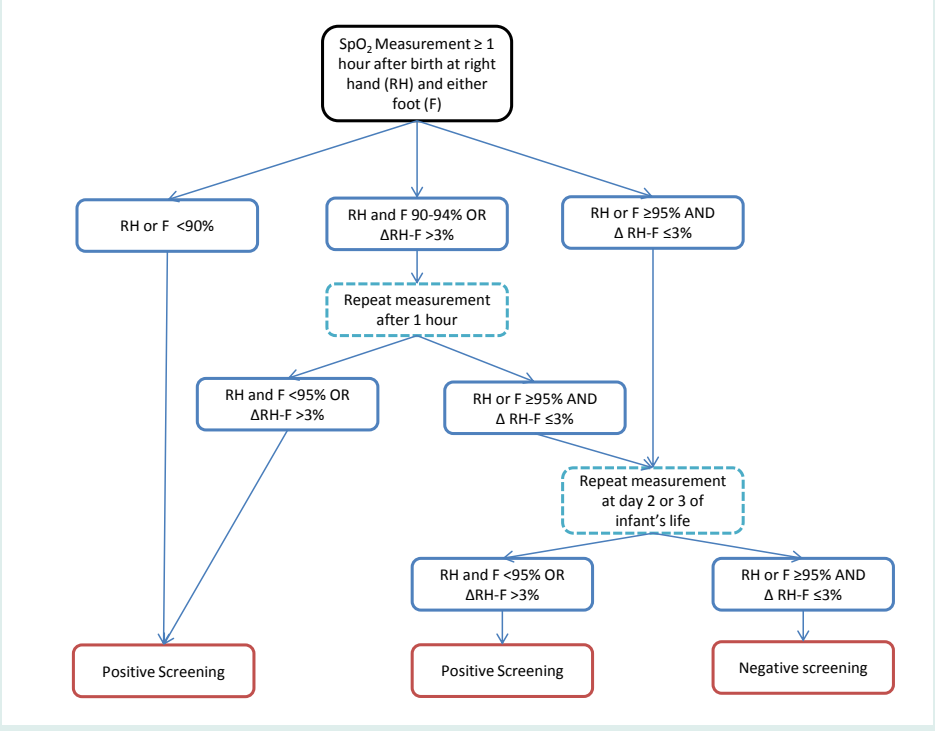
Next to early detection of CCHD, the use of PO at home could also play a role in detecting other potential life-threatening diseases. Indeed, in previous screening studies 27-70% of the false positive screenings were due to other pathology, such as early-onset sepsis or transitional problems.[1,4,12] It is vital that infants with those problems who were born at home are diagnosed and referred to hospital early in the course of the disease. Studies are required, but using pulse oximetry at home can have the potential to increase the safety of home births. A previous study with community based midwives has shown the feasibility of PO to assess infants born at home.[10]

A screening protocol that would take all the above-mentioned issues into account was needed and the current recommended protocol was adapted to the Dutch perinatal setting. The algorithm of the presented protocol (Figure 1) deviates in some aspects from the screening protocol proposed by an American work group of experts. The measurements will be performed at two time points, with a first measurement in the first hours (at least one hour) after birth and the second on day two or three. Another deviation is that the measurement is repeated only once instead of twice after being abnormal but above 90%.[11]. The oxygen saturation (SpO_2) is measured using a portable pulse oximeter (Nellcor™ N-65 portable pulse oximeter (Covidien, Dublin, Ireland)) with the probe placed at the right hand (pre-ductal) and consecutively at the right or left foot (post-ductal). The measurements are performed at least 1 hour after birth.

If the pre- or post-ductal SpO_2 at the measurement at least 1 hour after birth is <90%, the screening test is considered positive. If the pre- and post-ductal SpO_2 are 90-94% or if the difference between pre- and post-ductal SpO_2 is >3%, the test will be repeated after one hour. If the pre- or post-ductal SpO_2 is ≥5% and the difference between pre- and post-ductal

SpO_2 is ≤3%, the screening test will be repeated on day two or three. The screening test on day two or three of life is considered positive if the pre- and post-ductal SpO_2 are <95% or if the difference between pre- and post-ductal SpO_2 is >3%.

Figure 1. flowchart of pulse oximetry screening.



The decision tree of the protocol is shown. SpO_2: peripheral oxygen saturation; RH: right hand; F: either foot

There is no medical follow up for infants with a negative screening. In case of a positive screening, the infant will be referred to the paediatric department to rule out CCHD. Physical examination including pre- and post-ductal SpO_2 measurements will be performed. Echocardiography will be performed in the Leiden University Medical Center in case of persisting abnormal SpO_2 values.

This is the first screenings protocol adapted to a health care system with a high proportion of home births, with measurements taken in the first hours after birth and on day 2 or 3. Other early screening studies did not show a higher amount of false negatives or a lower sensitivity, but these studies were performed with a median screening time of at least 7 hours after birth.[1,4,12] As our first measurement is performed in the very first hours after birth, even 1

hour after birth, SpO_2 values of infants with CCHD may be just within the normal limits due to wide patency of the ductus arteriosus. The PO measurement at the second or third day of life allows for a second chance to detect CCHD with lower SpO_2 values during functional closure of the ductus. A possible advantage of early screening would be the early catch of cardiac and non-cardiac pathology, enabling early intervention and possible prevention of deterioration of the clinical state of the infant and shorter hospitalization.[1,4,12]

The protocol might be useful for other countries that are planning to perform CCHD screening after home birth or with early discharge from hospitals after a delivery.

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CHAPTER 4

Pulse oximetry screening for critical congenital heart disease after home birth and early discharge

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ABSTRACT

Objectives: Pulse oximetry (PO) screening for critical congenital heart defects (CCHD) is increasingly implemented worldwide. Feasibility of PO screening in settings with home births and very early discharge is unknown. We assessed this with an adapted protocol in the Netherlands.

Study design: PO screening was performed in the Leiden region in hospitals and by community midwives. Measurements were taken ≥ one hour after birth and on day two or three during the midwife visit. Primary outcome was the percentage of screened infants with parental consent. The time point of screening, oxygen saturation (SpO_2), false positive (FP) screenings, CCHD and other detected pathology were registered.

Results: In a one-year period 3625 eligible infants were born. Parents of 419 infants were not approached for consent and 44 refused the screening. PO screening was performed in 3059/3090 (99%) infants with obtained consent. Median (IQR) time points of the first and second screening were 1.8 (1.3-2.8) and 37 (27-47) hours after birth. In 394 infants with screening within one hour after birth the median pre- and post-ductal SpO_2 were 99% (98-100%) and 99% (97-100%). No CCHD was detected. The FP rate was 1.0% overall (0.6% in the first hours after birth). After referral, significant non-critical cardiac and other non-cardiac pathology was found in 62% of the FP screenings.

Conclusions: PO screening for CCHD is feasible after home births and very early discharge from hospital. Important neonatal pathology was detected at an early stage, potentially increasing the safety of home births and early discharge policy.

INTRODUCTION

Pulse oximetry (PO) as a screening method for critical congenital heart defects (CCHD) in newborns has been assessed in several large studies.[1-7] A systematic review and meta-analysis of studies, which involved approximately 230,000 screened infants, reported a high specificity, moderate sensitivity and low false positive (FP) rate.[8] PO screening is acceptable to both parents and medical staff, and has been shown to be cost effective in the UK and US.[1, 9] Since 2005, routine PO screening for CCHD has been recommended in Switzerland, Poland, the USA and the UK.[7, 10-13] Worldwide, PO screening is now increasingly common, either implemented nationwide or in pilot studies, with the highest coverage in the Nordic European countries.[4, 12, 14-16] The American Academy of Pediatrics now recommends performing PO screening between 24 and 48 hours of age, as the FP is higher if the screening is performed before 24 hours of age (0.5% versus 0.05%).[8, 10] Transition after birth might lead to lower oxygen saturations (SpO_2) when screening is performed in the first hours of life. However, in several countries infants are discharged earlier in case of uncomplicated deliveries, which means that screening <24 hours is preferable. In addition, the more recent large multi-center studies were not included in the meta-analysis and these studies showed a low false positive rate while performing <24 hours after birth.[7, 8, 17] Turska *et al.,* for example, screened at an average of seven hours after birth with a FP rate of 0.026%.[7] Interestingly, there is a secondary catch of significant clinical conditions which are also detected by screening, such as pneumonia, pulmonary hypertension, or sepsis.

Although PO screening is being implemented in several parts in the world, it has not been included in the Dutch universal screening program. The perinatal health care system in the Netherlands is unique due to its high incidence of home births and early discharge after uncomplicated deliveries. In total, 33% of all low risk deliveries are supervised by a community midwife, of which 55% occur at home and 45% at a birthing facility or policlinic.[18] A community midwife leaves approximately three hours after an uncomplicated home birth. After an uncomplicated delivery in hospital, mother and infant are discharged within five hours. In both scenarios, the community midwife will visit the mother and infant at home at the second or third day of life. For this reason it would not be feasible to use the PO screening protocol that is endorsed by the American Academy of Pediatrics.[10]

In order to implement CCHD screening in the Dutch perinatal care system, the protocol would need to be adjusted to coincide with the presence of a healthcare provider, and would thus necessitate screening in the first hours after birth. In addition, all 1850 community midwives would need to be provided with, and trained in the use of a pulse oximeter for screening in home settings. An appropriate logistic system for referrals after positive screenings at home

would also need to be established. Before testing the accuracy and cost effectiveness in a large implementation trial, we assessed the feasibility of PO screening for CCHD in the Dutch perinatal care system, using an adapted protocol.[19]

METHODS

Study design and population

Between October 2013 and October 2014, we performed a prospective study in the Leiden region. The study was conducted in 14 regional community midwifery practices, two regional hospitals (Rijnland Hospital Leiderdorp and Diaconessenhuis Leiden) and one academic hospital (LUMC, Leiden University Medical Centre). In this region, approximately 4,000 infants are born annually. The LUMC has a 24/7 echocardiography service with a paediatric cardiologist on call, and is the regional referral centre for infants with congenital heart defects.

All term infants (gestational age ≥37 weeks) who were not admitted at the paediatric or neonatal department and were not monitored with PO were eligible for this study. Parents were informed of the PO screening prenatally and written informed consent was obtained prior to performing the screening. The study was approved by the Leiden Medical Ethics Committee in September 2013.

Outcome measurements

For this feasibility study, the main outcome was the percentage of infants screened out of all infants with parental consent. PO screening was considered feasible if at least 90% of the infants with parental consent could be screened.

The secondary outcomes were the median SpO_2 values in the first hours after birth, false positive (FP) rate, and CCHD and other significant pathology diagnosed after screening. Defects that are classified as CCHD were hypoplastic left heart syndromes, pulmonary atresia with intact ventricular septum, simple transposition of the great arteries, interruption of the aortic arch, total anomalous pulmonary venous return, or tricuspid atresia; as well as all infants dying or requiring medical interventions within the first 28 days of life, with coarctation of the aorta, aortic valve stenosis, pulmonary stenosis, tetralogy of Fallot, double outlet right ventricle, Ebstein's anomaly, or pulmonary atresia with ventricular septal defect. The median (IQR) time of screening after births was assessed for the first screening moment and the screening moment on day two or three. Day one was defined as the day of birth. For both moments, the median (IQR) time was calculated overall, and also separately for measurements in hospital and for measurements at home, at the policlinic or in a birthing facility. We calculated the FP rate

and assessed the diagnoses that were found as a result of these FP screening tests and needed medical intervention or further monitoring. As a high FP rate could be anticipated when screening in the first hours after birth, we calculated the median (IQR) pre- and post-ductal SpO_2 each hour during the first three hours after birth.

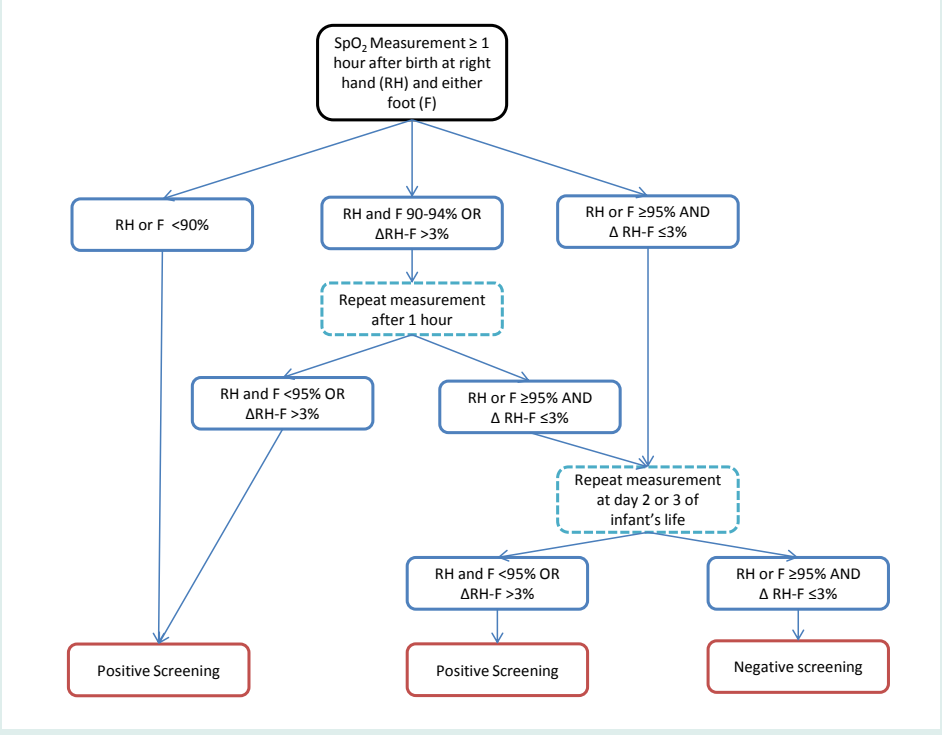
PO measurements

The protocol was adapted to the time of presence of community midwives after birth, so it would fit into the working scheme without the need for extra visits. PO measurements were obtained by a nurse or midwife at least one hour after birth and on day two or three, with the sensor placed on the right hand/wrist and either foot in a non-specified order. All screeners used a Nellcor™ N65 handheld pulse oximeter with reusable sensors and disposable adhesive sensor wraps (Covidien™, Dublin, Ireland).

PO screening was considered positive after one optimal signal quality pre- or post-ductal SpO_2 reading of <90%. The screening was also positive after two repeated measurements, with a one hour interval between them, of either <95% for both limbs or with an absolute difference of >3% between the pre- and post-ductal readings. When SpO_2 readings in the first measurement were normal, the pre- and post-ductal SpO_2 measurements were repeated on day two or three of the infant's life, either at the maternity ward or at home during the follow-up visit of the community midwife. Due to the limited available time during this visit on day two or three, no repeat measurement was performed during this visit after a reading of <95% for both limbs or an absolute difference of >3% (Figure 1).

Infants with positive PO screening were referred to the paediatric department where physical examination was performed by a paediatrician or paediatric resident and pre- and post-ductal PO was repeated. Echocardiography was performed in the LUMC if the SpO_2 readings remained abnormal and no other cause for hypoxaemia was found, or if the examination revealed cardiovascular symptoms.

Figure 1. Flowchart of measurements.



SpO_2: peripheral oxygen saturation; RH: right hand; F: either foot

False negative screenings

Since the LUMC is the regional referral and treatment centre for paediatric cardiology, all infants with false negative (FN) screenings could be detected. Also, mortality registries were consulted to assess for FN screenings. These registries were consulted up to three months after inclusion of the last infant.

Statistical analysis

Results are expressed as percentages, mean (SD) for normally distributed values, or median (IQR) and median (range) for non-normally distributed values. Data were analyzed with SPSS (IBM, version 20.0, 2012, IL, USA).

RESULTS

During the study period, 3,625 eligible infants were born, of which parents of 491 infants (14%) were not approached for consent and 44 (0.4%) were approached but refused the PO screening. Community midwives approached 97% of the parents with eligible infants, while the approach percentage was 89% in the regional hospitals and 70% in the academic hospital. Most reported reasons for not approaching for consent was high workload on the department. Parental consent was obtained for 3,090 infants, and screening was performed in 3,059/3,090 infants (99%).

Thus in 3,059/3,625 (84%) eligible infants PO screening was performed, of which 908 (30%) after home births or policlinical births supervised by a community midwife, and 2151 (70%) were born in hospital under the supervision of clinical midwives or gynaecologists.

The median (IQR) time point of the first PO screening was 1.8 (1.3-2.8) hours after birth, and 37 (27-47) hours after birth for the repeat screening on day two or three. Screening was performed earlier in infants born at home or at the policlinic (first measurement 1.3 (1.0-1.5) hours and late measurement 34 (26-47)) than in hospital (first measurement 2.0 (1.5-3.3) and late measurement 38 (28-47) hours). In 13% (394/3,059) of the infants the first screening was performed within one hour (15-60 minutes) after birth, and in these infants the median (IQR) pre-ductal SpO_2 was 99% (98-100%) and the post-ductal SpO_2 was also 99% (97-100%) (Table 1).

Table 1. SpO_2 values in the first three hours after birth.

Hours after birth	N	Pre-ductal SpO_2, %		Post-ductal SpO_2, %	
		p10	p50 (p25-p75)	p10	p50 (p25-p75)
0-1	394	97	99 (98-100)	96	99 (97-100)
1-2	969	97	99 (98-100)	96	99 (98-100)
2-3	346	96	99 (98-100)	96	99 (98-100)

10^{th} percentile and median (IQR) SpO_2 shown in percentage

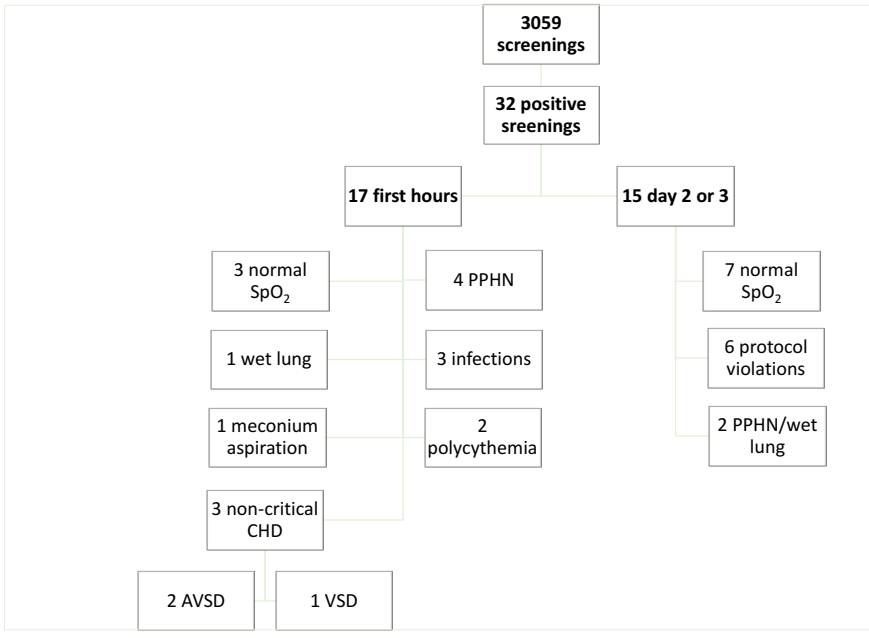
There were no FN screenings or true positive screenings during this study period. No deaths occurred in the cohort of screened infants. No CCHD was detected, nor were any cases missed by PO screening. One infant born in the academic hospital was diagnosed with a CCHD, but the parents were not approached for consent and the infant was not included in the study. The community midwife visited the infant at home for follow-up on day two and was alarmed by the colour of the baby, tachy-dyspnea, and intercostal retractions. The midwife measured a pre-ductal SpO_2 of 98% with the study PO device, but a post-ductal signal could not be detected. An interruption of the aorta was diagnosed after admission to the LUMC.

