Neonatal Hyperbilirubinaemia

Moving towards screening and treatment in primary care

Berthe van der Geest

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1.

General introduction

Neonatal jaundice is a physiologic phenomenon that occurs in approximately 60-80% of healthy near term and term neonates.[1] It is caused by elevated unconjugated bilirubin levels and usually occurs during the first week of life.[2] Unconjugated bilirubin is a breakdown product of haem, which mainly originates from haemoglobin in erythrocytes.[3-7] Unconjugated bilirubin levels are elevated in almost all neonates, because synthesis of unconjugated bilirubin is increased, breakdown of unconjugated bilirubin in the liver is decreased, and enterohepatic circulation is increased (see Figure 1).[8-11] In most neonates elevated bilirubin levels resolve spontaneously and treatment is not necessary. However, in some neonates bilirubin levels are highly elevated due to pathologic causes. Increased haemolysis cause by ABO incompatibility is a common reason, but haemolysis may also be increased by Rh D antagonism, presence of other maternal alloantibodies (e.g. anti-Rhesus c, anti-Kell), or non-immune causes (erythrocyte membrane defects, erythrocyte enzyme defects, and α-thalassemia).[12] Extravasation of blood (e.g. caephal haematoma), sepsis, polycythaemia, and macrosomia related to maternal diabetes may increase unconjugated bilirubin production as well.[10] Uridine diphosphate glucuronosyltransferase Family 1 Member A1 (UGT1A1), the enzyme that facilitates breakdown of unconjugated bilirubin in the liver, is less present in preterm born neonates and in neonates with Gilbert's syndrome.[13,14] Additionally, ethnic variation is seen in polymorphisms that are associated with UGT1A1 activity.[15,16] In neonates having Crigler-Najjar syndrome, UGT1A1 is permanently deficient.[17,18]

KERNICTERUS SPECTRUM DISORDER

Unconjugated bilirubin is neurotoxic and may, if unconjugated bilirubin levels are severely elevated, be deposited into the basal ganglia and brainstem nuclei of the neonatal brain.[2,19] The brain damage resulting from this bilirubin-induced neurotoxicity is nowadays called 'kernicterus spectrum disorder' (KSD).[20] KSD is a spectrum of neurological sequelae, ranging from acute bilirubin encephalopathy to long term consequences, and also encompasses 'classical' kernicterus. Although KSD is preventable by timely recognition and treatment of potentially severe hyperbilirubinaemia, it still occurs.[21] Extreme hyperbilirubinaemia is relatively rare in high income countries with an incidence of 3.7 per 10,000 live births, but occurs much more frequently in low and middle income countries with an incidence of 244 per 10,000 live births.[22]

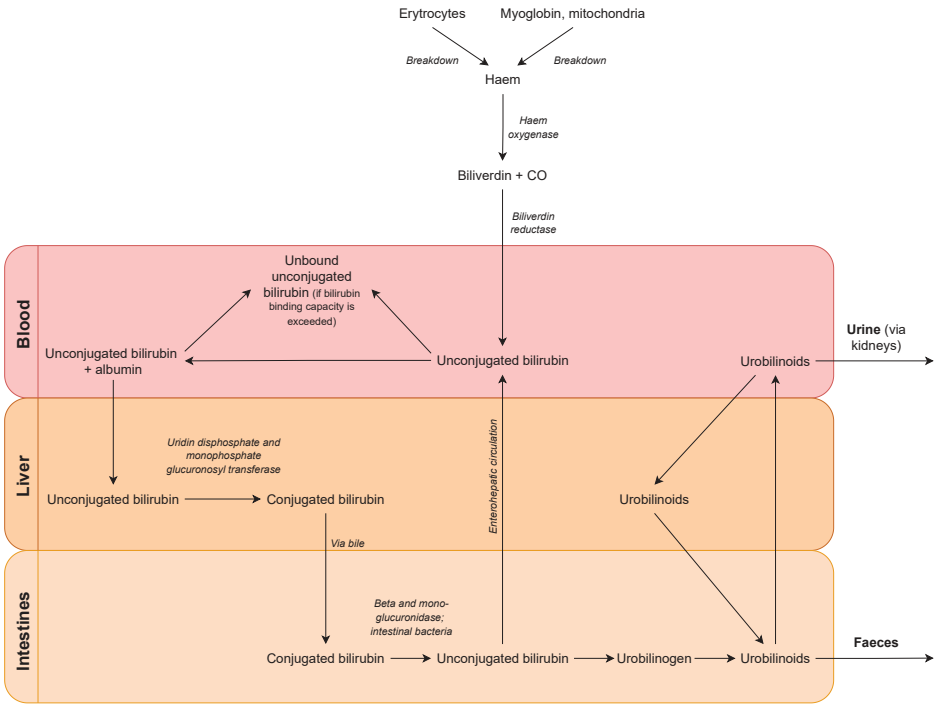

Figure 1. Bilirubin metabolism (adapted from Maisels 2006 and Dennery *et al*. 2001)[9,10]

RECOGNITION OF NEONATAL HYPERBILIRUBINAEMIA

The potential for lifelong disability makes a severely elevated unconjugated bilirubin level a serious threat to neonatal health and as such, this should be recognised and treated in time.[23] Traditionally and in most settings, screening for hyperbilirubinaemia is based on visual assessment. Deposition of bilirubin into the skin tissue leads to yellow discolouration of the skin (i.e. visible jaundice), which is often seen in neonates.[7] This discolouration is very roughly associated with bilirubin levels in the blood.[24] As the skin colour can be assessed non-invasively, screening methods are usually based on this visible aspect of neonatal hyperbilirubinaemia. Some countries have universal screening programmes in place based on a single total serum bilirubin (TSB) sample taken before discharge or during metabolic neonatal screening,[25-27] but usually TSB quantification is only performed if visual inspection is considered to indicate the need for it.

Visual inspection

Visual inspection of jaundice may raise suspicion of potentially severe neonatal hyperbilirubinaemia, but is unreliable in the prediction of TSB levels and thus in preventing KSD.[28] To objectify the degree of jaundice icterometers were developed. Icterometers are small Perspex rulers with reference stripes in different shades of yellow.[29] Although correlation between icterometer estimation and TSB is roughly moderate to good, it often does not provide a reliable measure of severity of neonatal hyperbilirubinaemia.[1,29-34]

Transcutaneous bilirubinometer

A transcutaneous bilirubinometer provides a total bilirubin level based on the amount of light absorbed by bilirubin in the skin (i.e. an algorithm converts the cutaneous and subcutaneous bilirubin into a total bilirubin level).[2,35] Nowadays, several transcutaneous bilirubinometers are commercially available and have been widely studied. Transcutaneous bilirubin (TcB) correlates well with TSB, but underestimation - especially at higher TSB levels - can occur.[36-41] The need for TSB quantification has been shown to decrease after implementation of selective TcB screening programmes in several studies.[37,42,43] Universal screening for neonatal hyperbilirubinaemia using a single TSB or TcB quantification (i.e. screening regardless of whether or not visual jaundice was observed) at a pre-set moment reduced the incidence of severe hyperbilirubinaemia in near term and term neonates in hospital and community settings.[42,44,45] However, Kuzniewicz *et al*. also showed that implementation of universal bilirubin screening resulted in a higher use of phototherapy.[44] Although transcutaneous bilirubinometers have been shown to be more reliable than visual inspection and to decrease the need for TSB sampling, they are not widely used yet. A significant barrier may be the high costs for purchasing and maintaining the devices, especially in primary care and low resource settings.

Smartphone applications

Mobile technology offers new opportunities to assess visual jaundice via a smartphone camera coupled to an application and may overcome the barrier of high costs of TcB quantification. The smartphone applications analyse the bio-optics (i.e. the discolouration) of the neonate's skin or sclerae. Some applications use a calibration card to account for variations in lightning condition.[46-50] Most studies investigated smartphone screening tools that assessed jaundice using a photograph of the neonatal sternum;[46-51] other studies used photographs of the forehead or sclerae.[52,53] Correlations between smartphone bilirubin estimation and TSB vary across different smartphone applications, but some showed good correlations.[46-53] Smartphone apps need to be improved and investigated further, but are a promising development towards objective and accessible non-invasive screening for neonatal hyperbilirubinaemia.

TREATMENT OF NEONATAL HYPERBILIRUBINAEMIA

Multiple treatment strategies for neonatal hyperbilirubinaemia have been developed and applied over the years. In this section, the treatment strategies currently considered as part of standard care are discussed.

Phototherapy

Phototherapy is the first choice of treatment if neonatal hyperbilirubinaemia is diagnosed.[2] The need for phototherapy is based on the TSB level, which is plotted on a postnatal age-specific nomogram and indicates the treatment threshold. Although phototherapy is typically provided during hospital admission, evidence suggests that it can be safely and effectively applied in primary care as well.[37,54-61]

Phototherapy reduces bilirubin levels in the skin and in the blood by exposure of the skin to light at wavelengths of 430-490 nm (i.e. blue light).[25,62] Following absorption of the blue light, unbound unconjugated bilirubin in the skin tissue and in the capillaries of the skin is converted into non-toxic breakdown products. These breakdown products are excreted through bile and urine.[63,64] An overview of the mechanism of phototherapy is depicted in Figure 2.

Phototherapy is a generally safe treatment to reduce bilirubin levels. However, phototherapy may be insufficient in reducing particularly high bilirubin levels in some neonates, who then need an exchange transfusion.

Exchange transfusion

An exchange transfusion is an invasive procedure in which the majority of blood of the neonate is replaced by reconstituted blood of a donor.[65] This reduces the TSB level rapidly by removing circulating bilirubin and antibody-coated erythrocytes.[2] The rapid decrease in bilirubin levels resulting from an exchange transfusion may reverse neurological symptoms, even in an intermediate phase.[66] Although exchange transfusions are important to rapidly decrease bilirubin levels and to avoid KSD, they are also associated with relatively high occurrence of adverse events. These may include sepsis, thrombocytopaenia, thrombosis or embolisms, hypoglycaemia, electrolyte imbalances, and necrotising enterocolitis.[65] Widespread implementation of phototherapy successfully reduced the number of neonates necessitating an exchange transfusion.[67] Nowadays, exchange transfusions are typically only performed in neonates having TSB levels close to or above exchange transfusion threshold and in whom phototherapy has failed to reduce bilirubin levels effectively or in neonates having acute clinical signs of KSD.[1,25]

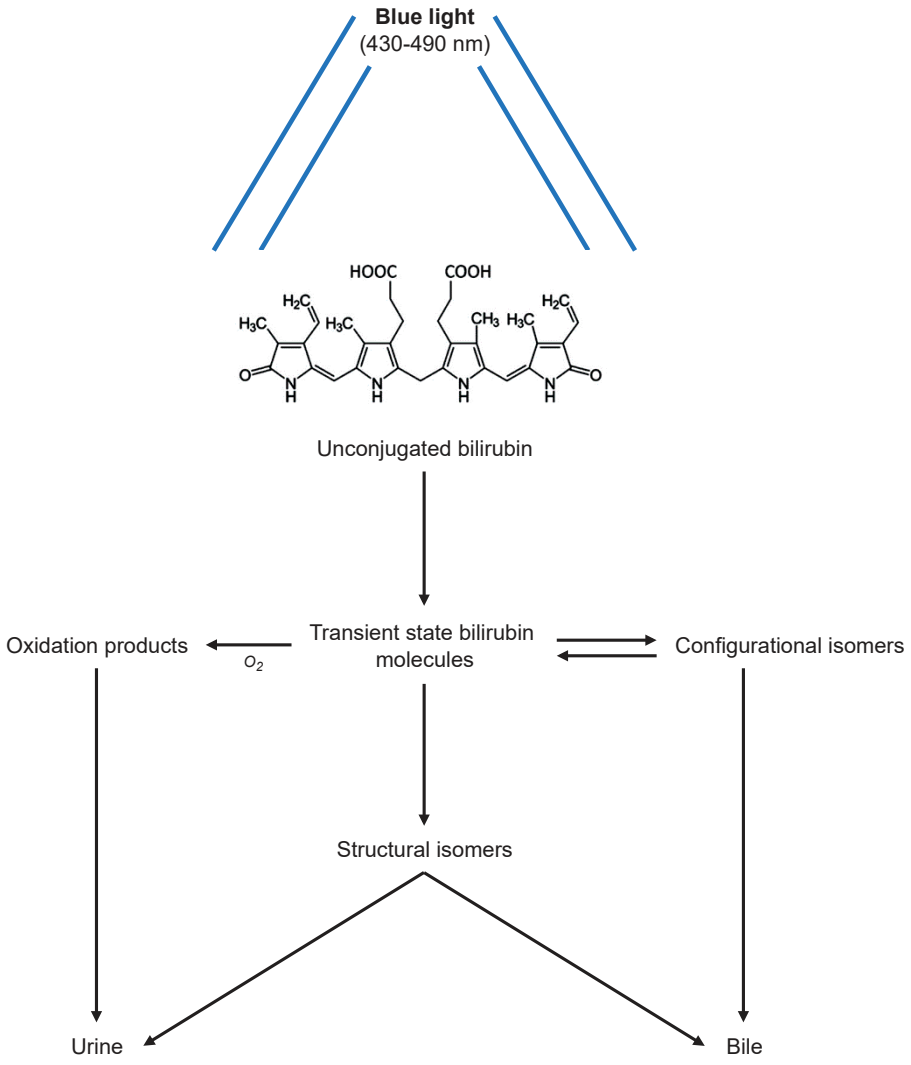

Figure 2. Mechanism of phototherapy (adapted from Maisels *et al*. 2008)[63]
Unconjugated bilirubin is converted into transient excited-state bilirubin molecules after absorption of blue light. These molecules can (1) react with oxygen and form colourless oxidation products (i.e. photo oxidation); (2) undergo rearrangement into structural isomers; or (3) undergo rearrangement to become configurational isomers. Structural isomerisation is irreversible, but slower than the reversible configurational isomerisation. The products of both isomerisation processes are less lipophilic than unbound unconjugated bilirubin and can be excreted via bile without glucuronidation. Configurational isomers convert back to unbound unconjugated unbound bilirubin when in the bile. Photo oxidation takes more time than isomer formation and products formed in this process are mainly excreted via urine. Structural isomers can also be excreted in urine.[63,64]

Intravenous immunoglobulin

Intravenous immunoglobulin (IVIg) may be used as an add-on therapy in neonates having severe hyperbilirubinaemia caused by alloimmune haemolytic disease (i.e. ABO or Rh antagonism).[2,68,69] IVIg is favoured over exchange transfusion, as it is less complicated, less labour intensive, and safer than exchange transfusions.[68] However, most neonates having alloimmune haemolytic disease can be treated with solely phototherapy and do not need IVIg.[70]

ASSESSMENT AND TREATMENT OF JAUNDICE IN THE DUTCH PERINATAL HEALTHCARE SYSTEM

In the Netherlands, more than 25% of women give birth in primary care and most women who gave birth in a hospital are discharged to primary care together with their neonate shortly after delivery.[71] As bilirubin levels usually peak between day 3 and 5 of life, most Dutch neonates are cared for in primary care then. In this setting, a community midwife holds responsibility for the mother-neonate dyad and visits them at least three time during the first week after delivery.[72] A maternity care assistant (MCA) provides daily postpartum care for at least three hours per day during the first eight days of life (i.e. in total at least 24 hours).[73] The MCA is supervised by the community midwife.

The MCA performs daily checks on the mother and the neonate. Visual inspection of neonatal jaundice, as advised by the national multidisciplinary guideline on hyperbilirubinaemia management,[74] is one of these checks. TcB quantification is not regularly used in primary care in the Netherlands, and a universal screening programme is absent. If hyperbilirubinaemia is suspected by the MCA (i.e. the neonate is considered 'too jaundiced'), the MCA is expected to consult the community midwife. The community midwife may decide to draw blood to quantify the neonate's TSB. The TSB level is then plotted on the Dutch TSB nomogram to determine the need for hyperbilirubinaemia treatment.[75] The need for treatment is based on TSB levels, combined with postnatal age and risk factors. If the TSB level exceeds the phototherapy treatment threshold or in case of another clinical problem regarding the neonate, the community midwife consults a paediatrician of a nearby hospital to decide whether phototherapy is indicated.

Recognition of potentially severe hyperbilirubinaemia in primary care in the Netherlands primarily relies on visual inspection. However, visual inspection is proven to be inaccurate to recognise potentially severe hyperbilirubinaemia.[28] Hence, diagnosis and treatment of hyperbilirubinaemia may be delayed, potentially exposing neonates un-

necessarily to dangerously elevated TSB levels. New strategies to improve recognition of potentially severe hyperbilirubinaemia in primary care are needed.

If a neonate needs hyperbilirubinaemia treatment and is admitted to the hospital, mother and child cannot always stay together. This is undesirable in terms of mother-child bonding and breastfeeding. Implementation of phototherapy in primary care may overcome the issue of mother-child separation and may reduce healthcare costs by avoiding hospital admission.

AIMS AND OUTLINE OF THIS THESIS

In this thesis, I describe several research projects aimed at assessing and improving current recognition and treatment of neonatal hyperbilirubinaemia in primary care. This includes a unique large-scale cluster randomised controlled trial evaluating screening and treatment of neonatal hyperbilirubinaemia in primary care.

The aims of this thesis are:

- To evaluate the extent of the problem of severe neonatal hyperbilirubinaemia in the Netherlands and assess contributing substandard care factors.
- To prospectively evaluate current practice of recognition of neonatal hyperbilirubinaemia in the primary care setting.
- To describe the rationale and design of a factorial stepped-wedge cluster randomised controlled trial to evaluate non-invasive universal screening for and treatment of neonatal hyperbilirubinaemia in primary care.
- To explore the facilitators and barriers of conducting this unique trial in a primary care setting and to describe the preliminary findings.
- To describe the rationale and design of a prospective cohort study evaluating screening for and diagnosis of neonatal hyperbilirubinaemia in the home setting.

Part one focuses on the problem of neonatal hyperbilirubinaemia in the Netherlands. Using data from the national perinatal audit, **Chapter 2** provides an overview of characteristics of neonates having severe neonatal hyperbilirubinaemia and associated substandard care factors that may have contributed to their condition. In a nationwide survey study described in **Chapter 3**, we evaluate the knowledge and skills of MCAs, who have an important role in recognising neonatal hyperbilirubinaemia.

Part two describes the Screening and TreAtment to Reduce Severe Hyperbilirubinaemia in Infants in Primary care (STARSHIP) Trial. This trial is the first randomised controlled

trial evaluating screening and treatment for neonatal hyperbilirubinaemia in primary care. **Chapter 4** describes the rationale for universal screening and treatment of neonatal hyperbilirubinaemia in primary care and the design of the STARSHIP Trial. In **Chapter 5**, we report the lessons learnt from conducting this unique trial with perinatal healthcare professionals in a primary care setting who previously had very little involvement in research. **Chapter 6** assesses standard practice in the assessment and management of neonatal hyperbilirubinaemia in healthy neonates cared for in primary care using data from the control phase of the STARSHIP Trial (i.e. when current standard practice was evaluated). In **Chapter 7**, we describe preliminary findings of the STARSHIP Trial, which at the time of writing was awaiting collection of the last data, by evaluating the effectiveness of implementing phototherapy in one of the seven participating primary care birth centres to avoid hospital admissions.

Part three describes next steps planned to further enhance screening for neonatal hyperbilirubinaemia in primary care, in particular the home setting. In **Chapter 8**, the rationale for and design of a prospective cohort study evaluating screening for and diagnosis of neonatal hyperbilirubinaemia at home is described.

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Part ONE

Neonatal hyperbilirubinaemia: a problem?

2.

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Severe neonatal hyperbilirubinaemia: Lessons learnt from a national perinatal audit

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ABSTRACT

Objectives To describe characteristics of neonates with severe neonatal hyperbilirubinaemia (SNH) and to gain more insight in improvable factors that may have contributed to the development of SNH.

Design and setting Descriptive study, based on national Dutch perinatal audit data on SNH from 2017 to 2019.

Patients Neonates, born after 35 weeks of gestation and without antenatally known severe blood group incompatibility, who developed hyperbilirubinaemia above the exchange transfusion threshold.

Main outcome measures Characteristics of neonates having SNH and corresponding improvable factors.

Results During the three-year period, 109 neonates met the eligibility criteria. ABO antagonism was the most frequent cause (43%). All neonates received intensive phototherapy and thirty neonates (28%) received an exchange transfusion. Improvable factors were mainly related to lack of knowledge, and poor adherence to the national hyperbilirubinaemia guideline, and to incomplete documentation and insufficient communication of the *a priori* hyperbilirubinaemia risk assessment among healthcare providers. *A priori* risk assessment, a key recommendation in the national hyperbilirubinaemia guideline, was documented in only six neonates (6%).

Conclusions SNH remains a serious threat to neonatal health in the Netherlands. ABO antagonism frequently underlies SNH. Lack of compliance to the national guideline including insufficient *a priori* hyperbilirubinaemia risk assessment, and communication among healthcare providers are important improvable factors. Implementation of universal bilirubin screening and better documentation of the risk of hyperbilirubinaemia may enhance early recognition of potentially dangerous neonatal jaundice.

INTRODUCTION

Severe neonatal hyperbilirubinaemia (SNH) is a known adverse outcome of the biologic phenomenon of elevated unconjugated bilirubin levels during the first days after birth. If SNH is left untreated, it may result in acute bilirubin encephalopathy (ABE) and may ultimately evolve further into kernicterus spectrum disorder (KSD).[1] Successful implementation of hyperbilirubinaemia management guidelines including universal or selective screening strategies, or *a priori* risk assessment and close follow up is key to reduce SNH.[2,3] A systems-based approach, such as a perinatal audit, is recommended to facilitate guideline implementation and change practice to ensure that SNH and imminent KSD are 'never-events'.[4] Unfortunately, SNH remains a global burden.[5,6] In the Netherlands, most neonates with SNH are born in a hospital, then discharged early, and subsequently readmitted from home (Supplementary Text Box 1).[6] The widespread reliance on visual jaundice assessment to identify potential SNH among neonates cared for at home may, among other factors, contribute to the persistent occurrence of SNH (Text Box 1).

Perinatal audits and hyperbilirubinaemia registries can be useful tools to improve the quality of perinatal care by identifying improvable factors and subsequently, formulating improvement actions by plan-do-check-act cycles. Results have already informed revision of the national guidelines and through doing so will optimise future quality of care.[7,8] Auditing case histories of neonates with SNH may help to identify whether care was given according to the national hyperbilirubinaemia guideline or not. The aim of this study was to gain more insight in improvable factors that contributed to SNH. We hypothesised that we would learn lessons from perinatal audits to improve diagnosis and quality of care for neonates with imminent SNH.

TEXT BOX 1: JAUNDICE ASSESSMENT IN THE NETHERLANDS

The Dutch neonatal hyperbilirubinaemia guideline recommends to document an *a priori* risk assessment for the development of hyperbilirubinaemia in every neonate before discharge from the hospital or primary care birth facility.[9] This *a priori* risk assessment is based on several risk factors, i.e. blood group antagonism; other haemolytic diseases; gestational age <38 weeks; (cephalic) haematomas; exclusive breastfeeding; siblings who received phototherapy (PT); large for gestational age associated with maternal diabetes; and East-Asian descent. The complete list of risk factors is freely available on www.babyzietgeel.nl (in Dutch). Neonates identified with an increased risk to develop hyperbilirubinaemia should be monitored more closely by all involved healthcare professionals.

Hence, it is of utmost importance that this risk assessment, one of the key recommendations of the national guideline, is documented clearly and communicated properly between different healthcare professionals.

Visual assessment of neonatal jaundice is one of the daily checks performed by the MCA.[10] Universal transcutaneous bilirubin or total serum bilirubin (TSB) screening is, in contrast to in other countries, not current practice in the Netherlands. If an MCA suspects hyperbilirubinaemia, the MCA is expected to inform the community midwife. The community midwife may decide to quantify TSB. A blood sample is then taken by the community midwife or a specialised home service, and sent to a laboratory. TSB test results are assessed by a laboratory specialist who informs the community midwife. If TSB exceeds the PT threshold (according to the Dutch nomogram, which is based on those of the American Academy of Pediatrics),[11] the neonate will be admitted to the hospital for treatment after consultation of a paediatrician. The Dutch hyperbilirubinaemia management guideline contains a flowchart on early recognition of hyperbilirubinaemia, including monitoring of high risk neonates (Flowchart 1 of the guideline).[9]

METHODS

Design

A descriptive study based on the national Perinatal Audit Assistant (PAA) database was conducted over a three-year period (2017-2019).

Setting

SNH was one of the pre-set themes of the nationwide perinatal audit from 1 January 2017 until 31 December 2019.[12,13] A case report is reviewed by the involved healthcare professionals during the audit meeting, and improvable factors are identified and improvement actions according to the plan-do-check-act cycle are initiated (Supplementary Text Box 2). An improvable factor is defined as care that deviates from professional requirements of standard care, national guidelines, or local protocols and that may negatively influence the outcome.[14]

Patients

Neonates were eligible for audit meetings on SNH if they:

- Were born after 35 weeks of gestation.
- Had SNH, i.e. a peak TSB level higher than the exchange transfusion (ET) threshold according to postnatal age and risk factors.[11]

Neonates were not eligible for audit meetings on SNH if they:

- Had hyperbilirubinaemia caused by antenatally known severe blood group incompatibility as defined by the national guideline.[15]
- Had a conjugated bilirubin level >10 µmol/L (>0.58 mg/dL) or >20% of TSB.

Variables, data collection and statistical analysis

All variables (Supplementary Table 1) were retrieved from the PAA database and exported to IBM SPSS Statistics (v25.0.0.1; IBM, New York, USA). Characteristics and improvable factors are summarised using descriptive statistics. Median and interquartile range (IQR) are shown for continuous, not normally distributed data. If the postnatal age of peak TSB was unknown, we assumed that peak TSB was reached at start of ET or, if no ET was performed, at start of PT. Missing data are presented in the results section.

Ethics

Perined manages data on behalf of the represented national professional organisations in obstetric and paediatric care. All data were anonymised. The Medical Research Ethics Committee of the University Medical Centre Groningen, the Netherlands, declared that this research was not subject to the Medical Research Involving Human Subjects Act (UMCG research register #202000584).

RESULTS

From 2017 to 2019, 507 perinatal audit meetings were convened. In total, 115 neonates with SNH were registered. Six cases were excluded from further analysis because they did not meet eligibility criteria. In total, 109 cases were used for further analysis (Figure 1).

The total number of live-born neonates with a gestational age ≥35+0 weeks in the Netherlands during the three-year study period was 475,901.[16] Accordingly, the incidence of SNH was 22.9 per 100,000 live-born neonates with a gestational age of 35 weeks or more.

Baseline characteristics

Table 1 shows the baseline characteristics of included neonates: 44 females and 65 males. Median gestational age was 38 weeks and 3 days (IQR 37+5 - 40+0). Median birth weight was 3300 grams (IQR 3000-3723). Most neonates were born vaginally and had blood group O, Rh D positive mothers. In seven neonates (6%) no maternity care was provided.

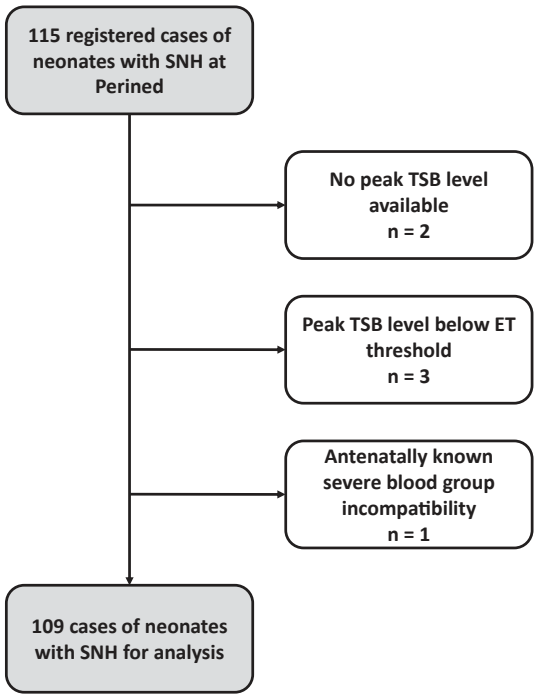

Figure 1. Flowchart of cases
ET, exchange transfusion; SNH, severe neonatal hyperbilirubinaemia; TSB, total serum bilirubin.
Flowchart made by first author (BAMG).

A priori risk assessment of hyperbilirubinaemia

Table 2 shows risk factors in neonates with SNH, listed as the *a priori* risk factors for developing SNH in the national guideline.[9] Approximately half of the neonates had blood group antagonism (defined as incompatible blood groups, with or without positive direct antiglobulin test), predominantly ABO, and most were breastfed. *A priori* hyperbilirubinaemia risk assessment was documented properly in the medical records of only 6 neonates (6%).

Hyperbilirubinaemia characteristics

Visual jaundice was noted for the first time at a median postnatal age of 42 hours (IQR 25-66; Table 3). Most neonates (76%) were (re)admitted from primary care after in-hospital birth and early discharge. The majority of neonates (67%) had a peak TSB level between 350 and 499 µmol/L. All neonates received intensive phototherapy (PT) and thirty neonates (28%) received one or more ETs at a median age of 55 hours (IQR 36-96). Nine neonates (9%) with peak TSB levels between 466 and 717 µmol/L had symptoms of ABE. Out of five neonates with clear symptoms of ABE, four neonates received an ET. Among the four neonates with mild symptoms of ABE, one neonate received an ET. ABO

antagonism was the commonest underlying cause of SNH (43%). Another important cause of SNH was dehydration (19%), defined as weight loss >7%. Eight (12%) out of sixty-seven neonates who received an (automated) auditory brainstem response test had an abnormal result. An MRI was performed in ten neonates, of which five (50%) had abnormalities (Supplementary Table 2). Five term-born neonates (5%) with peak TSB levels between 467 and 717 µmol/L had chronic bilirubin encephalopathy. Among the six excluded neonates, none received an ET, and MRI or (automated) auditory brainstem response test were not performed. Clinical follow-up was performed in three neonates: two were normal and one had mild abnormalities. It was unclear whether this was related to chronic bilirubin encephalopathy.

