Neonatal screening with pulse oximetry

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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.

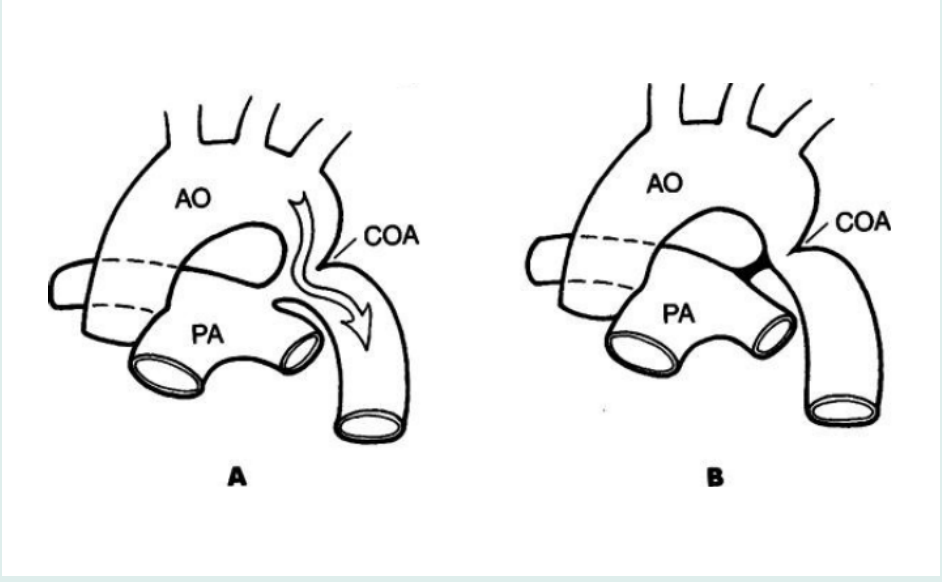
The early recognition of sepsis and respiratory morbidity by PO screening can be important in preventing worse outcome, and has the potential to reduce duration of hospitalisation and treatment, and importantly, neonatal morbidity and mortality.

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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