False positive screenings

PO screening was FP for CCHD in 32/3,059 infants (1.0%), of which 17 were obtained in the first screening and 15 in the second screening moment. Of these, 26/32 infants were referred to the hospital and significant other pathology was diagnosed in 16/26 (62%) infants (14/17 (82%) after the first and 2/9 (22%) after the second screening moment). Non-critical cardiac pathology was detected in 3/26 infants after referral, and in 13/26 infants other significant non-cardiac pathology was diagnosed (persistent pulmonary hypertension of the neonate, infection/sepsis, polycythaemia)(Figure 2). In 10/26 infants physical examination was normal and repeated PO after referral to the hospital showed normal values.

Referral did not take place in 6/32 infants with FP screening. This occurred only in the first half of the study period. In retrospect, the caregivers did not notice these positive screenings and all six infants were healthy at the age of >1 month.

Figure 2. Overview of positive screenings and their findings.



CHD: congenital heart defects; PPHN: persistent pulmonary hypertension of the neonate; SpO^2: oxygen saturation; AVSD: atrioventricular septal defect; VSD: ventricular septal defect.

DISCUSSION

Using an adapted protocol for PO screening, we were able to screen 99% of the infants when parental consent was obtained. There was no difference in FP between the early (≥ one hour after birth) and later (day two or three) measurement time point of the screening. Including a very early time point for screening, in the first hours after birth, did not lead to a high FP rate. Indeed, while screening in the first hours after birth is not recommended, as SpO_2 might not have reached normal values due to transition, we observed a normal range in SpO_2 even within the first 60 minutes after birth.[10] Although we did not detect a CCHD in this feasibility study, PO screening led to early detection of other potentially life-threatening pathology. Early detection of these morbidities is important, especially if infants are at home, and in this way PO screening has the potential to increase the safety of the current perinatal setting in the Netherlands and other countries with home birth or early hospital discharge after birth.
This is the first study with a CCHD screening protocol that is adapted to a setting with home births and early hospital discharge. The Netherlands is unique with 18% of deliveries occurring at home compared to other developed countries where the home birth rate is <2.5%.[18, 20-22] Other groups have assessed out-of-hospital screening,[16, 23] but the PO screening rate in our study was much higher when compared to the previous study of Lhost *et al* (99% vs 37.5%).[23] It demonstrates that the use of PO screening could be easily implemented in the daily routine of midwives attending home births; the rate of successful screening was higher after home births than in the hospitals. The prevalence of true FP screenings (no other morbidity and normal SpO_2 after referral to the hospital) was low: initially one to two per month but this declined after six months to one per two months.

The use of a very early PO screening time point was necessary to fit in the logistics. The time point of screening in our protocol was much earlier than that of previous studies, which demonstrates the feasibility of early screening (median 1.8 hour versus median ≥4 hours after birth).[7, 17] Furthermore, previous studies using early screening were performed in hospital and not at home. Very early screening is not recommended as there is a possibility that SpO_2 may not yet have reached >95% due to adaptation after birth and referral would take place unnecessary.[10] We did not observe a high FP rate, however, and we measured a median pre- and post-ductal SpO_2 of 99% already within one hour after birth. The pre-ductal SpO_2 is ≥95% in 90% of infants after vaginal delivery, which indicates that an infant should be evaluated for pathology even when this is measured within the first hour after birth.[24]

For this study, all infants with positive screening without the existence of a CCHD were classified as FP, since CCHD were defined as the screening target. Significant pathology, including pulmonary hypertension, infection, and non-critical cardiac defects was detected in

the majority of FP screenings, especially after PO screening in the first hours after birth (82%). In most of these cases it is likely that the infants benefit from early detection and treatment. It is well established that if persistent pulmonary hypertension of the neonate (PPHN) is not treated promptly there is risk for sudden deterioration, creating a need of more intensive treatment and an increased risk of an adverse outcome.[25, 26] Also, although most of the wet lungs are usually self-limiting, some of the infants may develop PPHN. For this reason, infants with wet lung should be adequately monitored, which is not possible in the home setting. Infection causes 5% of the perinatal mortality of term infants in the Netherlands.[27] Early detection and treatment of infection and sepsis before development of a full-blown disease, including shock and organ failure, considerably increases the chances of a favourable outcome.[28, 29] Taking into account the importance of the secondary early catch of other significant pathology, one might consider defining PPHN, wet lung, and infection/sepsis as targets for PO screening, and not defining these screenings FP in future studies.

In this study PO screening in the first hours after birth detected three significant septal defects, most likely due to transient right to left shunting shortly after birth. Infants with septal defects could also benefit from early diagnosis, as it would enable early treatment of heart failure and appropriate planning of surgical correction. Therefore, in addition to early detection of CCHD, early detection of other pathologies through PO screening, including non-critical cardiac pathologies, has the potential to increase the safety of early hospital discharge and home births.

Since there was limited time during the midwifery visit on day two or three, no repeat measurement was performed in case of abnormal measurements, and direct referral was recommended. Although our FP rate was no higher than that of previous studies, it is possible that omitting the repeat measurement could have led to a high true FP rate at the time of the second screening. In order to reduce this, a repeat measurement after a shorter time interval will be implemented in the protocol.

This study was carried out at a local level, but has much wider relevance. The Leiden region, is small, but densely populated. Since the Netherlands is small and has a good infrastructure, we predict that the results can be extrapolated to the rest of the country. Moreover, although the Netherlands has the highest home birth rate in the developed world, home births are also performed in other countries.[13, 20, 21] Similarly, there is an increasing tendency towards early discharge after uncomplicated deliveries in hospital. Our study shows that screening infants after home birth and early hospital discharge is both safe and feasible, and the protocol could therefore be applied for these settings in other countries.

Further research remains to be done to test if accuracy will be similar to PO screening in other countries.[1, 3, 4, 8] Previous cost effectiveness studies cannot be applied to this protocol

either, since all community midwives must be provided with a PO device to make sure that all infants receive SpO_2 measurements at both screening times.[9, 30] In order to screen all 33,000 infants that are born at home in the Netherlands annually, all community midwives in (over 1800 in the Netherlands) would need to be provided with a PO device. We are currently performing an implementation trial in the Amsterdam-Haarlem-Leiden region to assess cost-effectiveness and accuracy, aiming to screen at least 20,000 infants with our adapted screening protocol. This study (Pulse Oximetry screening Leiden-Amsterdam Region study) will then provide more insight into the need for implementation of PO screening in the Dutch healthcare system.

CONCLUSION

We have demonstrated that PO screening for CCHD using an adapted protocol is feasible in a perinatal care system with home births and early discharge. The FP rates in the first hours were comparable to other PO screening studies. Importantly, significant pathology- including infections, PPHN, and non-critical cardiac pathology- could be detected at an early stage. A larger implementation study is currently undertaken to assess the accuracy and cost-effectiveness of PO screening using the adapted protocol.

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CHAPTER 5

Accuracy of pulse oximetry screening for critical congenital heart defects after home birth and early postnatal discharge

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ABSTRACT

Background: pulse oximetry (PO) screening for critical congenital heart defects (CCHD) is increasingly implemented. PO screening was studied in the Netherlands, using an adapted protocol. Dutch perinatal care is characterised by a high home birth rate and early discharge after hospital deliveries.

Methods: Pre- and post-ductal oxygen saturation (SpO_2) were measured ≥ one hour after birth and on day two or three. Screenings were positive when SpO_2 measurement <90%, or a repeated pre- and post-ductal SpO_2 <95% and/or a pre-post-ductal difference of >3%. Positive screenings were referred for pediatric assessment. Primary outcomes were sensitivity, specificity and false positive rate of POS screening for CCHD. The secondary outcome was detection of other pathologies.

Findings: SpO_2 was obtained in 23,996 newborns and detected CCHD with a sensitivity of 70.2%(95%CI 56.0-81.4) and specificity of 99.1%(95%CI 99.0-99.2). The prenatal detection rate of CCHD was 73%. After excluding these cases and symptomatic CCHD 23,959 newborns were screened, 20,769 in the first hours, 14831 on day 2 or 3. In prenatally missed cases, PO screening detected five CCHD, while another five CCHD remained undetected with both prenatal ultrasound and PO screening. PO screening sensitivity in this cohort was 50.0% (95%CI 23.7-76.3), specificity was 99.1% (95%CI 99.0-99.2). In 221 infants PO screening screening was false positive for CCHD, of which 61% (134) had other serious illnesses, including infections (31) and respiratory pathology (88).

Interpretation: PO screening adapted for perinatal care in home births and early post-delivery hospital discharge detected CCHD in an early, asymptomatic stage. High prenatal detection led to a moderate sensitivity of PO screening. PO screening also detected other significant neonatal postnatal morbidities in 0.6% of all infants, including infection and respiratory morbidity, which led to early treatment without delay.

INTRODUCTION

Pulse oximetry (PO) is an accurate and cost-effective screening method for critical congenital heart defects (CCHD) in healthcare settings with in-hospital deliveries, and is acceptable to parents and caregivers.[1-5] PO also improves detection of other significant pathologies in neonates, including respiratory and infectious diseases.[6,7] As a result, PO screening is increasingly implemented as a standard care throughout the world.[7-9] However, the accuracy of PO screening in unique healthcare settings, for example where home births predominate or where early postnatal discharge after a hospital delivery is encouraged, has not been studied in a large cohort.

The length of post-delivery hospital stay in many European countries is relatively short with a trend towards discharge within 12 hours after an uncomplicated delivery.[8,10] In this situation, CCHD screening should be performed in the first hours after birth. Although most deliveries in developed countries occur in hospital, home births also occur. In Australia and New Zealand the home birth rate is stable at around 0.4% and 3.4% respectively, while these rates have increased in England and Wales (2.4%) and the US (1.4%) in the last decade.[11-14] In the Netherlands, the perinatal care system is unique with a very high home birth rate (18%) and early postnatal discharge (within five hours) after an uncomplicated vaginal hospital birth.[15] Community midwives supervise 33% of all deliveries in the Netherlands.[15,16] Furthermore, prenatal screening is well-structured, and only trained ultrasonographers perform the standard anomaly scans at 20 weeks of gestation. National implementation of PO screening in the Dutch perinatal care setting would require community midwives to perform the measurements at home. Consequently, all 1850 community midwives would need to have a pulse oximeter as part of their standard equipment. The timing of screening should also be adjusted to coincide with the presence of a perinatal caregiver; community midwives stay for less than three hours after birth following an uncomplicated delivery, and visit the mother and infant on day two or three of life for follow-up. Mothers and infants who are discharged home within five hours after an uncomplicated vaginal in-hospital delivery are also visited for follow-up by community midwives on day two or three of life.

We recently demonstrated the feasibility of screening for CCHD in this unique setting, with 99% screening rate of the infants with parental consent.[17] As already shown in previous studies, we also observed that PO screening detected other significant neonatal morbidities, such as perinatal infections and persistent pulmonary hypertension (PPHN), at an early stage. Early detection of these morbidities might be of extra importance since these infants are born at home or discharged early from hospital. However, this feasibility study was too small to analyze the accuracy of PO screening.

The aim of this study was therefore to assess the accuracy of PO screening for CCHD in a larger region in the Netherlands using an adapted protocol fitting the work patterns of community midwives. We also assessed the detection of other neonatal morbidities.

METHODS

Study design and population

Between July 2015 and December 2016, we performed a prospective trial in the Netherlands in the regions of Leiden, Haarlem, Hoofddorp, Amsterdam, Alkmaar and Purmerend. The study was conducted in 75 regional community midwifery practices, 11 regional hospitals, and three academic hospitals. Approximately 30,000 infants are born annually in this region.

All infants with a gestational age ≥35 weeks who were not admitted to the paediatric department with a clinical indication for PO monitoring were eligible for PO screening. Parents were informed of the PO screening by their caregiver before birth both verbally and by means of a flyer and website. An opt-out strategy was used.

Infants with prenatally diagnosed CCHD were not screened according to the protocol, but they were monitored with PO. The SpO_2 values one-two hours after birth and on day two or three were collected from the medical charts in order to assess if PO screening would have been positive in these infants. At the time of designing our study protocol the published prenatal detection rate in the studied region was 50%.[18]

Two cohorts were analysed for this study; the first cohort included all infants with and without a prenatal diagnosis of CCHD. The cases with prenatal detection or symptoms directly after birth were excluded in the second cohort.

The study was approved by the Leiden Medical Ethics Committee (Institutional Review Board) in January 2015.

Outcome measurements

The primary outcome was the accuracy of PO screening for CCHD, determined by the sensitivity, specificity, false positive (FP) rate, false negative (FN) rate, and positive and negative predictive value. CCHD was defined as all congenital heart defects that lead to death or require medical intervention within the first 28 days of life, including hypoplastic left heart syndrome, pulmonary atresia with intact ventricular septum, simple transposition of the great arteries, interrupted aortic arch, critical coarctation of the aorta, critical aortic or pulmonary valve ste-

nosis, critical tetralogy of Fallot, or total anomalous venous return. The secondary outcome was the detection of other pathologies with the screening.

Index test

The timing of PO screening was adapted to coincide with the regular home visits of community midwives after birth, thereby avoiding the need for extra visits. PO measurements were performed by a nurse or midwife on day one, at least one hour after birth, and on day two or three of life, with the sensor placed on the right hand/wrist and either foot in a non-specified order. For this study, all caregivers used a Nellcor™ PM10N handheld pulse oximeter with reusable sensors and disposable adhesive sensor wraps (Medtronic™, Dublin, Ireland).

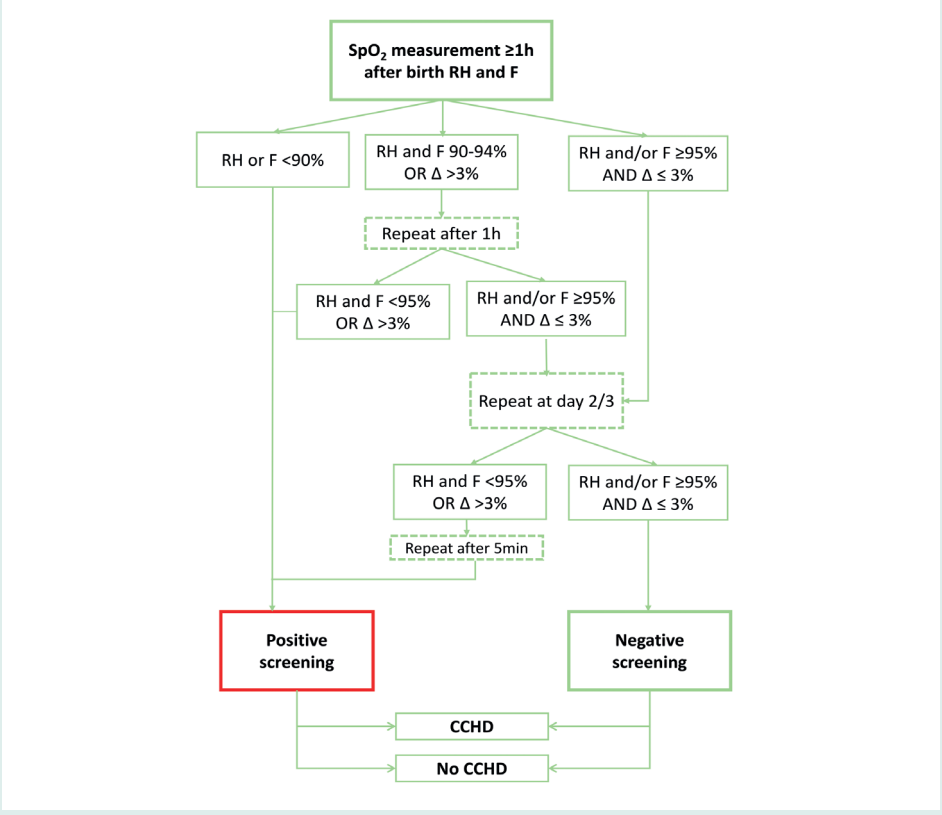
The first PO screening after birth was considered positive if: (1) the pre- or post-ductal SpO_2 reading was <90%; (2) two independent measurements, with at least a one hour interval, revealed an SpO_2 <95% for both limbs or an absolute difference of >3% between the pre- and post-ductal readings. When the first SpO_2 screening was normal (SpO_2 ≥95% in either limb and <3% difference between both limbs), the pre- and post-ductal SpO_2 measurements were repeated on day two or three of life, either in the maternity ward or at home during the follow-up visit of the community midwife. This second SpO_2 screening was considered positive if SpO_2 <95% in both limbs or in case of >3% difference between limbs (Figure 1).

Infants with positive PO screening were referred to the paediatric department for physical examination and repeated pre- and post-ductal PO measurement. Echocardiography was performed if the SpO_2 readings remained abnormal and no other cause for hypoxaemia was found, or if the physical examination revealed signs indicative of cardiovascular disease. It remains the practice of medicine for the practitioner to apply information provided to ultimately determine the most likely cause or guide the appropriate diagnostic work-up to determine the cause of low SpO_2.

Reference standard

The reference standard consisted of follow-up and echocardiography in screening positive infants without a non-cardiac explanation, as well as follow-up of screening negative infants. The PO screening was performed within the region of the Center for Congenital Heart Disease Amsterdam-Leiden (CAHAL), a collaboration of the three academic hospitals in Amsterdam and Leiden. All surgical and catheter interventions in newborns and infants with congenital heart defects were performed in the Leiden University Medical Center (LUMC) allowing the detection of FN screening results. Also, mortality registries were consulted to assess for FN screenings. These registries were consulted up to three months after the inclusion of the last infant.

Figure 1. Trial protocol.



Protocol adapted to the visiting scheme of community midwives in order to fit the Dutch perinatal care system with home births and early discharge after delivery in hospital. CCHD: critical congenital heart defects; SpO_2: peripheral oxygen saturation.

Data collection

All data were collected by the caregivers and entered in a validated web-based electronic database that fulfilled international standards for data management and quality assurance (ProMISe, LUMC Advanced Data Management, 2016). Privacy protection, by means of data encryption, was performed by a trusted third party (Trusted Reversible Encryption Service, ZorgTTP, 2012, Houten, the Netherlands). The data were extracted to SPSS for analysis (IBM, version 23.0, 2016, IL, USA).

Sample size

The prevalence of CCHD in the Netherlands is similar to other countries where screening has been performed (2/1,000 live births).[18] To obtain a level of accuracy similar to those of previous screening studies,[19] we calculated that a sample size of 20,000 neonates was needed to provide 82% power to detect a change in sensitivity from 52% to 75%, with a power of 95% to detect a change in specificity from 99.3% to 99.5% (both with one sided α=2.5%).

Statistical analysis

Results are expressed as percentages, mean (SD) for normally distributed values, or median (IQR) for non-normally distributed values. Accuracy parameters are expressed as percentages with a 95% confidence interval based on Wilson score intervals, and were calculated for day one only and for the combination of day one and day two or three. Data were analyzed with SPSS (IBM, version 20.0, 2012, IL, USA) and OpenEpi Software (OpenEpi, Version 3.01, 2013, FL, USA).