Table 1. Baseline characteristics

	Total (n=109)
Gestational age in weeks+days	38+3 (37+5 - 40+0)
<36 weeks	1 (1)
36 – 36+6 weeks	8 (7)
≥37 weeks	100 (92)
Female/male (%)	44/65 (40/60)
Birth weight in grams	3300 (3000-3723)
Place of birth	
Home	9 (8)
PCBC	10 (9)
Hospital, under supervision of community midwife	54 (50)
Hospital, medical indication	35 (32)
Unknown	1 (1)
Type of delivery	
Vaginal	98 (90)
Instrumental	8 (7)
C-section	3 (3)
Mother	
Parity	
Nulliparous	54 (50)
Multiparous	55 (50)
ABO blood group O	75 (69)
Rh D negative	16 (15)
Caucasian ethnicity	55 (51)
Unknown	1 (1)

Data are displayed as numbers (percentages) or medians (interquartile range). Due to rounding of percentages, some percentages may add up to 101%.
PCBC, primary care birth centre.

Table 2. A priori risk factors for hyperbilirubinaemia

	Total (n=109)
Risk assessment	
Documented	6 (6)
Not documented	90 (83)
Unknown	12 (11)
Missing	*1 (1)*
Gestational age	
<38 weeks	36 (33)
≥38 weeks	73 (67)
ABO antagonism	47 (43)
NO DAT test performed	2 (2)
Rh disease	3 (3)
Type of feeding	
Breastfeeding*	94 (86)
Exclusive formula feeding	15 (14)
Family history	
Having a multiparous mother and sibling(s) with hyperbilirubinaemia necessitating PT	23 (42)
Unknown	1 (1)
Missing	*1 (1)*
LGA after maternal diabetes	3 (3)

Data are displayed as numbers (percentages). Due to rounding of percentages, some percentages may add up to 101%. DAT, direct antiglobulin test; ET, exchange transfusion; LGA, large for gestational age (≥p90);[17] PT, phototherapy.
*Breastfeeding is defined as mothers who intended to give breastfeeding. Consequently, this group may also include neonates who were fed with a combination of breastfeeding and formula feeding, or who were temporarily formula fed.

Improvable factors

The PAA database included 147 improvable factors related to SNH (Table 4). In 33 neonates, no improvable factors related to SNH were formulated.

In total, 37 improvable factors (25%) were related to communication, 71 (48%) were related to knowledge deficits, which includes mainly deviation from the national guideline (n=56).[9] Twenty-three improvable factors (16%) were assessed as related to organisation of care.

Improvable factors represent a range of difficulties in observation and communication by both MCAs and community midwives, e.g. severity of jaundice was underestimated; no follow-up was provided in severe jaundice; neonates were not always assessed by the community midwife if an MCA reported severe jaundice; or the MCA did not mention the risks of SNH and urgent reasons for parents to ask for help outside working hours of the MCA. In eight out of twenty-three neonates having visual jaundice within 24 hours after

Table 3. Hyperbilirubinaemia characteristics

	Total (n=109)
Postnatal age in hours at first notion of jaundice[+]	42 (25-66)
Jaundice first recognised by*	
MCA	34 (31)
Community midwife	49 (45)
Nurse in hospital	16 (15)
Paediatrician	7 (6)
Parents	5 (4)
Unknown or missing	23 (23)
Encephalopathy	
Acute symptoms	9 (8)
Chronic symptoms	5 (5)
Peak TSB level	
<275 µmol/L	1 (1)
275-349 µmol/L	15 (14)
350-424 µmol/L	36 (33)
425-499 µmol/L	37 (34)
500-574 µmol/L	14 (13)
≥575 µmol/L	6 (6)
Age at peak TSB level (hours)	84 (48-111)
Admitted from primary care	83 (76)
Treatment	
PT	109 (100)
ET	30 (28)
Postnatal age in hours at:	
Start PT	77 (43-111)
Only PT (n=79)	92 (52-118)
PT and ET (n=30)	43 (27-90)
ET (n=30)	55 (36-96)
Presumed cause of hyperbilirubinaemia*	
ABO antagonism	47 (43)
Of which DAT positive	27 (57)
Rh disease	3 (3)
Of which DAT positive	3 (100)
Haemolytic anaemia	8 (7)
Related to prematurity	9 (8)
Dehydration	21 (19)
Of which breastfed	21 (100)
Birth trauma	1 (1)
Related to instrumental delivery	4 (4)

Table 3. Hyperbilirubinaemia characteristics (*continued*)

	Total (n=109)
Congenital hypothyroidism	1 (1)
Neonatal infection	2 (2)
(Suspicion of) inborn error of metabolism	2 (2)
Related to maternal diabetes	1 (1)
Delayed meconium passage	1 (1)
No cause identified	16 (15)
Missing	*1 (1)*

Data are displayed as numbers (percentages) or medians (interquartile range).
DAT, direct antiglobulin test; ET, exchange transfusion; MCA, maternity care assistant; PT, phototherapy; TSB, total serum bilirubin.
[+]Postnatal age at first notion of jaundice is missing in 5 neonates.
*Multiple answers possible.
Acute bilirubin encephalopathy is defined by internationally recognised criteria.[1] Chronic bilirubin encephalopathy is defined as neurological abnormalities at follow-up and a MRI of the brain with abnormalities.
ABO antagonism is defined as incompatibility of ABO blood groups.
Haemolytic anaemia is defined as hyperbilirubinaemia and evidence of haemolysis. This includes inherited erythrocyte cell membrane defects (e.g. spherocytosis, elliptocytosis), erythrocyte enzyme deficiencies (e.g. glucose-6-phosphate dehydrogenase deficiency, pyruvate kinase deficiency), and ABO or Rh disease combined with anaemia.
Prematurity was defined as born before 37 complete weeks of gestation with a gestational age based on early ultrasonography.

birth, this was not communicated to the community midwife or the community midwife was not aware of the urgent need for TSB quantification.

A priori hyperbilirubinaemia risk assessment was not documented in 90 neonates (Table 2), this was recorded as an improvable factor in only 24 cases. Lacking medical history regarding hyperbilirubinaemia of siblings, was reported as an improvable factor in five neonates, but occurred in 23 cases.

The process of TSB quantification itself led to delays of at least several hours in diagnosis of SNH. Sixteen improvable factors in the category organisation of care refer to a delay between quantification of TSB and report of the result. Nine improvable factors mention a delay in referral to the hospital or in start of treatment after report of the TSB result. Delays mainly occurred if the blood draw for TSB quantification was done at home. Other delays occurred when the urgency of hospital admission was not clear to the community midwife or to the parents. Also, delays happened after admission, e.g. TSB results remained unnoticed or blood for ET was not ordered.

Table 4. Improvable factors

	Total (n=147)
Improvable factors per case	1 (0-2)
Type of improvable factor*	
Communication	**37 (25)**
Insufficient communication	27 (18)
Insufficient documentation of PAA database variables	10 (7)
Knowledge deficit	**71 (48)**
Deviation from standard care	3 (2)
Deviation from national guideline neonatal hyperbilirubinaemia[9]	56 (38)
Deviation from local guidelines	4 (3)
Other	8 (5)
Organisation of care	**23 (16)**
Delay	10 (7)
Organisational problems	11 (7)
Insufficient testing	2 (1)
Other[+]	**18 (12)**
Category missing	*8 (5)*

Data are displayed as numbers (percentages) or medians (interquartile range).
*Multiple options per improvable factor possible.
[+]Improvable factors in this category included not having transcutaneous bilirubinometry, but also discrepancy in postnatal age calculation.
Some problems regarding delayed recognition of jaundice (e.g. if parents considered their neonate jaundiced, but no action was taken) were categorised in this category as well.

DISCUSSION

This study describes patient characteristics of 109 (near) term neonates who suffered from SNH and associated improvable factors as identified by perinatal audits. The incidence of SNH was 22.9 per 100,000 live-born neonates. In total, 8% of neonates had symptoms of ABE and ET was performed in 28%. At least five children developed chronic bilirubin encephalopathy. The main identified cause was ABO antagonism, of whom 57% had a positive direct antiglobulin test. Improvable factors revealed during audit meetings were mainly related to lack of compliance to the national guideline. This may reflect a knowledge deficit in the large majority perinatal healthcare professionals. Although *a priori* hyperbilirubinaemia risk assessment was very rarely documented, this was mostly not mentioned as improvable factor. Difficulties in communication and observation, and delay in TSB quantification were also frequently identified as improvable factors.

To the best of our knowledge, the Netherlands is the first country with a nationwide perinatal audit regarding neonatal hyperbilirubinaemia. The improvable factors that have been formulated in the audit meetings offer opportunities for improvement actions regarding timely recognition, diagnosis, and treatment of SNH. We consider the results of this study generalisable to other countries as well. Despite the different approaches in various countries to identify neonates at risk for developing severe hyperbilirubinaemia, timely detection of jaundiced neonates who need treatment remains a global deficit in all care practices.[5,8,18] The perinatal audit database is not a formal registry, and as such, underreporting is likely. Unfortunately, follow-up on improvement actions was not documented, and definitions of diagnoses and many laboratory tests were not recorded in the PAA database. Using an ICD classification and addition of few more obligatory characteristics will probably increase the appropriateness of this database for future studies.[19] Inherent to the retrospective nature of the analyses, some data were missing.

It appeared that less neonates in our study were born after instrumental delivery or a C-section than nationally (3% vs. 15-16%).[16] In line with previous studies, there was a slight male preponderance in neonates with SNH (60% vs. 51% nationally), and an overrepresentation of neonates with a non-Caucasian mother: 48% in our study vs. 13% nationally.[6,16,20-22] Seven mothers did not receive maternity care, of whom six were non-Caucasian. Lack of maternity care and the perceived difficulty of visual assessment of jaundice in non-White neonates may delay timely recognition of SNH.[23] Additionally, ABO blood group frequencies and incompatibilities, and other haemolytic diseases differ between ethnic groups.[24]

Our findings indicate that the *a priori* risk assessment for hyperbilirubinaemia is hardly ever documented in the medical records of neonates with SNH. Since 2008, *a priori* risk assessment, including documentation and communication, and close monitoring of neonates are key recommendations in the Dutch management guideline on hyperbilirubinaemia.[9] Our data indicate that this recommendation of the national guideline is not known or not adopted in clinical practice in 94% of the reported SNH cases. This concerning high percentage needs more extensive root cause analyses and consequently targeted implementation strategies. A long interval between the first notion of jaundice and initiation of treatment was observed in analogy to data from Rennie *et al*. who examined claims involving neonatal jaundice.[22] Visual inspection of jaundice is neither objective, nor accurate.[25-28] Additionally, and especially in the home setting, it may take several hours before TSB test result is obtained. Other potential explanations for the delay may be a wait-and-see approach and underestimation of the severity of hyperbilirubinaemia and its potential consequences in otherwise healthy neonates, which has also been shown in a nationwide survey among MCAs.[29] ET was performed

in only 28% of the neonates, whereas all neonates had a TSB level above ET threshold. This may be declared by the time needed to prepare an ET and the TSB reduction of TSB by intensive PT.

Improvable factors were registered in 76 neonates (70%). Remarkably, the lack of the *a priori* risk assessment of SNH was mostly not even documented as improvable factor. This may indicate a widespread lack of awareness, or lack of acknowledgement, of the importance of the *a priori* risk assessment or a knowledge deficit on this specific recommendation. This is important because universal bilirubin screening was not adopted in the Dutch guideline, since it was assumed that well-organised follow-up in the Dutch perinatal care system would guarantee the early recognition of imminent severe hyperbilirubinaemia.[9]
Deviation from guidelines seems a perennial issue. Alkén *et al*. showed that non-adherence resulted in kernicterus, whereas this could have been avoided in 11 neonates.[21] The importance of adherence to guidelines is underlined by Canadian data. Sgro *et al*. showed a reduction in incidence rates of SNH after implementation of a national hyperbilirubinaemia guideline.[30]
Additional examination and long-term follow-up were not performed in a substantial proportion of the neonates in our study. Whereas one might consider this as substandard care, recommendations on follow-up investigation after SNH are not part of the current guideline.[9]

We recommend, according to guidelines in other countries and advocated by other researchers, to add universal bilirubin screening using transcutaneous bilirubin or TSB measurement to the *a priori* risk assessment in the upcoming update of the next national guideline.[31,32] This may also shorten the time interval between first notion of jaundice and start of treatment. Another possible improvement action is the incorporation of a standard sentence in the (electronic) medical records that indicates whether the risk of developing hyperbilirubinaemia is normal or increased. Difficulties in communication between healthcare professionals and delays in the process of TSB quantification should be obviated by clear standard operating procedures (SOPs) in the local obstetric care networks and adequate adherence to these procedures. SNH should remain an event in which improvable factors are identified and improvement actions are formulated in a multidisciplinary setting, for example during a complication or critical incident review meeting.
Future research should focus on novel, preferably accessible and non-invasive, approaches for early identification of jaundice and underlying mechanisms regarding improvable factors.

CONCLUSIONS

Although SNH is largely preventable, it is still present in the Netherlands. Perinatal audit meetings are important to help identify improvable factors and formulate improvement actions (Text Box 2). Our data indicate that timely recognition – including universal bilirubin screening, improving knowledge, communication, acceptance and compliance to hyperbilirubinaemia guidelines – may reduce the occurrence of SNH.

TEXT BOX 2: OVERVIEW OF RECOMMENDATIONS

Communication and knowledge

- Implement universal transcutaneous bilirubin screening at a predefined time and act upon outcome of this screening.
- Facilitate documentation and communication of *a priori* risk assessment for hyperbilirubinaemia. For example, incorporate a standard sentence in the (electronic) medical records that indicates whether the *a priori* risk of developing neonatal hyperbilirubinaemia is normal or increased.
- Healthcare providers should accept and agree on local standard operating procedures regarding neonatal jaundice in primary care. These standard operating procedures should, among others, include responsibilities and timelines for the process of recognition of jaundice, total serum bilirubin quantification, obtaining the total serum bilirubin result, and hospital admission.
- Define severe neonatal hyperbilirubinaemia as an event in which improvable factors should always be identified and reviewed multidisciplinary at a pre-set moment. The paediatrician should hold responsibility for this process.

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SUPPLEMENTARY FILES

SUPPLEMENTARY TEXT BOX 1: ORGANISATION OF THE DUTCH PERINATAL CARE SYSTEM

In the Netherlands, a substantial proportion of healthy near term and term neonates are cared for in primary care, i.e. at home or in a primary care birth centre (PCBC), a 24/7 facility for postnatal care where babies and mothers (sometimes also partners) can stay up to eight days. Approximately 30% of women give birth in primary care and, additionally, many women who give birth in a hospital are discharged home or to a PCBC with their neonate within 24 hours.[1] Maternity care assistants (MCAs) provide daily care at home or in a PCBC for mother and neonate during the first eight days after birth.[2] A PCBC is a primary care delivery facility where MCAs are the primary care providers. PCBCs can be freestanding or affiliated with a hospital. Deliveries in the PCBC are supervised by community midwives. Some PCBCs also offer the possibility for women (and their partner) to spend the first few days of the postpartum period together with their baby in the facility (rather than at home). Both in a PCBC and at home a community midwife supervises the MCA and has the primary responsibility for mother and child. The community midwife visits the new family at least three times during the first week.[3] Both MCAs and community midwives have completed education on perinatal care, which also includes education on assessment and treatment of neonatal hyperbilirubinaemia according to the national multidisciplinary guideline on neonatal jaundice management. In case of a potential clinical problem, such as severe neonatal hyperbilirubinaemia, the community midwife will consult the paediatrician of a nearby hospital if treatment (phototherapy) is needed. Phototherapy is not provided in PCBCs.

SUPPLEMENTARY TEXT BOX 2: PERINATAL AUDIT

Perinatal audit meetings were introduced in the Netherlands by Perined in 2010. Perinatal audit meetings are biannual internal meetings (per obstetric care network (OCN)) in which provided care in cases that fall within one of the four pre-set themes is evaluated. The themes are determined by experts in perinatal healthcare and Perined, and change every two to three years.

Each audit meeting is prepared by a local team of an obstetrician, community midwife, clinical midwife, and paediatrician. A chronological report is constructed by the local team and registered in the Perinatal Audit Assistant (PAA) database. The report includes detailed information on maternal characteristics, obstetric history, and prenatal consultations, as well as a delivery report, data on the postpartum course, and maternal and neonatal follow up. The report is based on medical records kept by all involved perinatal healthcare professionals. The (presumed) causes of hyperbilirubinaemia are classified/categorised by the involved healthcare professionals. Additional laboratory tests are performed at the discretion of the involved healthcare professionals. Definition of diagnoses and documentation of the corresponding results are not included in the PAA database. Completeness of the data in PAA depends on the accuracy of medical record keeping of the involved healthcare professionals. The PAA database is managed by Perined.

For audit meetings, all perinatal healthcare professionals within an OCN (obstetricians, midwives, paediatricians, and obstetric nurses) are invited. During an audit meeting, usually two cases are evaluated. Every healthcare professional of an OCN may submit a case for evaluation. The local team decides which cases will be evaluated. Consequently, the PAA database is not a formal registry of all cases within a theme.

An audit meeting is chaired by an independent chair. All healthcare professionals involved in an OCN are invited to attend the meeting. Cases are anonymised and healthcare professionals involved in the case can stay anonymous as well. During an audit meeting, improvable factors are formulated. Every attendee may formulate a potential improvable factor or improvement action, but global consensus regarding (the formulation of) improvable factors and the corresponding improvement actions needs to be reached. After the audit meeting, improvable factors, their categorisation, responsible stakeholders, and improvement actions – according to the Plan-Do-Act principle, are registered in the PAA database by the local team. Feedback on the improvement actions is reported at the next perinatal audit meeting.

Supplementary Table 1. Variables used for analysis

Category	Variable
General characteristics	Year
	Number of SSFs
	Description of SSF
	Category of SSF
	Presence of maternity care
Maternal characteristics	Gestational age (days)
	Ethnicity Caucasian Non-Caucasian: North African; Other African (including Surinam/Antillean Creole); Turkish (including Kurdish); Hindu (including Surinam/Antillean Hindu); (Other) Asian; Latin American (including Surinam/Antillean other); Other (including mixed). Unknown
	ABO and Rh D blood group
	Parity
Delivery characteristics	Location and mode
Neonatal characteristics	Sex
	5' Apgar score
	Arterial umbilical cord pH
	Birth weight (grams)
	Birth percentile[4]
	Type of feeding
	Age at first discharge
Hyperbilirubinaemia characteristics	Hyperbilirubinaemia risk assessment
	Age at first notification of jaundice (hours)
	Person(s) who notified jaundice
	PT
	Age at start of PT (hours)
	Age at exceeding ET threshold (hours)[5]
	ET
	Age at first ET (hours)
	Highest TSB level
	Blood group antagonism
	DAT test
	Acute bilirubin encephalopathy
	Cause of hyperbilirubinaemia
	aABR
	MRI
	Age at discharge from hospital after treatment
	Follow-up

aABR, (automated) auditory brainstem response; DAT, direct antiglobulin test; ET, exchange transfusion; PT, phototherapy; SSF, substandard care factor.

Supplementary Table 2. Additional examinations

	Total (n=109)
(Automated) auditory brainstem response test performed	67 (61)
No abnormalities	59 (88)
Abnormalities	8 (12)
Not performed	39 (36)
Missing	*3 (3)*
MRI of brain performed	10 (9)
No abnormalities	5 (50)
Mild abnormalities	1 (10)
Kernicterus	4 (40)
Not performed	97 (89)
Missing	*2 (2)*

Data are displayed as numbers (percentages).
MRI, magnetic resonance imaging.

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Assessing knowledge and skills of maternity care professionals regarding neonatal hyperbilirubinaemia: a nationwide survey

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ABSTRACT

Background Neonatal hyperbilirubinaemia is a physiologic phenomenon, but, when severe, may cause lifelong disability. Maternity care assistants (MCAs) play an important role in timely recognition of severe neonatal jaundice. We assessed knowledge and skills of MCAs regarding neonatal hyperbilirubinaemia.

Methods All Dutch MCAs (n=9065) were invited to fill out a questionnaire assessing knowledge, expertise, and handling of neonatal jaundice. Additionally, we developed an e-learning and provided training sessions to a subgroup of MCAs (n=99), and assessed their knowledge on neonatal hyperbilirubinaemia before and after the training.

Results 1465 unique online questionnaires were completed (response 16.2%). The median number of correctly answered knowledge questions was 5 (out of six; IQR 1). Knowledge was significantly better when respondents had had in-service training on neonatal hyperbilirubinaemia in the previous year ($p=0.024$). Although 82% of respondents felt highly skilled or skilled to assess jaundice, accuracy of estimation of total serum bilirubin levels by assessing skin colour was generally poor and prone to underestimation. Participants who completed the e-learning had higher pre-training scores (5 (IQR 1) vs. 4 (IQR 2); $p<0.001$). The median post-training score was higher than pre-training (6 (IQR 1) vs. 5 (IQR 2); $p<0.001$).

Conclusions Background knowledge of MCAs regarding neonatal hyperbilirubinaemia was adequate, but can be improved by further training. Estimation of total serum bilirubin levels based on skin colour was often inadequate. Approaches to improve timely recognition of jaundiced neonates are needed.

BACKGROUND

Neonatal jaundice, caused by elevated total serum bilirubin (TSB) levels, occurs in approximately 60-80% of all live-born infants.[1] In Europe, 3.7 per 10,000 term and near term neonates develop severe hyperbilirubinaemia.[2] When TSB is highly elevated, bilirubin can cross the blood-brain barrier and may cause Kernicterus Spectrum Disorder (KSD).[3] Initially, KSD presents as acute bilirubin encephalopathy, which in severe cases may progress to 'classical kernicterus'. Although classical kernicterus is rare, consequences are severe and include motor dysfunction, visual and hearing impairment, seizures, and sometimes mental retardation.[4-6]

KSD and its devastating consequences are entirely preventable by timely recognition and treatment of potentially severe hyperbilirubinaemia. Some countries advise universal screening for neonatal hyperbilirubinaemia by quantifying TSB or transcutaneous bilirubin (TcB) levels at least once during the first week of life.[7] In most countries, including in the Netherlands, visual inspection by maternity care professionals is relied on as a first-line approach to identifying neonates requiring total bilirubin quantification.[8,9] However, visual estimation of jaundice is known to be inaccurate and therefore ineffective in preventing KSD.[8,10,11]

In the Netherlands, a significant proportion of neonates are born in a primary care setting or are discharged from the hospital within a few hours after birth.[12] A maternity care assistant (MCA, i.e. a skilled nurse with a lower secondary education degree) provides maternity care for the first eight days under supervision of a community midwife.[13] If potentially severe hyperbilirubinaemia is suspected, the MCA will consult the community midwife, who is responsible for the mother and the neonate. The community midwife may then decide to draw blood to have TSB quantified (usually in a laboratory of a nearby hospital). If the TSB level indicates the need for treatment (usually phototherapy) or in case of another potential clinical problem,[9] a paediatrician from a nearby hospital will be consulted. Traditionally, phototherapy is performed in the hospital.

Whereas theoretically entirely preventable, KSD still occurs in the Netherlands.[14] As MCAs have a first-line role in the recognition of potentially severe neonatal jaundice, we aimed to examine their current state of knowledge and skills regarding hyperbilirubinaemia. Accordingly, we propose recommendations for further training of maternity care professionals on the topic.

METHODS

Study design

We conducted a nationwide online survey among MCAs in the Netherlands to assess their knowledge regarding neonatal hyperbilirubinaemia and their skills regarding its assessment. In addition, from MCAs working in primary care and participating in training sessions provided as part of the Screening and TreAtment to Reduce Severe Hyperbilirubinaemia in Infants in Primary care (STARSHIP) Trial (NTR7187), we collected paper-based questionnaires assessing knowledge on hyperbilirubinaemia and on STARSHIP study procedures.[15] The STARSHIP Trial is an ongoing factorial stepped-wedge cluster randomised controlled trial aimed at assessing the effectiveness of (1) daily TcB screening to reduce the incidence of severe hyperbilirubinaemia, and (2) phototherapy provided in primary care birth centres to reduce the number of neonates admitted to hospital for hyperbilirubinaemia treatment.[15,16]

Setting

Nationwide online survey

The online survey was designed to assess the current state of knowledge on pathophysiology, risk factors, recognition and treatment of neonatal hyperbilirubinaemia, and professional experience with neonatal hyperbilirubinaemia of MCAs across the Netherlands. The nationwide survey was distributed via the Knowledge Centre of Maternity Care (*Kenniscentrum Kraamzorg*; KCKZ; www.kckz.nl) via a web link in their bimonthly newsletter, on the 29th of January 2018. In addition, the web link to the survey was posted on KCKZ's social media pages twice, on the 5th and the 13th of February 2018. The questionnaire was closed on the 28th of February 2018. The survey was constructed using LimeSurvey (version 2.06lts).[17]

STARSHIP training session questionnaire

Training sessions on neonatal hyperbilirubinaemia were provided to MCAs as part of the STARSHIP Trial.[15] Training sessions were aimed at increasing knowledge on pathophysiology, risk factors, recognition and treatment of neonatal hyperbilirubinaemia, and at providing information on STARSHIP study procedures (e.g. inclusion process, data collection). The training sessions were provided locally in each of the participating PCBCs.

Several weeks before and in preparation for each training session, all MCAs of the PCBCs were invited to complete an e-learning covering the same topics as the training session. Immediately prior to and following each training session, a paper-based questionnaire was filled out by participating MCAs to assess their knowledge on hyperbilirubinaemia

and to assess changes in knowledge following the training session itself. Time to fill out the questionnaire was not limited.

Participants

Online survey

The online survey was sent to all MCAs registered at KCKZ. At the time, 9065 MCAs were registered at KCKZ and all were subscribed to the electronic newsletter. These MCAs constitute 99.9% of all MCAs in the Netherlands. Approximately 99% of the MCAs registered at KCKZ work in primary care.

Training session questionnaire

The training session questionnaire was provided to all employees of the seven participating PCBCs who attended the training sessions of the STARSHIP Trial. The knowledge questions in the training session questionnaires were also used in the online survey. In order to prevent interference of the online questionnaire with the training session questionnaire, here we only report data from the training session questionnaires that had been filled out before the 29th of January 2018, i.e. the day the national questionnaire was published online.

Data collection

Online survey

The online survey started with questions on baseline characteristics of the MCA: i.e. age (in years), educational level (six categories, based on the definition of Statistics Netherlands[18]), type of maternity care education, experience in perinatal care (in years), working area (province and place; this was converted to urban vs. non-urban; a non-urban working area was defined as category 5 (less than 500 addresses per square kilometer) of the classification of urbanity of Statistics Netherlands[19]), working location (at home; in a primary care birth centre; in a hospital). See Supplementary file 1 and Supplementary file 2 for the Dutch and translated version of the online survey.

Following the baseline characteristics, the online survey continued with questions to assess MCAs' knowledge on pathophysiology, recognition and treatment of hyperbilirubinaemia, and questions assessing their professional experience with neonatal hyperbilirubinaemia. In addition, the questionnaire included three clinical case descriptions (with photos) of neonates with various degrees of jaundice. The photos displayed the neonate wearing a nappy only. Of each case, two photos were shown: one of the neonate's face and upper body (taken whilst gently stretching part of the neonate's skin using two fingers to allow for better colour assessment) and one of the neonate's whole body. All pictures were taken by an experienced professional medical photographer. Information

on sex, postnatal age, gestational age, and risk factors for severe hyperbilirubinaemia were also given (case characteristics are displayed in Table 1). For each case, MCAs were asked to: (1) visually assess skin colour (pink, slightly yellow, moderately yellow, quite yellow, very yellow); (2) estimate TSB level (by choosing a TSB range: <50 µmol/L (<2.92 mg/dL), 50-100 µmol/L (2.92-5.85 mg/dL), 100-200 µmol/L (5.85-11.70 mg/dL), 200-300 µmol/L (11.70-17.54 mg/dL), 300-450 µmol/L (17.54-26.32 mg/dL), >450 µmol/L (>26.32 mg/dL); and (3) determine their action plan accordingly (no action; no action but active surveillance; consultation of midwife; consultation of midwife to collect blood sample for quantifying TSB level; emergency consultation of midwife to collect blood sample for quantifying TSB level; other (please specify)). Treatment guidelines for each case are determined by age, gestational age and risk status according to Dutch national multidisciplinary guideline.[9]

Table 1. Characteristics of photo cases in online survey

Case	Sex	Ethnicity	Postnatal age (days)	Gestational age at birth (weeks)	Risk Factors*	TSB (µmol/L)	Threshold for phototherapy treatment (µmol/L)[20]
1	Male	Caucasian	3 (49-72 h)	38	None	256	270
2	Female	Non-Caucasian	3 (49-72 h)	41	None	145	290
3	Male	Caucasian	3 (49-72 h)	40	None	182	280

*Risk factors used in Dutch bilirubin nomogram: blood group antagonism; other haemolytic disease; asphyxia (Apgar score at 5 minutes <5 or umbilical cord pH in pH <7.0); ill, drowsy, or (suspicion of) infection or sepsis; serum albumin level <30 g/L (if quantified).[20]
TSB, total serum bilirubin.