Role of the funding source

Medtronic™ (Dublin, Ireland), ZonMw (The Hague, the Netherlands), and Stichting Hartekind (Zaandam, the Netherlands) monitored the progress of the study but had no role in study design, data collection, data analysis, data interpretation, or writing the report. The coordinating research team had full access to all data and had the final responsibility for the decision to submit for publication.

RESULTS

Cohort 1 (full cohort)

There were 23,998 infants eligible for this study, of whom 49 had an isolated CCHD. In 36 infants the CCHD was detected during prenatal screening (prenatal detection rate 73.5% (95%CI 59.7-83.8)). SpO_2 values were not measured in two infants with prenatally missed CCHD, so these cases were excluded from the analysis. In the remaining eligible 23,996 infants SpO_2 values were abnormal in 33 of 47 newborns with CCHD and were therefore considered screening positive cases according to the screening protocol. The sensitivity of PO screening when including the prenatally found cases was 70.2% (95%CI 56.0-81.4) with a specificity of 99.1% (95%CI 99.0-99.2%) (Figure 2, Table 1).

Table 1. Accuracy parameters in full cohort	
Parameter	**All screenings (n=23,996)**
True positives, n (%)	33 (0.1)
False negatives, n (%)	14 (0.06)
False positives, n (%)	221 (0.9)
True negatives, n (%)	23728 (98.9)
Sensitivity, % (95%CI)*	70·2 (56.0;81.4)
Specificity, % (95%CI)*	99·1 (99.0;99.2)
Positive predictive value, % (95%CI)*	13·0 (9.4;17.7)
Negative predictive value, % (95%CI)*	99·9 (99.9;100.0)
* Wilson Score CI.	

Cohort 2 (without prenatal diagnosed and symptomatic CCHD)

In the sub-cohort in which PO screening could affect postnatal management, infants with prenatally diagnosed CCHD were excluded. Furthermore, one infant had symptoms of cardiovascular disease directly after birth and was also excluded for analysis in this cohort. In total 23,959 infants were included of whom 20,769 had a PO measurement in the first hours after birth (median (IQR) screening time 116 (81-180) minutes), 14,831 were screened at the second screening moment (29 (22-40) hours), and 11,641 infants were screened at both time points (Figure 2). A community midwife supervised 26% of all deliveries, of which 42% were home births. The median (IQR) pre- and post-ductal SpO_2 was 99% (98-100%) and 99% (97-100%), respectively, in the first hours after birth and 99% (97-100%) and 98% (97-100%) at the second screening on day two or three.

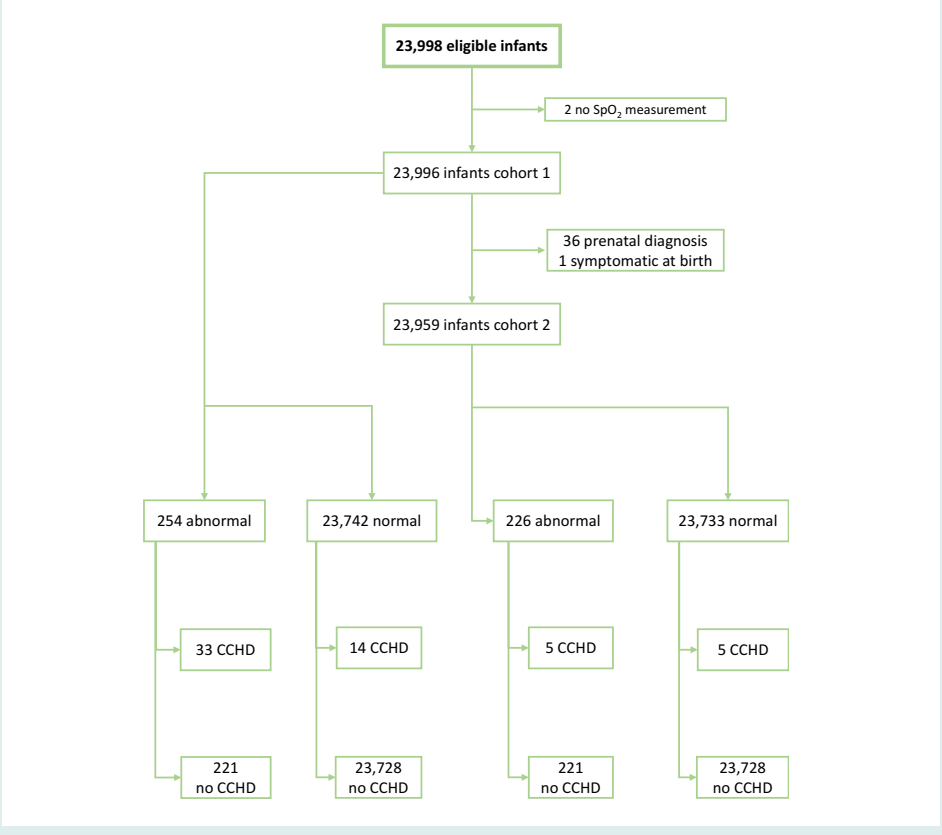
PO screening detected prenatally undetected CCHD in five of the remaining ten infants (two transpositions of the great arteries, two critical pulmonary valve stenosis, and one total abnormal pulmonary venous return (Figure 2, Table 2,3)), leading to a sensitivity of 50.0% (95%CI 23.7;76.3)). In the case of the other five infants with prenatally undetected CCHD, the screening result was FN (three coarctations of the aorta (CoA), one critical pulmonary valve stenosis, and one transposition of the great arteries (Table 1)). Adding PO screening to the existing screening methods (prenatal ultrasound and postnatal physical examination) increased the rate of timely diagnosis of newborns with CCHD from 79% to 89%.

Table 2. Accuracy parameters split per screening moments in cohort 2.

Parameter	All screenings (n=23,959)
True positives, n (%)	5 (0.02)
False negatives, n (%)	5 (0.02)
False positives, n (%)	221 (0.9)
True negatives, n (%)	23728 (99.0)
Sensitivity, % (95%CI)*	50·0 (23.7;76.3)
Specificity, % (95%CI)*	99·1 (99.0;99.2)
Positive predictive value, % (95%CI)*	2·2 (0.9;5.1)
Negative predictive value, % (95%CI)*	100·0 (100.0;100.0)

* Wilson Score CI.

Figure 2. Trial profile.



Overview of included newborns with screening outcome.
CCHD: critical congenital heart defects; SpO_2: oxygen saturation.

Table 3. All CCHD detected or missed with PO in cohort 2.

Diagnosis	Pre- and Post-ductal SpO_2		Detected / missed with PO	Age at diagnosis	Outcome at >3 months
	Day 1	Day 2/3			
TGA	60%- 70%	n/a	Detected	1h 10min	Alive
TGA	80%- 75%	n/a	Detected	1h 30min	Alive
PS	70%- 69%	n/a	Detected	1h 15 min	Alive
PS	82%- 85%	n/a	Detected	2h 15min	Alive
TAPVR	97%- 97%	93%- 90%	Detected	12h 30min	Alive
CoA	98%-97%	100%-99%	Missed	9 days	Alive
CoA	98%-96%	Not performed	Missed	9 days	Alive
CoA	100%-99%	Not performed	Missed	7 days	Alive
PS	97%-97%	98%-98%	Missed	11 days	Alive
TGA	98%-97%	98%-98%	Missed	49 days	Deceased
CoA	Not performed	Not performed	n/a	11 days	Deceased
CoA	Not performed	Not performed	n/a	11 days	Alive
TGA	Not performed	Not performed	n/a	Directly after birth	Alive

TGA: transposition of the great arteries; PS: critical pulmonary valve stenosis; TAPVR: total abnormal pulmonary venous return; CoA: coarctation of the aorta.

False positive screenings

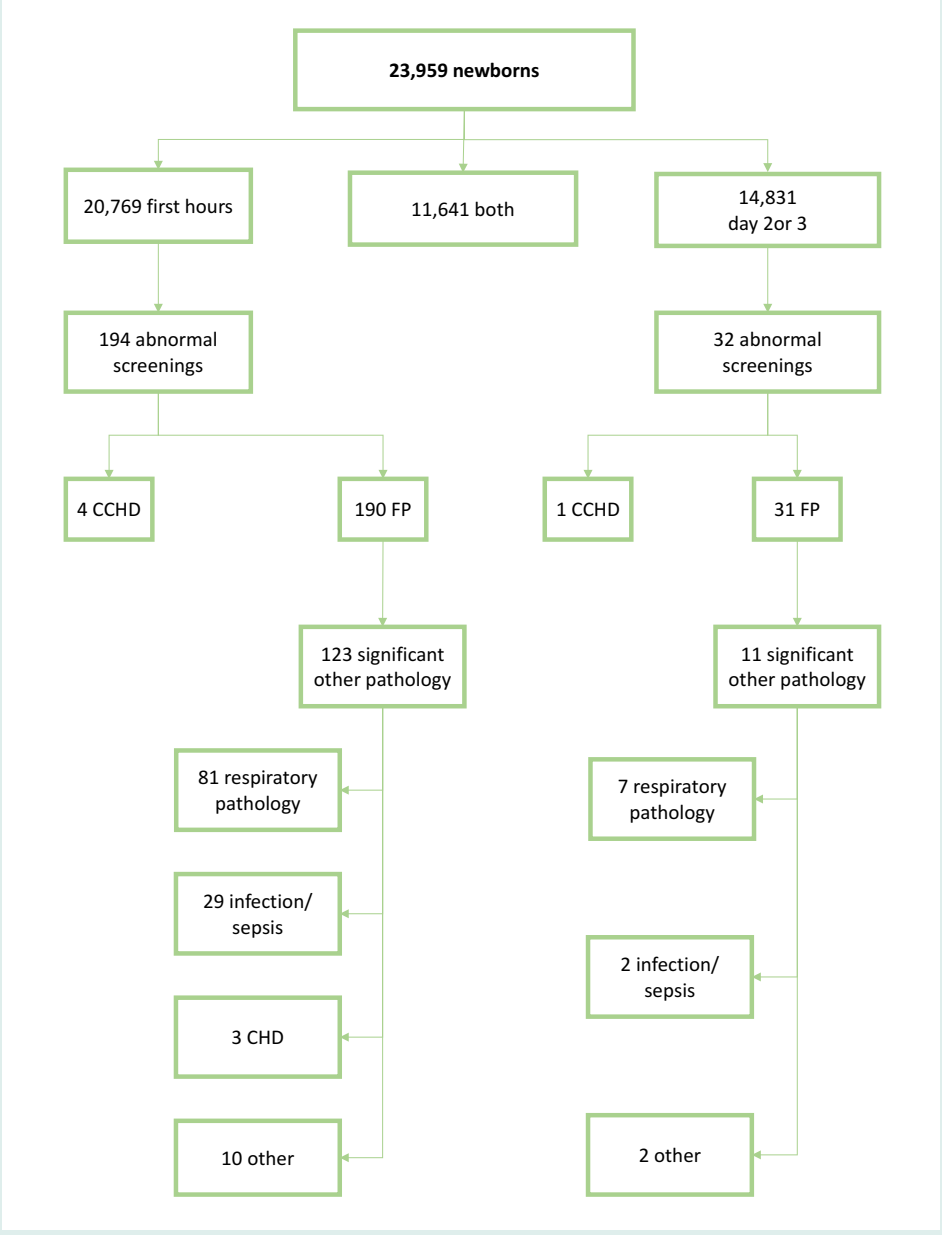
Overall, the FP rate of PO screening (no CCHD) in the second cohort was 0.92% (221/23,949 screenings), excluding prenatally detected CCHD. Most FP screenings for CCHD occurred on day one (190 on day one vs 31 infants on day two or three). The specificity of the screening test for CCHD was 99.1% (95%CI 99.0;99.2) (Table 2).

Importantly, 61% (134/221) of the infants with FP screenings proved to have significant morbidities requiring intervention and medical follow-up, including infection/sepsis (n=31), and persistent pulmonary hypertension of the neonate (PPHN) or transient tachypnoea of the newborn (TTN) (n=88) (Figure 3). The FP rate for CCHD or other morbidities was 0.36%. The detection of significant morbidities was also the highest on day one (65% vs 35% of false positive screenings on day two or three; Figure 3).

Referrals and ultrasounds

Abnormal PO screening led to 226 referrals to paediatricians (0.9% of screened infants), of which 139/226 (62%) infants needed treatment (five for CCHD). Echocardiography was performed on 45 infants of whom 25 showed abnormalities, including 5 cases of CCHD, 3 of CHD, and 17 of other pathologies such as PPHN.

Figure 3. Profile of positive screenings.



Pathology detected in the trial. Respiratory pathology includes transient tachypnoea of the newborn, persistent pulmonary hypertension of the newborn, pneumothorax, meconium aspiration and infant respiratory distress syndrome. Other pathology includes hypoglycemia, polycythemia, hemolytic anemia, thrombopenia, and anal and esofagal atresia. CCHD: critical congenital heart defects.

DISCUSSION

This is the first major prospective cohort study assessing the accuracy of PO screening for CCHD in a health care setting characterised by a significant number of home births and early discharge after uncomplicated in-hospital delivery. Although most mothers in developed countries give birth in hospital, home births occur with an increasing frequency in some countries, including England and the US.[11-14] There is also a trend in Europe towards a shorter postnatal stay after a hospital delivery.

We recently demonstrated the feasibility of the screening protocol in a home birth setting in the Netherlands in a smaller study, which was confirmed by research in the UK and in the plain communities in Wisconsin.[17,20,21] We now observe that PO screening in asymptomatic infants without a prenatal diagnosis in this setting detected CCHD with a moderate sensitivity (50.0%) and high specificity (99.1%). Adding PO to the regular screening program and care routine increased the rate of timely diagnosis from 79 to 89%. When we extrapolate this to the annual live birth rate in the Netherlands of 170,000, this indicates that CCHD could be diagnosed early by PO screening in 35 infants per year in the Netherlands.[22] Early recognition and treatment of CCHD reduces the risk for morbidity and mortality, as well as healthcare costs.[23,24] In this cohort, two out of seven infants with late diagnosis of CCHD died before surgery because of circulatory failure, emphasizing the importance of a timely diagnosis.

In addition to CCHD, other significant neonatal morbidities were diagnosed by PO screening in 0.6% of the infants in a timely manner; this may have prevented clinical deterioration over time and improved the outcome. In the Netherlands 5% of the mortality in term infants is caused by infection, and early detection via PO screening has the potential to reduce this rate.[25] In addition, approximately 10% of infants with TTN develop PPHN, a severe condition with a high mortality rate of 5-10%.[26-28] It has been shown that the clinical course of PPHN may be improved by prompt recognition and early treatment.[26] Although PO screening may be effective in preventing severe outcomes, it was not possible to make an assessment of this as there was no control group without treatment for these non-cardiac pathologies.

The detection rate of PO screening is related to the prenatal detection rate of CCHD. Prenatal screening is highly accessible, well-organised and centralised in the Netherlands, which improves the quality of fetal ultrasound screening. However, the prenatal detection rate of CCHD can vary between regions in the Netherlands, since screening programs and trainings are organised on a regional basis. When we started our study we assumed a prenatal detection

rate of 50%, which was based on an evaluation performed after introduction of the screening programme in 2007 until 2012.[18] However, after adding the three-vessel view to this prenatal screening in 2013, the detection rate of CCHD in our region has further increased, and during the study period the prenatal detection rate was much higher (73%). We were unaware of this increase when the study was planned. A higher prenatal detection rate led to a lower number of prenatally undetected cases that determined the effective sample size for calculation of the sensitivity in cohort two. The moderate sensitivity we observed was comparable to the screening study of Singh *et al.*, where the prenatal detection was also high.[6] In PO screening studies where the prenatal detection rate was low, a higher sensitivity of up to 84% was achieved.[5,7,29] Aortic coarctation (CoA) remains particularly difficult to detect prenatally, and is known to have been missed by PO screening as well.[18,30] We screened more than 13% of the annual birth rate in the Netherlands and therefore believe our sample size is representative of the Dutch perinatal care system. With a variable prenatal detection rate in the Dutch regions, we assume that when implementing the PO screening in the Netherlands the sensitivity is likely to be between 50-70%.

In accordance with other studies with early screening (before 24 hours after birth) our FP rate was higher than studies with screening >24 hours. However, in most FP measurements (61%) significant neonatal morbidities were detected. Singh *et al*. also reported a high rate of significant morbidities as a secondary target for PO screening on the first day of life.[6] Additionally, the studies with later screening reported that symptoms of cardiac pathology were already present in several cases before screening took place.[19,29] Early screening before CCHD becomes symptomatic is preferable, as it reduces cerebral hypoxia, organ-failure and death.[23]

This is also the first screening study with PO measurements at two separate time points: an early measurement in the first hours after birth and a late measurement on day two or three. This second measurement was added to the screening protocol with the consideration that infants with CCHD could have normal SpO_2 values in the first hours after birth due to a widely patent ductus arteriosus. Had we only made one measurement in the first hours after birth, the sensitivity would have been 40% instead of 50%. As mentioned above, CoA is difficult to detect both prenatally and postnatally with PO screening.[18,30] In our study, two out of three missed CoA had no second measurement, so it remains unclear whether the CoA could have been detected in these two infants by a measurement on day two or three. The fact that the screening protocol could be adapted with comparable outcomes to the unique and more complex Dutch perinatal care system implies that PO screening for CCHD is feasible in and adaptable to all perinatal care systems.

The large amount of incomplete screenings is a limitation of our study. A second measurement on day two or three was obtained in only 11,641 of 20,769 infants (56%) who were screened on day one, despite a successful feasibility study in the Leiden subregion.[17] In the region as a whole, many infants were discharged from hospitals with postnatal care performed by a midwife in a region or practice not participating in our study, making it more difficult to perform both screening moments. Another explanation might be the failure to register the second screening moment in the web-based database. Also, with a consent procedure based on opting out, caregivers might have felt less responsibility to perform the screening compared to cases in which parents had been asked to provide written consent. It is likely that the incomplete screening rate will be reduced in the case of national implementation, when it becomes standard care.

A cost-analysis is currently being performed and needs to be considered before implementing the screening in the Netherlands.

CONCLUSION

PO screening for CCHD using an adapted protocol to fit perinatal care with home births and early discharge after delivery in hospital detected CCHD at an early, asymptomatic stage. The prenatal detection rate was high, which led to a moderate sensitivity. PO also detected large numbers of other significant morbidities at an early stage and has the potential to increase the safety of home births and newborns who are discharged from hospital early. Neonatal PO screening for CCHD should focus on detecting postnatal morbidities as secondary targets.

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CHAPTER 6

Cost-effectiveness analysis of pulse oximetry screening for critical congenital heart defects in a setting with home births and short postnatal stay after in-hospital delivery

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Status: in preparation

ABSTRACT

Background: Pulse oximetry (PO) screening can be used to screen newborns for critical congenital heart defects (CCHD). Analyses performed in hospital setting suggest that PO screening is cost-effective. We aimed to assess the costs and cost-effectiveness of PO screening in the Dutch perinatal care setting, with home births and early postnatal discharge, compared to a situation without PO screening..

Methods: Data from a prospective accuracy study with 23,959 infants in the Netherlands were combined with a time and motion study and supplemented data were used in this healthcare cost evaluation. Costs and effects of the situations with and without PO screening were compared for a cohort of 100,000 newborns.

Results: Mean screening time per newborn was 4.9 minutes per measurement and 3.8 minutes for informing parents. The additional costs of screening were in total €14.71 per screened newborn (€11.00 for personnel costs and €3.71 for equipment costs). Total additional costs of screening and referral were €1,670,000 per 100,000 infants. This resulted in an incremental cost-effectiveness ratio of €139,000 per additional newborn with CCHD detected with PO, when compared to a situation without PO screening.

Conclusions: PO screening in the Dutch care setting would be cost-effective if considerable savings in lifetime treatment and, or substantial gains in Quality Adjusted Life Years are obtained per infant timely diagnosed with PO screening. Additional studies on treatment costs, life expectancy and quality of life of children with CCHD are needed to conclude whether addition of PO screening is cost-effective in the Netherlands.

INTRODUCTION

Pulse oximetry (PO) screening to detect critical congenital heart defects (CCHD) in newborns has been studied widely in the past years and was proven to be accurate, safe, easy, and acceptable in settings with delivery and screening in hospital.[1-3] Cost-effectiveness analyses performed in studies from the United States and United Kingdom also suggest that the screening might be cost-effective in their setting.[4,5]

Congenital heart defects are the most common congenital defect, affecting approximately 8 per 1,000 live births. One quarter of all congenital heart defects are critical and require surgery or catheter intervention in the first month of life.[6] Timely diagnosis of these CCHD, before signs of cardiovascular collapse, is pivotal in reducing morbidity and mortality. Around 50-80% of CCHD can be detected with prenatal screening.[7,8] Postnatal physical examination of remaining cases is hampered by the absence of clinical signs in the first days of life.[9-11] PO can be added to the regular screening program (prenatal ultrasound and postnatal examination) in order to reduce the cases with late diagnoses. It is known that a timely diagnosis of CCHD improves the chances of a favorable outcome with less mortality and morbidity.[9]

Although cost-effectiveness studies were performed in the United States and United Kingdom in settings with screening in hospital, costs might be different in settings with different perinatal care systems.[4,5] For example, the Netherlands is unique with a high rate of home births (18%) and discharge within 5 hours after an uncomplicated vaginal delivery in hospital.[12,13] Screening in this setting requires performance of PO at home by community midwives, as well as a referral system for positive screenings. Recently, an accuracy study in the Dutch perinatal care was performed including 23,959 infants.[14] We aimed to estimate the additional costs of PO screening in the Dutch perinatal care system, taking into account personnel time and equipment. The costs and cost effectiveness of a situation with PO screening were compared to the current setting, with effectiveness measured in terms of timely diagnosis (before death or signs of acute cardiovascular collapse).

METHODS

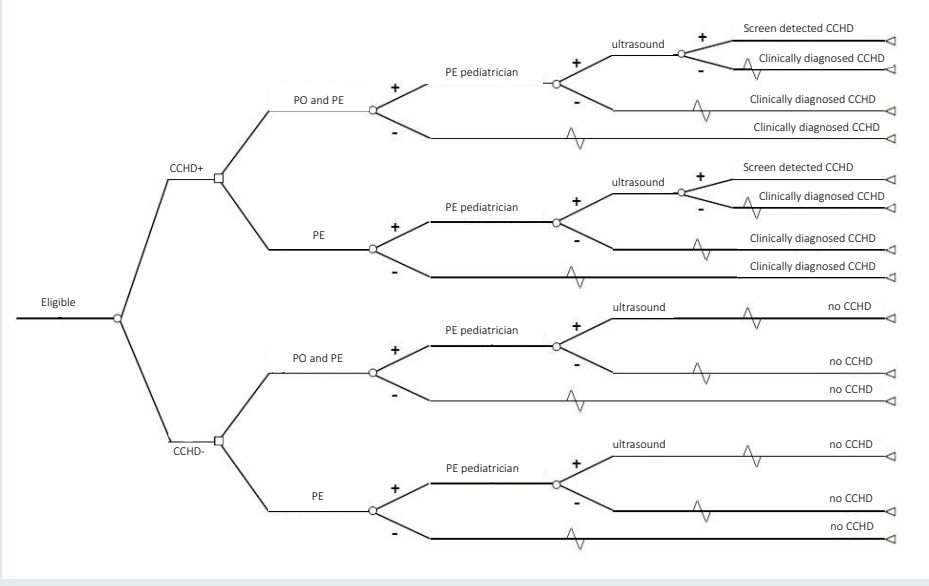
Screening strategies

The situation with PO screening as an adjunct to clinical examination was compared to usual care in which no PO screening was performed.

In the situation with PO screening, PO was added to physical examination of newborns and performed at home or in hospital at two moments: at least one hour after birth and on day two or three of the infant's life. Infants with abnormal screenings were referred to the paediatrician for physical examination and a cardiac ultrasound was made in case of persistent abnormal oxygen saturations in the absence of a non-cardiac explanation.

In a situation without PO screening a physical examination is performed by the midwife or the obstetric nurse. If this examination has an abnormal result, referral to the paediatrician for examination including a cardiac ultrasound will take place. In Figure 1 both screening strategies are shown.

Figure 1. Schematic representation of screening pathways.



CCHD: critical congenital heart defect
PE: physical examination
PO: pulse oximetry

Clinical data

Clinical data for the situation with PO screening were obtained from the Pulse Oximetry Leiden Amsterdam Region (POLAR) study. The protocol and results of this study are published in another article.[14] The study included 23,959 infants, six infants with CCHD were detected, five by abnormal PO results and one due to clinical symptoms, while five CCHD were missed (sensitivity 54.5%, specificity 99%). The false positive rate was 0.9%, but 61% of these infants had significant other pathology. Also, the percentage of referred neonates transported by an ambulance in a situation with PO screening were obtained from the POLAR study.

For the situation without PO, the number of physical examinations by midwives and obstetric nurses was assumed to be the same as in the situation with PO screening. Data on referrals were obtained from a review of patients' records before the introduction of PO. From all infants with CCHD that were not detected during antenatal anomaly scan, the records were reviewed in order to assess when the infants became symptomatic, if there was a timely diagnosis, and if postnatal physical examination revealed symptoms. The percentage of infants without CCHD with a false positive result in a situation with physical examination alone, was assumed to be 0.4%.[3]

The clinical parameters used in the model are summarised in Table 1.

Table 1. Model parameters for a situation with and without PO screening added to physical examination.

	Situation with PO screening		**Situation without PO screening**	
Parameter	Value	Source	Value	Source
CCHD positive children				
% screen positive by clinical examination and/or PO	54.5%	POLAR	25.8%	chart review
% transported by ambulance if screen positive	50.0%	POLAR	50.0%	POLAR*
% physical examination if screen positive	100%	POLAR	100%	expert opinion
% cardiac ultrasound if screen positive	100%	POLAR	100%	expert opinion
CCHD negative children				
% screen positive by PO	0.9%	POLAR	-	-
% screen positive by physical examination	0.4%	Ewer et al. (3)	0.4%	Ewer et al (3)
% transported by ambulance if screen positive	2.2%	POLAR	2.2%	POLAR*
% physical examination if screen positive	100%	POLAR	100%	expert opinion
% cardiac ultrasound if PO screen positive	18.1%	POLAR	-	-
% cardiac ultrasound if PE screen positive	100%	expert opinion	100%	expert opinion

*Assumed to be the same as in pulse oximetry and physical examination group. PO: pulse oximetry; POLAR: Pulse oximetry screening Amsterdam-Leiden region study.

Costs of screening and referral

The cost evaluation is performed from a healthcare perspective. All reported costs were converted to values for 2017, by means of the consumer price index.[15, 16] As the cost of physical examination was assumed to be the same in the situation with and without PO, only the additional costs of PO were assessed.

A total of 28 community midwives recorded the time of 190 PO screenings. Also, the duration of the parent information talks during the antenatal visit and at the first screening moment were measured. We assumed that these time measurements were also representative for PO screenings performed by obstetric nurses. Personnel costs of the screening were obtained by multiplying the time duration of the screenings by the hourly gross salary costs of respectively midwives (€ 59, personal communication Royal Dutch Organization of Midwives (KNOV)) and obstetric nurses (€32).[15]

Cost of equipment was based on the purchase price of the used pulse oximeter devices and reusable sensor with wraps requested at the vendor (PM10N handheld pulse oximeters with reusable OxiMax sensors, Medtronic, Ireland, Dublin). We assumed a depreciation period of eight years for the pulse oximeter and 6 months for the sensors. Cost of annual maintenance were assumed to be 5% of the purchase price.[15] The mean number of devices in midwife practices and hospitals was obtained from participating practices and hospitals in the study.[14] This was multiplied by the number of midwife practices and hospitals in the Netherlands and divided by the total number of infants screened per year to obtain the costs of the device per infant screened.[17-19]

The percentage of neonates with a repeat PO screening was obtained from the POLAR study. Respectively 1.0% and 0.3% tests at the first and second moment of screening were repeated.

Referral costs included the cost of an outpatient visit to the paediatrician (€102), ambulance transport (€621), and costs of cardiac ultrasounds (€ 490) for the subgroup of neonates with persistent abnormal oxygen saturations without a non-cardiac explanation.[15, 20]

Analysis

In the base case analysis, costs and effects of both the situation with and without PO screening are compared using the model parameters described above for a cohort of 100,000 neonates with a gestational age ≥35 weeks, that were not monitored with pre- and post-ductal SpO_2 in the first 24 hours of life and in whom no cardiac ultrasound was performed. The cost-effectiveness ratio was obtained by dividing the difference in costs in a situation with and without PO screening by the difference in number of timely diagnosed infants with CCHD.

Additionally, sensitivity analyses were performed to assess the impact of alternative assumptions for the model parameters on the incremental cost-effectiveness ratio.

In these sensitivity analyses the cost and effects of performing one measurement in the first hours after birth instead of two measurements was assessed. Performing only one measurement, leads to a lower sensitivity of 45.5%, a lower percentage of children without CCHD receiving a positive PO result (0.8%) and lower costs of screening. Furthermore, the effects and costs were assessed if a sensitivity of 70% was assumed for PO screening, which may also be likely for the Dutch situation.[14]

Also (univariate) sensitivity analyses on cost parameters were performed. In the base case analysis, a depreciation period of eight years for the pulse oximeter was assumed, this was changed in a five-year period in the sensitivity analysis, leading to higher material costs of screening (€4.32 per infant). The Dutch tariff for cardiac ultrasound in newborns is quite high compared to the costs assumed for the UK and the US,[4,5] therefore also a sensitivity analysis with lower costs for cardiac ultrasound of €250 was performed.

Analyses were performed using Microsoft Excel (Microsoft, Seattle, WA) 2010 software.

RESULTS

Screening costs

A total of 190 PO screenings were timed by community midwives. The mean screening time was 4.9 minutes (SD 2.7 min, range 1.0-15.0 min). The mean parental information time was 3.8 minutes (SD 2.5 min, range 1.5-12.0 min). The two screening moments and parental information together amount to time costs of €11.00 per infant screened. Costs of pulse oximeter devices and the reusable sensor with wraps amount to €3.71 per infant, resulting in additional costs of PO screening of €14.71.

Effects and cost of screening with and without PO

In the situation without PO, 11 per 100,000 infants with CCHD were timely diagnosed. Adding PO, resulted in an additional number of 12 CCHD per 100,000 infants. In the situation with PO screening estimated cost of the addition of PO screening and referral amount to € 1,922,000 per 100,00 infants, of which the additional costs of PO screening account for €1,471,000 (Table 2). In the situation without PO screening costs of referral including ambulance transport, paediatrician visit and cardiac ultrasound were € 201,000 per 100,000 infants. Therefore, the additional cost of screening and referral in a situation with PO screening were €1,670,000 per 100,000 infants compared to a situation without PO screening.

Table 2. Cost of PO screening and referral in a situation with and without the addition of PO to PE screening, per 100,000 infants (2017 €).

Cost category	Situation with PO screening	Situation without PO screening
PO screening	1,471,000	0
Referral	452,000	252,000
- Ambulance transport	25,000	9,000
- Paediatrician	138,000	42,000
- Cardiac ultrasound	289,000	201,000
Total cost of screening and referral	1,923,000	252,000

PO: pulse oximetry; PE: physical examination.

The resulting incremental cost-effectiveness ratio, representing the additional cost per additional timely detected infant with CCHD, was € 139,000.

Sensitivity analysis

The sensitivity analyses in which base case values of the model parameters were changed, did not lead to important changes in the cost-effectiveness ratio, except for assuming a higher PO sensitivity, which resulted in a considerable lower cost-effectiveness ratio (Table 3).

Table 3. Cost and effects in a situation with and without the addition of PO to PE screening for different assumptions of the model parameters, per 100,000 infants (2017 €).

Sensitivity analysis	Situation with PO screening		Situation without PO screening		Cost effectiveness ratio
	Costs	Effects	Costs	Effects	***Costs per additional timely detected infant with CCHD***
Only PO measurement on day 1	1,299,000	19	252,000	11	128,000
Higher sensitivity PO (70%)	1,677,000	30	252,000	11	86,000
Shorter depreciation period pulse oximeter (5 years)	2,025,000	23	252,000	11	148,000
Lower costs cardiac ultrasound (€250)	1,627,000	23	252,000	11	136,000
Base case	*1,922,000*	*23*	*252,000*	*11*	*139,000*

CCHD: critical congenital heart defect; PE: physical examination; PO: pulse oximetry

DISCUSSION

The additional costs of PO screening are €14.71 per screened newborn. Total additional costs of screening and referral are €1,670,000 per 100,000 infants. This would implicate that the annual costs for implementing PO screening in the Netherlands would be €2.4million. With an estimate of 12 extra timely detected CCHDs per 100,000, this resulted in a cost-effectiveness ratio of €139,000 per timely diagnosis CCHD, when compared to the current management with antenatal anomaly scan and postnatal physical examination. A Willingness-To-Pay (WTP) threshold of €20,000 per gained Quality Adjusted Life Year (QALY) in the Netherlands for prevention indicates that PO screening in the Dutch care setting would be cost-effective if considerable savings in lifetime treatment and/or substantial gains in QALYs would be obtained per infant timely diagnosed with PO screening.[21] It is known that the improved techniques of paediatric cardiac surgery and catheter interventions have considerably improved the outcome of children with CCHD in the last decades, with an improved life expectancy and quality of life.[22, 23] However, exact and recent data on gained QALYs by timely diagnosis are lacking. The majority of infants with CCHD survive at least up to adulthood, and it is expected that the majority of them have normal life expectancy.[22] Recent data have also shown that the short-term morbidity, mortality and length of hospital stay are reduced in case of timely diagnosis of CCHD.[9] An analysis of the importance of timely diagnosis of CCHD, performed in the United States and based on a birth defect registry, stated that potentially preventable death occurred in 1.8% of infants with late detected CCHD, and that a late diagnosis was associated with more and longer hospital admissions, and higher inpatient costs.[24]

PO screening performed in hospital setting in the US costed $14.19 (2011) per screened newborn, which was less than the costs for metabolic (Guthrie test) screening and hearing screening in their setting.[4] In a cost-effectiveness analysis of PO screening performed in the UK additional costs of PO screening were £6.24 (2009).[5] In our screening protocol a part of the screenings were performed at home, with referral to hospital in case of a positive screening. Furthermore, we adopted a two-step screening strategy with PO measurements at two time points, causing higher personnel costs. These factors partly explain the higher costs of PO screening per newborn in our setting. Also costs of referral, especially of cardiac ultrasounds, were assumed to be higher for the Dutch situation, which together with the higher screening cost attribute to the less favourable cost-effectiveness ratio compared to the UK estimate of £24,000 per extra timely diagnosis of CCHD when compared to physical examination alone. As shown in the sensitivity analyses, the prenatal detection rate of CCHD has a large impact on the cost-effectiveness ratio; a high prenatal detection rate of CCHD in our implementation

study resulted in less CCHD detected postnatally, when compared to the other studies.[14] This increases the costs per additional detected case as well.

A strength of this cost-effectiveness analysis is that it was based on data acquired by a large primary accuracy study, with an additional time and motion study to assess time duration of screening and informing parents.[14] Although there was no concurrent control group with physical examination only, we were able to evaluate the accuracy by assessing a retrospective cohort from our own patient population from the period before PO screening was introduced. Although we did assess the additional costs per detected newborn with CCHD, we could not assess the costs per QALY, which is of high importance for policy makers. No other cost-effectiveness analysis in other countries could assess this however, due to lacking up-to-date long-term outcomes of children with CCHD. Another limitation is that we did not include treatment costs in this analysis, but studies have shown that the duration and amounts of hospital admissions is higher in case of late detection of CCHD.[9, 24]

An extra value of PO screening is the detection of other pathology, such as infections and respiratory morbidity.[14, 25] Although these secondary targets were not included in cost-effectiveness analyses, it is likely that timely detection of these potentially life threatening pathologies can reduce morbidity and mortality in neonates.[26, 27]

CONCLUSION

This cost-effectiveness analysis assessed PO screening in the Dutch perinatal care setting with a high rate of home births and early postnatal discharge. We calculated that PO screening in the Dutch care setting would be cost-effective if considerable savings in lifetime treatment and/or substantial gains in QALYs would be obtained per infant timely diagnosed with PO screening. However, for this, additional studies on life expectancy, quality of life and treatment costs of children with CCHD are needed. The data we provided can be used by policy makers when considering implementation of PO screening.

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CHAPTER 7

Maternal acceptability of pulse oximetry screening at home after home birth or very early discharge

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ABSTRACT

Background: The Netherlands has a unique perinatal healthcare system with a high rate of home births and very early discharge after delivery in hospital. Although we demonstrated that pulse oximetry (PO) screening for critical congenital heart disease is feasible in the Netherlands, it is unknown whether parents find the screening acceptable when performed in home birth setting. We assessed the acceptability of PO screening to mothers after screening in home setting.

Methods: A questionnaire was sent electronically to mothers who gave birth and/or had postnatal care under supervision of a community midwife participating in the POLS study, a feasibility study of PO screening in the Dutch care system, performed in the Leiden region, the Netherlands. The questionnaire included questions based on satisfaction, general feelings and perceptions of PO screening.

Results: A total of 1172/1521 (77%) mothers completed the questionnaire. Overall, mothers were happy with the performance of the test (95%), thought their baby was comfortable during the screening (90%) and did not feel stressed while the screening was performed (92%). Most mothers would recommend the test to others (93%) and considered the test important for all babies (93%).

Conclusion: Mothers of newborns participating in the study found the PO screening acceptable when performed at home.

What is known:

- Pulse oximetry screening for critical congenital heart defects is (cost)effective and acceptable to mothers when performed in hospital.

What is new:

- Pulse oximetry screening for critical congenital heart defects is also acceptable for mothers when the screening is performed at home.

INTRODUCTION

Pulse oximetry (PO) is an accurate and cost-effective screening tool for critical congenital heart defects (CCHD) in newborns, and has the advantage to detect other important neonatal pathology as secondary targets.[1-4] However, PO screening has not been implemented in the Dutch universal screening program.[5] The Dutch perinatal health care system is unique, with a high rate of home births (18%) and very early discharge from hospital after uncomplicated deliveries (<5 hours). Community midwives supervise 33% of all deliveries in the Netherlands, either at home or at a birthing facility or hospital.[6] Their first follow-up visit of mother and newborn is on day two or three of life (day of birth is day one). With an adapted protocol the Pulse Oximetry Leiden Screening (POLS) study showed that the use of PO screening after home births and early hospital discharge is both safe and feasible and could be easily implemented in the daily routine of community midwives in the Leiden region in the Netherlands.[7, 8]

The burden of a screening is an important factor to consider when implementing a new screening strategy.[9] PO screening in hospital settings was proven to be acceptable to both mothers and clinical staff.[3, 10, 11] However, taking into account the unique perinatal healthcare system in the Netherlands, it is unknown whether mothers find the screening also acceptable when performed at home. A positive screening at home leads to referral to a hospital, which can be highly uncomfortable and disruptive for the childbed of a newborn and for the mother, since it requires transfer in the first days (sometimes even hours) after delivery, while they are still recovering from the delivery. Furthermore, parents can experience stress and insecurity about the condition of the baby. Therefore, it is possible that performing the screening at home might be less acceptable for mothers when compared to screening in hospital.