Training session questionnaire

The training questionnaire included baseline characteristics of the MCA (i.e. age (in years), experience in perinatal care (in years), educational level, type of maternity care education, working location (at home, in a primary care birth centre, in a hospital), whether or not the MCA was involved in doing intake interviews in the last year, and whether or not the MCA had assisted in deliveries in the last year), whether or not the MCA had (partially or fully) completed the e-learning, six questions on pathophysiology, recognition, and treatment of hyperbilirubinaemia, and five questions on the STARSHIP Trial and its study procedures. In order to facilitate comparison of the results from the online survey and the training sessions, only the six multiple-choice questions on pathophysiology, recognition, and treatment (i.e. the knowledge topics tested in the online survey as well) were analysed.

The questionnaire was used to assess a change in knowledge regarding neonatal hyperbilirubinaemia after the training session. For this purpose, two sets (A and B) were used. Within each set, each question was matched to a similar, but not identical, question (i.e. questions on the same topic and of the same difficulty level) of the other question set. After the training session, the questionnaire with the other set of questions was filled out by the MCA to evaluate a change in knowledge following the training session. To account for potential differences in difficulty level of the questions between sets A and B, the two question sets were used alternately before and after the training session. That is, approximately half the participants completed set A before the session and set B after, while the other half first completed B and then A.

Outcomes

Online survey

In case of duplicate responses to the online questionnaire, only the most recent response was included. Responses were defined as duplicate when either the submitted e-mail address or all baseline characteristics were exactly identical. In order to assess representativeness of the survey respondents, we compared the age and working area (province) distributions of the MCAs who filled out the online survey to the age distribution of all Dutch MCAs as provided by KCKZ, and to the province of residence of the Dutch population in general.[21] Level of knowledge on hyperbilirubinaemia was expressed as the number of questions answered correctly. Level of knowledge was defined as poor (≤2 correct answers out of six questions), moderate (3-4 correct answers), or good (5-6 correct answers).

For the three jaundice cases, descriptive statistics were used to describe visual assessment of the skin colour. For each case, we noted the number of ranges (see 'Data collection' above) by which MCAs were off when estimating TSB levels (i.e. correct estimation = off by zero ranges, estimation of one range higher or lower than correct TSB range = off by one range, etc.). The median number of ranges per MCA was calculated across the three cases.
The visual assessment of the skin colour was plotted against the MCA's action plan and the estimated TSB level. For this purpose, the three jaundice cases were taken together and the answers were treated like independent observations.

Training session questionnaire

Similar to the online survey, the level of knowledge was expressed as the number of correctly answered knowledge questions. For the training questionnaire, next to a wrong answer, answers were considered incorrect when: 1) the question was unanswered, 2)

it was unclear or doubtful which answer was selected, or 3) more than one answer was selected.

Question sets A and B were used alternately. We compared the number of correctly answered questions between question sets A and B pre-training to identify whether there was a difference in difficulty between the sets. To evaluate the change in knowledge regarding hyperbilirubinaemia following the training sessions, the difference in the number of correct answers before and after the training session was calculated.

Statistical analysis

All data were analysed using SPSS Statistics (v25.0.0.1). Data are summarised using descriptive statistics. Mean and standard deviation (SD) are provided for continuous and (approximately) normally distributed data. Median and interquartile range (IQR) are provided for continuous, non-normally distributed data. Comparisons for non-normally distributed continuous data were performed using Wilcoxon signed rank test and Mann-Whitney U test. Categorical data were compared using $\chi 2$-tests or Fisher's exact test as appropriate. Two-sided p-values of <0.05 are considered to indicate statistical significance.

RESULTS

Online survey

The web-portal was accessed 1706 times. After removal of 74 duplicates, there were 1465 unique questionnaires with at least all baseline characteristics having been filled out. Data from 1167 completed and 298 partially completed questionnaires were analysed (in total 16.2% of all Dutch MCAs) (Figure 1). Sample frequencies for age and province of working area of survey respondents were comparable to national data, indicating that our sample was representative (See Supplementary file 3).

There were no relevant differences in MCAs' baseline characteristics according to whether an MCA had or had not fully completed the questionnaire. We used both completed questionnaires and completed sections of partially completed questionnaires for further analyses. Baseline characteristics are displayed in Table 2.

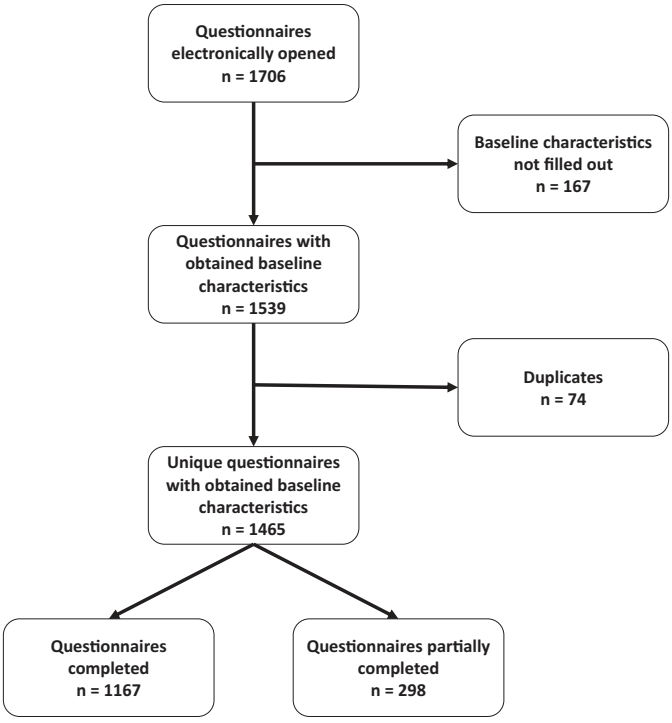

Figure 1. Flowchart online survey

Knowledge regarding hyperbilirubinaemia

One thousand three hundred sixty-six respondents completed all knowledge questions. The median number of correctly answered questions was 5 (out of 6; IQR 1). MCAs who had attended an in-service training on neonatal hyperbilirubinaemia in the last year (related or unrelated to the STARSHIP Trial) were more likely to have a higher level of knowledge on hyperbilirubinaemia (i.e. low, medium, or high) than MCAs who had not attended an in-service training on neonatal hyperbilirubinaemia (p=0.024; Table 2). The vast majority of MCAs (90%) felt that their knowledge on hyperbilirubinaemia was adequate. However, 63% of the MCAs still expressed an additional training need to increase their knowledge on hyperbilirubinaemia (Table 3).

Table 2. Baseline characteristics of maternity care assistants attending the online survey by knowledge on hyperbilirubinaemia

	Level of knowledge on hyperbilirubinaemia (n = 1366)		
	Poor: ≤2 correct answers (n = 64) *mean (SD)*	**Moderate: 3-4 correct answers (n = 515)** *mean (SD)*	**Good: 5-6 correct answers (n = 787)** *mean (SD)*
Age (years)	50 (12)	49 (11)	47 (11)
Experience (years)	21 (16)	17 (12)	17 (11)
	n (%)	**n (%)**	**n (%)**
Educational level†			
Low	12 (19)	55 (11)	69 (9)
Medium	46 (72)	398 (78)	643 (82)
High	1 (2)	31 (6)	42 (5)
Missing	5 (8)	31 (6)	33 (4)
Working at client's home			
Yes	63 (98)	505 (98)	741 (94)
No	1 (2)	10 (2)	46 (6)
Working in a birth centre/hotel/clinic			
Yes	2 (3)	33 (6)	75 (10)
No	62 (97)	482 (94)	712 (90)
Working in a hospital			
Yes	4 (6)	39 (2)	77 (10)
No	60 (94)	476 (98)	710 (90)
Urbanisation level of working area‡			
Urban	53 (83)	470 (92)	734 (93)
Rural	3 (5)	17 (3)	12 (2)
Unknown	8 (13)	24 (5)	41 (5)
Delivery assistant in the past 12 months			
Yes	40 (63)	388 (75)	603 (77)
No	21 (33)	110 (21)	167 (21)
Has been working for <12 months	3 (5)	17 (3)	17 (2)
Had (in-service) training on hyperbilirubinaemia in the past 12 months			
Yes	10 (19)	101 (21)	198 (26)
No	44 (81)	389 (79)	569 (74)
Came in contact with neonate in need of treatment for hyperbilirubinaemia in the past 12 months			
Yes	23 (42)	279 (57)	421 (55)
No	32 (58)	211 (43)	346 (45)

MCA, maternity care assistant; SD, standard deviation.

†Educational level based on the definition of Statistics Netherlands.[18]

‡Rural working area is defined as category 5 of the classification of urbanisation of Statistics Netherlands.[19]

Table 3. Frequencies of answers given to questions on experience with and current knowledge regarding neonatal hyperbilirubinaemia

	n = 1313 **n (%)**
Number of times cared for a jaundiced neonate who had to be admitted to the hospital for hyperbilirubinaemia treatment in the last year	
Never	589 (45)
1-2 times	575 (44)
3-5 times	104 (8)
6-10 times	20 (2)
11-20 times	11 (1)
More than 20 times	13 (1)
Self assessed capability of recognising jaundice by MCA	
Totally incapable	1 (0)
Incapable	9 (1)
Neutral	231 (18)
Capable	922 (70)
Very capable	150 (11)
In my experience, jaundiced neonates are usually recognised and treated in time	
All neonates	999 (76)
Most of the neonates	303 (23)
Some neonates	8 (1)
No neonates	2 (0)
Missing	*1 (0)*
What are common causes for jaundice not being recognised in time *(multiple options possible)*	
Delay in recognition by MCA	122 (39)
Delay in recognition by midwife	242 (77)
Delay in TSB quantification	44 (14)
Delay due to consultation of paediatrician	11 (4)
Delay in transferring neonate to hospital	28 (9)
Other	11 (4)
My knowledge regarding neonatal hyperbilirubinaemia is:	
More than sufficient	211 (16)
Sufficient	970 (74)
Insufficient	130 (10)
Largely insufficient	2 (0)
I would like to learn more about neonatal hyperbilirubinaemia	
Yes	820 (63)
I do not know	81 (6)
No	411 (31)

MCA, maternity care assistant; TSB, total serum bilirubin.

Assessment of jaundice

Out of 1313 MCAs who completed the questionnaire's section on their experience with jaundice assessment, 82% considered themselves very capable or capable to visually assess neonatal jaundice. Virtually all MCAs (99%) felt that the vast majority of neonates with hyperbilirubinaemia is diagnosed on time in the Netherlands. If a jaundiced neonate was not timely recognised, MCAs primarily identified insufficient visual assessment (i.e. late recognition or inaccurate visual assessment) by a midwife or MCA to be the main cause of late diagnosis. Other causes were identified less frequently: late/delayed blood sample collection (14%), late/delayed referral to secondary or tertiary care (9%), and late/delayed consultation with a paediatrician (4%). See Supplementary file 4.

Results from visual assessment of the three cases of various degrees of jaundice by MCAs are shown in Figure 2. There was substantial variation in the degree to which MCAs felt the cases did or did not have visible jaundice. Twelve MCAs noted that the skin colour made assessment more difficult in the non-Caucasian neonate.

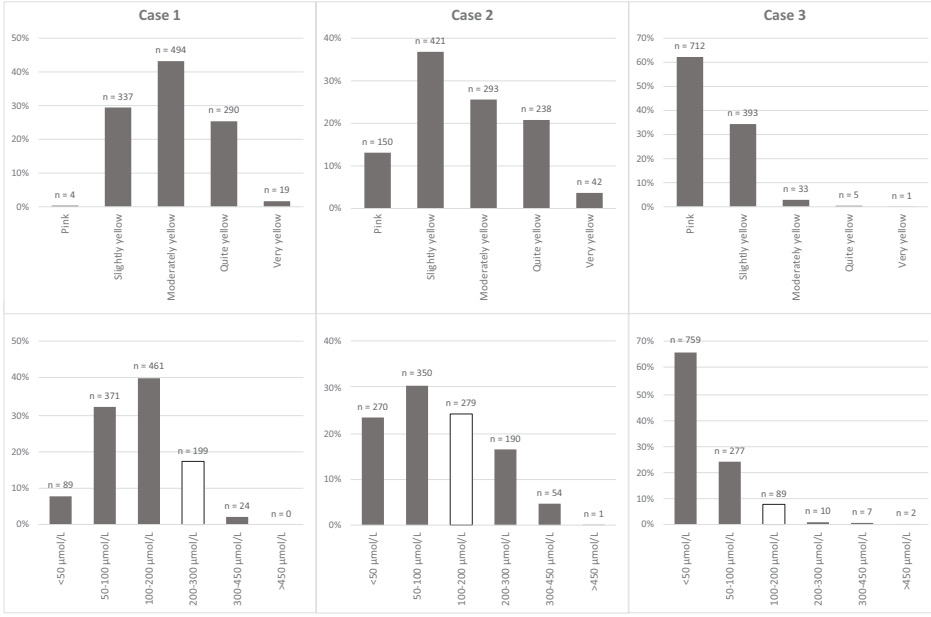

Figure 2. Visual skin colour assessment of photo cases (above) and estimated TSB level per photo case (below) by maternity care assistants who participated in the online survey.
The white bars indicate the correct TSB range.
MCA, maternity care assistant; TSB, total serum bilirubin.

Estimation of TSB range by MCAs based on visual inspection of the photographs was rarely in accordance with the actual TSB level in blood samples (Figure 2). Only 22 of 1144 MCAs (2%) estimated TSB in the correct range for all three cases, and the majority (62%) did not estimate TSB range correctly in any of the cases. As shown in Figure 2, there was a structural underestimation of TSB levels by MCAs across the three cases based on visual inspection. The adequacy of estimation of TSB was not different in MCAs having different levels of knowledge (p=0.067).

When asked for their action plan, MCAs were more likely to choose 'no action (and active surveillance)' when they assessed the skin colour of the neonates in the three photo cases to be pink or only slightly yellow or if they estimated the TSB level to be low (p<0.001; Figure 3 and Figure 4). The more yellow the MCAs assessed the skin colour of the neonates, the more likely they were to choose an active action plan. At the same time, a large proportion (63%) of the MCAs indicated that they would not have a blood sample collected for TSB quantification from a neonate despite their assessment indicating that the neonate was quite or very yellow. There was a positive association between MCAs' assessment of the degree of jaundice and the estimated TSB range (Chi square for trend p<0.001 for each case; Figure 5).

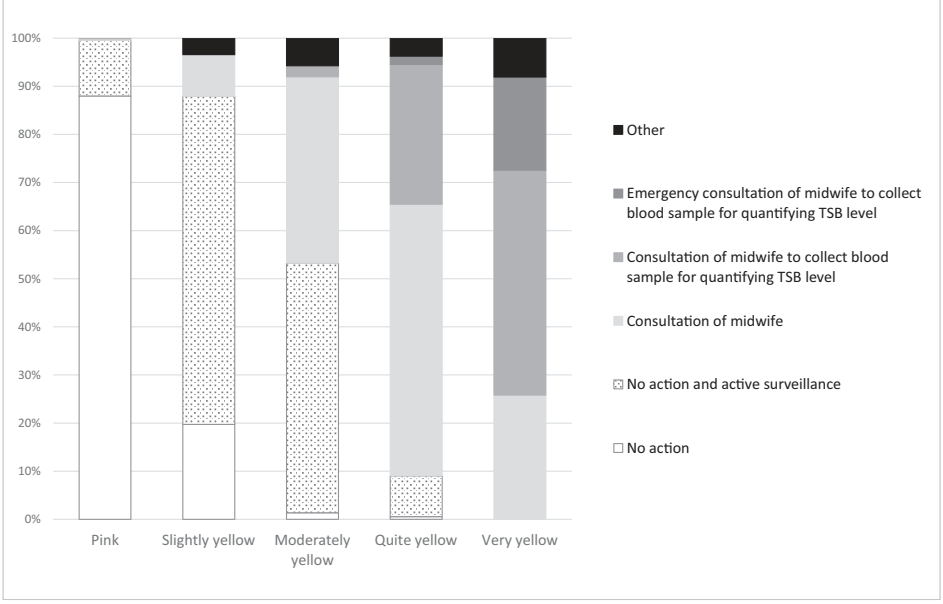

Figure 3. Maternity care assistant's action plan according to neonate's skin colour as assessed visually
TSB, total serum bilirubin.

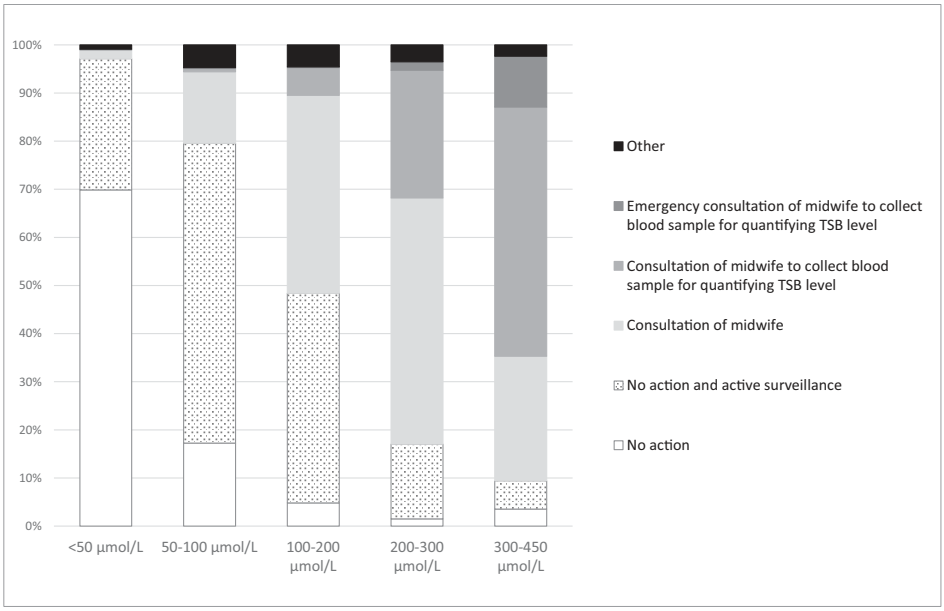

Figure 4. Maternity care assistant's action plan according to estimated total serum bilirubin level
TSB, total serum bilirubin.

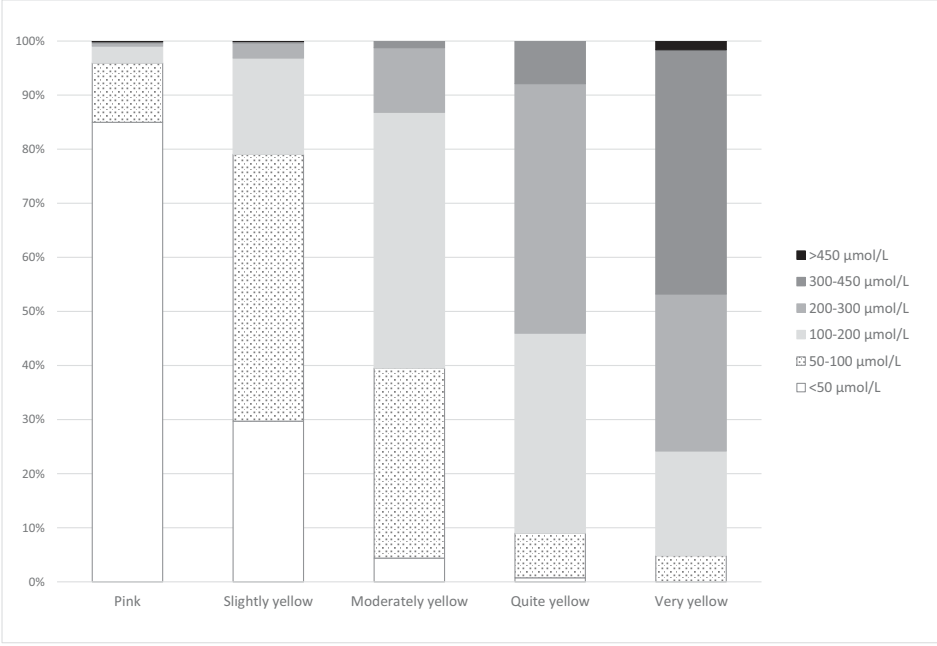

Figure 5. Estimated total serum bilirubin level according to estimated skin colour

There was no association between MCAs' self-rated capability to assess jaundice and their actual ability to correctly estimate TSB ranges in the three cases based on visual inspection (Figure 6; p=0.794).

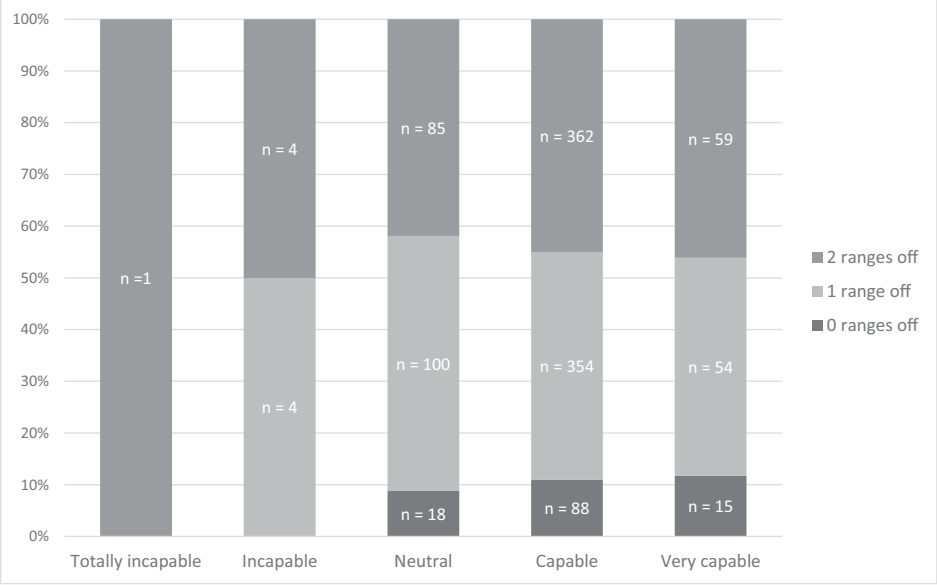

Figure 6. Self-assessed versus actual ability of maternity care assistants to estimate total serum bilirubin via visual inspection

Maternity care assistants (MCAs) were asked to estimate the total serum bilirubin (TSB) level of a neonate based on two photographs. For each case, we noted the number of 50 µl/L ranges by which MCAs were off when estimating TSB levels. The median number of ranges per MCA was calculated across the three cases. In this figure, the self-assessed capability of recognising jaundiced neonates in time was plotted against the median number of ranges by which the specific MCA was off.

Training session questionnaire

In December 2017 and January 2018 a total of 11 training sessions in five PCBCs were organised with a total of 102 attendees. Three questionnaires were excluded from further analysis as one attendee was not an MCA and two attendees did not fill out all pages of the questionnaire (Figure 7).

Baseline characteristics of the respondents of the included questionnaires are displayed in Table 4.

There was no relevant difference between the median pre-training scores for the two different question sets A and B (5 (IQR 1) vs. 5 (IQR 2), see Supplementary file 4), indicating that fair comparison of pre- and post-training scores is possible.

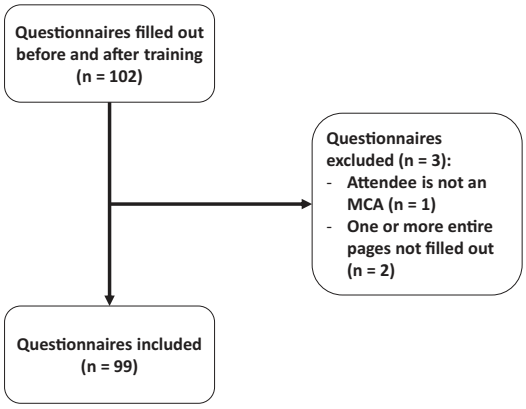

Figure 7. Flowchart of training session questionnaire inclusion
MCA, maternity care assistant.

Median test scores were higher following the training session (5 (IQR 2) pre-training versus 6 (IQR 1) post-training; p<0.001). There was no association between MCAs' age or years of experience and improvement in the scores (p=0.819 and p=0.934). MCAs who had completed the e-learning prior to the actual training session had a higher median pre-training score than those who did not complete the e-learning (median score 5 (IQR 1) vs. 4 (IQR 2), respectively; p<0.001). The post-training score did not differ between MCAs who had completed the e-learning and those who did not (median score 6 (IQR 1) vs. 6 (IQR 1), respectively; p=0.656).

DISCUSSION

Being alert to identify term and near term neonates with potential hyperbilirubinaemia is daily practice for MCAs. In this study, we examined the knowledge and skills of MCAs regarding neonatal hyperbilirubinaemia. We found that background knowledge on neonatal hyperbilirubinaemia among MCAs was generally adequate, with further evidence indicating that this knowledge could be improved by training or e-learning. The estimation of TSB levels based on skin colour was, however, often inadequate, generally leading to underestimation.

There have been very few previous assessments of knowledge regarding neonatal hyperbilirubinaemia among maternity care professionals. We are aware of one Egyptean study, which demonstrated knowledge deficits among primary healthcare physicians in multiple areas, including screening methods, symptoms of complications, and treat-

Table 4. Baseline characteristics of maternity care assistants who filled out the training session questionnaire

	n = 99 ***Mean (SD)***
Attendees per training session (n)	11 (4)
Age (years)	44 (10)
Experience as MCA (years)	17 (10)
	%
Work location	
Birth Hotel Haga	24
Birth Hotel Maasstad	37
Maternity Care Hotel Noord	17
Birth Centre Sophia	7
Birth Clinic Westeinde	14
Workplace(s)	
In a primary care birth centre/hotel/clinic	92
In a primary care birth centre/hotel/clinic and at client's home	8
Delivery assistant	
Yes	81
No	19
Interviewer for client's first intake	
Yes	12
No	87
Unknown	1
Completed e-learning before training session	
Yes	71
Partly	12
No	16

MCA, maternity care assistant.

ment of hyperbilirubinaemia.[22] In the Netherlands, primary healthcare physicians are rarely involved in perinatal healthcare, limiting comparability of the findings of this study with ours.

Earlier studies have already demonstrated that visual inspection of jaundice is inaccurate for estimating the degree of hyperbilirubinaemia.[7,11] Our results support this claim and also indicate that MCAs generally overestimated their own ability to estimate TSB via visual inspection. Their structural underestimation of TSB levels and their predominantly applied wait-and-see approach is particularly striking, whereby potentially severe neonatal hyperbilirubinaemia can be missed in these neonates. Missed diagnoses increase the risk of neonates going on to develop severe hyperbilirubinaemia

and KSD, and there are multiple examples of this still happening in everyday perinatal care even in high-income countries including in the Netherlands.[2,23] Hence, other approaches to timely identification of potentially severe hyperbilirubinaemia, such as TcB measurement, are needed. Our study also shows that MCAs whose level of knowledge on hyperbilirubinaemia was poor tended to have a lower ability to accurately estimate TSB levels based on visual inspection.

Together, this indicates that better knowledge on neonatal hyperbilirubinaemia may help increase MCAs' awareness regarding the risks of potentially severe hyperbilirubinaemia and their accuracy of visual inspection. Knowledge can be increased further by training, as supported by various aspects of our study. In the national survey, knowledge was better when MCAs had received training on hyperbilirubinaemia in the previous year. Furthermore, pre-post training comparisons of MCAs' knowledge on hyperbilirubinaemia in the STARSHIP training sessions indicate that these trainings, as well as the preceding e-learning, effectively increased MCAs' knowledge. According to Lahti *et al*., e-learning can be as effective as traditional learning methods regarding knowledge, skills, and satisfaction of nurses and student nurses.[24] This suggests that e-learning can be used as an alternative for traditional training to further increase the knowledge of MCAs regarding neonatal hyperbilirubinaemia.

In the interpretation of our study it is important to consider a number of strengths and limitations. For the online survey, we were able to obtain a very large and – importantly – representative sample of all Dutch MCAs. Despite the large number of respondents, the response rate was only 16%. Other surveys among MCAs in the Netherlands have had response rates of 20-30%.[25,26] The low response rate may have introduced nonresponse bias, as in that respondents might represent a selected sample of all MCAs in the Netherlands. Respondents may have been more interested in neonatal hyperbilirubinaemia beforehand than non-respondents, and may have had more knowledge on neonatal hyperbilirubinaemia, potentially leading to overestimation of the knowledge of MCAs regarding the topic. On the other hand, the realisation of MCAs that they lack knowledge on neonatal hyperbilirubinaemia and might learn something about it, may have resulted in overrepresentation of MCAs with less knowledge on neonatal hyperbilirubinaemia. It is not possible to assess the direction of any bias, if present, although the representativeness of the sample is somewhat reassuring. In the current study, we were unable to collect data on knowledge and skills regarding neonatal hyperbilirubinaemia among all maternity care professionals in the Netherlands, such as obstetric nurses, midwives, obstetricians, and paediatricians. Nevertheless, as MCAs are mainly relied on for the first-line recognition of neonatal jaundice in the Dutch primary care setting, we consider these results highly relevant for clinical practice.

To allow assessment of knowledge and skills regarding neonatal hyperbilirubinaemia in a large cohort, we created a short online survey. This survey consisted of six knowledge questions covering different topics in the field of neonatal hyperbilirubinaemia. We acknowledge that the discriminative value of this short questionnaire to assess differences between the levels of knowledge among MCAs maybe somewhat limited, although the findings indicate that relevant differences in knowledge could in fact be identified and that these also appear to translate into variation in skills. In the online survey, we emphasised that the participants should not look up the correct answers, however we were unable to ensure that looking up the answers did not happen. If it did, this may have resulted in an overestimation of MCAs' knowledge level and this should be taken into account when interpreting our results. Also, it is important to note that our study may in itself have served to raise awareness of the importance of appropriate jaundice assessment and improved knowledge on the topic among MCAs through the Hawthorne effect. Not only was the theoretical knowledge established in the online survey, but also clinical performance was tested using three cases of jaundice with photographs taken by a medical photographer. The colouration of these photographs may have differed among respondents according to the quality and the settings of their computer screen, although this is unlikely to have influenced our findings.