We aimed to assess the acceptability of PO screening for the mothers participating in the POLS study in the Leiden region.

MATERIALS AND METHODS

Participants and procedures

The POLS study was performed between October 2013 and October 2014 in the Leiden region, the Netherlands. This prospective study was conducted in one academic hospital (Leiden University Medical Center (LUMC)), two regional hospitals (Rijnland Hospital Leiderdorp and Diaconessenhuis Leiden) and 14 regional community midwifery practices. PO measurements were performed pre- and post-ductally at two moments; at least one hour after birth (median 1.8 hours after birth) and on day two or three of life, at home during the first follow-up visit of the community midwife, or in hospital in case of prolonged hospital admission. The screening was abnormal in case of a pre- or post-ductal oxygen saturation below 90%, or with either a difference between the two limbs of >3%, and/or if the measurements at both limbs were <95%.[7,8]

In Dutch perinatal care a community midwife is responsible for the postnatal care of a mother and newborn in the first 8-10 days following childbirth, when the mother and newborn are at home (after hospital discharge or in case of home birth). Mothers who gave birth and/or had postnatal care under supervision of a community midwife during the POLS study were invited by email by their midwife to complete a questionnaire online. This questionnaire consisted of selected and translated questions from the questionnaire for mothers that was used in the PulseOx study in the United Kingdom (Table 1).[3]

Outcome

The outcome of this study was maternal acceptability. The questions focused on maternal perceptions during the measurement of the PO screening (happiness with test, comfort of baby, perceived stress), the extent to which mothers would recommend the test to someone else, and whether they thought the test was important for their or all babies. Higher scores

Table 1 Maternal perception on pulse oximetry screening.

	[a]Strongly agree [b]Yes, definitely, n (%)	[a]Agree [b]Yes, probably, n (%)
Overall, I was happy with the way the test was done [a]	523 (45)	585 (50)
My baby was very comfortable when the test was done [a]	536 (46)	513 (44)
I did not feel stressed while the test was being done [a]	591 (50)	491 (42)
Do you think it was important for your baby to have the test? [b]	683 (58)	340 (29)
Do you think it is important for all babies to have the test? [b]	781 (67)	306 (26)
Would you recommend the test to someone else? [b]	804 (69)	286 (24)

First three questions: [a] strongly agree-strongly disagree. Last three questions: [b] yes, definitely- definitely not

implied more positive perceptions.

Statistical Analyses

Data are presented as numbers and percentages. Statistical analyses were performed with SPSS (IBM SPSS Statistics, version 23.0, 2016, IL, USA).

Ethical considerations

The Medical Ethical Committee of the LUMC approved this study.

RESULTS

Participation in questionnaire study

In the POLS study 3,059 babies were included of which in 1,521(50%) infants at least one screening was performed at home (908 (60%) both screenings, 613 (40%) only second screening). The mothers of the babies where screening was performed at home were invited to complete the questionnaire of which 1172/1521 (77%) mothers completed the questionnaire.

Maternal acceptability

Table 1 shows the perceptions of mothers for the screening test. The majority of mothers were happy with how the test was performed (95%) and did not feel stressed during the test (92%). Most mothers (90%) thought that their babies were comfortable when the screening was performed. The majority of the mothers considered the test was important for the wellbeing of their own baby (87%) and for all (also other) babies (93%). The vast majority of mothers (93%) would recommend the test to someone else, while only 1% would not.

[a]Neither agree or disagree [b]I do not know, n (%)	[a]Disagree [b]Probably not, n (%)	[a]Strongly disagree [b]Definitely not, n (%)	Total, n (%)
45 (4)	16 (1)	3 (0.3)	1172 (100)
82 (7)	36 (3)	5 (0.4)	1172 (100)
56 (5)	31 (3)	3 (0.3)	1172 (100)
116 (10)	31 (3)	2 (0.2)	1172 (100)
76 (7)	8 (0.7)	1 (0.1)	1172 (100)
72 (6)	9 (0.8)	1 (0.1)	1172 (100)

DISCUSSION

Since an adapted protocol was used in the POLS study to facilitate PO screening after home births and with early discharge in the Netherlands, the acceptability of mothers was assessed. The vast majority of mothers were satisfied with the screening; most mothers considered it important for their babies and other babies and would recommend the test to others. Based on these results, our study implicates that the implementation of PO screening at home would be acceptable for the mothers.

Acceptability for neonatal PO screening has been assessed before, although this was in different settings, after hospital deliveries.[10, 11]However, their findings are comparable to ours. In a large study in the United Kingdom false positive results did not increase anxiety and mothers were overall satisfied with the PO test.[3]

The general maternal acceptability in our study might be explained by several factors. First, it was not mandatory to test one's baby and therefore participation after informed consent was a conscious and voluntary choice. For this reason, mothers were probably positively disposed towards the PO screening before participation. Other aspects of the test, as being not time-consuming and non-invasive will also positively influence the acceptability. The PO screening is painless and not dangerous for the baby. There are no known risks and the parents were informed about the safety of the measurement before screening. Furthermore, the measurement was performed by the mother's own healthcare provider. The possibility of early detection of potential life-threatening pathology may also have influenced the acceptability due to the possibility of prompt treatment before deterioration.

There were some limitations in this study. For example, the decoded (anonymous) storage of data in order to guard the privacy of the mothers entering the online questionnaire, made it impossible to link the test results to the participants. As a result, this study did not distinguish between mothers of newborns with false positive, true positive and true negative screening. However, the numbers of false positives were low and there were no true positives or false negatives in the POLS study, which makes it difficult to make a valid comparison between the true and false positive and negatives.

This study was conducted in the Leiden region, a middle-sized city in the urban agglomeration of Netherlands, and might therefore not be representative for the rest of the country, including the larger cities or rural areas.

In conclusion, PO screening at home was acceptable to mothers participating in the POLS study.

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CHAPTER 8

Low signal quality pulse oximetry measurements in newborn infants are reliable for oxygen saturation but underestimate heart rate

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ABSTRACT

Aim: We assessed the influence of system messages (SyM) on oxygen saturation (SpO_2) and heart rate measurements from infants after birth to see if clinical decision-making changed if clinicians included SyM data.

Methods: Heart rate and SpO_2 of term infants were recorded using Masimo pulse oximeters. Differences in means and standard deviations (SD) were calculated. Permutation corrected the non-random distribution and inter-subject variation. SpO_2 and heart rate centile charts were computed with, and without SyM.

Results: Pulse oximetry measurements from 117 neonates resulted in 28,477 data points. SyMs occurred in 46% of measurements. Low signal quality accounted for 99.9% of SyMs. Mean SpO_2 with SyM was lower ($p<0.001$), while the SpO_2 SD was similar to data without SyMs. The SpO_2 centile charts were approximately 2% lower with SyMs included, but they were not more dispersed. Mean heart rate was lower ($p<0.001$) and more dispersed ($p<0.001$) when a SyM occurred. The heart rate centile charts were lower, with increased variability, when SyMs were included.

Conclusion: A SyM occurred frequently during pulse oximetry in term infants after birth. SpO_2 measurements with low signal quality proved reliable for monitoring an infant's clinical condition. However, heart rate could be underestimated by low signal quality measurements.

Key notes:

- This study assessed the influence of system messages (SyMs) on the oxygen saturation (SpO_2) and heart rate measurements of 117 term infants after birth to see if clinical decision-making changed if clinicians included data with SyMs.
- Low quality signals occurred often, indicating lower heart rate and SpO_2.
- There was little difference between measurements with, and without low-quality SpO_2 signals, but heart rate could be underestimated by low signal quality.

BACKGROUND

Current international neonatal resuscitation guidelines recommend the use of pulse oximetry (PO) to evaluate an infant's condition when resuscitation is indicated.[1-3] PO provides objective and accurate values of the saturation of peripheral oxygen (SpO_2) and heart rate in a continuous manner.[4, 5]

PO measurements of the SpO_2 and heart rate of infants needing no resuscitation have been used to develop reference ranges.[6-11] In these studies measurements with an alarm message or system message (SyM) on the pulse oximeter were excluded; in some studies almost half of all collected data were excluded.[7, 10] However, when evaluating infants at birth, very little distinction is made between the signals with and without SyM in daily clinical use. When resuscitation or stabilisation is needed, it can be difficult for clinicians to note the SyM and exclude these measurements while evaluating the infant's condition. This raises an important question: are measurements of heart rate and SpO_2 with a SyM obtained by pulse oximetry valid and useful for clinical decision-making. Furthermore, the feasibility of pulse oximeter measurements of heart rate and SpO_2 can be questioned, as almost half of the data on the pulse oximeter screen are considered to be of poor quality and should be excluded from clinical decision-making.

The Masimo Radical pulse oximeter provides a number of possible SyM messages: low signal

identification and quality (SIQ), low perfusion, sensor off and ambient light. A message of low perfusion appears when there are very low amplitude arterial pulsations. SIQ is a measure of confidence in the measurement by the oximeter's algorithm. The Masimo Radical oximeter determines signal quality as a range from zero to one and an SIQ of less than 0.3 is defined as low SIQ.[12, 13] While studies reporting PO measurements have excluded measurements with SyM from analysis, the manufacturer (Masimo) indicates that measurements with low perfusion values can be used. However, caution needs to be taken when the low SIQ message is shown, as the degree of confidence decreases.[6-11, 15] The manufacturer has also stated that measurements with low SIQ have a high probability of being correct. However, clinicians should proceed with caution and efforts should be undertaken to rule out sensor displacement, malpositioning, light interference, and combination of poor perfusion or motion artefacts for the cause of a measurement accompanied by SyM.[15] Therefore, the manufacturer has recommended that clinicians should exclude measurements with a low SIQ message when the oximeter is used for clinical research.[14]

A SyM is often obtained in PO measurements performed soon after birth; it is therefore useful for the clinician to know if all displayed values, including the measurements with SyMs, will influence the evaluation of the infant's condition using the current reference ranges. We

investigated the differences between SpO_2 and heart rate measurements with, and without SyMs from a Masimo pulse oximeter to determine the validity of data obtained with a SyM. We also assessed whether the currently used reference charts would change significantly when SyM data were incorporated.

PATIENTS AND METHODS

For this study we used the PO recordings from a prospective observational study performed by 27 midwives in seven community midwifery practices in the Leiden region. Midwives supervised uncomplicated vaginal births at home, in birthing facilities, or in hospital.[16, 17] During the 10-month period from April 2011 to February 2012 the midwives used a Masimo Rad-8 hand held pulse oximeter (Masimo Corporation, Irvine, California), and obtained measurements directly after birth. The devices contained Signal Extraction Technology (SET, V.7.8.0.1) and were set to give a measurement every two seconds, with two-second averaging intervals and maximal sensitivity.

Midwives were provided with a timer, which was synchronised with the pulse oximeter, enabling time of birth and initiation of PO to be recorded accurately. Midwives placed a disposable sensor (Masimo Low Noise Cable Sensor (LNCS®) Newborn Sensor) around the infant's right hand. Preductal SpO_2 and heart rate were obtained for a minimum of ten consecutive minutes. Delayed cord clamping was standard care in these healthy term deliveries.

The study was approved by the Leiden Medical Ethics Committee in February 2011. As PO is non-invasive, the measurements were observational, and the pulse oximeter measurements were not used in clinical decision making by the midwives, only verbal parental consent was required as approved by the Ethics Committee. The consent was documented in the mother's medical record.

The PO data were downloaded using Trendcom software, which transfers rough data into an Excel spreadsheet (2003, Microsoft), with data points every two seconds including whether SyM occurred at that data point. All data, including those with SyM (low perfusion, sensor off, ambient light and low SIQ), were included for analysis.

Statistical analysis

We calculated the means and standard deviations (SD) for both heart rate and SpO_2 for signals with, and without SyMs and then compared them to assess whether there was a difference between signals with, and without SyMs. It is not possible to compare data with, and without a SyM at one time point within one patient, because only one of these alternatives is possible at

each time point. Therefore, we computed the difference of the means and standard deviations between the data, with and without SyMs and added these differences across all time points. This resulted in four values for the systematic difference between data with, and without SyMs: for mean SpO_2, standard deviation of SpO_2, mean heart rate, and standard deviation of heart rate. To correct for the statistical dependence between measurements within a subject, and for the non-random patterns of SyMs, we performed permutation by randomly reassigning the observed patterns of SyMs between the subjects.[18] We repeated this reassignment 1,000 times, and each time we recomputed the means and standard deviations of heart rate and SpO_2. By reassigning the SpO_2 and heart rate values randomly, any association between subject and SpO_2 or heart rate was nullified. Finally, we compared the original, unpermuted values of the means and standard deviations of SpO_2 and heart rate to the corresponding 1,000 permuted values in order to obtain *p* values.

Data points were incorporated into LMSChartMaker Light Version 2.3 (Medical Research Council, UK; 2006) to produce centile charts for all measurements with and without SyM in order to assess whether reference ranges would change when data with SyM was included.[19]

Statistical significance was found if $p<0.05$. Calculations were performed using the statistical programme R.2.14.0 (R foundation for statistical computing, Austria; 2011).

RESULTS

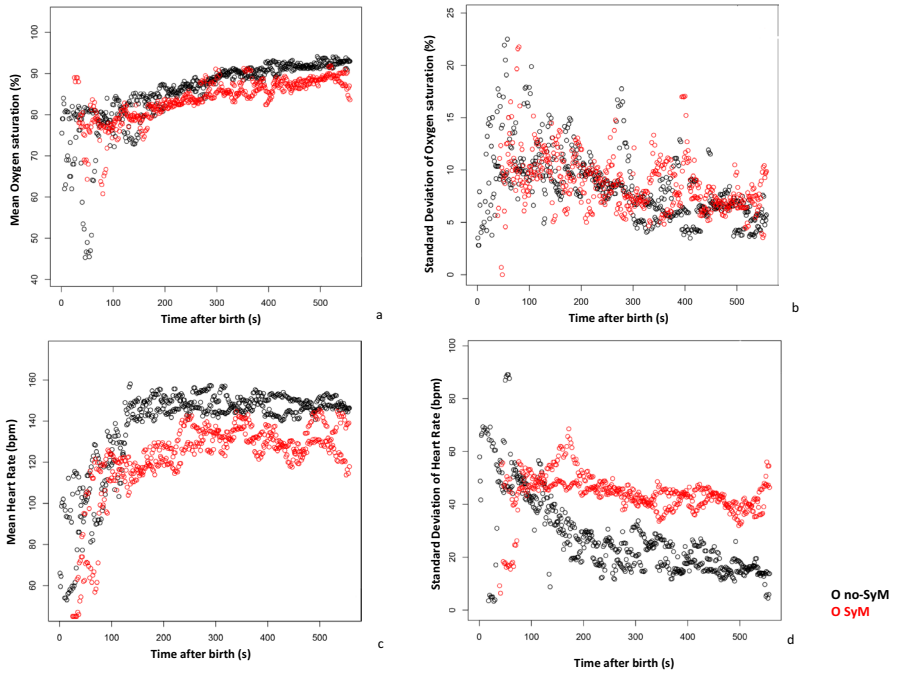
Between April 2011 and February 2012 we recorded PO measurements from 117 neonates. A total of 28,477 measurements were collected, of which 12,970 (46%) were labelled with a SyM and 15,507 (54%) had no SyM. Of all the SyM data 12,963 measurements (99.9 %) were labelled as low SIQ and the remaining seven measurements were labelled as low perfusion. No other SyM occurred. None of the SyMs occurred in the first minute. In the following two to ten minutes SyMs occurred in 27%, 60%, 56%, 46%, 47%, 42%, 39%, 40% and 39% of the data respectively. In addition, we recorded the time from the birth of the infant until the umbilical cord was clamped in 45 infants, which showed that this occurred at a median of five minutes with an interquartile range of three to seven minutes.

Oxygen saturation

The means and standard deviations for SpO_2 measurements from one to ten minutes after birth are shown in Figure 1A and 1B, respectively. The mean SpO_2 was significantly lower when the measurement was obtained with a SyM ($p<0.001$). There was no significant difference in the standard deviation for the SpO_2 measurements obtained with, and without SyMs ($p=0.30$).

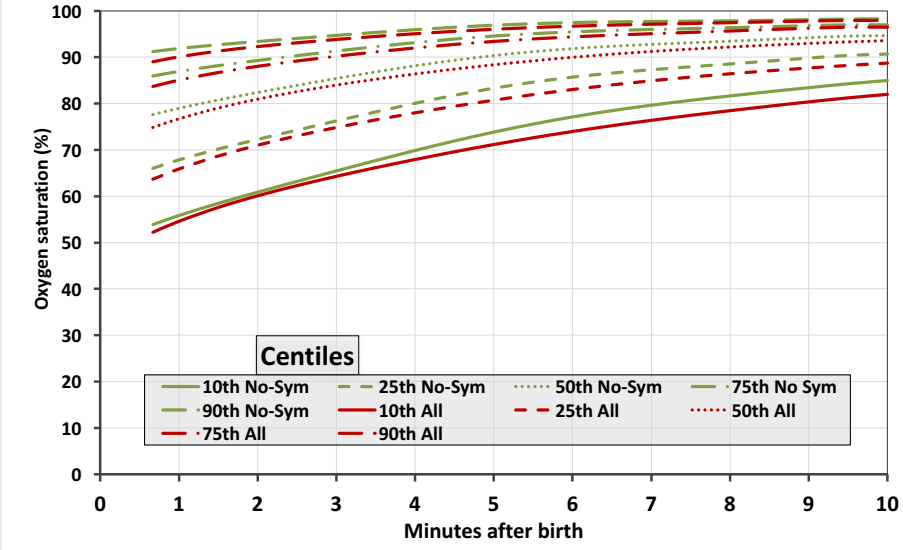
The centile charts from SpO_2 with, and without SyMs for one to ten minutes after birth are shown in Figure 2. On average, those measurements with SyMs were 2% lower than those with no SyM. The centiles were equally distributed and not more dispersed when SyM measurements were included.

Figure 1. Mean and standard deviation of oxygen saturation and heart rate per time point in seconds.



A) Mean SpO_2 in percentage per time point in seconds. B) SD of SpO_2 per time point in seconds. C) Mean heart rate in bpm per time point in seconds. D) SD of heart rate per time point in seconds. Every circle represents the mean or SD SpO_2 or HR at that certain time point. Black circles represent measurements obtained without SyM. Red circles represent measurements obtained with SyM.

Figure 2. Centile charts for oxygen saturation per minute for all signals and no-SyM signals.



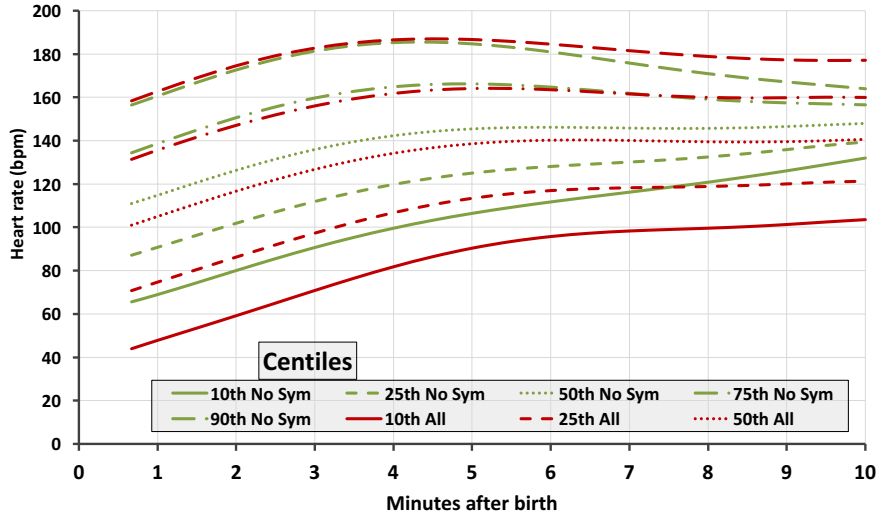
10th, 25th, 50th, 75th and 90th centile for SpO_2 are given for all signals in red and for no-SyM signals in green.

Heart Rate

The means and standard deviations of heart rate are shown in Figures 1C and 1D, respectively. The means and standard deviations of heart rate with SyMs was significantly lower than the heart rate obtained without SyM (p<0.001). The standard deviation of heart rate obtained with SyMs was significantly higher than the heart rate measurements obtained without SyMs (p <0.001).

The centile charts of heart rate without SyM signals and for all signals are shown in Figure 3. The 10th to 75th centiles of heart rate were lower when SyM data were included and the difference was highest in the lower centiles. The 90th centile was slightly higher in the first minutes after birth when we used all the data. In the last minutes, centiles of data without SyM signals converged, while centiles with all data diverged, showing more variability in heart rate when SyM data were included.

Figure 3. Centile charts for heart rate in beats per minute for all signals and no-SyM signals.



10th, 25th, 50th, 75th and 90th centile for HR are given for all signals in light red and for no-SyM signals in green.

DISCUSSION

This is the first study on healthy term infants not receiving interventions that compares PO SpO_2 and heart rate measurements with SyMs to those without SyMs. We observed that SyMs occurred in almost half of the measurements, which were mostly marked with low SIQ messages. This could make it difficult for a caregiver to interpret SpO_2 and heart rate measurements when using pulse oximetry for evaluating an infant after birth. It is useful to know if measurements obtained with SyMs are valid and usable for clinical decision making.

Mean SpO_2 was lower when obtained with SyMs compared to data obtained without SyMs. Although the difference in mean SpO_2 was small, it was statistically significant, probably due to the large number of measurements in this study. The standard deviation was not different when SpO_2 measurements with SyMs were compared to measurements without SyMs, indicating that there was no more variation in SpO_2 measurements for data with SyMs. The centiles produced for SpO_2 were also consistently lower, by around 2%, when SyM data were included, meaning that there was no more variability in SpO_2 when using all the data. Furthermore, this small absolute difference fell within the defined 2% margin of error of Masimo pulse oximetry and was, therefore, not clinically relevant.[20] The centiles were almost identical after inclusion

of SyM data. For these reasons, clinical management will probably not be influenced by using all data, including measurements with SyMs. Therefore, it may be less important to note signal quality when evaluating SpO_2 at birth with PO.

We found that the mean heart rate with SyMs was significantly lower than the mean heart rate without SyMs. We have shown that there was a large range of heart rate measurements when signal quality was questionable. Additionally, when measurements with SyMs were included, the heart rate centiles were lower in the first minutes and became wider over time. In the lower heart rate range (10^{th} and 25^{th} centile) there was a potentially clinically significant difference in heart rate when SyM data were included. This means that clinicians should be aware of SyMs when interpreting heart rate with PO, especially when the heart rate is low. If a low SIQ message is not noted, it is possible that clinicians may underestimate an infant's heart rate.

SyM frequently occurred when using a pulse oximeter to measure heart rate and SpO_2 in newborns. The occurrence of SyMs in almost half of our data is comparable to previous studies in the same population.[6, 10] SyM predominantly indicated low SIQ (99.9%). Low perfusion occurred infrequently and no other messages occurred. It is possible that when other messages occur, for example in the Neonatal Intensive Care Unit, this might lead to other differences between measurement with, and without SyMs. For this reason, the difference observed in this study only refers to SyMs with low SIQ.

The high proportion of SyM signals might go unnoticed by clinicians when evaluating newborns. We hypothesise that clinicians look at the numbers, but may not take into account the quality of the signal. Consequently, they may not try to gain a better signal by re-siting the oximeter sensor. Moreover, when we consider the similarities in centile charts with all signals included and compare them to those with no SyM signals, it is also possible that the given values obtained with SyM met the normal values. Therefore, there might not have been a priority to improve the signal.

Previous studies using pulse oximetry excluded measurements obtained with SyMs for analysis, as has been recommended by the manufacturer.[6-11] However, very little data is available concerning the confidence level when there are measurements with low SIQ. Lang *et al.* analysed 10 neonatal files to assess whether low SIQ messages obtained with a Masimo Radical pulse oximeter reliably indicated compromised data integrity. This study showed that a low SIQ message demonstrated high sensitivity in detecting poor signal quality, without being displayed for an excessive amount of the monitoring time.[21] However, SpO_2 values were considered erroneous in the Lang *et al.* study if they deviated >10% from measurements obtained with other motion resistant pulse oximeters. Hence, findings from the Lang study must be interpreted with caution as they did not compare SpO_2 measurements against a gold

standard. Masimo has stated that measurements with low SIQ have a high probability of being correct.[15] This might be true for SpO_2 where we observed little difference between data with, and without SyMs. In addition, the centile charts ranges (Figure 2) for SpO_2 were very similar for data with, and without SyMs, while we observed larger differences for heart rate.

In contrast to what we expected, few signals with SyMs occurred in the first minutes. It is possible that delayed umbilical cord clamping, with a median time of five minutes, influenced the quality of the signal. Therefore, the first heart rate and SpO_2 measurements were recorded before the cord was clamped.[16, 17] In a study of preterm lambs, Bhatt *et al.* demonstrated that ventilation before cord clamping stabilised the haemodynamic transition at birth by increasing pulmonary blood flow before the umbilical venous return was lost. This allows the supply of preload to the left ventricle to immediately switch from umbilical to pulmonary venous return when the cord is clamped.[22] No temporary decrease in left ventricular output and increase in systemic vascular resistance would occur in the first minutes. The pulse oximeter may find a signal more quickly before the cord is clamped. It is difficult to compare our findings with previous studies, as they do not report when SyMs occurred and they do not report the time of cord clamping.

It is impossible to obtain data with, and without SyMs for each infant at each time point. Therefore, we compared measurements of each subject against measurements from other infants obtained at the same time points. Inter-subject variation in heart rate and, or SpO_2, and variations in the amount of measurements with SysM is possible and could have influenced our findings. In addition, there was no random distribution in the occurrence of SyM. We performed a permutation test to nullify these potential effects of bias. Another limitation was the use of solely one model of oximeter. We therefore cannot be certain if our findings can be generalised to all pulse oximeters.

CONCLUSION

This study showed that SyMs occurred frequently during PO at birth using Masimo, predominantly displaying a low SIQ message. Mean SpO_2 and heart rate measurements obtained with low SIQ are lower than measurements without SyMs. The absolute difference in SpO_2 measurement with poor signal quality versus those with good signal quality was small, and they lay within the margin of error of Masimo pulse oximetry. The occurrence of low signal quality for SpO_2 measurements is, therefore, unlikely to affect clinical practice. However, the absolute difference in heart rate measurements with poor signal quality versus those with good signal quality was variable. Heart rate measurements with poor signal quality should be used with

caution, as the possible underestimation of heart rate might affect clinical practice, especially in the lower range. The effect of signal quality on pulse oximetry should be further examined to provide more insight into the effect of signal quality on SpO_2 and heart rate measurements.

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CHAPTER 9

General Discussion

Critical congenital heart defects (CCHD) occur in approximately 2/1,000 newborns and require invasive medical intervention within the first month of life. When CCHD is not timely diagnosed it will lead to severe cyanosis, acidosis, cardiovascular collapse, organ failure, hypoxic-ischemic brain injury, and eventually to death.[1] A timely diagnosis and prompt treatment reduces the risk of mortality and (short and long term) morbidity, increasing the chance for a favorable outcome.[2, 3] However, despite implementation of the prenatal screening using ultrasonography in perinatal care plans, still approximately 30-50% of all CCHD remain undiagnosed during pregnancy.[4] Physical examination is routinely performed after birth but the clinical symptoms of CCHD are often not noticed, since murmurs are often absent and cyanosis is difficult to detect with the human eye.[2, 5] As a consequence still around 10-20% of newborns with CCHD are diagnosed late and usually present with cardiovascular collapse when the ductus arteriosus closes.[6]

To increase the number of timely diagnoses, studies on screening newborns for CCHD using pulse oximetry (PO) have been performed since 2000 and led to an increasing implementation of PO screening across all continents.[7, 8] This non-invasive screening method was proven to be reliable, easy to perform and easy to implement in hospitals. Although studies only investigated the costs, without the long-term benefits, the screening is likely to be cost-effective and studies using questionnaires have shown that the screening was acceptable for parents and caregivers.[8-11]

However, all studies performed so far were in hospital settings and with a postnatal stay of more than five hours. In contrast, the Netherlands has a different perinatal care setting with the highest rate of home births (18%), which are supervised by community midwives.[12] The midwives stay for approximately three hours after birth and come back for their first follow-up visit on day two or three after birth (day of birth is day one). Also, in the Netherlands mother and newborn are discharged early (within five hours) after uncomplicated vaginal delivery in hospital. For these reasons, the published protocols used in other countries do not match with the Dutch perinatal logistics and it is not possible to extrapolate the results of other PO screening studies to the Dutch perinatal care setting. We therefore performed studies with an adapted PO screening protocol to fit home births and early discharge in the Dutch unique perinatal care setting.

After publication of the meta-analysis on PO screening in the Lancet in 2012 it was stated that in the Netherlands it would be difficult to train all 1850 community midwives in performing PO measurements and to provide them all PO devices.[13] Although the Dutch Association of Pediatrics (NVK) recommends the use of PO in case of resuscitation of a newborn, PO has not been implemented as standard practice in community midwifery.[14, 15]The Netherlands has a history of having a high rate of 'natural' deliveries at home, without medical intervention.[16]

Community midwives in the Netherlands are traditionally trained in clinical assessment and intervention with little use of technical devices.[15] However, in the Leiden region there is a well organised clinical and research collaboration between hospitals and community midwives. The midwives participated in a study with recording PO measurements at birth at home. The midwives were trained in one afternoon session and experienced no problems with the use of PO during the study. The study showed that using the PO at home birth was feasible and almost all midwives were enthusiastic about having a PO available, especially in situations with a suboptimal condition of the newborn.[15] We considered the Leiden region the optimal region to pilot PO screening in the Dutch perinatal care setting.

The screening protocol used in the United States and Scandinavia needed to be adapted and make it fit with the visiting scheme of community midwives in the Netherlands.[17,18] Instead of performing one pre- and post-ductal SpO_2 reading 24-48 hours after birth, we decided to perform these measurements at two separate time points: the first measurement at least one hour after birth, and the second measurement on day two or three of the newborn's life (day of birth is day one). The first measurement should be performed in the first hours after birth, since community midwives stay for approximately three hours after a delivery and because of discharge within five hours after in-hospital delivery. We were aware that performing screening early (before 24 hours) is accompanied with a higher false positive (FP) rate, due to transitional circulation.[8] However, studies also demonstrated that when the screening was performed after 24 hours of life, some CCHD already presented with severe symptoms before the screening was performed.[11, 19] The intention of screening is to detect pathology before symptoms occur, making early screening pivotal. Early screening also enables timely detection of other significant pathology, such as infections and respiratory morbidity. We added the second measurement on day two or three of life, at the first follow-up visit of the community midwife, because it is possible that a widely patent ductus arteriosus can cause normal SpO_2 values in newborns with CCHD in the first hours of life.

We first piloted the adapted protocol in a feasibility study in the Leiden region, in which one academic hospital, two regional hospitals, and 14 midwifery practices are situated.[20] In this study, the Pulse Oximetry Leiden Screening (POLS) study, screening could only be performed after parental consent. Almost all parents who were approached consented and 99% (3,059/3,090) of the newborns with parental consent were screened. It was reassuring to observe that during the first screening moment in most of the healthy term newborns the pre- and post-ductal SpO_2 were already above 95% in the first hours after birth (Table 1). This implicates that newborns with SpO_2 values below 95% should be evaluated when they are measured at least one hour after birth. Indeed, in 50% of the newborns with a FP screening

result other morbidities than CCHD were diagnosed, including infections, wet lungs, PPHN or non-critical congenital heart defects.

Table 1. SpO_2 values in the first three hours after birth.

Hours after birth	N	Pre-ductal SpO_2, %		Post-ductal SpO_2, %	
		p10	p50 (p25-p75)	p10	p50 (p25-p75)
0-1	394	97	99 (98-100)	96	99 (97-100)
1-2	969	97	99 (98-100)	96	99 (98-100)
2-3	346	96	99 (98-100)	96	99 (98-100)

10^{th} percentile and median (IQR) SpO_2.

We then assessed the acceptability of performing PO screening at home amongst 1,172 mothers participating in the POLS study by using questionnaire.[21] In this group screening measurements were performed at least once at home by their community midwife. The response rate was acceptable (77%) and the vast majority (93%) of mothers considered the screening test important for all babies and would recommend the test to someone else.

We concluded that PO screening for CCHD, using the adapted protocol, was feasible in the Dutch perinatal care setting and that screening at home is acceptable to mothers.[20, 21]

In order to assess the accuracy of the adapted PO screening we performed an implementation study in a larger cohort in a much larger region (Leiden-Amsterdam Region (POLAR) study).[22] This study was carried out in three academic hospitals, 11 regional hospitals and 75 midwifery practices and included 23,996 newborns. The sensitivity of PO screening for all newborns with CCHD was 70% with a specificity of 99%. The prenatal detection rate was 73% and after excluding the 36 newborns with CCHD that were prenatally detected and one newborn that was already symptomatic at birth the sensitivity decreased to 50%. Serious illnesses such as infections and respiratory pathology were detected in 61% of all newborns with FP screening results. This study demonstrated that PO screening adapted to home births and early post-delivery hospital discharge contributes to the detection of CCHD in an early, asymptomatic stage. The early detection of CCHD, but also other significant pathology, such as infections and respiratory morbidity, could be considered as a safety net when newborns are born at home or early discharged after delivery in hospital. In that view, the PO screening has the potential to decrease morbidity and mortality of newborns in the Netherlands.

Before screening programs can be recommended for universal implementation, cost effectiveness should be considered. Cost analyses have shown that PO screening is likely to be

cost effective, but only screening in hospitals were taken into account.[9, 10, 23] In the way our screening was set up, all community midwives would require a pulse oximeter, and positive screenings at home should be transported and referred to hospital. This is likely to increase the costs when performing the screening in the Dutch perinatal care system as compared to settings with deliveries and screening in hospital. In a cost-effectiveness analysis our calculations demonstrated that PO screening would cost €14,71 per screened newborn and approximately €2.4 million annually to screen all newborns born at a gestational age of at least 35 weeks, or €139.000 per timely detected CCHD. The outcome of children after paediatric cardiac surgery has considerably improved in the last decades, but recent data on gained Quality Adjusted Life Years are lacking. However, it is known that a timely diagnosis of CCHD decreases the risk of mortality and morbidity, and also the length of hospital stay.[2, 24]

It is sometimes not possible to obtain optimal PO readings, which might complicate making decisions when the screening is performed at home. In these cases, community midwives performing the screening at home would have to use the values with low signal quality. This might then lead to unnecessary referrals if the actual SpO_2 would be higher when the measurement was not hampered by low signal quality. PO is now recommended to obtain SpO_2 and heart rate during stabilisation of newborns at birth.[14, 25] While the developed normograms for SpO_2 are based on high quality data only, caregivers often have to deal with both low and high quality signals during clinical use.[26, 27]We therefore assessed the validity of SpO_2 and heart rate obtained with low signal quality and found that SpO_2 was approximately 2% lower with inclusion of data with low signal quality, while the heart rate showed lower values with more variability when compared to optimal readings only.[28] Although an optimal reading should always be aimed for, we concluded that SpO_2 readings with low signal quality can be used in decision making if an optimal signal quality cannot be obtained. Using measurements with low signal quality in the PO screening protocol might however lead to more referrals.

Prenatal detection and sensitivity of PO screening

PO screening is not a replacement for other screening moments for CCHD, but should be considered as an addition to prenatal screening and physical examination. An early prenatal diagnosis of CCHD allows the parents to be mentally prepared, and gives them the opportunity to terminate the pregnancy. Furthermore, it allows the medical team to prepare a treatment strategy and the delivery can be planned in a congenital heart disease center with a third level Neonatal Intensive Care Unit (NICU) facility to enable acute surgical or catheter interventions. Prenatal detection varies between countries, and regions within countries, and can be improved with training and logistic interventions.[29] The sensitivity of PO screening is correlated

with the prenatal detection rate of CCHD, which ranged from 0-82% within performed accuracy studies.[30] Fetal screening with structural anomaly scan is well organised and highly accessible in the Netherlands; there are strict nationwide requirements regarding the performance of the fetal ultrasounds. Intensive training and audit programmes are regionally organised. The prenatal detection rate of CCHD was high (73%) in the region where the implementation study was performed,[22] but the prenatal detection rate in other regions of the Netherlands is currently unknown.

Although the overall prenatal detection of CCHD is high, specific defects remain difficult to detect prenatally, such as transposition of the great arteries (TGA), total anomalous pulmonary venous return (TAPVR), pulmonary valve stenosis, aortic valve stenosis and coarctation of the aorta (CoA).[4, 29] PO screening is efficient in detection of lower SpO_2 caused by TGA, TAPVR, and pulmonary valve stenosis, but left sided obstructive lesions, such as CoA are frequently missed with PO screening (see below).[8, 31, 32] It remains challenging to detect CoA in an early stage even in combination with antenatal screening, PO screening and neonatal physical examination. In conclusion, PO is an effective screening method for diagnosing CCHD, but results of PO screening are correlated with the prenatal detection rate of CCHD. When we implement the PO screening in the Netherlands and we anticipate a variable prenatal detection rate in the Dutch regions, the sensitivity is likely to be somewhere between 50 and 70%.[22]

False positive screenings

Sepsis is one of the leading causes of newborn mortality and can be missed in an early stage due to the non-specific clinical presentation.[33] Hypoxia can be one of the first symptoms in newborns with infection, caused by an increased oxygen demand of the infected cells and functional shunting in the microcirculation.[34] PO screening detected infection and sepsis as a part of the FP screenings, enabling prompt treatment in an early stage.