To the best of our knowledge, this is the first study to have investigated the knowledge and skills of MCAs regarding neonatal hyperbilirubinaemia. The findings indicate that MCAs overestimate their ability to assess TSB via visual inspection, at the same time confirming that visual inspection to assess hyperbilirubinaemia is inaccurate and prone to underestimation. We furthermore show that knowledge on hyperbilirubinaemia can be improved via training, potentially leading to improved ability to assess neonatal jaundice and to initiate appropriate action. Further research is needed to assess the knowledge and skills regarding neonatal hyperbilirubinaemia among other maternity care professionals, and to explore opportunities to improve recognition of neonatal hyperbilirubinaemia in the primary care setting, for example via screening programmes. Based on our findings, setting up regular training programmes for MCAs to update their knowledge and skills regarding neonatal hyperbilirubinaemia is recommended. Increased awareness among maternity care professionals caring for otherwise healthy neonates in primary care and more accurate approaches to recognition of hyperbilirubinaemia in these neonates are needed to help improve early recognition of potentially severe hyperbilirubinaemia and prevent the occurrence of KSD.

CONCLUSIONS

In this national survey, knowledge of MCAs regarding neonatal hyperbilirubinaemia was generally adequate. Our findings indicate that knowledge can be improved further by an e-learning or providing training sessions. Visual assessment of TSB levels was often inaccurate and structurally underestimated. This confirms that, based on visual assessment, potentially severe neonatal hyperbilirubinaemia may be missed. This study suggests that increased awareness of the potential pitfalls of visual assessment and more accurate approaches are needed to improve early identification of potentially severe hyperbilirubinaemia.

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SUPPLEMENTARY FILES

Supplementary file 1: Dutch version of online survey

Geelzucht bij pasgeborenen; kennis van kraamverzorgenden

Algemeen

1. Bent u op dit moment werkzaam als kraamverzorgende?
   a. Ja
   b. Nee
2. Werkt u in Nederland?
   a. Ja
   b. Nee

Uw gegevens

3. Wat is uw leeftijd? ____ jaar
4. Wat is het niveau van uw hoogst afgeronde opleiding?
   a. Vmbo
   b. Havo
   c. Vwo
   d. Mbo
   e. Hbo
   f. WO
   g. Anders, namelijk
5. Welke opleiding tot kraamverzorgende heeft u gevolgd?
   a. Verzorgende IG met uitstroomvariant/branche verbijzondering van Kraamzorg
   b. Verzorgende IG zonder kraamdifferentiatie met aanvullende opleiding 311/313 en 650 uur BPV (beroepspraktijkvorming)
   c. Brancheopleiding kraamverzorgende
   d. MDGO-VZ, uitstroom kraam
   e. Verkorte opleiding kraamverzorgende met erkend certificaat ROC, verplichte BPV 650 uur
   f. Internaat (kraamverzorgende oude stijl tot 1987)
   g. OVDB
   h. Rijkskweekschool voor vroedvrouwen
   i. Ik ben nog in opleiding
   j. Anders, namelijk:
6. Hoeveel jaar bent u werkzaam als kraamverzorgende? ___ jaar
7. In welke provincie werkt u (voornamelijk)?
   a. Drenthe
   b. Flevoland

   c. Friesland
   d. Gelderland
   e. Groningen
   f. Limburg
   g. Noord-Brabant
   h. Noord-Holland
   i. Overijssel
   j. Utrecht
   k. Zeeland
   l. Zuid-Holland
8. Wat is de plaatsnaam van uw voornaamste werklocatie?
9. Waar werkt u als kraamverzorgende? *Meerdere antwoorden mogelijk*
   a. Bij mensen thuis
   b. In een geboortecentrum/geboortehotel/geboortekliniek/kraamhotel
   c. In het ziekenhuis
10. Heeft u in het afgelopen jaar partusassistentie als kraamverzorgende verricht?
   a. Ja
   b. Nee
   c. Ik ben korter dan een jaar werkzaam als kraamverzorgende, maar ik heb wel partusassistentie gedaan.
   d. Ik ben korter dan een jaar werkzaam als kraamverzorgende en ik heb geen partusassistentie gedaan.
11. Heeft u in het afgelopen jaar intakegesprekken gedaan voor de kraamzorg?
   a. Ja
   b. Nee
   c. Ik ben korter dan een jaar werkzaam als kraamverzorgende, maar ik heb wel intakegesprekken gedaan.
   d. Ik ben korter dan een jaar werkzaam als kraamverzorgende en ik heb geen intakegesprekken gedaan.
12. Deze vragenlijst hangt samen met een onderzoek over hyperbilirubinemie bij pasgeborenen dat in een aantal centra in Nederland wordt opgezet. Werkt u in een van de deelnemende centra van de STARSHIP Trial?
   a. Ja *(ga naar vraag 13)*
   b. Nee *(ga naar vraag 16)*

Onderzoek hyperbilirubinemie

13. In welk centrum werkt u?
   a. GeboorteHotel Maasstad, Rotterdam
   b. Kraamzorghotel Noord, Rotterdam

c. Geboortecentrum Sophia, Rotterdam
d. GeboorteHotel Haga, Den Haag
e. Geboortekliniek Westeinde, Den Haag
f. Geboortecentrum Livive, Tilburg
g. Kraamafdeling Isala Kliniek, Zwolle

14. Heeft u de e-learning gemaakt over het onderzoek naar hyperbilirubinemie bij pasgeborenen in de eerste lijn?
    a. Ja, volledig
    b. Ja, deels
    c. Nee, maar de e-learning is wel naar mij verstuurd
    d. Nee, ik heb (nog) geen e-learning ontvangen
15. Heeft u de training op locatie gevolgd over het onderzoek naar hyperbilirubinemie bij pasgeborenen in de eerste lijn?
    a. Ja, volledig
    b. Ja, deels
    c. Nee

Kennis hyperbilirubinemie

16. Waar komt bilirubine in het bloed vandaan?
    a. Bilirubine ontstaat bij een tekort aan rode bloedcellen.
    b. Bilirubine ontstaat bij een tekort aan witte bloedcellen.
    c. Bilirubine ontstaat bij de afbraak van rode bloedcellen.
    d. Bilirubine ontstaat bij de afbraak van witte bloedcellen.
17. Wat is geen mogelijke oorzaak van hyperbilirubinemie?
    a. Een bloeduitstorting bij de baby, ontstaan bij de geboorte
    b. Bloedgroepantagonisme (moeder en baby hebben niet dezelfde bloedgroep)
    c. Het eten van veel wortelen tijdens de zwangerschap
    d. Een verstopte darm bij het kind
18. Hoe vaak komt het voor dat een baby geel ziet?
    a. Vaak; meer dan de helft van de baby's wordt geel
    b. Regelmatig, iets minder dan de helft van de baby's wordt geel
    c. Zelden, baby's worden bijna nooit geel
19. Wat is geen alarmsymptoom van hyperbilirubinemie?
    a. Geelzucht binnen 24 uur na de geboorte
    b. Veel drinken
    c. Suf zijn
    d. Liggen met een holle rug
20. Welke blijvende schade kan ontstaan door hyperbilirubinemie?
    a. Kaalheid

b. Gele kleuring van de huid
c. Onvruchtbaarheid
d. Doofheid

21. Welke behandeling kan een arts gebruiken bij hyperbilirubinemie?
    a. Fototherapie, ook wel lichttherapie
    b. Alleen bijvoeden
    c. Baby bij het raam leggen
    d. Alle bovenstaande antwoorden zijn goed.

Uw ervaring met hyperbilirubinemie

22. Hoe vaak heeft u de afgelopen 12 maanden een baby met geelzucht gezien, die daarvoor behandeling nodig heeft gehad in het ziekenhuis?
    a. Nooit
    b. 1 of 2 keer
    c. 3 tot 5 keer
    d. 6 tot 10 keer
    e. 11 tot 20 keer
    f. Meer dan 20 keer
23. Heeft u in de afgelopen 12 maanden (bij)scholing gehad over geelzucht bij baby's?
    a. Ja, alleen voor het onderzoek naar de huidmeter en fototherapie op mijn werklocatie (zie helptekst hieronder)
    b. Ja, maar niet voor het hierboven genoemde onderzoek
    c. Ja, zowel de scholing voor het hierboven genoemde onderzoek als een andere (bij)scholing/andere (bij)scholingen
    d. Nee
24. Als kraamverzorgende beoordeelt u de kleur van de huid en kijkt u of het kind geel ziet. Hoe deskundig voelt u zich om (de mate van) geelzucht vast te stellen?
    a. Zeer deskundig
    b. Deskundig
    c. Neutraal
    d. Niet deskundig
    e. Helemaal niet deskundig
25. Naar uw mening, welk deel van de baby's met ernstige geelzucht waar u voor zorgt, wordt op tijd gehandeld?
    a. Bij alle baby's waar ik voor zorg, wordt op tijd gehandeld. *(ga naar vraag 27)*
    b. Bij de meeste baby's waar ik voor zorg, wordt op tijd gehandeld. *(ga naar vraag 26)*
    c. Bij weinig baby's waar ik voor zorg, wordt op tijd gehandeld. *(ga naar vraag 26)*

d. Bij geen enkele baby waar ik voor zorg, wordt op tijd gehandeld. *(ga naar vraag 26)*

26. Als er niet op tijd wordt gehandeld bij ernstige geelzucht, aan welke factor ligt dit dan voornamelijk? *1 of 2 antwoorden mogelijk.*
    a. Moeilijke of verkeerde inschatting van de ernst van de geelzucht door u of een andere kraamverzorgende
    b. Moeilijke of verkeerde inschatting van de ernst van de geelzucht door de verloskundige
    c. Vertraging door bloed prikken (moeilijk te prikken, lang wachten op iemand om te prikken, lang wachten op de uitslag, enz.)
    d. Vertraging door overleg met de kinderarts
    e. Moeite met/vertraging bij het doorsturen van de baby voor behandeling
    f. Anders, namelijk:
27. Naar uw mening, weet u voldoende over geelzucht en hyperbilirubinemie bij pasgeborenen?
    a. Ja, ruim voldoende
    b. Ja, voldoende
    c. Nee, onvoldoende
    d. Nee, ruim onvoldoende
28. Zou u meer willen weten over geelzucht en hyperbilirubinemie bij pasgeborenen?
    a. Ja
    b. Weet ik niet
    c. Nee
29. Wat zou u nog willen weten/willen leren over geelzucht en hyperbilirubinemie bij pasgeborenen?
30. Wanneer u met de verloskundige overlegt of er bloed geprikt moet worden bij een gele baby, hoe vaak zit u dan met de verloskundige op één lijn?
    a. Altijd *(ga naar vraag 32)*
    b. Regelmatig *(ga naar vraag 31)*
    c. Af en toe *(ga naar vraag 31)*
    d. Zelden *(ga naar vraag 31)*
    e. Nooit *(ga naar vraag 31)*
    f. Ik overleg niet met de verloskundige over een baby die geel ziet. *(ga naar vraag 32)*
31. U heeft aangegeven niet altijd met de verloskundige op één lijn te zitten. Waar ligt dit meestal aan in uw ogen?
    a. De verloskundige onderneemt over het algemeen sneller actie bij een baby met geelzucht dan ik zou doen.

b. De verloskundige onderneemt over het algemeen minder vaak actie bij een baby met geelzucht dan ik zou doen.
c. Anders, namelijk:

32. Heeft u nog opmerkingen over de samenwerking met de verloskundige met betrekking tot geelzucht bij pasgeborenen?

Foto's van pasgeborenen

Pasgeborene 1

Hieronder ziet u twee afbeeldingen van dezelfde baby. Het is een jongen van XX uur oud (tussen de 49 en 72 uur), geboren na een zwangerschap van 38+X weken. De bevalling is ingeleid. Verder zijn er geen bijzonderheden. Er zijn geen risicofactoren voor geelzucht bij dit kind.

Foto 1 van pasgeborene 1: foto van het gehele lichaam
Er is geen toestemming voor het verspreiden van identificerende gegevens en foto's van de baby's voor andere doeleinden dan het tonen van de foto's in de vragenlijst.

Foto 2 van pasgeborene 1: foto van het gezicht en bovenlichaam van de baby (genomen terwijl een deel van de huid van de baby zachtjes gerekt wordt om een betere inschatting van de kleur mogelijk te maken)
Er is geen toestemming voor het verspreiden van identificerende gegevens en foto's van de baby's voor andere doeleinden dan het tonen van de foto's in de vragenlijst.

33. Wat vindt u van de kleur van de huid?
    Ik beoordeel dit als…
    a. Roze
    b. Vleugje geel
    c. Matig geel
    d. Redelijk geel
    e. Zeer geel
34. Op basis van de kleur van de huid, wat zou u doen met deze baby als u voor deze baby zou zorgen?
    a. Ik zou geen actie ondernemen.
    b. Ik zou nu geen actie ondernemen, maar de kleur van de huid zeer goed in de gaten houden.
    c. Ik zou de verloskundige om advies vragen.

d. Ik zou met de verloskundige overleggen om bloed te prikken.
e. Ik zou zo snel mogelijk de verloskundige bellen om met spoed bloed te prikken.
f. Anders, namelijk:

35. Stel dat er bij deze baby bloed wordt geprikt, welke waarde zou u dan verwachten van het bilirubine-gehalte in het bloed?
    a. Minder dan 50 µmol/L
    b. Tussen de 50 en 100 µmol/L
    c. Tussen de 100 en 200 µmol/L
    d. Tussen de 200 en 300 µmol/L
    e. Tussen de 300 en 450 µmol/L
    f. Meer dan 450 µmol/L

Pasgeborene 2

Hieronder ziet u twee afbeeldingen van dezelfde baby. Het is een meisje van XX uur oud (tussen de 49 en 72 uur), geboren na een zwangerschap van 41+X weken. Er zijn geen bijzonderheden. Er zijn geen risicofactoren voor geelzucht bij dit kind.

Foto 1 van pasgeborene 2: foto van het gehele lichaam
Er is geen toestemming voor het verspreiden van identificerende gegevens en foto's van de baby's voor andere doeleinden dan het tonen van de foto's in de vragenlijst.

Foto 2 van pasgeborene 2: foto van het gezicht en bovenlichaam van de baby (genomen terwijl een deel van de huid van de baby zachtjes gerekt wordt om een betere inschatting van de kleur mogelijk te maken)
Er is geen toestemming voor het verspreiden van identificerende gegevens en foto's van de baby's voor andere doeleinden dan het tonen van de foto's in de vragenlijst.

36. Wat vindt u van de kleur van de huid?
    Ik beoordeel dit als…
    a. Roze
    b. Vleugje geel
    c. Matig geel
    d. Redelijk geel
    e. Zeer geel
37. Op basis van de kleur van de huid, wat zou u doen met deze baby als u voor deze baby zou zorgen?

a. Ik zou geen actie ondernemen.
b. Ik zou nu geen actie ondernemen, maar de kleur van de huid zeer goed in de gaten houden.
c. Ik zou de verloskundige om advies vragen.
d. Ik zou met de verloskundige overleggen om bloed te prikken.
e. Ik zou zo snel mogelijk de verloskundige bellen om met spoed bloed te prikken.
f. Anders, namelijk:

38. Stel dat er bij deze baby bloed wordt geprikt, welke waarde zou u dan verwachten van het bilirubine-gehalte in het bloed?
    a. Minder dan 50 µmol/L
    b. Tussen de 50 en 100 µmol/L
    c. Tussen de 100 en 200 µmol/L
    d. Tussen de 200 en 300 µmol/L
    e. Tussen de 300 en 450 µmol/L
    f. Meer dan 450 µmol/L

Pasgeborene 3

Hieronder ziet u twee afbeeldingen van dezelfde baby. Het is een jongen van XX uur oud (tussen de 49 en 72 uur), geboren na een zwangerschap van 40+X weken. Er zijn geen bijzonderheden. Er zijn geen risicofactoren voor geelzucht bij dit kind.

Foto 1 van pasgeborene 2: foto van het gehele lichaam
Er is geen toestemming voor het verspreiden van identificerende gegevens en foto's van de baby's voor andere doeleinden dan het tonen van de foto's in de vragenlijst.

Foto 2 van pasgeborene 2: foto van het gezicht en bovenlichaam van de baby (genomen terwijl een deel van de huid van de baby zachtjes gerekt wordt om een betere inschatting van de kleur mogelijk te maken)
Er is geen toestemming voor het verspreiden van identificerende gegevens en foto's van de baby's voor andere doeleinden dan het tonen van de foto's in de vragenlijst.

39. Wat vindt u van de kleur van de huid?
    Ik beoordeel dit als…
    a. Roze
    b. Vleugje geel
    c. Matig geel

d. Redelijk geel
e. Zeer geel

40. Op basis van de kleur van de huid, wat zou u doen met deze baby als u voor deze baby zou zorgen?
    a. Ik zou geen actie ondernemen.
    b. Ik zou nu geen actie ondernemen, maar de kleur van de huid zeer goed in de gaten houden.
    c. Ik zou de verloskundige om advies vragen.
    d. Ik zou met de verloskundige overleggen om bloed te prikken.
    e. Ik zou zo snel mogelijk de verloskundige bellen om met spoed bloed te prikken.
    f. Anders, namelijk:
41. Stel dat er bij deze baby bloed wordt geprikt, welke waarde zou u dan verwachten van het bilirubine-gehalte in het bloed?
    a. Minder dan 50 µmol/L
    b. Tussen de 50 en 100 µmol/L
    c. Tussen de 100 en 200 µmol/L
    d. Tussen de 200 en 300 µmol/L
    e. Tussen de 300 en 450 µmol/L
    f. Meer dan 450 µmol/L

Supplementary file 2: Translated version of online survey

Jaundice in newborns; knowledge of maternity care assistants

General

1. Do you currently work as a maternity care professional?
   a. Yes
   b. No
2. Do you work in the Netherlands
   a. Yes
   b. No

Your characteristics

3. What is your age? ____ years
4. What is the highest level of education you have completed?
   a. Pre- vocational secondary education
   b. Senior general secondary education
   c. Pre-university education
   d. Secondary vocational education
   e. Higher professional education
   f. University education
5. Which training for maternity care assistants have you done?
   a. Nurse assistant individual care with branch specification of maternity care
      'Verzorgende IG met uitstroomvariant/branche verbijzondering van Kraamzorg'
   b. Nurse assistant individual care without maternity care differentiation with additional training 311/313 and 650 hours practical training
      'Verzorgende IG zonder kraamdifferentiatie met aanvullende opleiding 311/313 en 650 uur BPV (beroepspraktijkvorming)'
   c. Maternity care assistant branch training
      'Brancheopleiding kraamverzorgende'
   d. Secondary vocational education, sector services and healthcare, health department, care, outflow maternity care
      'MDGO-VZ, uitstroom kraam'
   e. Shortened training for maternity care assistants with a recognised ROC certificate, mandatory practical training 650 hours
      'Verkorte opleiding kraamverzorgende met erkend certificaat ROC, verplichte BPV 650 uur'
   f. Boarding school (maternity care assistant old style, until 1987)
      'Internaat (kraamverzorgende oude stijl tot 1987)'
   g. Training for care and service professions
      'OVDB'

h. State training college for midwives
   'Rijkskweekschool voor vroedvrouwen'
i. I am currently in training
j. Other, please specify:

6. How many years have you been working as a maternity care assistant? ___ years
7. In which province do you work (mainly)?
   a. Drenthe
   b. Flevoland
   c. Friesland
   d. Gelderland
   e. Groningen
   f. Limburg
   g. Noord-Brabant
   h. Noord-Holland
   i. Overijssel
   j. Utrecht
   k. Zeeland
   l. Zuid-Holland
8. In which city/town do you work (mainly)?
9. Where do you work as maternity care assistant? *Multiple options possible*
   a. At client's home
   b. In a primary care birth centre
   c. In a hospital
10. Did you provide delivery assistance in the past year?
    a. Yes
    b. No
    c. I have been working as maternity care assistant for less than one year, but I have provided delivery assistance
    d. I have been working as maternity care assistant for less than one year and I have not provided delivery assistance
11. Did you conduct maternity care intake interviews in the past year?
    a. Yes
    b. No
    c. I have been working as maternity care assistant for less than one year, but I have conducted intake interviews
    d. I have been working as maternity care assistant for less than one year and I have not conducted intake interviews
12. Do you work in one of the participating primary care birth centres of the STARSHIP Trial?

a. Yes *(go to question 13)*
b. No *(go to question 16)*

Research hyperbilirubinaemia

13. In which primary care birth centre do you work?
    a. Primary care birth hotel Maasstad, Rotterdam
    b. Maternity care hotel Noord, Rotterdam
    c. Primary care birth centre Sophia, Rotterdam
    d. Primary care birth hotel Haga, Den Haag
    e. Primary care birth clinic Westeinde, Den Haag
    f. Primary care birth centre Livive, Tilburg
    g. Maternity ward Isala, Zwolle
14. Did you complete the e-learning regarding research on neonatal hyperbilirubinaemia in primary care?
    a. Yes, in its entirety
    b. Yes, partly
    c. No, but I did receive the web link of the e-learning
    d. No, I have not received the web link to the e-learning
15. Have you attended an in-service training regarding research on neonatal hyperbilirubinaemia in primary care?
    a. Yes, completely
    b. Yes, partly
    c. No

Knowledge hyperbilirubinaemia

16. Where does bilirubin come from?
    a. Bilirubin originates from a shortage in red blood cells
    b. Bilirubin originates from a shortage in white blood cells
    c. Bilirubin originates from the breakdown of red blood cells
    d. Bilirubin originates from the breakdown of white blood cells
17. Which of the following is not a potential cause of hyperbilirubinaemia?
    a. A bruise in the baby, caused during birth
    b. Blood group antagonism (mother and baby do not have the same blood group)
    c. Eating many carrots during pregnancy
    d. A bowel obstruction in the neonate
18. How common is it for a baby to be jaundiced?
    a. Very common; more than half of the babies becomes jaundiced
    b. Often; slightly less than half of the babies becomes jaundiced
    c. Rarely; babies almost never become jaundiced

19. Which of the following is not a red flag when regarding hyperbilirubinaemia?
    a. Jaundice occurring within 24 hours after birth
    b. Drinking a lot
    c. Being drowsy
    d. Lying with arched neck and trunk
20. What permanent damage can result from hyperbilirubinaemia?
    a. Baldness
    b. Jaundiced skin tone
    c. Infertility
    d. Deafness
21. Which treatment can a doctor apply for hyperbilirubinaemia?
    a. Phototherapy, also known as light therapy
    b. Supplemental feeding
    c. Putting the baby near the window
    d. All of the above

Your experience with hyperbilirubinaemia

22. How often have you seen a jaundiced neonate necessitating treatment in the hospital in the past 12 months?
    a. Never
    b. 1 to 2 times
    c. 3 to 5 times
    d. 6 to 10 times
    e. 11 to 20 times
    f. More than 20 times
23. Have you attended an in-service training about neonatal jaundice in the past 12 months?
    a. Yes, only related to the study about the skin device and phototherapy at my work location
    b. Yes, but not related to the aforementioned study
    c. Yes, both a training related to the aforementioned study and other training sessions
    d. No
24. How competent do you feel in assessing (the degree of) neonatal jaundice?
    a. Very competent
    b. Competent
    c. Neutral
    d. Not very competent
    e. Not at all competent

25. In your opinion, which proportion of newborns with severe jaundice you care for is recognised in time?
    a. All babies I care for are timely recognised and treated *(go to question 27)*
    b. Most babies I care for are timely recognised and treated *(go to question 26)*
    c. Few babies I care for are timely recognised and treated *(go to question 26)*
    d. No babies I care for are timely recognised and treated *(go to question 26)*
26. If action is not taken in time when newborns are severely jaundiced, what is the main cause? *1 or 2 answers possible*
    a. Difficult or inadequate assessment of severity of jaundice by you or another maternity care assistant
    b. Difficult or inadequate assessment of severity of jaundice by the midwife
    c. Delay in total serum bilirubin quantification (difficulties during heel prick, long waiting time for the person who's performing the heel prick, long waiting time for the result)
    d. Delay in consultation of a paediatrician
    e. Difficulties with/delay in admission of the neonate to the hospital
    f. Other, please specify:
27. In your opinion, do you have sufficient knowledge about neonatal hyperbilirubinaemia?
    a. Yes, more than sufficient
    b. Yes, sufficient
    c. No, insufficient
    d. No, very insufficient
28. Would you like to learn more about neonatal jaundice and hyperbilirubinaemia?
    a. Yes *(go to question 29)*
    b. I do not know *(go to question 30)*
    c. No *(go to question 30)*
29. What would you like to learn about neonatal jaundice and hyperbilirubinaemia?
30. When you consult a midwife or total serum bilirubin needs to be quantified in a jaundiced neonate, how often do you and the midwife agree?
    a. Always *(go to question 32)*
    b. Usually *(go to question 31)*
    c. Occasionally *(go to question 31)*
    d. Very rarely *(go to question 31)*
    e. Never *(go to question 31)*
    f. I do not consult a midwife about a jaundiced baby *(go to question 32)*
31. You have indicated that you and the midwife do not always agree. What is most often the cause of this?

a. The midwife tends to take action sooner than I would do when a neonate is jaundiced.
b. The midwife tends to take action later than I would do when a neonate is jaundiced.

32. Do you have any remarks regarding your collaboration with the midwife in relation to neonatal jaundice?

Photographs of newborns

Newborn 1

Below, two photographs of the same baby are displayed. It is a boy, he is XX hours (between 49 and 72 hours) old and born at a gestational age of 38+X weeks. The delivery was induced. There are no further abnormalities. There are no risk factors for neonatal jaundice.

Photo 1 of newborn 1: photo of baby's whole body *No informed consent for distribution of identifying characteristics or photographs other than via the questionnaire was obtained.*

Photo 2 of newborn 1: photo of the baby's face and upper body (taken whilst gently stretching part of the baby's skin using two fingers to allow for better colour assessment) *No informed consent for distribution of identifying characteristics or photographs other than via the questionnaire was obtained.*

33. How would you assess the skin colour?
    I would assess this as…
    a. Pink
    b. Slightly yellow
    c. Moderately yellow
    d. Quite yellow
    e. Very yellow
34. Based on the skin colour, what would you do if you would take care of this baby?
    a. I would not do anything
    b. I would not do anything at the moment, but I would watch the skin colour very closely
    c. I would consult the midwife

d. I would consult the midwife for bilirubin quantification
e. I would consult the midwife immediately for urgent bilirubin quantification
f. Other, please specify:

35. If bilirubin was quantified in this baby, what level of bilirubin in the blood would you expect?
    a. Less than 50 µmol/L (<2.92 mg/dL)
    b. Between 50 and 100 µmol/L (2.92 - 5.85 mg/dL)
    c. Between 100 and 200 µmol/L (5.85 - 11.7 md/dL)
    d. Between 200 and 300 µmol/L (11.7 - 17.54 mg/dL)
    e. Between 300 and 450 µmol/L (17.54 - 26.32 mg/dL)
    f. More than 450 µmol/L (>26.32 mg/dL)

Newborn 2

Below, two photographs of the same baby are displayed. It is a girl, she is XX hours (between 49 and 72 hours) and born at a gestational age of 41+X weeks. There are no abnormalities. There are no risk factors for neonatal jaundice.

Photo 1 of newborn 2: photo of baby's whole body
No informed consent for distribution of identifying characteristics or photographs other than via the questionnaire was obtained.

Photo 2 of newborn 2: photo of the baby's face and upper body (taken whilst gently stretching part of the baby's skin using two fingers to allow for better colour assessment)
No informed consent for distribution of identifying characteristics or photographs other than via the questionnaire was obtained.

36. How would you assess the skin colour?
    I would assess this as…
    a. Pink
    b. Slightly yellow
    c. Moderately yellow
    d. Quite yellow
    e. Very yellow
37. Based on the skin colour, what would you do if you would take care of this baby?
    a. I would not do anything

b. I would not do anything at the moment, but I would watch the skin colour very closely
c. I would consult the midwife
d. I would consult the midwife for bilirubin quantification
e. I would consult the midwife immediately for urgent bilirubin quantification
f. Other, please specify:

38. If bilirubin was quantified in this baby, what level of bilirubin in the blood would you expect?
    a. Less than 50 µmol/L (<2.92 mg/dL)
    b. Between 50 and 100 µmol/L (2.92 - 5.85 mg/dL)
    c. Between 100 and 200 µmol/L (5.85 - 11.7 md/dL)
    d. Between 200 and 300 µmol/L (11.7 - 17.54 mg/dL)
    e. Between 300 and 450 µmol/L (17.54 - 26.32 mg/dL)
    f. More than 450 µmol/L (>26.32 mg/dL)

Newborn 3

Below, two photographs of the same baby are displayed. It is a boy, he is XX hours (between 49 and 72 hours) and born at a gestational age of 40+X weeks. There are no abnormalities. There are no risk factors for neonatal jaundice.

Photo 1 of newborn 3: photo of baby's whole body
No informed consent for distribution of identifying characteristics or photographs other than via the questionnaire was obtained.

Photo 2 of newborn 3: photo of the baby's face and upper body (taken whilst gently stretching part of the baby's skin using two fingers to allow for better colour assessment)
No informed consent for distribution of identifying characteristics or photographs other than via the questionnaire was obtained.