PO screening also detected respiratory morbidity in newborns, such as wet lung, persistent pulmonary hypertension of the neonate (PPHN) and pneumothorax. Wet lung, or transient tachypnea of the neonate, is a clinical diagnosis caused by the delayed clearance of fetal lung fluid.[35] Low SpO_2 values can be the first symptom, followed by symptoms of respiratory distress, such as tachypnea or retractions. Although wet lung is often self-limiting, it can progress to PPHN in approximately 10% of affected newborns. PPHN is a severe condition, caused by right-to-left shunting with reduced pulmonary flow, and has a mortality rate of 5-10%.[36, 37]

Non-cardiac causes of cyanosis in newborns can be relatively benign, such as transitional circulation, but can also be caused by more severe pulmonary, infectious or haematologic pathology. It is possible that detection of this non-cardiac pathology leads to overtreatment. Indeed, in the case of suspicion of infection or wet lung, it is not clear in which newborns the

symptoms are self-limiting and in whom the condition will deteriorate into sepsis or PPHN. The duration of admission and respiratory support will be short in case of self-limiting wet lungs, so the burden for the newborn and parent will be limited in this situation.

All newborns with FP screenings had objectively measured cyanosis. If the SpO_2 was normalised at paediatric assessment, no admission or follow-up was required. However, in the case of persistent low SpO_2 values the cause should be assessed and it is common clinical practice to treat cyanosis in newborns. The clinicians judged that treatment was required in all newborns diagnosed with significant pathology in our implementation study.

Also, the burden of unneeded admissions and diagnostics of FP screenings was assessed in the UK in a national pilot, involving 32,836 newborns with pre-discharge screening, targeted to be performed between 4-8 hours after birth.[38] Comparable to our studies, the screen positive rate was 0.73%. Significant pathology was detected in 38% (87/231) of FP screens, and 48% (114/239) newborns with positive screens were admitted to the neonatal unit, of which 22 newborns (19%) were considered healthy. Clinical investigations were performed in 18/135 (13%) newborns with a FP screening without significant pathology detected. In summary, PO screening in this UK pilot led to unnecessary hospital admittance in 0.07% of screened newborns and to clinical investigations in 0.05% of healthy screened newborns.[38] This implicates that the burden of unneeded investigations and admittances is low.

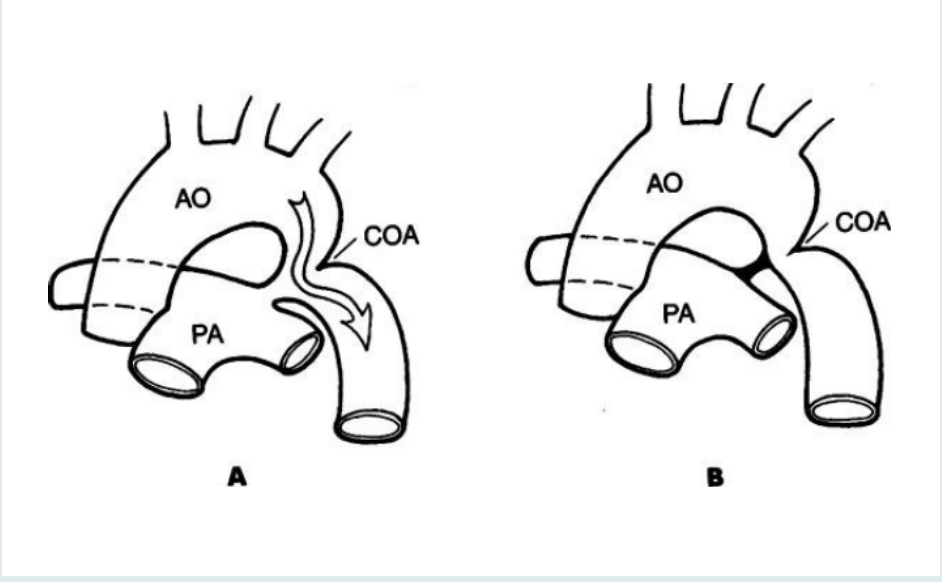
The early recognition of sepsis and respiratory morbidity by PO screening can be important in preventing worse outcome, and has the potential to reduce duration of hospitalisation and treatment, and importantly, neonatal morbidity and mortality.

False negative screenings

Most CCHD are immediately dependent on mixing of the systemic and pulmonary circulation by shunting structures, such as septal defects or a patent ductus arteriosus. In these conditions, the oxygen poor and oxygen rich blood will be mixed and the SpO_2 will already be low in an early stage. In left-sided obstructive lesions, such as CoA, the blood is well oxygenated in the lungs, but a high pulmonary pressure causes right-to-left shunting across the patent ductus arteriosus. For this reason, the SpO_2 in the lower extremities can be lower, but the difference between the upper and lower extremities might not exceed 3%, because of sufficient antegrade flow of oxygen rich blood in the aorta, and therefore PO screening results can be normal. In the specific case of CoA the obstruction is usually located juxtaductally, allowing for sufficient lumen as long as the ductus arteriosus is open (Figure A). The SpO_2 values as well as the physical examination can then be normal in this situation. However, upon closure of the ductus arteriosus, this extra lumen at the aortic end of the ductus disappears and the flow to the descending aorta is compromised (Figure B), causing poor circulation in the lower body,

severe acidosis and circulatory failure.[39] Furthermore, there are theories of extending ductal tissue in the aortic arch, which cause constriction upon ductal closure.[40] For these reasons, PO screening is not the optimal screening tool to detect CoA.

Figure 1. Pathophysiology of coarctation of the aorta and clinical deterioration upon ductal closure.



Source: Park, Pediatric Cardiology for Practitioners, 5th edition 2008, page 259.

Comparison with other studies

Several studies on PO screening in hospital were performed which led to implementation in many countries. We performed the first studies, including a feasibility study and a large implementation study, with an adapted protocol for PO screening in a perinatal care system with home births and early postnatal discharge from hospital. Smaller pilot studies on PO screening out-of-hospital settings were performed in the United Kingdom (n=90) and in the plain community in Wisconsin (n=440).[41, 42] In the Netherlands, only women with low-risk pregnancies can choose for home births, while in the plain community in Wisconsin place of birth is not selected based on risk profile. Instead it is culturally, religiously or financially based and many pregnant women in the plain community do not perform prenatal screening. The detection of CCHD in this group will probably be higher when compared to our population of home birth deliveries.

This was the first screening set up where two separate screening moments were used. Also, the first screening moment was earlier when compared to other early screening studies.[8, 30] In general it is not recommended to perform PO screening in the first hours after birth, because of the probability of having a higher FP rate due to transitional circulation. In our Leiden pilot study however we demonstrated that SpO_2 values in healthy newborns were above 95% within the first hour of life.[20] In the POLAR study we demonstrated that in 65% of FP screenings obtained in the first hours were due to significant non-cardiac pathology, which is consistent with other early screening studies.[38, 43] he true FP screening rate, defined as the percentage of positive screenings without the presence of an underlying condition explaining cyanosis was 0.36% (87/23,959) in the POLAR study, which was comparable to other studies.[38, 43]

The costs of PO screening are higher in our setting, when compared to other studies. This can be explained by the work time needed for two screening moments, but mostly by supplying all community midwives with PO devices. The amount of screenings per device is higher in hospitals, where only two or three devices were needed to screen all babies born, while the amount of births and childbeds supervised per midwife is lower. However, guidelines of the Dutch Association of Pediatrics (NVK) already recommend the use of PO in case of resuscitation, and the usefulness in suboptimal neonatal clinical conditions was endorsed by community midwives in the Leiden region.[14] Incorporation of PO devices in community midwifery could therefore purpose for more than only CCHD screening.

Strengths and limitations of the studies

After publication of the meta-analysis of 13 studies assessing accuracy on PO screening and recognition of implementation of the screening in many countries, we acknowledged the need to assess the feasibility and accuracy of the screening in the Dutch perinatal care setting.[7, 8, 44] concluded that the Netherlands could not lack behind in a proven neonatal screening that detects life threatening conditions because of logistic barriers. We managed to adapt the international protocol to the working schema of community midwives, while it remained suitable for secondary and tertiary hospital settings as well. In order to do this, we discussed the best protocol options with community midwives, paediatricians, obstetricians and paediatric cardiologists. The implementation in clinical practice in different care paths and disciplines without the need for extra personnel is a strength of our studies. Furthermore, we studied different aspects of PO screening in our unique perinatal care setting, including feasibility, accuracy, costs and acceptability to mothers. These aspects can be considered in decision making regarding universal or regional screening policy.

A limitation was the high rate of incomplete screening moments in the implementation study. We did not foresee this as the pilot study in the Leiden region was very successful in

completing the screening. There are a few explanations for these incomplete screenings. In retrospect, we were more often dealing with postnatal discharges to non-participating practices outside the studied region. Also, fusions between hospitals and transition from paper to electronic patient files occurred during the study period, which increased the work load for obstetric nurses and research could have had less priority. In addition, an opt-out procedure could have caused less responsibility to perform the screening compared to the feasibility study where parents gave written consent. Nevertheless, we were able to screen more than ten percent of the annual birth rate in the Netherlands and it is likely that the incomplete screening rate will be reduced in case of national implementation, when it becomes standard care.

In the acceptability study, we were unable to compare the results between true negative, FP, true positive and false negative screenings, because of the anonymity in the web-based questionnaire and the absence of true positive and false negative screenings in the pilot study in the Leiden region. However, the overall acceptability was high: 93% of mothers would recommend the screening to others.

The control group in the cost analysis was a retrospective cohort from 2012, which makes it more difficult to compare the situation with and without PO screening. Furthermore, long term benefits in outcome and costs were not available for our cohort. However, it is known from other studies that the outcome of newborns with prenatal detection is better when compared to a late, symptomatic diagnosis of CCHD. Also, the societal and medical costs on long term are likely to be less in case of timely detection.[10, 24]

Wilson and Jungner criteria for universal screening

In 1968 Wilson and Jungner published screening criteria in a World Health Organisation report.[45] These criteria were developed to guide the selection of conditions for which universal screening is suitable. Below we will discuss the criteria when it comes to PO screening in the Dutch perinatal care setting.

1. **The condition sought should be an important health problem.**
   Congenital heart defects (CHD) are the most common congenital malformations and contribute to 3-7.5% of all infant mortality. CCHD occurs in approximately 2 per 1,000 newborns and without timely medical intervention newborns with CCHD will die within their first month of life.[46-48]
2. **There should be an accepted treatment for patients with recognised disease.**
   Timely treatment with prostaglandins, catheter and surgical interventions have considerably improved the outcome of newborns with CCHD. These treatments are well established.

3. **Facilities for diagnosis and treatment should be available.**
   Echocardiography performed by paediatric cardiologists and specialised paediatricians is available in all academic hospitals and in some regional hospitals. Newborns can be referred if echocardiography is necessary. Prostaglandin can be started in all hospitals and surgical or catheter treatments of CCHD is available in specialised CHD centers.
4. **There should be a recognizable latent or early symptomatic stage.**
   Cyanosis and symptoms of tachydyspnea are present before the acute cardiovascular collapse. However, these symptoms are not always recognised with physical examination.[6, 39]
5. **There should be a suitable test or examination.**
   PO screening detects 70% of all CCHD and 50% if prenatal detected cases of CCHD are excluded. Addition of PO to the existing fetal anomaly scan and postnatal examination increases the rate of timely detection of CCHD from 79% to 89%.[22]
6. **The test should be acceptable to the population.**
   PO screening was proven to be acceptable to mothers in hospital setting before, and we demonstrated the acceptability of the screening to mothers when performed at home by community midwives.[11, 21]
7. **The natural history of the condition, including development from latent to declared disease, should be adequately understood.**
   The pathophysiology and natural course of all CCHD is well understood.
8. **There should be an agreed policy on whom to treat as patients.**
   The diagnosis of CCHD can be accurately made with echocardiography and all newborns with CCHD should be treated as patients.
9. **The costs of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.**
   PO screening in our setting costs less than €15 per newborn and €139.000 per CCHD case diagnosed with the screening. This is likely to be cost-effective on the long term.
10. **Case finding should be a continuous process and not a 'once and for all' project.**
    Case finding will be a continuous process when the screening would be universally implemented, since the incidence of CCHD remains stable.

Taking into account the results of this thesis and the above-mentioned criteria for universal screening, we conclude that PO screening to detect CCHD can and should be implemented in the Netherlands.

After finalising the studies, a large part of the caregivers did not want to await a governmental decision regarding top-down universal implementation, which can take several years. Bottom-up implementation has already begun in the studied region using the logistics that was set up for the study; the screening is continued in all but two participating hospitals in the POLAR study, as well as by 36% of all participating community midwifery practices, and this rate is still increasing. The perinatal caregivers in these hospitals and practices were convinced of the usefulness of PO screening.

GENERAL CONCLUSIONS

PO screening for CCHD is feasible to perform and acceptable to mothers in the Dutch perinatal care setting with an adapted protocol for home births and early postnatal discharge from hospital. The screening detects CCHD at an early symptomatic stage with the extra benefit of detecting other significant and potentially life-threatening morbidities, such as infections and respiratory pathology. Implementation of PO screening for CCHD and other morbidities has the potential to decrease infant morbidity and mortality and increase the safety of newborns born at home or discharged from hospital in the first hours of life. Based on the findings in this thesis a nation-wide implementation of the PO screening is recommended.

FUTURE PERSPECTIVES

When PO screening is implemented, regionally or nationwide, continuous auditing of screening results and outcome should be established. Therefore, a universal database for collection of the screening results is needed. Also, more knowledge on the long-term outcome of children with CCHD should be acquired, and the outcomes of the different detection pathways (prenatal, PO, physical examination, late diagnosis) should be compared. A follow-up program would be required for this, and with this information the long-term benefits can be assessed. Furthermore, technical improvements for performing the screening should be sought. For example, screening protocols and instructions can be incorporated in a software application of PO devices, and guide screening performers through the process. In this case, the screening result is automatically given by the device which can decrease protocol misinterpretation. The use of PO applications for mobile devices and tablets is also increasing and could be used for PO screening as well.

CoA remains difficult to detect both prenatally and postnatally with physical examination and PO screening. More research should be performed to enable timely diagnosis of this condition.

Screening newborns admitted at the NICU should also be considered when PO screening is implemented. Studies have been performed and showed that it is feasible to screen the NICU population before discharge, but the rate of FP screenings was high because of underlying pathology.[49, 50] Also, the timing of the screening should be considered in this special population. More studies are needed to assess PO screening at the NICU.

It is often difficult for parents, midwives and general practitioners to judge severity of diseases or symptoms in babies. Babies can suffer from a large variety of diseases, varying from mild to severe. A validated scoring system for parents and doctors has been developed in the 90s to quantify the severity from diseases in infants.[51-55] This scoring system, called BabyCheck, provides the parents and caregivers with an advice on time frame in which the baby should be referred. As was demonstrated in this thesis, a low SpO_2 can be a symptom in many different morbidities, such as infections, CHD and pulmonary pathology. The use of PO in combination with the BabyCheck scoring system could then provide an objective measure for parents, midwives and doctors to assess illness in babies. As a next step in improving care for babies we would like to assess the predictive value of a combined score of BabyCheck and PO in assessing severity of illnesses.

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CHAPTER 10

Summary
Nederlandse samenvatting

SUMMARY

Pulse oximetry (PO) screening for critical congenital heart defects (CCHD) was proven to be an effective, acceptable and cost-effective screening method in hospital setting. For this reason, the screening has been implemented in many countries across the world. However, these factors are currently unknown for the Dutch perinatal care system with a high home birth rate and early discharge from hospital after uncomplicated deliveries.

The general aim of this thesis was to assess the feasibility, accuracy, acceptability and costs of PO screening for CCHD with a protocol that is adapted to the Dutch perinatal care system. We also aimed to assess the rate of detection of other pathologies by PO screening, such as infections and respiratory pathology.

Chapter 2 provides an overview of all aspects of PO screening that need to be considered before implementing it in a specific setting. In this narrative review we concluded that the screening is effective, simple, quick, reliable, cost-effective, and does not lead to extra burden for parents and caregivers. However, test accuracy is influenced by several factors. For example, early timing of screening is accompanied with an increase in false positive (FP) screenings, but has the advantage to detect pathology in an earlier stage, preventing worse outcome. Furthermore, in 35-74% of the FP screenings significant non-CCHD pathology is diagnosed. When a pre-ductal measurement is added more cases of CCHD will be identified when compared to measuring post-ductal SpO_2 only. More FP screenings are obtained at higher altitudes when using the same cut-off values as used at (near) sea level. It is feasible to screen newborns at Neonatal Intensive Care Units and newborns born out-of-hospital, but the accuracy in these settings should be further investigated. The quality of PO screening for CCHD can be optimised by training caregivers, simplifying the algorithm, and using computer-based interpretation tools.

It is important to consider all the above-mentioned aspects when choosing an optimal screening protocol for implementation in a specific setting.

In **Chapter 3** we describe our protocol for PO screening for CCHD that was adapted to the Dutch perinatal care setting, with home births and early postnatal discharge. International screening protocols were adjusted to fit the working schema of community midwives.
Two time points for pre- and post-ductal SpO_2 measurements were used: at least one hour after birth and on day two or three. If the pre- or post-ductal SpO_2 at the measurement one hour after birth is <90%, the screening test is considered positive. In case of a repeated measurement with one hour interval with pre- and post-ductal SpO_2 <95% or a difference between

pre- and post-ductal SpO_2 of >3%, the screening test is also considered positive. If the pre- or post-ductal SpO_2 is ≥ 95% and the difference between pre- and post-ductal SpO_2 is ≤ 3%, the screening test will be repeated on day two or three. The screening test on day two or three of life is considered positive if the pre- and post-ductal SpO_2 are <95% or if the difference between pre- and post-ductal SpO_2 is >3%. Newborns with positive screenings are referred for paediatric assessment and an echocardiogram is performed in case of persistent abnormal SpO_2 values. The protocol we provided might also be useful for other countries with home births or early discharge from hospital.

Chapter 4 reports the results of a pilot study of the adapted protocol described in chapter 3, performed in the Leiden region. Primary outcome in this feasibility study was the percentage of screened newborns with parental consent. We also registered the time point of screening, distribution of SpO_2, FP screenings, and detection of CCHD and other pathology. With the adapted protocol PO screening was performed in 3,059/3,090 (99%) newborns for whom parental consent was obtained. Median (IQR) time points of the first and second screening were 1.8 (1.3-2.8) and 37 (27-47) hours after birth. We observed that the median (IQR) pre- and post-ductal SpO_2 in the 394 newborns with screening within one hour after birth were 99% (98-100%) and 99% (97-100%). No CCHD was detected or missed. The FP rate was 1.0% overall (0.6% in the first hours after birth), but significant non-CCHD pathology, such as non-critical CHD, infections and respiratory pathology, was found in 62% of the FP screenings. We concluded that PO screening for CCHD with this adapted protocol is feasible after home births and early postnatal discharge from hospital. The screening detected important neonatal pathology at an early stage, which has the potential to increase the safety of home births and early discharge policy after delivery in hospital.

After demonstrating the feasibility, the objective of the study described in **Chapter 5** was to assess the accuracy of PO screening in the Dutch perinatal care setting in a larger implementation study. In order to reduce the FP rate on day two or three, a repeat measurement was added to this screening moment if the pre- and post-ductal SpO_2 were <95% and/or if there was a pre-post-ductal difference of >3%. Also, an echocardiogram was only indicated in case of persistent abnormal SpO_2 values in the absence of a non-cardiac explanation.

We analysed two cohorts: the first cohort also included newborns with a prenatal diagnosis of CCHD and with symptoms of CCHD before screening took place. In this cohort of 23,996 newborns PO screening detected CCHD with a sensitivity of 70.2% (95%CI 56.0-81.4) and specificity of 99.1% (95%CI 99.0-99.2). The prenatal detection rate of CCHD was 73%. In cohort two these prenatal detected cases as well as symptomatic CCHD were excluded. In this

second cohort 23,959 newborns were screened. The sensitivity of PO screening for CCHD in this second cohort was 50.0% (95%CI 23.7-76.3), with a specificity of 99.1% (95%CI 99.0-99.2). The screening was FP for CCHD in 221 newborns, of which 61% had other serious illnesses, including infections and respiratory pathology.