39. How would you assess the skin colour?
    I would assess this as…
    a. Pink
    b. Slightly yellow
    c. Moderately yellow
    d. Quite yellow

   e. Very yellow

40. Based on the skin colour, what would you do if you would take care of this baby?
    a. I would not do anything
    b. I would not do anything at the moment, but I would watch the skin colour very closely
    c. I would consult the midwife
    d. I would consult the midwife for bilirubin quantification
    e. I would consult the midwife immediately for urgent bilirubin quantification
    f. Other, please specify:
41. If bilirubin was quantified in this baby, what level of bilirubin in the blood would you expect?
    a. Less than 50 µmol/L (<2.92 mg/dL)
    b. Between 50 and 100 µmol/L (2.92 - 5.85 mg/dL)
    c. Between 100 and 200 µmol/L (5.85 - 11.7 md/dL)
    d. Between 200 and 300 µmol/L (11.7 - 17.54 mg/dL)
    e. Between 300 and 450 µmol/L (17.54 - 26.32 mg/dL)
    f. More than 450 µmol/L (>26.32 mg/dL)

Supplementary file 3

Supplementary Table 1. Frequencies of age and province for maternity care assistants in the national survey sample and in the Netherlands

	MCA respondents in national survey sample (%)	All MCAs in the Netherlands (%)
Age in years		
<20	0	0
20-24	4	6
25-29	4	8
30-34	5	8
35-39	8	11
40-44	10	10
45-49	15	15
50-54	19	16
55-59	22	17
60-64	11	8
≥65	2	1
Province of working area		
Zuid-Holland	23	21
Noord-Holland	15	16
Noord-Brabant	15	15
Gelderland	11	12
Overijssel	7	7
Utrecht	7	8
Limburg	6	7
Friesland	5	4
Flevoland	3	2
Groningen	2	3
Drenthe	3	3
Zeeland	2	2

MCA, maternity care assistant.

Supplementary file 4

Supplementary Table 2. Comparison of question sets of training session questionnaire

	Set A in part I n = 53	**Set B in part I n = 46**
Pre-training score; median (IQR)	5 (1)	5 (2)
Age in years; mean (SD)	45 (10)	44 (11)
Experience as MCA in years; mean (SD)	17 (9)	18 (11)
	n (%)	**n (%)**
Participated in e-learning before training session		
Yes, completed	40 (76)	31 (67)
Yes, only partially completed	6 (11)	6 (13)
No	7 (13)	9 (20)
Location of training		
Birth Hotel Maasstad	19 (36)	18 (39)
Birth Hotel Haga	13 (25)	11 (24)
Maternity Care Hotel Noord	9 (17)	8 (17)
Birth Clinic Westeinde	8 (15)	6 (13)
Birth Centre Sophia	4 (8)	3 (7)

IQR, interquartile range; MCA, maternity care assistant; SD, standard deviation.

Appendix A.

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Management of neonatal jaundice in low- and lower-middle-income countries

Mir SE, van der Geest BAM, Been JV

More than 85% of newborns develop some degree of jaundice during the first days of life. Often a benign condition, the yellowish discolouration of the skin, sclerae, and mucous membranes in newborn infants is caused by unconjugated hyperbilirubinaemia, which may result from increased production of bilirubin, limited ability to conjugate bilirubin, and/or slow hepatic-enteric clearance of bilirubin.[1] A small proportion of newborns develops extreme hyperbilirubinaemia, that is, a total serum bilirubin (TSB) level of 25 mg/dL (428 µmol/L) or more. When it is not timely recognised or treated, extreme unconjugated hyperbilirubinaemia may lead to acute bilirubin encephalopathy. This in turn carries a risk of developing a spectrum of long-term neurological sequelae known as kernicterus spectrum disorders (KSD), encompassing 'classical kernicterus' but also milder forms of permanent brain damage caused by bilirubin neurotoxicity.[1,2] Worldwide, it is estimated that extreme hyperbilirubinaemia affects at least 481,000 late-preterm and term newborn infants annually, resulting in 114,000 deaths and more than 63,000 survivors with moderate or severe long-term disability.[1,3] More than 75% of affected infants live in low-income and lower-middle-income countries. Moreover, in South Asia severe hyperbilirubinaemia is the seventh leading cause of neonatal mortality.[1]

When timely recognised, clinically significant hyperbilirubinaemia can be treated with conventional phototherapy and in more severe cases exchange transfusion, thus reducing the risk of KSD. Relatively uncommon in high-income countries, exchange transfusions are performed regularly in low-income and lower-middle-income countries.[3] In these countries early recognition of hyperbilirubinaemia can be difficult. In low-resource settings, home births are common, and for institutional deliveries, early post-discharge follow-up controls are not always feasible. In addition, parental unawareness and logistical challenges may result in poor care-seeking behaviour. In these settings infants often present with extreme hyperbilirubinaemia and moderate to severe stages of acute bilirubin encephalopathy, resulting in high mortality and morbidity rates.[1,3] Traditionally, neonatal jaundice is determined by visual inspection. If clinically relevant jaundice is suspected, TSB is quantified in blood to assess the need for treatment. However, visual inspection of neonatal jaundice correlates poorly with the TSB level, particularly in non-Caucasian infants.[1] Moreover, in areas with limited resources laboratory testing can be challenging due to the high cost and lack of trained technical personnel. Transcutaneous bilirubin (TcB) devices have been developed as potential non-invasive alternatives to visual inspection. Several observational studies have shown a good correlation between TSB and TcB measurements. TcB can be performed by nurses or trained health workers with limited education. Coordinated TcB screening in a Canadian community setting was associated with a 55% reduction in severe hyperbilirubinaemia compared with visual inspection alone.[4]

Shah *et al*. have evaluated a care improvement initiative in a large hospital in Karachi, the largest city in Pakistan.[5] TcB screening of visibly jaundiced, otherwise well babies was implemented and clinical characteristics and jaundice-related outcomes were compared in the 6 months before vs. 6 months after implementation. There was a 79% reduction in the number of blood samples taken for TSB quantification following TcB implementation; at the same time the proportion of infants receiving phototherapy increased (6% after vs. 4% before implementation of TcB). Overall, this is a useful uncontrolled before-after study, and the first to investigate the effectiveness of using a TcB device to diagnose neonatal jaundice in a Pakistani population. The considerable reduction in TSB sampling following TcB implementation as compared with other studies (in general reduction of 40% to 50%), was attributed to excessive sampling due to the high incidence of severe hyperbilirubinaemia in South Asia. The increased use of phototherapy in the post-implementation period suggests improved recognition of hyperbilirubinaemia, although it is possible that this includes some over-treatment. In this study, the vast majority of infants were indeed screened, suggesting a low threshold for selection for screening. It is however important to note that selective screening based on visible jaundice still carries a risk of under-diagnosis. Universal TcB screening may be a valuable approach to avoid this risk and is currently under investigation in the primary care setting (Netherlands Trial Register: NTR7187). In the Pakistani study, it would have been informative to have other indicators evaluated as well to determine added value and/or safety aspects, such as changes in exchange transfusions, duration of phototherapy, or duration of hospital admission. The mean TSB peak was relatively low in this study population, 9.2 mg/dL before and 10.2 mg/dL after TcB implementation.[5] Most likely these low-risk infants are not representative of the large proportion of infants with severe hyperbilirubinaemia admitted to non-private, non-tertiary care hospitals in Pakistan. Some other limitations of this study were the small sample size, short duration of the study (12 months) and the single centre design. Whether TcB devices can impact the high incidence of severe hyperbilirubinaemia at the population level in low-income and lower-middle-income countries like Pakistan is doubtful. That is, the majority of patients with extreme hyperbilirubinaemia and moderate to severe stages of acute bilirubin encephalopathy present from home. As such, early recognition of clinically relevant hyperbilirubinaemia is particularly needed in primary care/community based settings. Whereas the current study indicates that TcB screening may be useful in a large institution, the price of TcB devices and logistical challenges are obvious barriers to implementation in primary healthcare settings in low-income and lower-middle-income countries. Low-cost and minimally invasive tools for hyperbilirubinaemia recognition including smartphone technology and point-of-care TSB quantification have emerged and may hold promise for early detection of hyperbilirubinaemia in poor-resource settings.[1] Proper education of communities and healthcare providers remains essential to

increase awareness of the main risk factors for severe hyperbilirubinaemia, and facilitate early recognition, timely referral for evaluation and treatment, and adequate follow-up.

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Part TWO

STARSHIP Trial:
towards a solution?

4.

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Screening and treatment to reduce severe hyperbilirubinaemia in infants in primary care (STARSHIP): a factorial stepped wedge cluster randomised controlled trial protocol

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ABSTRACT

Introduction Jaundice, caused by hyperbilirubinaemia, is a physiological phenomenon in the neonatal period. However, severe hyperbilirubinaemia – when left untreated – may cause kernicterus, a severe condition resulting in lifelong neurologic disabilities. Although commonly applied, visual inspection is ineffective in identifying severe hyperbilirubinaemia. We aim to investigate whether, among babies cared for in primary care: (1) transcutaneous bilirubinometry (TcB) screening can help reduce severe hyperbilirubinaemia, and (2) primary care-based (versus hospital-based) phototherapy can help reduce hospital admissions.

Methods and analysis A factorial stepped-wedge cluster randomised controlled trial will be conducted in seven Dutch primary care birth centres (PCBCs). Neonates born after 35 weeks of gestation, cared for at a participating PCBC during at least two days within the first week of life are eligible, provided they have not received phototherapy before. According to the stepped-wedge design, following a phase of 'usual care' (visual assessment and selective total serum bilirubin (TSB) quantification), either daily TcB measurement or, if indicated, phototherapy in the PCBC will be implemented (phase 2). In phase 3, both interventions will be evaluated in each PCBC. We aim to include 5500 neonates over 3 years.
Primary outcomes are assessed at 14 days of life: (1) the proportion of neonates having experienced severe hyperbilirubinaemia (for the TcB screening intervention), defined as a TSB above the mean of the phototherapy and the exchange transfusion threshold, and (2) the proportion of neonates having required hospital admission for hyperbilirubinaemia treatment (for the phototherapy intervention in primary care).

Ethics and dissemination This study has been approved by the Medical Research Ethics Committee of the Erasmus MC Rotterdam, the Netherlands (MEC-2017-473). Written parental informed consent will be obtained. Results from this study will be published in peer-reviewed journals and presented at (inter)national meetings.

Trial registration number: NTR7187 (Dutch Trial Registry)

INTRODUCTION

In newborns, severe hyperbilirubinaemia may cause brain damage when it is not recognised or is left untreated.[1,2] This spectrum of neurological sequelae is called kernicterus spectrum disorders (KSD) with acute bilirubin encephalopathy and its consequences at the extreme end and more subtle disorders at the other.[1,3] KSD also encompasses 'classical kernicterus', a chronic, irreversible, neuropathological disorder involving neuromotor dysfunction, auditory disorders, and oculomotor impairments.[1-4]

In high income countries an estimated 1 in 67,000 neonates develops classical kernicterus.[5,6] Timely recognition of potentially severe jaundice, caused by hyperbilirubinaemia, is essential to prevent KSD.[7,8] Traditionally, jaundice is identified via visual inspection by maternity care professionals, midwives or parents. If potentially severe jaundice is suspected, total serum bilirubin (TSB) is quantified in blood taken via a skin prick to assess the need for treatment.[9] However, visual inspection of neonatal jaundice is proven to be inaccurate in detecting hyperbilirubinaemia [10,11] and therefore ineffective in preventing kernicterus.[12]

Guidelines in several high-income countries advise universal screening for jaundice in newborns using TSB or transcutaneous bilirubin (TcB) measurement.[10,13] Several observational studies have shown a good correlation between TSB and TcB measurements in the neonatal period.[14,15] A programmatic evaluation of a TcB-based screening programme in Canada demonstrated a 55% reduction in severe hyperbilirubinaemia and related healthcare utilisation as compared to visual inspection with selective TSB quantification.[16] Similar findings were obtained in a retrospective multicentre study evaluating a screening program using standard versus selective TSB or TcB measurement in the US.[17] Universal screening for neonatal jaundice in the primary care setting has the potential to reduce the incidence of severe hyperbilirubinaemia.[2,18] This would also bring down the number of patients who require exchange transfusion, which is a highly invasive treatment that carries significant health risks and substantial costs.

Hyperbilirubinaemia is usually treated with phototherapy in a hospital setting which may be applied via various modalities.[2] Fibreoptic phototherapy using a underneath device (i.e. mattress) is effective in reducing TSB levels, is safe,[19] and meets existing guidelines.[9] There is some evidence to suggest that fibreoptic phototherapy may safely and effectively be used in the primary care setting as well.[14,20,21] Institution of phototherapy in the primary care setting may reduce the number of neonates admitted to hospital for hyperbilirubinaemia treatment and reduce associated costs.[22]

Whereas universal TcB screening for neonatal hyperbilirubinaemia and phototherapy provided in primary care have the potential to be effective and cost-effective via reducing the incidence of severe hyperbilirubinaemia and the need for hospitalisation,[14,23] evidence to support these assertions is currently lacking, while in today's healthcare arena cost-effectiveness considerations are becoming increasingly important.

We hypothesise that non-invasive screening for neonatal hyperbilirubinaemia using TcB and application of phototherapy in primary care will (cost-)effectively reduce the incidence of severe hyperbilirubinaemia and the need for hospital admission for hyperbilirubinaemia treatment. Here, we present our protocol for a factorial stepped-wedge cluster randomised controlled trial (RCT) among newborns cared for in primary care to test these hypotheses.

METHODS AND ANALYSIS

Study design

We will conduct a factorial stepped-wedge cluster RCT in seven primary care birth centres (PCBCs) in the Netherlands to evaluate among newborns the effectiveness of: (1) screening for hyperbilirubinaemia using daily TcB quantification to reduce the incidence of severe hyperbilirubinaemia, and (2) treatment of hyperbilirubinaemia (if indicated) using phototherapy instituted within the PCBC to reduce the need for hospital admission. Accordingly, each PCBC will start with (1) a control phase in which usual care is evaluated, followed by (2) a second phase in which one of both interventions is evaluated, followed by (3) a final phase in which both interventions are evaluated in parallel. More detail is provided below.

Dutch perinatal care system

In the Netherlands, a significant proportion of women (30% in 2016) give birth in a primary care setting (i.e. at home or in a PCBC) under supervision of a community midwife.[24] In addition, many who deliver in a hospital setting are discharged home or to a PCBC within 24 hours after delivery. Maternity care assistants provide maternity care when the neonate and the mother are at home or in a PCBC, under supervision of the community midwife (who will visit at least 3 times in the first week).[25] Only healthy neonates will be cared for at home or in a PCBC (i.e. neonates with congenital infection or other diseases will receive initial treatment in the hospital). The community midwife will consult the paediatrician of an affiliated nearby hospital if a potential clinical problem such as hyperbilirubinaemia presents in the neonate. Neonates with a gestational age

(GA) above 35 weeks who have been discharged from the hospital are especially at risk of developing severe unconjugated hyperbilirubinaemia.[26]

Participants

Study sites

This study will be performed in seven PCBCs in the Netherlands. In these PCBCs altogether, approximately 5000 neonates and their mothers are admitted for at least 48 hours each year. Each of the five largest PCBCs will be considered a cluster in the context of our cluster RCT. The two smallest PCBCs will be paired and will form a cluster together. A PCBC was selected for the study if it facilitated provision of maternity care during the first days postpartum (that is, some PCBCs only facilitate deliveries and do not provide care beyond the first 24 hours after delivery).

Patient eligibility

Neonates are eligible for inclusion in the study if:

- The neonate was born after 35 completed weeks of gestation.
  Note: Only neonates with a GA of 37 weeks or higher are born in primary care; Nevertheless, a neonate may be eligible when born in the hospital between 35 and 37 weeks GA and then discharged to a PCBC within seven days after birth.
- The neonate is admitted to a participating PCBC within the first week of life.
- The neonate is expected to remain admitted for at least two days (to allow for serial TcB measurements to take place).
- Signed informed consent (IC) is provided by parent(s) or primary caregiver(s).

Neonates are not eligible if:

- The neonate received phototherapy previously or is currently receiving phototherapy (reliability of TcB measurement is reduced in neonates who are receiving or have received phototherapy).[14]
- Parents do not have sufficient understanding of the Dutch language to be able to comprehend the patient information sheet and questionnaire.

The enrolment of participants has started in July 2018 and is planned to be completed in July 2021.

Interventions and control

In this study, two interventions will be assessed in a 2x2 factorial design to determine the effectiveness of each intervention separately. Timing of implementation of each intervention will be allocated at the PCBC level.

Control group: usual care

During this initial study phase, usual care will be evaluated. Accordingly, visual inspection is used to identify jaundice, as advised in the Dutch national guideline for neonatal hyperbilirubinaemia.[9] When potentially severe jaundice is suspected, a skin prick will be performed to determine TSB. The TSB level will be plotted on the Dutch nomogram[27] (which is similar to the nomogram of the American Academy of Pediatrics and explained in Text Box 1) and be discussed with the affiliated paediatrician, according to local procedures. If treatment for hyperbilirubinaemia is indicated, as judged by the affiliated paediatrician, the neonate will be admitted to the hospital for this purpose.

Intervention 1: TcB measurement as a non-invasive screening tool

During the study phase in which this intervention is tested, TcB will be measured daily starting from 24 hours of age using the Dräger JM-105, a CE marked, and validated handheld bilirubinometer, in all included neonates admitted to a PCBC allocated to this intervention.[28-31] If TcB exceeds the phototherapy threshold, as determined by the Dutch TSB nomogram for neonates born after 35 weeks of gestation,[9] TSB will be quantified. Because the nomograms were originally designed to be applied to TSB measurements and because TcB measurements have an inaccuracy of maximally 50 µmol/L (i.e. 2.9 mg/dL),[14,32] TSB will also be quantified if TcB is less than 50 µmol/L below the phototherapy treatment threshold. The TSB level obtained will be discussed with an affiliated paediatrician (of the nearby hospital) in order to determine the need for phototherapy, again based on the Dutch nomogram.[9] A second TcB measurement on the same day may be performed at the discretion of the maternity care professional (e.g. if the TcB level is close to the threshold for measuring TSB).

Following institution of phototherapy, bilirubin levels will be monitored using TSB rather than TcB given the reduced reliability of TcB in neonates receiving or having received phototherapy.[14]

TEXT BOX 1: THE DUTCH TSB NOMOGRAM[27]

The Dutch TSB nomogram has the same values as the nomogram of the American Academy of Pediatrics. The nomogram consists of three risk categories: lower risk, medium risk and higher risk. The risk assessment is based on gestational age and several risk factors (blood group antagonism, other haemolytic disease, birth asphyxia, suspicion of infection/sepsis, the neonate being ill or drowsy, and serum albumin level below 30 g/L). The need for phototherapy and exchange transfusion depend on the risk assessment and the postnatal age of the neonate. A translated version of the Dutch TSB nomogram is depicted in Figure 1.

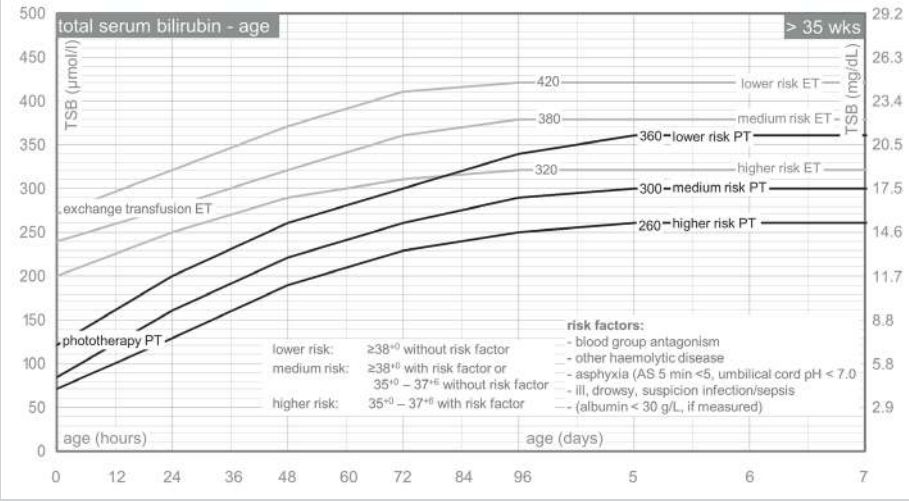

Figure 1. Phototherapy and exchange transfusion thresholds for neonates with a gestational age of 35 weeks or more (AS, Apgar score; ET, exchange transfusion; PT, phototherapy; TSB, total serum bilirubin). Translated from Dutch.
The Dutch nomogram can be downloaded from http://babyzietgeel.nl/kinderarts/hulpmiddelen/diagnostiek/bili-curve35wkn.php.

Intervention 2: phototherapy in the PCBC

During this study phase, the default location for application of phototherapy – if clinically indicated – will be the PCBC, rather than the hospital. The indication for phototherapy is made by a paediatrician in the affiliated hospital based on the TSB level, according to the Dutch nomogram.[9] Phototherapy in the PCBC will be provided using the GE Healthcare BiliSoft Large, a commercially available, CE marked and validated phototherapy mattress using blue LED-light.[33] This phototherapy mattress is suitable for application in primary care as well as in the hospital setting.

The affiliated paediatrician will decide whether other blood tests have to be performed to determine the cause of hyperbilirubinaemia and at what time points follow-up TSB measurements need to be taken. Based on the results of these TSB measurements (dis)continuation of phototherapy and further follow-up is determined by the affiliated paediatrician. The affiliated paediatrician may decide to admit a neonate to the hospital for further hyperbilirubinaemia treatment at any time if there are strong reasons to do so; these reasons will be recorded. Phototherapy will not be applied in the PCBC in neonates who have hyperbilirubinaemia above the phototherapy threshold within 24 hours after birth, since this is considered to represent a likely pathologic cause of hyperbilirubinaemia and bilirubin levels may rise swiftly in these neonates.[9]

Each PCBC will start with a time period without any intervention (control period), followed by a time period with only one of the interventions, and then a time period with both interventions. The inclusion of neonates will take 2.5 years per PCBC. The sequence and the timing at which the PCBC will switch over to the next intervention period will be determined by random allocation. The allocation scheme with the possible sequences of the interventions is depicted in Figure 2. The time blocks will take 4 months, except for the first and the last block. These two blocks will cover 5.5 months, because, to be able to make a comparison within a cluster, a sufficient number of participants in the control period (C) and in the period with both interventions (I1+I2) should be included, even when a smaller PCBC is randomised to time line 1 or 6.

Cluster	Time →						
1	C	I1	I1	I1	I1	I1	I1 + I2
2	C	C	I1	I1	I1	I1 + I2	I1 + I2
3	C	C	C	I1	I1 + I2	I1 + I2	I1 + I2
4	C	C	C	I2	I1 + I2	I1 + I2	I1 + I2
5	C	C	I2	I2	I2	I1 + I2	I1 + I2
6	C	I2	I2	I2	I2	I2	I1 + I2

Figure 2. Allocation scheme (C, control; I1, intervention 1: TcB measurement; I2, intervention 2: phototherapy in PCBC)

A flowchart with an overview of the study procedures with the different intervention phases and possible orders of intervention phases from the perspective of a participant is displayed in Figure 3.

Primary outcomes

The two interventions each have their own primary outcome. The primary outcome for TcB measurement as a screening tool for jaundice will be the proportion of neonates having severe hyperbilirubinaemia at any time point within the first 14 days of life. Severe hyperbilirubinaemia is defined as a TSB level above the mean of the phototherapy and exchange transfusion threshold, according to the Dutch nomogram;[9] that is:

$$TSB > \frac{\textit{phototherapy threshold} + \textit{exchange transfusion threshold}}{2}$$

For the second intervention, phototherapy in the PCBC, the primary outcome will be the proportion of neonates requiring hospital admission for hyperbilirubinaemia treatment within the first 14 days of life. Hyperbilirubinaemia treatment will be considered the indication for hospital admission if the neonate received phototherapy or an exchange transfusion for hyperbilirubinaemia within 24 hours after hospital admission.

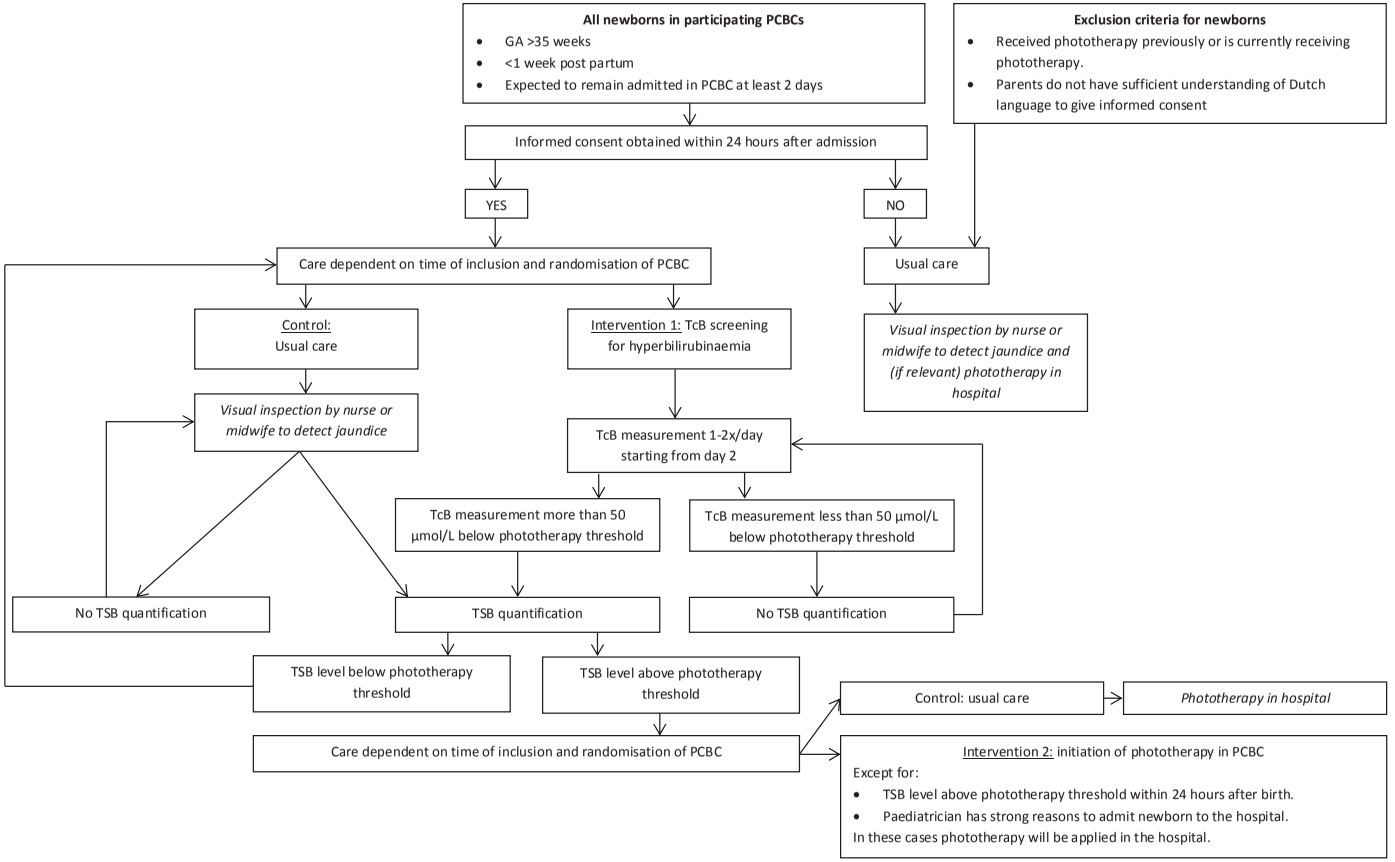

Figure 3. Flowchart for study inclusion
GA, gestational age; PCBC, primary care birth centre; TcB, transcutaneous bilirubin; TSB, total serum bilirubin.

Secondary outcomes

The secondary outcomes will also be assessed within the first 14 days of life (except for kernicterus) and are listed in Table 1.

Cost-effectiveness analysis

A cost-effectiveness analysis (CEA) will be performed from the healthcare perspective. In the CEA, the costs and outcomes of the interventions, compared to 'usual care', will be identified, measured, and valued.

For all of the following items, healthcare use will be measured: TSB and TcB tests, phototherapy in the hospital, phototherapy in the PCBC, exchange transfusions, PCBC and/or hospital admission days, and ambulance transportation to a hospital. These data will be recorded during the study and/or retrieved from the electronic information systems of the participating PCBCs and affiliated hospitals.
Then, integral unit prices will be calculated using real economic cost prices or using standard cost prices for health economic evaluations.[34] Unit prices will be multiplied by the quantities for each resource used and summed over the separate types of resource to give a total cost per patient.

Regarding the outcomes, the CEA will look at the number of neonates with severe hyperbilirubinaemia (as defined above) and the number of hospital admissions. Data on costs and outcomes will be measured throughout the 14-day observation period. As the final outcome measure of the CEA, incremental cost-effectiveness ratios (ICERs) will calculated, expressed as incremental costs per case of severe hyperbilirubinaemia or hospitalisation avoided. Uncertainty in the estimation of the ICERs will be illustrated through cost-effectiveness planes. Where relevant, sensitivity analyses will be performed to assess the robustness of the analyses to certain assumptions.

Sample size

Two sample size calculations are required since two interventions, each with their own outcome, are evaluated. The interventions are considered to be independent of each other and therefore the largest sample size among the two sample size calculations is considered appropriate for the entire study. Sample size calculations are based on detecting superiority rather than non-inferiority.

The estimated incidence of severe hyperbilirubinaemia in term neonates in the Netherlands is 1.2% per year.[9] A previous study in Canada regarding screening for unconjugated hyperbilirubinaemia using transcutaneous bilirubinometry among healthy neonates ≥35 weeks of gestation showed a relative reduction in severe hyperbilirubinaemia of

Table 1. Secondary outcomes

Secondary outcomes		
Assessed in	**Outcome**	**Recorded by**
All neonates	Number of times TcB quantified	Maternity care professional
	Individual TcB readings	Maternity care professional
	Highest TSB level	Maternity care professional and/or EMR in hospital
	Number of neonates having TSB quantified	Maternity care professional
	Number of times blood taken for TSB quantification	Maternity care professional and/or EMR in hospital
	Individual TSB levels	Maternity care professional and/or EMR in hospital
	Number of times blood taken for TSB quantification before start of phototherapy	Maternity care professional and/or EMR in hospital
	Number of neonates receiving phototherapy	Maternity care professional and/or EMR in hospital
	Duration (hours) of phototherapy	Maternity care professional and/or EMR in hospital
	Number of neonates having a TSB level above exchange transfusion threshold[9]	Maternity care professional and/or EMR in hospital
	Number of neonates who actually received an exchange transfusion	EMR in hospital
	Number of neonates having kernicterus*	EMR in hospital and/or EMR at general practitioner
	Duration of stay in the PCBC	Maternity care professional
	Duration of hospital stay following initial PCBC admission (if relevant)	EMR in hospital
	Number of transfers between PCBCs/hospitals	Maternity care professional and parental questionnaire
	Number of times affiliated paediatrician consulted	Maternity care professional
	Experience of parents regarding hyperbilirubinaemia assessment and treatment	Parental questionnaire
	Experience of attending maternity care personnel regarding the daily practice of hyperbilirubinaemia assessment and treatment during control and intervention periods, including facilitators and barriers for implementation	Maternity care assistant questionnaire
Within the group included in the intervention period with phototherapy in the PCBC	The number of neonates in whom phototherapy was initiated in the hospital, including reasons for this hospital admission	EMR in hospital
	The number of neonates requiring subsequent hospital admission for hyperbilirubinaemia treatment (i.e. after initiation of phototherapy in the PCBC), including reasons for this 'treatment failure'	EMR in hospital

EMR, electronic medical record; PCBC, primary care birth centre; TcB, transcutaneous bilirubin; TSB, total serum bilirubin.
**The diagnosis of kernicterus will be made by combining clinical signs and symptoms and additional investigations (e.g. cerebral ultrasound, MRI) up to one year after birth in every neonate who had a TSB level above the exchange transfusion threshold level.*

55% following implementation.[16] We therefore hypothesise that the TcB screening intervention will decrease the incidence of severe hyperbilirubinaemia from 1.2% to 0.5% (i.e. by 0.7% points; a relative reduction of 58%). At a power of 80% and a two-sided alpha of 0.05, 2691 neonates per arm are needed to identify this effect.

The estimated proportion of neonates needing phototherapy is 4%.[9] We anticipate that approximately 50% of the neonates with hyperbilirubinaemia will have an indication to be admitted to the hospital (e.g. feeding difficulties in addition to hyperbilirubinaemia or need for intensive phototherapy). Therefore, we hypothesise that the planned application of phototherapy in the PCBC will decrease the need for hospital admission for hyperbilirubinaemia by 2% points (i.e. 50% relative reduction). At a power of 80% and a two-sided alpha of 0.05, 1136 neonates per arm are needed to identify this effect. While our study is a cluster RCT, given the cross-sectional nature of a stepped-wedge design the effect of intracluster correlation on power is minimal, therefore we did not adjust for intracluster correlation.[35]

Based on the largest sample size of 2691 neonates per arm, 5382 neonates are needed in total. We aim to include 5500 neonates to account for a degree of missing data.

Randomisation and blinding

Each of the participating PCBCs will be randomised to one of the predefined timelines (as depicted in Figure 2 above) by an online randomisation module (www.randomization.com). The two smallest PCBCs will be paired and randomised to the same timeline (see Figure 2).

Given the nature of the treatment in the intervention groups and the control group, blinding of participants (and parents) and healthcare personnel is not possible. Analyses will be performed by a researcher who is blinded to the PCBC allocation scheme.

Study procedures

All PCBCs in the Netherlands that provide maternity care to mothers and neonates in the first days after delivery were invited to participate. Eligibility of neonates admitted to the PCBC will be assessed by the maternity care or study personnel based on the inclusion and exclusion criteria. IC of parents will be obtained by the maternity care professional. Research nurses and study personnel will support the maternity care professionals in obtaining IC and collecting data.

Depending on the allocation and the moment of admission in the PCBC during the study period, the neonate is included in the control period, in a time period where one

of the interventions is implemented, or in a time period where both interventions are implemented. Standard operating procedures (SOPs) for each study phase have been developed.

Maternity care personnel of all PCBCs will be trained in the SOPs and in using the transcutaneous bilirubinometer and the phototherapy mattress to ensure the interventions are applied in a professional standardised manner. For this purpose, an e-learning module has been developed (available from: https://xoteur.12change.eu/play.php?template_id=798); in addition, during the study period three training sessions for maternity care professionals are held at each PCBC prior to the start of each subsequent study phase (i.e. intervention implementation).

Data collection

Data collection at the PCBC will be performed by maternity care personnel. Together with the training for using the transcutaneous bilirubinometer and the phototherapy mattress, maternity care personnel will be trained in adequate data collection. Data collection is described in the SOPs as well.

After inclusion, a maternity care professional of the PCBC will record baseline characteristics of the mother and the neonate (see Table 2) using a standardised registration form at a secured internet page. All participants will receive an anonymised study number.

The maternity care professionals will record several measurements during PCBC stay. These measurements are noted in Table 3. All data will be recorded in standardised case report forms. The study team, the study monitor, and (inter)national supervisory authorities will have access to the data and the final dataset.

A questionnaire for the parents/caregivers to evaluate their experience will be sent by e-mail 14 days after birth of the neonate. This questionnaire will assess parental satisfaction, burdensomeness of interventions for the neonate, and experienced competence of maternity care professionals. If parents do not have access to the internet or do not respond to the questionnaire by email, they will be approached by regular mail or by phone. The community midwife and/or the general practitioner will be approached if parents do not respond at all. Both after the control and after each intervention period, maternity care personnel will be invited to complete a questionnaire about their experiences regarding the daily practice of hyperbilirubinaemia assessment and treatment during these periods (e.g. facilitators and barriers for implementation, sense of competence regarding applying the new interventions, integrating the new interventions in routine care, and the content of the training regarding the new interventions).

Table 2. Baseline characteristics

Baseline characteristics	
Parental characteristics	Maternal age
	Maternal ethnicity
	Maternal blood group
	Paternal ethnicity
	Presence of haemolytic disease (other than blood group antagonism) in mother or father
Characteristics of pregnancy and birth	Parity
	Maternal atypical red-cell alloantibodies during pregnancy
	Gestational age at birth
	Type of delivery: vaginal delivery, vacuum-assisted vaginal delivery, forceps-assisted vaginal delivery, caesarean delivery without vacuum or forceps extraction (before or during delivery), caesarean delivery with vacuum or forceps extraction (before or during delivery).
Neonatal characteristics	Date of birth
	Time of birth
	Sex
	Birth weight (in grams)
	Presence of birth trauma
	Type of feeding
	Neonatal blood group (if known)
	Foetal or neonatal Rhesus factor (if known)
	Direct antiglobulin (Coombs) test (if known)
	Presence of haemolytic disease (other than blood group antagonism)
	Presence of birth asphyxia: Apgar score <5 at 5 minutes or pH <7.0 in umbilical cord blood
	Suspicion of sepsis
	Neonate being ill or drowsy
Other characteristics	Siblings who experienced neonatal hyperbilirubinaemia (and cause of hyperbilirubinaemia, if known)

Statistical analysis

We will use cluster specific methods because randomisation will be performed at the PCBC level rather than at the individual level. For both primary objectives an intention-to-treat analysis will be performed.

To evaluate whether the occurrence of the primary outcomes of both interventions are different between the study periods with and without the intervention(s), generalised linear mixed models (GLMMs) will be used. GLMMs account for the systematically different observation periods and for clustering in the data.[36] In case of missing data, multiple

Table 3. Daily measurements in PCBC

Daily measurements	
Control period	Skin colour: pink, slightly yellow, moderately yellow, quite yellow, very yellow
	Weight (in grams)
	Risk factors for hyperbilirubinaemia (if present)
	TSB values with date and time of measurement (if relevant)
	Decisions made based on TSB (if relevant)
Period with TcB screening (extra measurements in addition to control period)	TcB values measured at forehead and sternum together with date and time of measurement (once a day or two times if indicated)
Phototherapy in PCBC (extra measurements in addition to control period)	Start and end date and time of phototherapy
	Decisions made by the affiliated paediatrician regarding phototherapy

PCBC, primary care birth centre; TcB, transcutaneous bilirubin; TSB, total serum bilirubin.

imputation using chained equations will be used. Relative risks, risk differences, and relative risk reduction with corresponding 95% confidence intervals will be calculated from the GLMMs.

Subgroup analyses to evaluate the effect of the interventions in neonates of different ethnicities (Caucasian and non-Caucasian) and different gestational age groups (<38 weeks of gestation and ≥38 weeks of gestation) will be performed.
We will perform a per-protocol analysis to assess the impact of potential contamination during the first days of a new intervention period as a sensitivity analysis in addition to the intention-to-treat analysis.

Safety

Adverse events noticed by parents or maternity care professionals will be recorded in the case report forms by the maternity care assistant or study personnel. Serious adverse events will be communicated to the study team within 4 days. The study team will investigate this event and report it to the sponsor and the Medical Research Ethics Committee of the Erasmus MC Rotterdam. Insurance has been taken out for every participant in this study. The insurance covers any damage caused by the study.

The medical technical service department of the Erasmus MC-Sophia will provide technical maintenance of the phototherapy mattresses (at least two times per year). Once a year, calibration of the TcB devices will be carried out by the manufacturer.

A Data Safety Monitoring Board will not be established, given that the risks of this study are considered negligible. Monitoring of the study will be carried out according to the Guideline for Good Clinical Practice by an independent, qualified monitor at least once a year per PCBC.[37]

Patient and public involvement

The study protocol, study procedures and patient information form were discussed with the regional patient involvement board of the Rijnmond Obstetric District Platform ('District Verloskundig Platform'; DVP) and patient representatives of the Child & Hospital foundation ('Stichting Kind & Ziekenhuis': https://www.kindenziekenhuis.nl/). They consider the project highly relevant from a patient perspective and have agreed to be involved throughout execution, analysis and interpretation, dissemination to patients and implementation. The involved patient panels have considered the burden of the interventions negligible and underline the potential benefits of the study.

ETHICS AND DISSEMINATION

This study has been approved by the Medical Research Ethics Committee of the Erasmus MC Rotterdam (MEC-2017-473). Collected data will be coded. Only investigators will have access to identification list. Study documents and data will be stored for 15 years after completion of the study. Written informed consent is provided by parents of neonates included in the study. The study is registered in the Dutch Trial Registry (NTR7187).

The full protocol will be shared at request. Results of this study including the statistical code will be published in peer-reviewed scientific journals and be presented at (inter) national meetings. The results of the study will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) Statement guidelines.[38] We intend to provide an anonymised version of the dataset at request. Authorship will be determined according to the guidelines of the International Committee of Medical Journal Editors (ICMJE).[39] No professional writers will be used.

DISCUSSION

Identification and (referral for) treatment of neonatal jaundice is daily practice for maternity care professionals. The continuing occurrence and devastating consequences of KSD underline the urgent need for more effective identification and treatment of at-risk neonates.[1,7] This pragmatic study aims to evaluate the (cost-)effectiveness of (1) TcB

measurement as a screening tool for jaundice in a primary care setting and (2) application of phototherapy in the PCBCs in the Netherlands. To the best of our knowledge, this RCT will be the first to assess the (cost-)effectiveness of these diagnostic and treatment modalities in a primary care setting.

The study design allows all participating PCBCs to implement both interventions during the study and as such all PCBCs will have implemented the interventions as standard care toward the end of the study. This process will provide valuable information about the facilitators and barriers for implementation that will help upscaling of the interventions if (cost-)effectiveness is confirmed.

A limitation of this study is that parents and care providers cannot practically be blinded to allocation of the interventions. As a result, maternity care personnel or paediatricians may act differently in control and intervention periods. We will try to identify this via the questionnaires addressed at the maternity care assistants and the recording of the underlying reasons for paediatricians to divert from the new practice of applying phototherapy in the PCBC, if relevant. We will furthermore record the number of times TSB is quantified to evaluate whether this may change following implementation of the screening programme.

For this study, we take advantage of the fact that neonates receive primary care within PCBCs rather than at home. This centralised primary care provision is efficient in terms of feasibility of training the maternity care professionals and of minimising costs of transcutaneous bilirubinometers and phototherapy mattresses (i.e. groups of neonates can be covered with individual devices). Moreover, although the Dutch perinatal healthcare system is quite unique, care provision in PCBCs in the Netherlands is comparable to regular maternity care in many other high-income countries, which promotes generalisability.

We expect the interventions to be similarly effective in the home setting as in the PCBC setting, since the population in the PCBCs in the Netherlands does not differ from that the home setting. The costs in the PCBC setting may however differ from the home setting. Generalisability of the results to other countries and the home setting depends on several aspects, such as characteristics of the population, organisation of the maternity care system, presence of an effective screening program for neonatal hyperbilirubinaemia, and proximity and availability of sufficient healthcare. A future study to investigate the feasibility and effectiveness of the interventions in the home setting is needed if the current study is successful.

In conclusion, our study will generate useful data about the (cost-)effectiveness of TcB measurement as a universal screening tool for jaundice, potentially reducing the incidence of severe neonatal hyperbilirubinaemia. Several guidelines have highlighted the lack of research into the prevention of severe hyperbilirubinaemia.[9,10,13,40] Although most of these guidelines do not specify where phototherapy should be instituted, it is standard practice in most high-income countries – including the Netherlands – to do so in the hospital setting.[9,10,40] As such, institution of phototherapy in the primary care setting has significant potential to reduce healthcare costs associated with hospital admission. Furthermore, it promotes mother-child bonding by allowing mother and child to remain together in the same location.

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Learning from a factorial stepped-wedge cluster randomised controlled trial in primary care

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ABSTRACT

Neonatal hyperbilirubinaemia is a common phenomenon during the first days after birth. However, severe hyperbilirubinaemia may cause brain damage when not timely recognised and treated. Visual inspection, the traditional first-line approach to identifying hyperbilirubinaemia, is unreliable. The STARSHIP Trial was designed to assess the effectiveness of: (1) daily screening for neonatal hyperbilirubinaemia using transcutaneous bilirubin measurement in reducing severe hyperbilirubinaemia, and (2) application of phototherapy in primary care in reducing hospital admissions. A factorial stepped-wedge cluster randomised controlled trial is conducted in primary care birth centres in the Netherlands. Each cluster starts with a control phase of 'usual' care, followed by a phase in which one of the two interventions (i.e. daily transcutaneous bilirubin quantification or phototherapy in primary care) is applied. In the last phase, both interventions will be applied. The factorial design allows us to assess the effectiveness of two interventions in the same trial and is therefore time- and cost-efficient. Both interventions will implemented stepwise during the study. Towards the end of the trial, all clusters will have implemented both interventions. This offers the opportunity to learn from the implementation of the interventions during the study. Our initial experiences are that healthcare providers in the primary care setting are unfamiliar with conducting research, and extensive support is needed to assist them in their tasks.
In this case study these and other pros and cons of a factorial stepped-wedge cluster randomised controlled trial in primary care are outlined.

PROJECT OVERVIEW AND CONTEXT

Neonatal jaundice, caused by elevated serum bilirubin levels, is a physiological phenomenon during the first few days of life. However, severe hyperbilirubinaemia may cause brain damage (kernicterus spectrum disorder; KSD) when not timely recognised or left untreated.[1,2] KSD is a spectrum of neurological sequelae ranging from acute bilirubin encephalopathy and kernicterus at the extreme end to milder forms (e.g. mild hearing loss, delayed speech, mild abnormal muscle tone or gross motor delays) at the other end.[2-4] Timely recognition and treatment of potentially severe hyperbilirubinaemia is essential to prevent KSD.[5,6]

In most countries the primary approach to identifying potentially severe hyperbilirubinaemia is via visual inspection of the neonate's skin.[7,8] If the neonate is considered jaundiced, a heel prick is usually performed to quantify total bilirubin (TB) in blood to assess the need for treatment.[1,8] However, visual inspection is proven to be unreliable to detect potentially severe hyperbilirubinaemia[9,10] and, consequently, ineffective in preventing KSD as it may cause significant delay in the recognition of severe hyperbilirubinaemia.[11] Universal screening to timely detect neonatal hyperbilirubinaemia requiring treatment has the potential to reduce the incidence of severe hyperbilirubinaemia.[1,12] Transcutaneous bilirubin (TcB) measurements have been shown to correlate well with TB in the neonatal period.[13,14] Implementation of a TcB-based screening program in Canada was associated with a 55% reduction in severe hyperbilirubinaemia and related resource utilisation compared to visual inspection and selective TB measurement in healthy (near) term neonates.[15] A retrospective study in the United States comparing standard versus selective TB or TcB quantification in a hospital setting showed a similar reduction in the proportion of neonates having severe hyperbilirubinaemia.[16]

Phototherapy is the first line treatment for neonatal hyperbilirubinaemia.[1] Fibreoptic phototherapy using an underneath mattress is safe and effective to reduce TB levels.[17] Some studies suggest that fibreoptic phototherapy may be performed in a primary care setting as well.[13,18,19] Phototherapy for neonatal hyperbilirubinaemia applied in the primary care setting has the potential to reduce the need for hospital admission for phototherapy and accordingly, reduce associated costs.[20]

Evidence from randomised studies to support the assertions that universal TcB screening and application of phototherapy in primary care may reduce the incidence of severe hyperbilirubinaemia and the need for hospitalisation, respectively, is lacking. The Screening and TreAtment to Reduce Severe Hyperbilirubinaemia in Infants in Primary care (STARSHIP) Trial aims to address this knowledge gap.[21]

Section summary

- *Neonatal hyperbilirubinaemia is a physiologic phenomenon, but may cause brain damage when severe.*
- *Screening for hyperbilirubinaemia via visual inspection is unreliable.*
- *More effective approaches to recognising potentially severe hyperbilirubinaemia are needed.*
- *The first choice of treatment for hyperbilirubinaemia is phototherapy.*
- *Phototherapy is usually applied in-hospital.*
- *Evidence suggests that hyperbilirubinaemia can be treated safely and effectively in primary care.*
- *The STARSHIP trial is designed to evaluate the effectiveness of screening for hyperbilirubinaemia and of phototherapy in neonates cared for in primary care.*

RESEARCH DESIGN

The STARSHIP Trial was designed as a factorial stepped-wedge cluster randomised controlled trial (RCT) in primary care birth centres (PCBCs) in the Netherlands. The effectiveness of (1) daily screening for neonatal hyperbilirubinaemia using TcB measurement to reduce the incidence of severe hyperbilirubinaemia and of (2) phototherapy, as a treatment for neonatal hyperbilirubinaemia, instituted in PCBCs to reduce the need for hospitalisation, will be evaluated.

The study is performed in seven PCBCs in the Netherlands. In the Netherlands, approximately 30% of term deliveries are supervised by a community midwife in primary care (i.e. in a PCBC or at home).[22] In addition, many healthy (near) term neonates who were born in hospital are discharged home or to a PCBC within 24 hours after birth. Maternity care assistants (MCAs) provide maternity care at home or in a PCBC on a daily basis during the first 8 days after delivery.[23] The community midwife carries primary responsibility of the postpartum period in this situation and will visit the new family at least three times during the first week.[24] The community midwife may consult the paediatrician of an affiliated, nearby hospital if a potential clinical problem presents in the neonate.

The STARSHIP Trial has six clusters. Each of the seven participating PCBCs is allocated to a cluster; the two smallest PCBCs are paired and form a cluster together. Within each cluster, the two interventions are implemented in a stepwise fashion (according to the stepped-wedge design). Each cluster starts with a control phase where no intervention is implemented and in which care as usual is evaluated. In the next phase, one of the two interventions is implemented, and in the last phase both interventions are implemented

and their impact on the outcomes is evaluated. This is the 2x2 factorial aspect of the trial. Between the clusters, there is variation in the duration of each phase, and in which of the two interventions is implemented first (i.e. in phase two), according to schedules which were defined *a priori* (Figure 1). These sources of variation facilitate optimal comparison of the effectiveness of interventions in routine practice across the clusters. The allocation of the schedules depicted in Figure 1 to the different clusters is randomised.

Cluster	Time→						
	Time period 1	Time period 2	Time period 3	Time period 4	Time period 5	Time period 6	Time period 7
1	C	I1	I1	I1	I1	I1	I1 + I2
2	C	C	I1	I1	I1	I1 + I2	I1 + I2
3	C	C	C	I1	I1 + I2	I1 + I2	I1 + I2
4	C	C	C	I2	I1 + I2	I1 + I2	I1 + I2
5	C	C	I2	I2	I2	I1 + I2	I1 + I2
6	C	I2	I2	I2	I2	I2	I1 + I2

Figure 1. Allocation scheme
C, control; I1, intervention 1: transcutaneous bilirubin measurement; I2, intervention 2: phototherapy in primary care birth centre.

Control phase: standard care

During the control phase, standard care according to the Dutch national multidisciplinary guideline on neonatal hyperbilirubinaemia is assessed. Accordingly, visual inspection will be performed daily to identify potentially severe hyperbilirubinaemia. When potentially severe hyperbilirubinaemia is suspected, a heel prick will be done to quantify TB. The TB level will be plotted on the Dutch nomogram[25] and the community midwife will discuss the TB level with the affiliated paediatrician, according to the local procedures. The neonate will be admitted to the hospital if treatment for hyperbilirubinaemia is indicated.

Intervention 1: TcB quantification as a non-invasive screening tool for hyperbilirubinaemia

During this study phase, TcB will be quantified daily starting from 24 hours of age in all participating neonates in a PCBC allocated to this intervention. TcB has a maximum inaccuracy of 50 µmol/L (2.9 mg/dL) compared to TB.[13,26] Hence, TcB is considered to be elevated if the TcB level is above the phototherapy threshold (according to the Dutch nomogram[25]) minus 50 µmol/L (2.9 mg/dL). If TcB is elevated, a heel prick to quantify TB is performed. The obtained TB level will be assessed by the community midwife, who may consult the affiliated paediatrician if phototherapy is needed.

Intervention 2: phototherapy in the PCBC

During this study phase, the default location for application of phototherapy, if indicated, is the PCBC rather than the hospital. The need for phototherapy is assessed by a paediatrician of an affiliated hospital based on the TB level. The paediatrician will decide at what time points follow-up TB samples need to be taken, and – based on the TB level – when discontinuation of phototherapy is required. The affiliated paediatrician may decide to admit the neonate to the hospital at any time if there are strong reasons to do so.

Section summary

- *The STARSHIP Trial is a factorial stepped-wedge cluster RCT.*
- *Two interventions are assessed in the STARSHIP Trial:*
  - *Daily screening for neonatal hyperbilirubinaemia using TcB measurement (versus visual inspection).*
  - *Phototherapy treatment, applied in primary care (versus phototherapy in hospital).*

RESEARCH PRACTICALITIES

Aims and hypothesis

The aim of the study is to evaluate the effectiveness of (1) universal TcB screening in primary care to reduce severe hyperbilirubinaemia and (2) application of phototherapy in primary care to reduce the need for hospital admission for hyperbilirubinaemia. Severe hyperbilirubinaemia is defined as a TB level above the mean of the phototherapy and exchange transfusion threshold as defined by the Dutch national guideline.[8,21] We hypothesise that universal screening for neonatal hyperbilirubinaemia using TcB and application of phototherapy in primary care will (cost-)effectively reduce the incidence of severe hyperbilirubinaemia and the need for hospitalisation for hyperbilirubinaemia treatment.

Setting

We chose to conduct the research in PCBCs and not at home, because clustering of neonates within these facilities increased the feasibility in terms of the number of maternity care professionals who needed training regarding the study and the number of TcB and phototherapy devices that had to be purchased.

A PCBC was selected to participate in the study if it facilitated provision of maternity care during at least 48 hours postpartum. All eligible PCBCs in the Netherlands participated in the study.

Eligibility

Neonates are eligible if:

- The neonate was born after 35 weeks of gestation.
- The neonate is admitted to a participating PCBC.
- The neonate is expected to remain admitted in the PCBC for at least 2 days.
- Signed informed consent is provided by parent(s) or primary caregiver(s).

Neonates are not eligible if:

- The neonate received phototherapy previously or is currently receiving phototherapy.
- Parents do not have sufficient understanding of the Dutch language to be able to comprehend the patient information sheet.

Sample size

Two sample size calculations are needed, because two interventions, each with their own outcome, are assessed. We considered the two interventions independent of each other and therefore the larger sample size among the two sample size calculations is considered appropriate for the entire study. Sample size to demonstrate superiority rather than non-inferiority was calculated.

Based on an anticipated incidence of severe hyperbilirubinaemia of 1.2%,[8] 2691 neonates per arm are needed to identify a relative reduction of 55% following implementation of TcB screening with a power of 80% and an alpha of 0.05.[15] Based on an anticipated incidence of hospital admissions for phototherapy of 4%,[8] 1136 neonates per arm are needed to identify a relative reduction of 50% in hospital admissions for phototherapy following implementation of phototherapy in primary care with a power of 80% and an alpha of 0.05.

Based on the larger sample size of the two and accounting for a low degree of lost-to-follow-up, we aim to include 5500 neonates.

Data collection

The STARSHIP Trial is conducted in seven PCBCs at several locations across the Netherlands. Financial resources were not sufficient to appoint dedicated study personnel who could perform data collection and other study procedures on a daily basis within each of the PCBCs. MCAs working in each of the PCBCs where therefore extensively trained to perform these tasks. Study personnel is present in the PCBCs approximately twice per month to support the MCAs, and more frequently during crucial phases of the trial (e.g. when a next phase is entered where a new intervention is implemented). MCAs obtain

informed consent of the parents after eligibility of the neonate has been assessed and perform data collection. Research nurses and other study personnel (e.g. PhD student, medical students) support the MCAs in obtaining informed consent and collecting data.

Section summary

- *We hypothesise that*
  - *Universal transcutaneous bilirubin screening for neonatal hyperbilirubinaemia will (cost-)effectively reduce the proportion of neonates having severe hyperbilirubinaemia.*
  - *Application of phototherapy in primary care birth centres will (cost-)effectively reduce the proportion of neonates admitted to the hospital for neonatal hyperbilirubinaemia.*
- *The STARSHIP Trial is conducted in seven primary care birth centres.*
- *We aim to include 5500 neonates.*
- *Data collection is performed by MCAs.*

METHOD IN ACTION

All MCAs of the participating PCBCs were trained on various aspects of neonatal hyperbilirubinaemia (pathophysiology, risk factors, recognition and treatment) and study procedures. Several weeks before each training session participating MCAs were invited to complete a preparatory e-learning covering the same topics as the training session. The training sessions were held before the start of the study: from December 2017 to May 2018.

Approval of the Medical Research Ethics Committee (MREC) was obtained in April 2018 and enrolment in the first PCBC started in July 2018. The other participating PCBCs started enrolment in the following months. In January 2019, the final PCBC started enrolling neonates for the study. We initially aimed to start enrolment in all PCBCs within a time period of maximum 3 months in order to minimalise a potential confounding effect of calendar time. Calendar time may potentially influence the prevalence of a disease studied, the effectiveness of the interventions, and/or the outcomes. Hypothetically, for example, jaundiced neonates may be recognised earlier in summer, because more daylight may improve visual recognition. If the control period is mainly during the summer months and the period with TcB device is mainly studied during the winter months, this may affect effectiveness of the TcB intervention as determined in the study. The balanced allocation scheme aims to minimise such influence of calendar time (that is, the interventions are implemented in a stepwise fashion and across varying time

frames and hence the participants in the different phases with different interventions are distributed equally over calendar time). To minimise the impact of calendar time we had therefore planned to start enrolment in another PCBC every other week. However, following initiation of the study it soon became clear that implementation of enrolment and study procedures in each PCBC was more challenging and time-consuming than expected. Several barriers to implementation of the study procedures were experienced:

- The training sessions for MCAs had been organised in anticipation of MREC approval. Unfortunately, this approval was delayed by several months, causing a time gap between the training sessions and the actual start of the study. Accordingly, the MCAs needed extra explanation and support to refresh their awareness and knowledge on the study procedures when the study started. This was very labour-intensive and time-consuming.
- To address the knowledge gap regarding early recognition and treatment of hyperbilirubinaemia in the primary care setting, this trial is conducted in PCBCs. Healthcare professionals in the primary care setting and especially in the primary perinatal care setting are not used to conducting research. In fact, MCAs involved in the STARSHIP Trial had never before played an active role in a research project. Accordingly, they were inexperienced in typical clinical research tasks such as informing parents about a study, obtaining informed consent, and collecting and recording data. Also, the general educational level of MCAs is typically lower than that of other healthcare workers more typically involved in conducting research activities in perinatal care (i.e. physicians, midwives, nurses). Within the Netherlands, there currently is a shortage of MCAs and accordingly MCAs generally were already experiencing a relatively high workload within the PCBCs. As the study and its procedures constituted an extra task for the MCAs, these tasks were typically the first tasks to omit when the experienced workload was high. Consequently, MCAs' need for support regarding the study procedures was larger than anticipated, which complicated and delayed implementation of the study procedures in routine daily practice. Insufficient funds were available to cover expenses of additional research personnel to address this unanticipated barrier.