Our findings implicate that PO screening with an adapted protocol for home births and early postnatal hospital discharge detects CCHD, but the sensitivity was moderate because of a high prenatal detection in our study. The early detection of other significant pathology in newborns enables early treatment and can reduce morbidity and mortality in newborns as well.

In **Chapter 6** we presented the results of the cost-effective analysis of PO screening for CCHD in the Dutch perinatal care setting using the adapted protocol. We used the data from the implementation study as well as input from other sources. The screening costs €14,71 per newborn or €139,000 per timely detected CCHD with PO screening, in comparison with the current practice of fetal anomaly scan and postnatal physical examination. PO screening in the Dutch care setting would be cost-effective if considerable savings in lifetime treatment and, or substantial gains in Quality Adjusted Life Years would be obtained per newborn timely diagnosed with PO screening. Additional studies on treatment costs, life expectancy and quality of life of children with CCHD are needed to conclude whether addition of PO screening is cost-effective in the Netherlands.

The maternal acceptability of PO screening in home setting was described in **Chapter 7**. The acceptability of the screening was already demonstrated in hospital setting, but we assessed this for screenings performed at home by community midwives in the Leiden pilot study by sending out an online questionnaire. The questionnaire included questions based on satisfaction, general feelings and perceptions of PO screening and was responded by 77% of approached mothers.

Overall, mothers were happy with the performance of the test (95%), thought their baby was comfortable during the screening (90%) and did not feel stressed while the screening was performed (92%). Most mothers would recommend the test to others (93%) and considered the test important for all babies (93%). We therefore concluded that PO screening performed at home is acceptable to mothers.

The objective of **Chapter 8** was to assess the differences of SpO_2 and heart rate between measurements with and without system messages at PO, and if reference ranges would change with inclusion of data with system messages. We observed that system messages occurred frequently (46% of 28,477 data points) in the first 10 minutes after birth and almost all (99.9%)

were caused by a low signal quality. Mean SpO_2 with system messages was lower ($p<0.001$), while SD of SpO_2 was similar to data without system messages. With system messages included, centile charts of SpO_2 are approximately 2% lower, but not more dispersed. Mean heart rate was also lower ($p<0.001$) and more dispersed ($p<0.001$) when system messages occurred. Centile charts of heart rate are lower and have increased variability when including system messages.

We concluded that during PO in term newborns at birth system messages occurred frequently. The findings implicate that SpO_2 measurements with low signal quality are reliable for monitoring a newborn's clinical condition. However, heart rate measurements with low signal quality might underestimate a newborn's heart rate.

Finally, in **Chapter 9** we discuss the results of our studies, draw general conclusions based on these results, and also discuss perspectives for future research. Based on the studies in this thesis we have shown that PO screening for CCHD after home births and early postnatal discharge with an adapted protocol is feasible and acceptable for mothers. The sensitivity was moderate, probably due to a high prenatal detection, with a high specificity. PO screening also detects other significant neonatal pathology in an early stage, such as infections and respiratory morbidity. This can be of extra importance for newborns who are at home already on the first day of life and could decrease infant mortality and morbidity. The screening is likely to be cost-effective in the Dutch perinatal care setting.

We conclude that PO screening in the Dutch perinatal care setting complies to the Wilson and Jungner screening criteria and we recommend that PO screening should be implemented as a universal screening in the Netherlands.

NEDERLANDSE SAMENVATTING

Studies hebben aangetoond dat neonatale screening door middel van saturatiemeting op kritische aangeboren hartafwijkingen (PO screening) effectief, acceptabel en kosteneffectief is als het uitgevoerd wordt in een ziekenhuissetting. Om die reden is de screening in veel landen op de wereld ingevoerd als standaardzorg voor pasgeborenen. Het is echter onbekend of de bovengenoemde factoren ook van toepassing zijn op het Nederlandse perinatale zorgsysteem, dat gekenmerkt wordt door een hoog percentage thuisbevallingen en vroeg ontslag van moeder en kind na een ongecompliceerde geboorte in het ziekenhuis.

De doelstelling van dit proefschrift was om de haalbaarheid, betrouwbaarheid, tevredenheid van moeders en kosten te evalueren voor PO screening met een protocol dat is aangepast aan het Nederlandse perinatale zorgsysteem. Daarnaast wilden we ook de detectie van andere pathologie, zoals infecties en respiratoire morbiditeit, door deze screening onderzoeken.

Hoofdstuk 2 geeft een overzicht van alle aspecten van PO screening die in overweging genomen moeten worden voordat de screening in een specifieke zorgsetting geïmplementeerd wordt. In dit literatuuroverzicht concludeerden we dat de screening effectief, eenvoudig, snel, betrouwbaar en kosteneffectief is, zonder dat het leidt tot extra belasting voor ouders en zorgverleners. De betrouwbaarheid van de test wordt beïnvloed door meerdere factoren; screening op een vroeger tijdstip gaat bijvoorbeeld gepaard met een stijging van het aantal fout-positieve screenings, maar heeft het voordeel om pathologie in een eerder stadium te detecteren en kan zo een slechtere uitkomst voorkomen. Daarnaast werd in 35-74% van de fout-positieve screenings andere pathologie dan kritische aangeboren hartafwijkingen gevonden. Wanneer naast een post-ductale saturatiemeting ook een pre-ductale meting wordt toegevoegd, worden meer kritische aangeboren hartafwijkingen opgespoord. Op grotere hoogte worden, bij gebruik van dezelfde afkapwaarden, meer fout-positieve screenings verkregen in vergelijking met screening op zeeniveau. Het is mogelijk om pasgeborenen op Neonatale Intensive Care Units of pasgeborenen die buiten het ziekenhuis zijn geboren te screenen, maar de betrouwbaarheid van de screening in deze specifieke settings moet uitgebreider onderzocht worden. De kwaliteit van PO screening kan worden geoptimaliseerd door de zorgverleners te trainen, het algoritme te simplificeren en door het gebruik van automatische interpretatiemiddelen. Het is belangrijk om alle bovengenoemde aspecten te overwegen bij het bepalen van een optimaal screeningsprotocol voor de implementatie in een specifiek zorgsysteem.

In **Hoofdstuk 3** beschrijven we ons protocol voor PO screening dat is aangepast aan het Nederlandse perinatale zorgsysteem met thuisbevallingen en vroeg ontslag na een bevalling in

het ziekenhuis. Internationale protocollen zijn hiervoor aangepast om aan te sluiten bij het werkschema van eerstelijns verloskundigen.

Op twee tijdstippen worden pre- en post-ductale saturatiemetingen verricht: minimaal een uur na de geboorte en op levensdag twee of drie. De screening op het eerste screeningsmoment is positief als 1) de pre- of post-ductale saturatie lager dan 90% is, of 2) er twee herhaalde metingen zijn met een uur interval waarbij de pre- en post-ductale saturatie lager dan 95% zijn of het verschil tussen beide groter dan 3% is. Als de pre- of post-ductale saturatie minimaal 95% is en het verschil tussen de metingen maximaal 3%, vindt herhaling van de metingen plaats op levensdag twee of drie. Bij dit tweede meetmoment is de screening afwijkend als de pre- en post-ductale saturaties lager dan 95% zijn of het verschil tussen de metingen groter dan 3% is. Alle pasgeborenen met een positieve screening worden verwezen naar de kinderarts voor beoordeling en een echocardiogram wordt gemaakt als de saturaties bij beoordeling door de kinderarts afwijkend blijven.

Het beschreven protocol kan ook van toepassing zijn voor andere landen met thuisbevallingen of vroeg ontslag na een ziekenhuisbevalling.

In **Hoofdstuk 4** worden de resultaten gerapporteerd van een haalbaarheidsstudie in de Leidse regio met het aangepaste protocol dat beschreven wordt in Hoofdstuk 3. De primaire uitkomst van dit onderzoek was het percentage van pasgeborenen, waarbij ouders toestemming hebben gegeven, waarbij de screening is uitgevoerd. Ook onderzochten we het tijdstip van de screening, de distributie van saturaties, de fout-positieve screenings en de detectie van kritische aangeboren hartafwijkingen en andere pathologie. Met het aangepaste protocol zijn 3059/3090 (99%) van de pasgeborenen gescreend waarbij toestemming van de ouders is verleend. Het mediane (IQR) tijdstip van de eerste en tweede screening was 1.8 (1.3-2.8) en 37 (27-47) uur na de geboorte. De mediane (IQR) pre- en post-ductale saturatie van de 394 pasgeborenen met screening binnen het eerste levensuur waren 99% (98-100%) en 99% (97-100%). Er werd geen kritische aangeboren hartafwijking gedetecteerd of gemist met de screening. Het percentage fout-positieve screenings was 1.0% (0.6% in de eerste uren na geboorte), maar significante pathologie (anders dan kritische aangeboren hartafwijkingen) werd gevonden in 62% van de fout-positieve screenings, waaronder niet-kritische aangeboren hartafwijkingen, infecties en respiratoire pathologie. We concludeerden dat PO screening met het aangepaste protocol haalbaar is na thuisbevallingen en vroeg ontslag na een ziekenhuisbevalling. De screening detecteerde belangrijke pathologie bij pasgeborenen in een vroeg stadium, wat potentieel de veiligheid kan verhogen van thuisbevalling en een vroeg ontslagbeleid na ziekenhuisbevallingen.

Na het aantonen van de haalbaarheid, was het doel van het onderzoek beschreven in **Hoofdstuk 5** om de diagnostische waarde van PO screening in het Nederlandse zorgsysteem te evalueren in een grotere implementatiestudie. Om het aantal fout-positieve uitslagen op levensdag twee of drie te verlagen, werd een herhaling van de meting toegevoegd bij dit screeningsmoment als de pre- en post-ductale saturatie lager dan 95% waren en/of het verschil tussen de pre- en post-ductale saturatie groter dan 3% was. Ook was een echocardiogram alleen geïndiceerd in het geval van persisterend abnormale saturaties zonder een duidelijke non-cardiale verklaring.

Twee cohorten werden geanalyseerd: in het eerste cohort werden ook de pasgeborenen geïncludeerd met een prenatale diagnose van een kritische aangeboren hartafwijking of met symptomen die hierbij pasten direct na de geboorte. In dit cohort van 23,996 pasgeboren detecteerde PO screening kritische aangeboren hartafwijkingen met een sensitiviteit van 70.2% (95%BI 56.0-81.4) en specificiteit van 99.1% (95%BI 99.0-99.2). De prenatale detectiegraad van kritische aangeboren hartafwijkingen was 73%. In cohort twee, waarbij de prenataal gedetecteerde cases en symptomatische kritische aangeboren hartafwijkingen geëxcludeerd, werden 23,959 pasgeborenen gescreend met een sensitiviteit van 50.0% (95%BI 23.7-76.3) en een specificiteit van 99.1% (95%BI 99.0-99.2). De screening was fout-positief voor kritische aangeboren hartafwijkingen bij 221 pasgeborenen, waarvan 61% andere significante pathologie hadden, het merendeel daarvan waren infecties en respiratoire pathologie.

We concludeerden dat PO screening met een aangepast protocol voor thuisbevallingen en vroeg ontslag na een ziekenhuisbevalling kritische aangeboren hartafwijkingen detecteert, maar door een hoge prenatale detectie was de sensitiviteit gemiddeld. Door vroege detectie van andere significante pathologie bij pasgeborenen kan behandeling gestart worden in een vroeg stadium, wat potentieel de morbiditeit en mortaliteit bij pasgeborenen kan verlagen.

In **Hoofdstuk 6** beschrijven we de resultaten van een kosteneffectiviteitsanalyse van PO screening met het aangepaste protocol voor het Nederlandse perinatale zorgsysteem. We gebruikten hiervoor de gegevens van de implementatiestudie (Hoofdstuk 5) en input van andere studies. Per pasgeborene kost de screening €14,71 en de screening kost €139,000 per vroegtijdige detectie van één kritische aangeboren hartafwijking, ten opzichte van de huidige zorg, met de 20-weken echo en lichamelijk onderzoek na de geboorte. De screening zou kosteneffectief zijn in het Nederlandse zorgsysteem, indien er een substantiële winst in overleving, kosten voor behandeling en/of winst in Quality Adjusted Life Years verkregen wordt door tijdige diagnoses door de screening. Meer studies over deze uitkomsten zijn nodig om te concluderen of PO screening kosteneffectief is in Nederland.

De tevredenheid van moeders over PO screening thuis wordt beschreven in **Hoofdstuk 7.** De tevredenheid van de screening was al aangetoond in de ziekenhuissetting, maar we onderzochten dit nu voor de screenings die in de Leidse pilotstudie thuis werden uitgevoerd door eerstelijns verloskundigen. Hiervoor gebruikten we een online vragenlijst, die vragen bevatte over tevredenheid, algemene gevoelens en percepties over de PO screening. De vragenlijst is ingevuld door 77% van de moeders die benaderd zijn. Over het algemeen waren de moeders tevreden over de uitvoer van de test (95%), vonden ze dat hun baby comfortabel was tijdens de screening (90%) en voelden zij geen stress tijdens de uitvoering ervan (92%). Het merendeel van de moeders zou de test aanraden aan anderen (93%) en was van mening dat de test belangrijk is voor alle (ook andere) baby's (93%). We concludeerden daarom dat het thuis screenen van pasgeborenen op kritische aangeboren hartafwijkingen acceptabel is voor moeders.

De doelstelling van **Hoofdstuk 8** was om de verschillen tussen zuurstofsaturatie en hartfrequentie tussen metingen met en zonder systeemfoutmeldingen tijdens saturatiemetingen te evalueren, en om te onderzoeken om de referentiewaarden zouden veranderen als data met systeemfoutmeldingen geïncludeerd werden. Systeemfoutmeldingen kwamen vaak voor bij metingen van a termen in de eerste 10 minuten van het leven (bij 46% van de 28,477 datapunten) en deze werden bijna allemaal (99.9%) veroorzaakt door een lage signaalkwaliteit. De gemiddelde saturatie was lager bij data met systeemfoutmeldingen ($p<0.001$), terwijl de standaarddeviatie van de saturatie gelijk was aan data zonder systeemfoutmeldingen. Met inclusie van data met systeemfoutmeldingen waren de percentielgrafieken van zuurstofsaturatie ongeveer 2% lager, zonder een verschil in variabiliteit. De gemiddelde hartfrequentie was ook lager ($p<0.0001$) en meer verspreid ($p<0.001$) wanneer systeemfoutmeldingen zich voordeden. De percentielgrafieken van de hartfrequentie waren lager en toonden meer variabiliteit wanneer data met systeemfoutmeldingen werden geïncludeerd.

We concludeerden dat systeemfoutmeldingen frequent voorkwamen tijdens saturatiemeting van a terme pasgeborenen. De bevindingen impliceerden dat saturatiemetingen met lage signaalkwaliteit betrouwbaar zijn voor het monitoren van de klinische conditie van pasgeborenen. De metingen van de hartfrequentie met een lage signaalkwaliteit kunnen echter de hartfrequentie van een pasgeborene onderschatten.

Tenslotte bespreken we in **Hoofdstuk 9** de resultaten van onze studies, trekken daarbij algemene conclusies gebaseerd op deze resultaten en bespreken ook de perspectieven voor toekomstig onderzoek. Gebaseerd op de onderzoeken in dit proefschrift hebben we aangetoond dat PO screening om kritische aangeboren hartafwijkingen te detecteren haalbaar is en acceptabel voor moeders wanneer deze met een aangepast protocol wordt uitgevoerd na

thuisbevallingen en vroeg ontslag na een ziekenhuisbevalling. De sensitiviteit van de screening was gemiddeld, waarschijnlijk door een hoge prenatale detectiegraad, met een hoge specificiteit. PO screening detecteert ook andere significante neonatale pathologie in een vroeg stadium, zoals infecties en respiratoire morbiditeit. Dit kan extra belangrijk zijn voor pasgeborenen die al op de eerste levensdag thuis zijn en mogelijk kan deze screening de mortaliteit en morbiditeit onder pasgeborenen verlagen. Ook is de screening naar waarschijnlijkheid kosteneffectief in het Nederlandse zorgsysteem.

We concluderen dat PO screening in het Nederlandse zorgsysteem voldoet aan de Wilson and Jungner criteria voor universele screening en bevelen universele implementatie in Nederland aan.

APPENDIX

List of Abbreviations
Publications
Curriculum Vitae
Dankwoord

LIST OF ABBREVIATIONS

AVSD	Atrioventricular septal defect
BPM	Beats per minute
CAHAL	Center for congenital heart defects Amsterdam and Leiden
CCHD	Critical congenital heart defects
CHD	Congenital heart defects
CoA	Coarctation of the Aorta
F	Either foot
FN	False negative
FP	False positive
HR	Heart rate
KNOV	Koninklijke Nederlandse Organisatie van Verloskundigen
	Royal Dutch Organization of Midwives
LUMC	Leiden University Medical Center
NICU	Neonatal Intensive Care Unit
NVK	Nederlandse Vereniging van Kinderartsen
	Dutch Association of Pediatrics
PE	Physical examination
PO	Pulse oximetry / pulse oximeter
POLAR	Pulse Oximetry screening Leiden-Amsterdam Region
POLS	Pulse Oximetry Leiden Screening
PPHN	Persistent pulmonary hypertension of the newborn
PS	Pulmonary valve stenosis
RH	Right hand
QALY	Quality Adjusted Life Year
SIQ	Signal identification and quality
SpO_2	Peripheral oxygen saturation
SyM	System message
TAPVR	Total anomalous pulmonary venous return
TGA	Transposition of the great arteries
TTN	Transient tachypnea of the neonate
VSD	Ventricular septal defect
WTP	Willingness-to-pay

PUBLICATIONS

Narayen IC, te Pas AB, Blom NA, van den Akker-van Marle ME.
Cost-effectiveness analysis of pulse oximetry screening for critical congenital heart defects in a setting with home births and short postnatal stay after in-hospital delivery.
Submitted

Narayen IC, Blom NA, van Geloven Nan, Blankman EIM, van den Broek AJM, Bruijn M, Clur SAB, van den Dungen FA, Havers HM, van Laerhoven H, Mir SE, Muller MA, Polak OM, Rammeloo LAJ, Ramnath G, van der Schoor SRD, Kaam AH, te Pas AB on behalf of the POLAR study group.
Accuracy of pulse oximetry screening for critical congenital heart defects after home birth and early postnatal discharge.
Submitted and under review

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CURRICULUM VITAE

Ilona Christina Narayen was born on April 17th 1989 in Zoetermeer. A few weeks later she moved to Spaarndam with her parents, brother Yuri and sister Nadia, where she grew up. She graduated cum laude for grammar school at the Mendel college in Haarlem. Hereafter she studied Medicine at Leiden University, from which she graduated cum laude in 2013. After a clinical and scientifical internship at the Neonatal Intensive Care Unit of the Leiden Universitary Medical Center, she started as a PhD candidate at this department in December 2013, under supervision of dr. Arjan te Pas and prof.dr. Nico Blom. This thesis represents the research performed in that period.

Ilona has been a member of the European working group on pulse oximetry screening since 2014 and has been a board member of the Royal Dutch Medical Association in Leiden region since 2011.

Ilona married Siryl in September 2016 and on July 26th 2017 their daughter Julie was born.

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