According to the stepped wedge design, all PCBCs had to start with a control phase to evaluate performance of usual care. During this phase, parents and their neonate do not experience potential benefits of participating in the study. The same applies for the MCAs during the control phase: they do not apply new interventions (which is the part they typically enjoy and experience as being relevant), but do need to obtain informed consent and collect data, tasks that are added to their daily routine and take time. This may have complicated successful enrolment of neonates in the control phase. In addition, MCAs have expressed that they experience the control phase as being very

lengthy. This reinforces their feeling that the study is very time-consuming. In addition, it appears that MCAs are more enthusiastic about the TcB intervention than the application of phototherapy in the PCBC. That is, visual inspection as a screening tool for neonatal hyperbilirubinaemia is part of their everyday routine and hence they regularly experience the drawbacks of this method of screening. Obviously, daily application of TcB screening directly addresses this issue in their perception. In contrast, the other intervention (application of phototherapy in the PCBC) is anticipated to be required in only 4% of (near) term neonates.[8] Accordingly, implementation of this intervention in daily practice may not be experienced as a major change in practice by MCAs, and certainly not on a daily basis.

So far, the inclusion rate in the STARSHIP Trial has been lower than needed in order to reach the required sample size in 2.5 years. We sought to address this by prolonging study inclusion, however given the factorial stepped-wedge design this is not straightforward. In a classic (parallel cluster) RCT, extending participant inclusion can simply be attained by extending the inclusion period. In our factorial stepped-wedge trial, however, extension of the trial in the final phase would result in extension of the phase with two interventions only. This would only increase the number of participants who were allocated to both interventions, whereas the group of participants who were allocated to one intervention or who were in the control period would remain the same, causing an imbalance in the number of participants. It is favourable for statistical power to keep a balance within the allocation scheme in order to equally distribute the number of participants over the different phases and interventions.[27] According to our allocation scheme (Figure 1), balanced extension of the inclusion period could only be attained by prolonging phase two and/or by proportionally prolonging both phase one and three. In March 2019, a decision was therefore made to prolong the trial's inclusion period by extending Time period 3 and 5 with 1 month and to extend Time period 4 with 2 months, resulting in a balanced extension of the study (see Figure 2). Although a longer extension, keeping the balance of the allocation scheme in mind, would have been possible, this was not desirable as this would lengthen the control phase in Time line 3 and 4 even more. As it was already difficult to keep the MCAs motivated during the control phase, this would have negatively influenced the attitude of the MCAs regarding the study, resulting in increasing the risk of a lower inclusion rate. The new allocation scheme is depicted in Figure 2.

These issues are some examples of potential issues encountered in a stepped-wedge design. Obviously, however the stepped-wedge design also has advantages, and we highlight a few below.

Cluster	Time→						
	Time period 1	Time period 2	Time period 3	Time period 4	Time period 5	Time period 6	Time period 7
1	C	I1	I1	I1	I1	I1	I1 + I2
2	C	C	I1	I1	I1	I1 + I2	I1 + I2
3	C	C	C	I1	I1 + I2	I1 + I2	I1 + I2
4	C	C	C	I2	I1 + I2	I1 + I2	I1 + I2
5	C	C	I2	I2	I2	I1 + I2	I1 + I2
6	C	I2	I2	I2	I2	I2	I1 + I2

Figure 2. Allocation scheme after extension of the study
C, control; I1, intervention 1: transcutaneous bilirubin measurement; I2, intervention 2: phototherapy in primary care birth centre.

In a stepped-wedge trial, the interventions are implemented in a stepwise manner, which allows personnel to gradually become acquainted with the study procedures and to incorporate them into daily practice. Furthermore, the stepwise schedule allows us to learn from the implementation of the interventions in the PCBCs and apply these lessons in the PCBCs that not have implemented that intervention yet. In addition, this knowledge is also very helpful when implementing these interventions on a larger scale after the trial, should (cost-)effectiveness of the interventions indeed be demonstrated. Another advantage is that, as a result of the stepped-wedge design (and opposed to for example a parallel cluster-RCT), all PCBCs will have implemented both interventions by the end of the study. If (cost-)effectiveness of the interventions has been proven, these PCBCs can easily continue to incorporate the interventions as part of standard care. Also, as compared to a parallel cluster RCT, centres may be more willing to participate in a stepped-wedge cluster RCT because every centre will be assigned to the intervention at some point.[28]
Another methodological advantage of the stepped-wedge design is that each cluster has a control phase and, therefore, can serve as a control for itself. This minimises the issue of intracluster correlation as compared to a parallel cluster RCT. Furthermore, the intervention phase in a particular cluster can be compared to its own control phase and thus the effectiveness of each intervention can be determined within a particular cluster as well.[28,29]

In a classic RCT with randomisation at the participant level rather than the cluster level (in this case the PCBC), contamination of interventions can occur.[30] For example, when some participants are randomised to the TcB device while others are not, midwives or MCAs may be tempted to use the device also in control participants if their experience is positive, particularly if the device is at already at their disposal. Randomisation at

the PCBC level prevents this contamination to occur (that is, the devices necessary to deliver the interventions are not available in the PCBC in the control phase).

The 2x2 factorial design of this study is also worth discussing briefly. The factorial design is a cost- and time-efficient method of research, since two independent interventions can be assessed at the same time in the same group of participants.[31] This design allows to study the individual and the combined effect of the interventions (in phase 2 and 3, respectively). Also, in the phase in which only one intervention is applied (i.e. Phase 2 for each PCBC), the participants function as control group for the other intervention, resulting in a shorter period without any intervention.[32]

Section summary

- *It is difficult for healthcare providers to implement study procedures into daily practice when they are unfamiliar with conducting research.*
- *It is important to realise that healthcare providers and parents may not experience benefits of being part of the control phase.*
- *Balancing of the duration of each study phase requires attention when prolonging a stepped-wedge cluster randomised controlled trial in case of lower-than-expected participant inclusion.*
- *The 2x2 factorial design allows assessment of the effectiveness of two interventions in the same trial.*
- *All clusters will have implemented both interventions toward the end of the study.*

PRACTICAL LESSONS LEARNED

The combination of a factorial stepped-wedge cluster RCT design and the primary care setting results in a number of challenges and accordingly in lessons learned for future research using the same design or conducted in a similar setting:

- Conducting research in settings where research is uncommon, for example, in primary perinatal care, provides a lot of opportunities: new groups of potential participants can be approached and relevant research questions pertaining to these participants addressed; research findings can be implemented in these settings and personnel that is not used to performing research can learn how to engage in research. However, when healthcare providers are not familiar with conducting research, requirement of extra personnel and time should be taken into account to provide support. This support includes clearly communicating and emphasising the importance of the study for clinical practice, providing extensive training to healthcare providers to perform the study procedures, helping the healthcare providers to implement

the study procedures in their routine daily practice, monitor the performed study procedures (e.g. check whether informed consent forms are filled out completely), and taking over study procedures when these procedures exceed the capability of the healthcare providers.

- In stepped-wedge cluster RCTs, (nearly) simultaneous start of enrolment at the different participating sites is ideally needed.[29] In order to enable this, each site preferably needs their own study personnel to provide daily support to optimise the start of enrolment.
- In a stepped wedge RCT, healthcare providers need to be prepared for starting the study with a control phase in which there is little incentive for parents and healthcare providers to participate in the study. Clear explanation of the study and its aims to parents is required to help parents understand why their participation is important in every phase of the study. Small incentives for the healthcare providers, such as a treat when a certain number of participants has been included, have been used in our study and may increase the effort of the healthcare providers for the study and consequently the inclusion rate.
- The 2x2 factorial design allows implementing two interventions in the same study. This is efficient in terms of time and costs, but implementation of two interventions also makes the study more demanding. Training sessions on study procedures in each study phase are needed. In addition, healthcare providers need to implement more study procedures in their routine daily practice. To facilitate this, ample support should be provided to the healthcare providers.
- The inclusion rate has to be monitored closely. When the inclusion rate is lower than expected and extension of the study is necessary, this should be done as soon as possible (no later than when half of the study period has passed) to allow extension while maintaining balance in the allocation scheme.

Section summary

- *Extensive support is needed when conducting research in settings where healthcare providers are unfamiliar with conducting research.*
- *In this stepped-wedge trial, each cluster starts with a control phase. It is important to clearly highlight the importance of the study in this phase.*
- *Prolongation of a stepped-wedge cluster randomised controlled trial at the end of the trial will result in an imbalance of participants over the different phases of the study. Therefore, potential prolongation of the study needs to be considered in time.*

CONCLUSION

A factorial stepped-wedge cluster RCT design offers opportunities to implement multiple interventions in a time- and cost-efficient manner. However, this design is also challenging, because it is less flexible when inclusion is behind schedule. For obvious reasons, research should be performed in a similar setting as the one in which the implementation will eventually take place (if efficacy has been proven). This is a particular challenge in the primary care setting or other settings where research is uncommon, and accordingly, sufficient support to facilitate personnel in conducting a trial in such settings is essential. Timely identification of such challenges is required in order to address and overcome them. If this is adequately handled, a factorial stepped-wedge cluster RCT design in primary care can be an unconventional but methodologically strong, very much needed, and promising method of research.

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Assessment and management of neonatal jaundice in healthy neonates cared for in primary care: a prospective cohort study

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ABSTRACT

Jaundice caused by hyperbilirubinaemia is a common phenomenon during the neonatal period. Population-based studies evaluating assessment, management, and incidence of jaundice and need for phototherapy among otherwise healthy neonates are scarce. We prospectively explored these aspects in a primary care setting via assessing care as usual during the control phase of a stepped wedge cluster randomised controlled trial.

We conducted a prospective cohort study embedded in the Screening and TreAtment to Reduce Severe Hyperbilirubinaemia in Infants in Primary care (STARSHIP) Trial. Healthy neonates were included in seven primary care birth centres (PCBCs) in the Netherlands between July 2018 and March 2020. Neonates were eligible for inclusion if their gestational age was ≥35 weeks, they were admitted in a PCBC for at least 2 days during the first week of life, and if they did not previously receive phototherapy. Outcomes were the findings of visual assessment to detect jaundice, jaundice incidence and management, and the need for phototherapy treatment in the primary care setting.

860 neonates were included of whom 608 (71.9%) were visibly jaundiced at some point during admission in the PCBC, with 20 being 'very yellow'. Of the latter, four (20%) did not receive total serum bilirubin (TSB) quantification. TSB levels were not associated with the degree of jaundice (p=0.416). Thirty-one neonates (3.6%) received phototherapy and none received an exchange transfusion. Five neonates did not receive phototherapy despite having a TSB level above phototherapy threshold.

Jaundice is common in otherwise healthy neonates cared for in primary care. TSB quantification was not always performed in very jaundiced neonates, and not all neonates received phototherapy when indicated. Quality improvement initiatives are required, including alternative approaches to identifying potentially severe hyperbilirubinaemia.

Trial registration: NL6997 (Dutch Trial Register; Old NTR ID 7187), registered 3 May 2018.

Neonatal hyperbilirubinaemia is a common condition during the first days of life and typically presents as visible jaundice.[1] Hyperbilirubinaemia in the neonatal period is usually benign. In some neonates, unconjugated bilirubin may reach hazardous levels and cause acute bilirubin encephalopathy and later kernicterus spectrum disorder (KSD) when not timely recognised and treated.[2]

In several countries and settings, the first-line recognition of hyperbilirubinaemia is based on visual inspection of jaundice, followed by selective total serum bilirubin (TSB) quantification (i.e. if considered necessary). Transcutaneous bilirubin (TcB) quantification is not widely used in the primary care setting. TSB levels are plotted on a nomogram to determine the need for treatment (Text Box 1).[3-5] Phototherapy is a safe and effective treatment to decrease bilirubin levels and is usually applied in-hospital.[1] When bilirubin levels are extremely high or continue to increase despite intensive phototherapy, one or more exchange transfusions may be needed to decrease bilirubin levels.

TEXT BOX 1: THE DUTCH TSB NOMOGRAM

The Dutch TSB nomogram is adapted from the American Academy of Pediatrics.[3] Treatment thresholds are based on postnatal age and risk assessment. Gestational age (<38 weeks or ≥38 weeks) and risk factors (blood group antagonism, haemolytic disease; birth asphyxia; suspicion of infection; drowsy or ill neonate; and serum albumin level below 30 g/L) are combined to assess the risk category: lower, medium, or higher risk. See Figure 1.

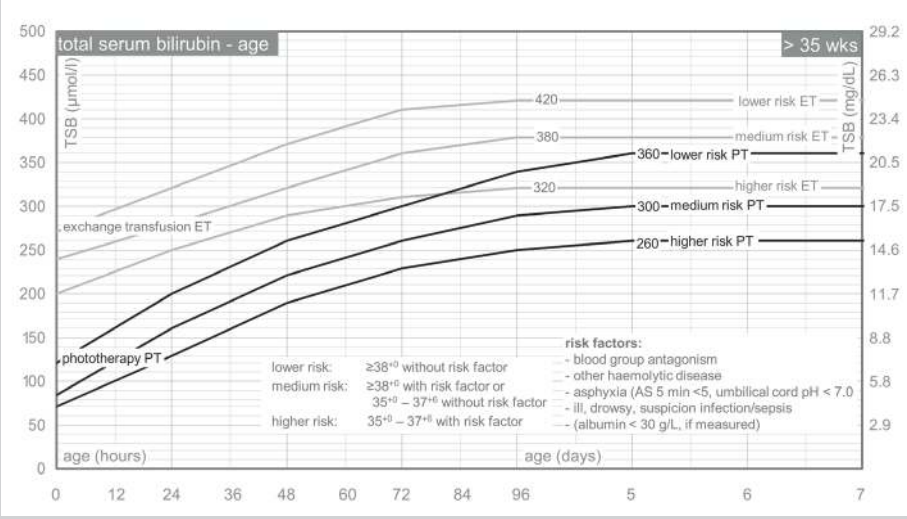

Figure 1. Phototherapy and exchange transfusion thresholds for neonates born after more than 35 weeks of gestation.

AS, Apgar score; ET, exchange transfusion; PT, phototherapy; TSB, total serum bilirubin. Translated from Dutch. The Dutch nomogram is available at http://babyzietgeel.nl/kinderarts/hulpmiddelen/diagnostiek/bilicurve35wkn.php.

Although neonatal jaundice is commonly observed, population-based data on the assessment, management, and incidence of visual jaundice and need for phototherapy among healthy neonates, especially if cared for in primary care, are scarce. Whereas the inaccuracy of visual inspection of jaundice to estimate TSB levels has previously been demonstrated,[6,7] the associations of visual jaundice assessment to the decision whether or not to quantify TSB, and of visual jaundice assessment to whether or not a neonate exceeded the individual phototherapy treatment threshold in primary care are unknown. Also, most population-based studies focus on hospitalised neonates having severe neonatal hyperbilirubinaemia or KSD.[8-11] Hence, these studies do not cover the complete scope of assessment, management, incidence, and burden of neonatal hyperbilirubinaemia. In addition, definitions of severe hyperbilirubinaemia vary, resulting in a wide variation in reported incidences of neonatal hyperbilirubinaemia between studies.[12-17]

The Screening and TreAtment to Reduce Severe Hyperbilirubinaemia in Primary care (STARSHIP) Trial is an ongoing factorial stepped-wedge cluster randomised controlled trial in seven Dutch primary care birth centres (PCBCs). It aims to assess the effectiveness of universal TcB screening and of phototherapy applied in primary care.[18] See Text Box 2. In each participating PCBC, the initial phase of the STARSHIP Trial evaluates usual care (i.e. no interventions are implemented). This provides a unique opportunity to explore the assessment, management, and incidence of neonatal jaundice and phototherapy in primary care among children included during this initial phase.

METHODS

Study design

Prospective cohort study embedded in the factorial stepped-wedge cluster randomised controlled STARSHIP Trial.[18]

Setting

In the Netherlands, most healthy neonates are either born in primary care or discharged to primary care (i.e. the home or a PCBC) within the first few hours to days of life.[19] A maternity care assistant (MCA) provides postpartum care to mother and neonate during daytime for the first eight days after delivery.[20] The MCA is supervised by a community midwife, who visits the family at least three times in the first week.[21] The MCA assesses each day whether the neonate is visually jaundiced and if so, to which degree. The MCA is expected to consult the community midwife if she considers the neonate 'too jaun-

diced' or if she feels that there are other reasons to quantify TSB. Medical doctors are only involved in the care of otherwise healthy neonates if consulted by the community midwife. The current national multidisciplinary guideline on neonatal hyperbilirubinaemia does not include universal screening, but alternatively states that each involved perinatal healthcare professional should be aware of a neonate's *a priori* risk for developing hyperbilirubinaemia and that this risk should be documented and communicated among all involved perinatal healthcare professionals.[4] According to the guideline, the midwife can have blood taken to quantify TSB levels if hyperbilirubinaemia is suspected based on visual inspection (e.g. a neonates is assessed 'too jaundice'). The guideline does not provide objective criteria for having TSB quantified.[4] One of the PCBCs and a small number of primary care midwifery practices participating in the STARSHIP Trial used selective transcutaneous bilirubin (TcB) screening (i.e. TcB quantification if a neonate is assessed 'too jaundiced', followed by TSB quantification if the TcB level is above or <50 µmol/L below the phototherapy threshold). TSB levels are plotted on the Dutch TSB nomogram (Text Box 1), which is based on the American Academy of Pediatrics guidelines.[3] A paediatrician of a nearby affiliated hospital can be consulted when hyperbilirubinaemia is confirmed, and this is then usually treated in the hospital.

The STARSHIP Trial is conducted in seven PCBCs throughout the Netherlands where MCAs provide postpartum care, supervised by community midwives. Women can choose to receive their care either at home or in a PCBC if the neonate is healthy. Neonates included in the control phase of the STARSHIP Trial, when usual care was evaluated, were included in this cohort. The control phase of the STARSHIP Trial ran between 2 July 2018 and 8 March 2020 (Supplementary Table 1).[18]

TEXT BOX 2: STARSHIP TRIAL

The Screening and TreAtment to Reduce Severe Hyperbilirubinaemia in Infants in Primary care (STARSHIP) Trial is a factorial stepped-wedge cluster randomised controlled trial. In the STARSHIP Trial, universal transcutaneous bilirubin screening and phototherapy in primary care are evaluated. The STARSHIP Trial is conducted in seven primary care birth centres (PCBCs) in the Netherlands. MCAs provide postpartum care supervised by community midwives in PCBCs. Medical doctors are not involved in providing care, although in some PCBCs they can be consulted if a problem arises. According to the factorial stepped-wedge cluster design of the STARSHIP Trial, each PCBC is allocated to a predefined timeline with three phases. Each PCBC starts with a control phase in which all included neonates receive standard care according to the national multidisciplinary hyperbilirubinaemia guideline (i.e. visual inspection of jaundice and selected TSB quantification to screen for hyperbilirubinaemia, and phototherapy in the hospital if treatment is indicated).[4] The control phase is followed

by a second phase in which one intervention is implemented (i.e. transcutaneous bilirubin screening *or* phototherapy in the PCBC rather than in-hospital) and eventually by a final phase in which both interventions are implemented (i.e. transcutaneous bilirubin screening *and* phototherapy in the PCBC).[18]

Participants

Neonates were eligible for inclusion in the STARSHIP Trial if:

- Born ≥35+0 weeks of gestation;
- Admitted to a participating PCBC during the first week of life;
- Expected to remain admitted to the PCBC for at least 2 days;
- Signed informed consent from parent(s) or primary caregiver(s) was obtained.

Neonates were not eligible if:

- The neonate previously received phototherapy;
- Parents did not have sufficient understanding of the Dutch language to be able to comprehend the patient information form.

For the analyses presented in this manuscript, all neonates included in the control phase of the STARSHIP Trial were eligible. Inclusion of the neonates was performed at admission to the PCBC and irrespective of the degree of jaundice of the neonate.

Variables

Outcomes of this study are: findings of assessment of jaundice by MCAs (ranging from 'not yellow at all' to 'very yellow'; in the Netherlands no standardised colour scale is used for visual jaundice assessment), the number of neonates in whom TSB was quantified; TSB level; management of neonatal hyperbilirubinaemia (i.e. what treatment is needed and what treatment is performed); the incidence of neonatal hyperbilirubinaemia and of receiving phototherapy treatment; and risk factors associated with receiving phototherapy. An overview of all variables used for the current analyses and definitions of variables is shown in Supplementary Table 2.

Data sources

Baseline data regarding mother and neonate, and daily data regarding findings of screening and treatment of neonatal hyperbilirubinaemia were collected by MCAs of the participating PCBCs and by study personnel of the STARSHIP Trial and stored in a Limesurvey/Gemstracker database.[22] Additionally, parent(s) of all included neonates were asked to fill out a questionnaire, 2 weeks after discharge from the PCBC, that included questions regarding hospital admission for hyperbilirubinaemia. If a neonate was admitted to the hospital for neonatal hyperbilirubinaemia, additional information

from the medical records regarding likely underlying causes, TSB levels, and treatment of hyperbilirubinaemia was requested from this hospital.

Statistical analysis

Analyses were performed using SPSS Statistics version 25.0. Data were summarised using descriptive statistics. Mean and standard deviation (SD) were calculated for continuous, normally distributed data. For non-normally distributed data, median and inw terquartile range (IQR) were calculated. As phototherapy treatment thresholds vary according to postnatal age and individual risk assessment for each neonate (Text Box 1), the difference between a neonate's TSB level and the corresponding phototherapy threshold for each individual neonate was calculated.[4,5] In the absence of information on individual risk factors determining phototherapy thresholds, such as blood group incompatibility, the risk factor is generally considered to be absent. To compare whether or not TSB was quantified, and the difference between neonates' TSB levels and corresponding phototherapy thresholds among neonates having different degrees of visual jaundice, χ^2 and Kruskal-Wallis test were performed as appropriate. Logistic regression was performed to analyse which risk factors were independently associated with hyperbilirubinaemia necessitating treatment. A p-value <0.05 was considered to indicate statistical significance.

Ethics

The STARSHIP Trial has been reviewed and approved by the Medical Research Ethics Committee of Erasmus MC Rotterdam, the Netherlands (MEC2017-473). The trial was performed in accordance with the Declaration of Helsinki.[23]

Consent to participate

Parents provided written informed consent before participation of their neonate in the study.

RESULTS

In total, 860 neonates were included in the control phase of the STARSHIP Trial. Baseline characteristics are shown in Table 1. Median gestational age was 39.3 weeks (IQR 1.9) and mean birth weight was 3399 grams (SD 487). Most neonates were born after a vaginal, non-instrumental delivery, had a Western ethnicity and a Rh D positive mother. Apgar score at 5 minutes was below 5 in 18 neonates (2.1%) and umbilical cord pH was below 7.0 in 11 (2.5%) out of 441 neonates in whom umbilical cord pH was quantified.

Table 1. Baseline characteristics

		n = 860
Sex		
Female	*n (%)*	398 (46.7)
Male	*n (%)*	454 (53.3)
Missing	*n*	*8*
Gestational age (weeks)	*Median (IQR)*	39.3 (1.9)
Missing	*n*	*10*
Birth weight (grams)	*Mean (SD)*	3399 (487)
Missing	*n*	*8*
Mode of delivery		
Vaginal, non-instrumental	*n (%)*	477 (56.1)
Vaginal, instrumental	*n (%)*	68 (8.0)
C-section, non-instrumental	*n (%)*	298 (35.0)
C-section, instrumental*	*n (%)*	8 (0.9)
Missing	*n*	*9*
Apgar score <5 at 5 minutes	*n (%)*	18 (2.2)
Missing or unknown	*n (%)*	*24*
Umbilical cord pH quantified	*n (%)*	441 (64.7)
Of which, umbilical cord pH <7.0	*n (%)*	11 (2.5)
Umbilical cord pH not quantified	*n (%)*	241 (35.3)
Missing or unknown	*n*	*178*
Maternal Rh D negative	*n (%)*	119 (16.3)
Of which, foetal Rh D positive	*n (%)*	42 (35.3)
Missing or unknown maternal Rh D	*n*	*131*
Non-western ethnicity neonate[#]	*n (%)*	200 (28.1)
Missing	*n*	*149*
Type of feeding		
Exclusive breastfeeding	*n (%)*	533 (62.6)
Exclusive formula feeding	*n (%)*	176 (20.7)
Combination	*n (%)*	143 (16.8)
Missing	*n*	*8*
PCBC[+]		
Fam, Tilburg	*n (%)*	56 (6.5)
Haga, The Hague	*n (%)*	98 (11.4)
Isala, Zwolle	*n (%)*	207 (24.1)
Maasstad, Rotterdam	*n (%)*	219 (25.5)
Noord, Rotterdam	*n (%)*	83 (9.7)
Sophia, Rotterdam	*n (%)*	187 (21.7)
Westeinde, The Hague	*n (%)*	10 (1.2)

IQR, interquartile range; PCBC, primary care birth centre; SD, standard deviation.
*C-section, instrumental refers to (1) a vaginally, instrumental delivery that failed and subsequently a C-section was performed or (2) the use of vacuum extraction or forceps during C-section to assist the delivery of the neonate's head.
[#]According to the definition of Statistics Netherlands.[24]
[+]Duration of inclusion period differed per PCBC. See Supplementary Table 1.

Assessment and incidence of neonatal hyperbilirubinaemia

The majority of neonates (n=608, 71.9%) had some degree of jaundice at any point during admission in the PCBC; the maximum degree of jaundice was 'slightly yellow' in the vast majority of jaundiced neonates (n=442, 72.7%). In most neonates, jaundice was first noted on postnatal day one or two (n=390, 75.0% of neonates having some degree of jaundice); two neonates (0.3%) were jaundiced within 24 hours after birth (i.e. on postnatal day 0). TSB was quantified at least once in 129 neonates (15.0%). Twenty-three neonates (2.7%) had a TSB level above the phototherapy threshold during PCBC admission, at a median age of 57 hours (IQR 43).[4] In an additional five neonates, TSB level was above phototherapy threshold after discharge home from the PCBC (postnatal age range: 40-142 hours), see Table 2.

In total, 165 TcB and 171 TSB quantifications were performed during admission in the PCBC. Figure 2 shows the association between visual jaundice assessment by the MCA and whether or not TcB or TSB quantification was performed. Although there was a clear increase in the proportion of neonates having TcB or TSB quantified as jaundice was considered more severe (χ^2 trend test $p<0.001$), still no TcB or TSB was quantified in 44% of the neonates considered 'quite yellow' and in 20% in of the neonates considered 'very yellow'.

The difference between individual phototherapy treatment thresholds and TSB levels according to the visually assessed degree of jaundice is shown in Figure 3. TSB was below the treatment threshold for all four assessments resulting in TSB being quantified in the absence of jaundice. There was no clear association between the degree of jaundice and the TSB level in those having TSB quantified (p=0.416).

Management of hyperbilirubinaemia

Table 3 shows the management of hyperbilirubinaemia in neonates who received treatment. During the control period of the STARSHIP Trial, 33 neonates (3.8%) had a TSB level above the phototherapy treatment threshold.[4] Phototherapy was performed in 31 neonates (3.6%) with a median duration of 22 hours (IQR 22.5). Three neonates (0.3%) received phototherapy despite having a TSB level below the phototherapy threshold, whereas five neonates (0.6%) did not receive phototherapy despite having a TSB level above the phototherapy threshold.[4] TSB levels of the latter five exceeded phototherapy threshold with a maximum of 31 µmol/L (1.81 mg/dL). One of these neonates was admitted to the hospital for another reason than hyperbilirubinaemia treatment. TSB levels exceeded the threshold for exchange transfusion (with a maximum of 71 µmol/L; 4.15 mg/dL) during admission in the PCBC in three neonates (0.3%) and during hospital admission in one additional neonate (0.1%),[4,5] but no exchange transfusions were per-

formed. The neonates with TSB levels that exceeded the exchange transfusion threshold during admission in the PCBC were slightly yellow (n=2) and very yellow (n=1). None of these neonates had a TSB quantified in the PCBC prior to exceeding the exchange transfusion threshold.

Table 2. Assessment and incidence of neonatal hyperbilirubinaemia

		n = 860
Neonates having any degree of jaundice as assessed by MCA; maximum degree:	*n (%)*	608 (71.9)
Slightly yellow	*n (%)*	442 (72.7)
Moderately yellow	*n (%)*	91 (15.0)
Quite yellow	*n (%)*	61 (10.0)
Very yellow	*n (%)*	14 (2.3)
Missing visual jaundice assessment	*n*	*14*
First postnatal day of jaundice during admission in PCBC (n=608)*		
Day 0 (0-23 h)	*n (%)*	2 (0.9)
Day 1-2 (24-71 h)	*n (%)*	390 (75.0)
Day 3-5 (72-143 h)	*n (%)*	202 (73.2)
Day 6-8 (144-215 h)	*n (%)*	8 (23.5)
Missing first day of jaundice	*n*	*6*
Neonates who had TcB quantified in PCBC	*n (%)*	116 (13.5)
1 TcB quantification	*n (%)*	80 (9.3)
2 or more TcB quantifications	*n (%)*	36 (4.2)
Neonates who had TSB quantified in PCBC (before start of phototherapy, if indicated)	*n (%)*	129 (15.0)
1 TSB quantification	*n (%)*	96 (11.1)
2 or more TSB quantifications	*n (%)*	33 (3.8)
Bilirubin nomogram risk category		
Lower risk	*n (%)*	664 (77.2)
Medium risk	*n (%)*	172 (20.0)
Higher risk	*n (%)*	14 (1.6)
Missing	*n*	*10*
Highest TSB level during admission in PCBC (µmol/L; n=124)	*Mean (SD)*	223 (68)
TSB level missing	*n*	*5*
Neonates having a TSB level above phototherapy threshold during admission in PCBC[#]	*n (%)*	26 (3.0)
TSB level missing	*n*	*2*
Postnatal age when exceeding phototherapy threshold in PCBC (hours; n=23)	*Median (IQR)*	57 (43)
Neonates having a TSB level above phototherapy threshold after discharge home	*n (%)*	7 (0.8)
Missing	*n*	*148*

IQR, interquartile range; MCA, maternity care assistant; PCBC, primary care birth centre; SD, standard deviation; TSB, total serum bilirubin.

*Percentage according to number of participating neonates that had some degree of jaundice during admission in the PCBC and were admitted in a participating PCBC at the time.

[#]Phototherapy threshold according to the Dutch TSB nomogram.[4,5]

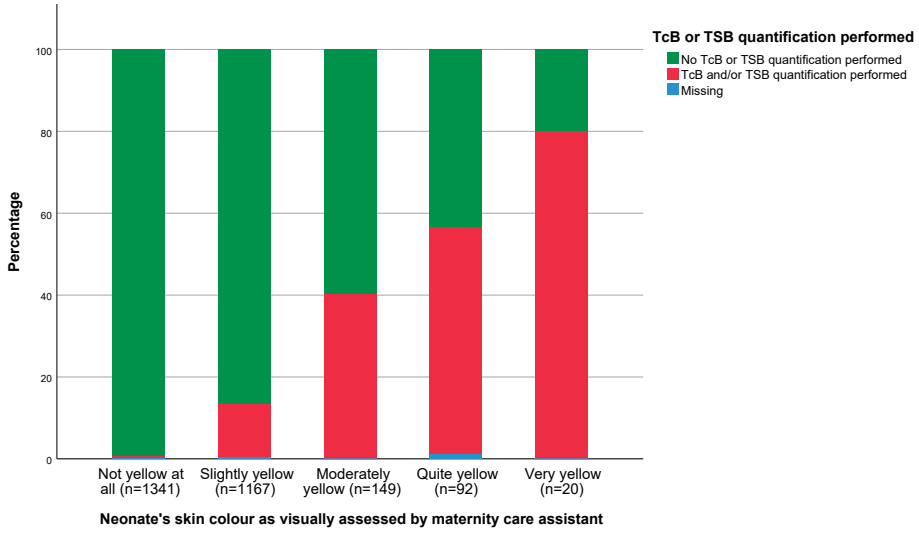

Figure 2. Proportion of assessment resulting in TcB or TSB being quantified according to degree of visible jaundice

TcB, transcutaneous bilirubin; TSB, total serum bilirubin.

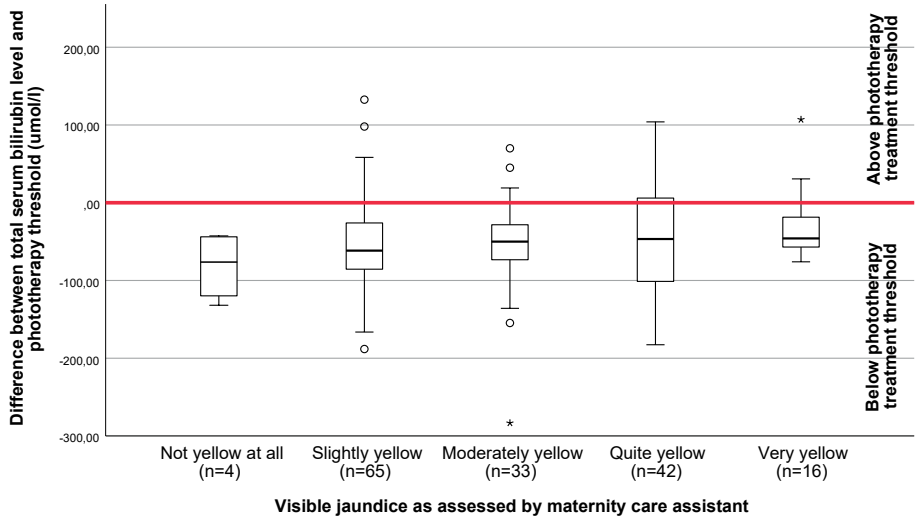

Figure 3. Difference between individual phototherapy treatment threshold and total serum bilirubin level according to degree of jaundice as visually assessed.

The area above the red bar indicates a total serum bilirubin level above phototherapy treatment threshold.

Table 3. Hyperbilirubinaemia management

		n = 858*
Neonates having hyperbilirubinaemia above the treatment threshold[4,5]	*n (%)*	33 (3.8)
Highest TSB level overall if necessitating treatment (µmol/L)	*Mean (SD)*	318 (50)
Phototherapy performed	*n (%)*	31 (3.6)
Total duration of phototherapy (hours)	*Median (IQR)*	22 (22.5)
Missing duration of phototherapy	*n*	*1*
Exchange transfusion threshold exceeded[#]	*n (%)*	4 (0.5)
Exchange threshold exceeded in PCBC	*n (%)*	3 (0.3)
Exchange threshold exceeded in hospital	*n (%)*	1 (0.1)
Exchange transfusion performed	*n (%)*	0 (0.0)

IQR, interquartile range; SD, standard deviation.
*The need for phototherapy was unknown for two neonates, as daily measurements and parental questionnaire were not filled out. These neonates were excluded from these analyses.
[#]Phototherapy threshold according to the Dutch TSB nomogram.[4,5]

Risk factors for receiving phototherapy treatment

Neonates who received phototherapy were more often born before 38 weeks of gestation when compared to neonates not receiving hyperbilirubinaemia treatment (56.7% vs. 12.8%; p<0.001). The proportion of neonates born after an instrumental delivery was higher in the group receiving phototherapy than in the group not receiving phototherapy (26.7% vs. 8.3%; p=0.004). Birth weight percentile,[25] perinatal asphyxia, Rh D incompatibility, type of feeding, sibling(s) who received phototherapy, and ethnicity were not significantly different between neonates who received phototherapy and those who did not (Table 4).

DISCUSSION

In our prospective cohort study evaluating the assessment, management, and incidence of neonatal hyperbilirubinaemia and the need for phototherapy among neonates cared for in primary care, we found that approximately 70% of neonates became jaundiced at any point during the first days of life and that 3.6% received treatment for hyperbilirubinaemia. However, not all neonates who had a TSB level that exceeded the phototherapy threshold received phototherapy. Also, TcB or TSB levels were not quantified in a substantial proportion of neonates assessed as moderately to severely jaundiced. Visual jaundice assessment was not reliable in estimating TSB levels.

Table 4. Association of risk factors with receiving treatment for hyperbilirubinaemia

	Received phototherapy (n = 31)	Did not receive phototherapy (n= 827)	Total (n = 858)+	p value
Gestational age				<0.001*
< 38 weeks	17 (56.7)	105 (12.8)	122 (14.4)	
> 38 weeks	13 (43.3)	713 (87.2)	726 (85.6)	
Missing	*1*	*9*	*10*	
Mode of delivery				0.004*
Non-instrumental	22 (73.3)	751 (91.7)	773 (91.0)	
Instrumental	8 (26.7)	68 (8.3)	76 (9.0)	
Missing	*1*	*8*	*9*	
Birth weight percentile[25]				0.398
< p10	5 (16.7)	88 (10.8)	93 (11.0)	
p10 – p90	25 (83.3)	647 (79.1)	672 (79.2)	
> p90	0 (0.0)	83 (10.1)	83 (9.8)	
Missing	*1*	*9*	*10*	
Presence of perinatal asphyxia*				0.191
Yes	2 (7.1)	27 (3.3)	29 (3.5)	
No	26 (92.9)	783 (96.7)	809 (96.5)	
Missing	*3*	*17*	*20*	
Presence of Rh D incompatibility				0.920
Yes	2 (7.1)	40 (6.2)	42 (6.2)	
No	26 (92.9)	608 (93.8)	634 (93.8)	
Missing or unknown	*3*	*179*	*182*	
Type of feeding				0.673
Exclusive breastfeeding	17 (56.7)	516 (62.9)	284 (34.5)	
Non-exclusive or no breastfeeding	13 (43.3)	304 (37.1)	540 (65.5)	
Missing	*1*	*9*	*10*	
Sibling received hyperbilirubinaemia necessitating treatment				0.964
Yes	4 (13.8)	33 (4.8)	37 (5.2)	
No	25 (86.2)	649 (95.2)	674 (94.8)	
Missing	*2*	*145*	*147*	
Ethnicity neonate				0.154
Western	22 (75.9)	489 (71.7)	511 (71.9)	
Non-Western	7 (24.1)	193 (28.3)	200 (28.1)	
Missing	*2*	*147*	*149*	

*Defined as Apgar score <5 at 5 minutes and/or umbilical cord pH <7.0. According to the definition of the Dutch total serum bilirubin nomogram.

+The need for phototherapy was unknown for two neonates, as daily measurements and parental questionnaire were not filled out. These neonates were excluded from this analysis.

To the best of our knowledge, this study is the first to prospectively describe the full scope of assessment, management, and corresponding incidence of hyperbilirubinaemia in otherwise healthy neonates cared for in primary care. This provides insight in the overall burden of neonatal hyperbilirubinaemia in primary care. We were able to identify neonates requiring phototherapy following discharge home by using parental questionnaires. Using parents as a source for data also has some pitfalls. First, if parents indicated that their neonate received phototherapy after discharge from the PCBC, this was not always in agreement with the actual data from the medical records in the hospital. Second, despite the prospective nature of the study, a proportion of included neonates had missing data, primarily due to missing parental questionnaires (17.3%). This may have led to an underestimation of the proportion of neonates who needed treatment. However, among the 711 (out of 860) neonates whose parents did respond, only five extra neonates who received treatment were identified using the questionnaires. Thus, we expect minimal influence of the missing data on this outcome. Neonates born after a C-section were overrepresented in our study (36% vs. 15% nationally),[26] probably because their mothers were more likely to stay (longer) in the PCBC. As C-section is not known as a protective or risk factor for neonatal hyperbilirubinaemia, we expect negligible impact on our results. Additionally, the informed consent procedure may have induced selection (e.g. neonates whose parents refused participation in the STARSHIP Trial may have had other demographic characteristics). In contrast, overestimation of the proportion of neonates receiving hyperbilirubinaemia treatment in the whole population may have occurred as well. This is because we were dependent on parental consent for participation of their neonate in the STARSHIP Trial and parents having a previous child with hyperbilirubinaemia may have been more likely to provide informed consent. Unfortunately, we were unable to assess the incidence of receiving phototherapy and associated risk factors (e.g. siblings having received phototherapy) among neonates without consent. Other findings may also have been influenced by the trial itself. Before the start of the STARSHIP Trial, all maternity care professionals were trained regarding neonatal hyperbilirubinaemia and study procedures. The training and the trial may have raised awareness on neonatal hyperbilirubinaemia, potentially resulting in a lower threshold to assess the neonate as jaundiced and to quantify TSB. From a clinical perspective, this can be considered a positive development in the context of preventing severe hyperbilirubinaemia.

The incidence of visible jaundice in our study is comparable to other studies in (near) term neonates in which 60-90% became jaundiced.[27-29] The finding that visual jaundice assessment is not reliable to estimate TSB levels is in line with other studies describing the inaccuracy of visual jaundice assessment.[6,7] Strikingly, in a substantial proportion of neonates being assessed as ‘quite yellow’ or ‘very yellow’, no TcB or TSB was quantified.

This observation corresponds with a previous study among MCAs regarding neonatal hyperbilirubinaemia, which showed structural underestimation of TSB levels and common application of a so-called 'wait-and-see approach' in visibly jaundiced neonates.[30] Moreover, despite being strongly recommended by the national guideline,[4] TSB was not quantified in two neonates who developed visible jaundice within 24 hours after birth. Also, five neonates did not receive phototherapy despite having a TSB level that exceeded the phototherapy threshold as defined by the national guideline.[4] Our evaluation of standard practice in this cohort highlights significant gaps in guideline application. In the current study, we did not prospectively explore the considerations underlying these decisions. Previous studies indicate that lack of knowledge on guideline recommendations,[31,32] and systematic underestimation of the severity of jaundice based on visual assessment likely contributed.[30] Other potential reasons for non-compliance may include a belief that the recommendations in the guideline do not reflect the best care for the neonate (e.g. a healthcare provider may consider the phototherapy thresholds too conservative as evidence on exact phototherapy thresholds is lacking,[33] and TSB quantification is avoided to keep the neonate in primary care), or practical challenges regarding feasibility of guideline compliance in daily practice. Research focused on these considerations may be useful to improve guideline adherence. This non-compliance to neonatal jaundice guidelines can have potentially severe consequences, as demonstrated by Rennie *et al*. in a Swedish study where KSD was (potentially) avoidable in 11 out of 13 neonates having KSD.[9] Additionally, a national audit indicated that non-compliance to the guideline was an important contributing factor to severe neonatal hyperbilirubinaemia in the Netherlands.[34]

Most studies assessing the burden of neonatal hyperbilirubinaemia focused on severe neonatal hyperbilirubinaemia or on KSD.[12-17] Studies assessing the hospitalisation rate for neonatal hyperbilirubinaemia showed incidences for hyperbilirubinaemia treatment ranging from 0.55 to 2.62%.[35-39] The retrospective nature of these studies in which the researchers depended on correct registration of the diagnosis of hyperbilirubinaemia may have contributed to the lower published incidence. Studies having phototherapy use as secondary outcome when assessing the institution of a bilirubin screening programme found (slightly) higher percentages in their control group (4.2-6.1%).[38-40] The difference in the percentage of neonates necessitating hyperbilirubinaemia treatment between these studies and ours may also be attributed to other hyperbilirubinaemia assessment and management strategies. In the Netherlands, neonates are typically screened visually for neonatal hyperbilirubinaemia, followed by selective TSB quantification; universal TcB or TSB screening is not performed. Additionally, in the Netherlands a relatively high proportion of neonates are cared for in primary care shortly after birth, where transcutaneous bilirubinometers are not widely used yet. Our current evaluation

of care-as-usual indicates that TcB or TSB is often not quantified even in neonates who were considered quite yellow or very yellow. As such, it is possible that some neonates requiring phototherapy were not identified. In other countries, most neonates remain admitted in the hospital for several days after birth and TcB or TSB is quantified before discharge.[3,15]

Potential risk factors for developing severe hyperbilirubinaemia have been widely investigated.[3,33] Whereas gestational age <38 weeks is a well-known risk factor, instrumental delivery itself is not widely investigated as risk factor.[16,41-43] Most studies focus on bruising and cephalic haematomas, that may arise from an instrumental delivery, which increases the risk for severe neonatal hyperbilirubinaemia.[16,41] Instrumental delivery may be a marker for another risk factor (e.g. large for gestational age; LGA).[44] However, we did not find a higher LGA incidence in neonates receiving phototherapy. Other well-known risk factors for hyperbilirubinaemia, such as Rh D incompatibility, previous siblings who received phototherapy, and exclusive breastfeeding, did not differ significantly between neonates who received phototherapy and those who did not. This may in part be due to limited power.

Findings from this study are useful for perinatal healthcare providers in primary care as well as in secondary and tertiary care (e.g. if a neonate is admitted together with mother). Data on the incidence of jaundice and the need for hyperbilirubinaemia treatment can help raise awareness regarding the extent of the problem. This awareness should also include the inaccuracy of visual jaundice assessment. Although this inaccuracy has been demonstrated previously,[29,45,46] our current study indicates that many healthcare professionals still strongly rely on visual assessment, and this is in fact in line with the current Dutch guideline, which is currently now undergoing revision. Although not every case of severe hyperbilirubinaemia results in KSD, KSD is entirely preventable and should clearly be a never-event. As such, regarding severe hyperbilirubinaemia as a healthcare system failure may strengthen implementation of new strategies to prevent KSD.[47] More objective approaches to universal hyperbilirubinaemia screening, for example using a transcutaneous bilirubinometer, should be considered to improve early recognition of potentially severe hyperbilirubinaemia.[3,48,49] Even though the PCBCs and their healthcare professionals took part in a trial focused on hyperbilirubinaemia assessment and management, the recommendations of the national guideline regarding TSB quantification and start of phototherapy treatment were not adhered to in some cases. Hence, more knowledge regarding risk factors for hyperbilirubinaemia, when to quantify TSB, treatment thresholds, and adherence to the national guideline are important as well. Future research should focus on objective approaches of universal screening for potentially severe neonatal hyperbilirubinaemia in a primary care setting. The STARSHIP Trial

will present results from implementing a universal screening programme in primary care using TcB in the next year or two.

In this prospective cohort study embedded in the STARSHIP Trial, assessment, management and incidence of neonatal jaundice and the need for phototherapy were evaluated. We demonstrated that the vast majority of neonates had some degree of jaundice during admission and that phototherapy was provided in 3.6% of neonates. Also, we showed that visual jaundice assessment was inaccurate in determining hyperbilirubinaemia and that compliance to the guideline requires improvement. We suggest that awareness regarding neonatal hyperbilirubinaemia and its potentially devastating consequences should be raised. Additionally, the benefits of objective universal screening to improve recognition of hyperbilirubinaemia need to be assessed in an attempt to reduce the burden of neonatal hyperbilirubinaemia.

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SUPPLEMENTARY FILES

Supplementary Table 1. Start and end dates control phase STARSHIP Trial

PCBC	Start date control phase	End date control phase
Fam, Tilburg	21 November 2018	26 May 2019
Haga, The Hague	3 August 2018	12 May 2019
Isala, Zwolle	14 January 2019	8 March 2020
Maasstad, Rotterdam	13 September 2018	10 November 2019
Noord, Rotterdam	5 November 2018	1 May 2019
Sophia, Rotterdam	2 July 2018	14 April 2019
Westeinde, The Hague	23 January 2019	18 March 2019*

PCBC, primary care birth centre.
*The planned end date of the control phase in PCBC Westeinde was 10 July 2019. However, as of 18 March 2019 this PCBC was permanently closed due to unforeseen circumstances.

Supplementary Table 2. Variables used for analysis

Category	Variable
Maternal characteristics	Gestational age (days)
	Maternal birth country
	Maternal Rh D factor
	Parity
Family characteristics	Paternal birth country
	Siblings with history of neonatal hyperbilirubinaemia
Delivery characteristics	Mode of delivery (vaginal non-instrumental; vaginal, with vacuum; vaginal, with forceps C-section, non-instrumental; C-section, instrumental)
Neonatal characteristics at baseline	Sex (male; female; indistinct)
	Apgar score <5 after 5 minutes (no; yes; unknown)
	Arterial umbilical cord pH quantified (no; yes; unknown)
	Arterial umbilical cord pH <7.0 (no; yes; unknown)
	Birth weight (grams)
	Type of feeding (multiple answers possible: Breastfeeding on demand; Breastfeeding on schedule; Mother's milk via bottle or finger feeding; Formula feeding)
	Foetal Rh D factor (not determined; Rh D positive; Rh D negative; unknown)
Daily measurements	Skin colour (not yellow at all; slightly yellow; moderately yellow; quite yellow; very yellow)
	Weight (grams)
	Risk factors for hyperbilirubinaemia (Blood group or Rh antagonism; Other haemolytic disorder; Asphyxia; Ill or drowsy neonate; Other, namely)
	TSB levels in µmol/L with age of neonate in hours at measurement (if relevant)
	Decisions made based on TSB (if relevant)
	Admission to hospital (no; yes)
Parental questionnaire	Hospital admission after admission in PCBC (yes; no)
Data requested from hospital (if relevant)	Duration of hospital admission in nights
	Duration of phototherapy (in hours)
	Exchange transfusion performed
	Number of exchange transfusions performed
	All laboratory quantifications during admission with age of neonate in hours at quantification
	Blood group and Rh D factor neonate
	Blood group and Rh D factor mother
	Risk factors for neonatal hyperbilirubinaemia (as described in medical records)

Supplementary Table 2. Variables used for analysis (*continued*)

Category	Variable
Variables composed for analysis	Any degree of jaundice: neonate having any degree of jaundice as assessed by MCA (i.e. slightly yellow, moderately yellow, quite yellow, or very yellow) during admission in PCBC.
	Maximum degree of jaundice: maximum intensity of jaundice of neonate during admission in PCBC.
	First postnatal day of visual jaundice during admission in PCBC: first day on which any degree of jaundice (i.e. slightly yellow, moderately yellow, quite yellow, or very yellow) was noted during admission in PCBC.
	Presence of perinatal asphyxia: Apgar score <5 at 5 minutes and/or umbilical cord pH <7.0*
	Exclusive breastfeeding: neonate was exclusively breastfed (i.e. no pumped mother's milk, no finger feeding). Non-exclusive breastfeeding or formula feeding: neonate was fed with pumped mother's milk or formula feeding by bottle or finger feeding (sometimes in combination with being breastfed).
	Western neonatal ethnicity: mother and father (if known) are born in a Western birth country. Non-Western neonatal ethnicity: mother or father (if known) are born in a non-Western birth country.[#]
	Age at discharge from the PCBC home or to the hospital: difference between discharge date and time and birth date and time in hours. *If discharge date missing: day after last measurements in PCBC was considered as discharge date,* *If discharge time was missing: 10.00h was considered as discharge time.*

MCA, maternity care assistant; PCBC, primary care birth centre; TSB, total serum bilirubin.
*As defined in the Dutch bilirubin nomogram.[1]
[#]According to the definition of Statistics the Netherlands.[2]

SUPPLEMENTARY REFERENCES

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Part THREE

Towards new strategies for hyperbilirubinaemia screening at home

8.

BMJ Open. Accepted.

Better assessment of neonatal jaundice at home (BEAT jaundice@ home): an observational, prospective multicentre study protocol

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ABSTRACT

Introduction Severe neonatal hyperbilirubinaemia can place a neonate at risk for acute bilirubin encephalopathy and kernicterus spectrum disorder. Early diagnosis is essential to prevent these deleterious sequelae. Currently, screening by visual inspection followed by laboratory-based bilirubin (LBB) quantification is used to identify hyperbilirubinaemia in neonates cared for at home in the Netherlands. However, the reliability of visual inspection is limited. We aim to evaluate the effectiveness of universal transcutaneous bilirubin screening as compared to visual inspection to: (1) increase the detection of hyperbilirubinaemia necessitating treatment, and (2) reduce the need for heel pricks to quantify bilirubin levels. In parallel, we will evaluate a smartphone app (Picterus®), and a point-of-care device for quantifying total bilirubin (Bilistick®) as compared to LBB.

Methods and analysis We will undertake a multicentre prospective cohort study in nine midwifery practices across the Netherlands. Neonates born at a gestational age of 35 weeks or more are eligible if they: (1) are at home at any time between day two and eight of life; (2) have their first midwife visit prior to postnatal day six; and (3) did not previously receive phototherapy. TcB and the Picterus® app will be used after visual inspection. When LBB is deemed necessary based on visual inspection and/or TcB reading, Bilistick® will be used in parallel. The co-primary endpoints of the study are: (1) hyperbilirubinaemia necessitating treatment; (2) the number of heel pricks performed to quantify LBB. We aim to include 2310 neonates in a two-year period. Using a decision tree model, a cost-effectiveness analysis will be performed.

Ethics and dissemination This study has been approved by the Medical Research Ethical Committee of the Erasmus MC Rotterdam, the Netherlands (MEC-2020-0618). Parents will provide written informed consent. The results of this study will be published in peer-reviewed journals.

Study registration: Netherlands Trial Register (NL9545).

INTRODUCTION

Neonatal jaundice, caused by elevated levels of unconjugated bilirubin, is a common phenomenon during the first few days of life. This unconjugated hyperbilirubinaemia is generally transient and considered benign. However, when very high bilirubin levels are left untreated, non-protein bound bilirubin may pass the blood-brain barrier and damage the neonate's developing brain. Hence, severe neonatal hyperbilirubinaemia may result in acute bilirubin encephalopathy. Neonates with acute bilirubin encephalopathy urgently require treatment as they are prone to develop a chronic phase with irreversible brain damage, known as kernicterus spectrum disorder.[1] Kernicterus spectrum disorder consists of a variety of severe pathologic conditions including motor, cognitive, and auditory disorders with life-long sequelae.[2,3] Phototherapy is often successful in reducing bilirubin to non-hazardous levels, and may also revert early stages of acute bilirubin encephalopathy.[4] When phototherapy is unsuccessful in treating severe neonatal hyperbilirubinaemia, one or more exchange transfusions are necessary to lower circulating bilirubin levels. However, exchange transfusions are invasive, high-risk procedures that should be avoided if possible. Thus, timely recognition of neonates with imminent severe hyperbilirubinaemia is essential.

In the Netherlands, the majority of neonates born at a gestational age of 35 weeks or more are eventually cared for at home, irrespective of the place of birth.[5] Daily postpartum care at home is provided by maternity care assistants during the first week after birth, who are supervised by community midwives. The community midwife visits mother and neonate at home usually at least three times in the first week after birth.[6] As per the current multidisciplinary Dutch national guideline for identification and treatment of neonatal jaundice, visual inspection is used as first-line screening in neonates cared for at home.[7] If potentially severe hyperbilirubinaemia is suspected based on visual inspection, the community midwife may decide to have bilirubin levels checked in the neonate's blood, taken by the midwife or a specialised laboratory home service. Based on this laboratory-based bilirubin (LBB) level, the need for treatment of hyperbilirubinaemia is assessed using the nomogram of the Dutch national guideline, adapted from the American Academy of Pediatrics 2004 guideline.[6,7] If the LBB level indicates the need for treatment, this is usually applied in-hospital.

Several studies have shown that visual inspection is not a reliable screening tool for neonatal hyperbilirubinaemia.[8,9] In a significant proportion of neonates admitted from home with severe hyperbilirubinaemia and/or acute bilirubin encephalopathy, neonatal jaundice either went unnoticed or was misclassified by maternity care assistants, midwives, and/or parents.[9-11] Moreover, neonatal hyperbilirubinaemia is one of the most

common indications for hospital (re)admission in the neonatal period.[4] Hence, there is an urgent need for more effective approaches towards timely recognition of clinically relevant jaundice in neonates cared for at home.

Hospital-based screening programmes have been shown to be effective in preventing severe hyperbilirubinaemia via timely quantification of LBB or transcutaneous bilirubin (TcB).[12,13] A Dutch randomised controlled trial in the hospital setting showed that selective TcB screening (i.e. when visually jaundiced) reduced the need for heel pricks to quantify LBB by 38% as compared to only visual assessment.[14] The effectiveness of universal TcB screening compared to only visual inspection in preventing severe hyperbilirubinaemia is currently being investigated in the STARSHIP Trial in seven Dutch primary care birth centres.[15] The BEAT jaundice@home study extends this work by focusing on screening and diagnosis of neonatal hyperbilirubinaemia in the home setting and adding additional screening (i.e. Picterus®) and diagnostic (i.e. Bilistick®) tools in an attempt to improve early recognition and diagnosis of potentially severe hyperbilirubinaemia. Picterus® is a smartphone application that provides a bilirubin reading based on photographs of the neonate's skin overlying the sternum, and Bilistick® is a point-of-care (POC) test for total bilirubin in whole blood.[16-18]

In this prospective study, our main aim is to evaluate the effectiveness of universal TcB screening in neonates cared for at home to increase the timely detection of hyperbilirubinaemia necessitating treatment while reducing the need for heel pricks to quantify bilirubin levels in blood. Using a decision tree model, an additional cost-effectiveness analysis will be performed. In parallel, we will evaluate the diagnostic accuracy, user convenience, and (cost-)effectiveness of the Picterus® app and Bilistick® in the same population.

METHODS AND ANALYSIS

Study design and setting

We will conduct a prospective multicentre cohort study in nine community midwifery practices across two regions in the Netherlands. Three approaches for screening (i.e. TcB and Picterus®) and diagnosis (i.e. Bilistick®) of neonatal hyperbilirubinaemia in the home setting will be evaluated in parallel with standard care (i.e. visual inspection followed by LBB quantification in case of jaundice). The study inclusions have started in July 2021, with an anticipated inclusion period of two years.

Participant eligibility

Neonates are considered eligible for inclusion if they: (1) are born at a gestational age of 35 weeks or more, (2) are at home at any time between day two and eight of life, and (3) have their first midwife visit at home prior to postnatal day six. Neonates are excluded if they: (1) previously received phototherapy, or (2) have parents who are unable to understand the patient information sheet due to insufficient understanding of the Dutch language.

Recruitment

Participants will be recruited in the community midwifery practices by the midwives. Parents will be informed about the study at the regular antenatal care by the community midwife and/or upon the first midwife visit following delivery. Written parental informed consent is obtained by the community midwife during the first postnatal visit at home.

Interventions

We will evaluate three universal screening tools in parallel: (1) visual inspection (standard care); (2) TcB (Dräger JM-105, Lübeck, Germany); and (3) a smartphone-based mobile health application (Picterus® app, Trondheim, Norway). TcB and Picterus® app will be applied in all included neonates directly following visual inspection (standard care) during each midwife home visits in the following order: (1) visual inspection, (2) TcB, (3) Picterus® app. The Picterus app is a novel screening tool for neonatal hyperbilirubinemia, and may be a cheaper alternative to the TcB tool depending on its performance. Moreover, we will evaluate two diagnostic tools: (1) LBB quantification (standard care); and (2) a hand-held POC device for quantifying total bilirubin in whole blood (Bilistick®, Trieste, Italy). Bilistick® will only be used if LBB quantification is indicated by the presence of visual jaundice and/or an elevated TcB reading. Its place is distinct from that of Picterus, which is a screening tool, whereas Bilistick® is evaluated as a diagnostic tool. Figure 1 displays a flowchart with an overview of the timeline per participant. During each midwife visit this participant flow is followed, except when treatment for neonatal hyperbilirubinaemia is started.

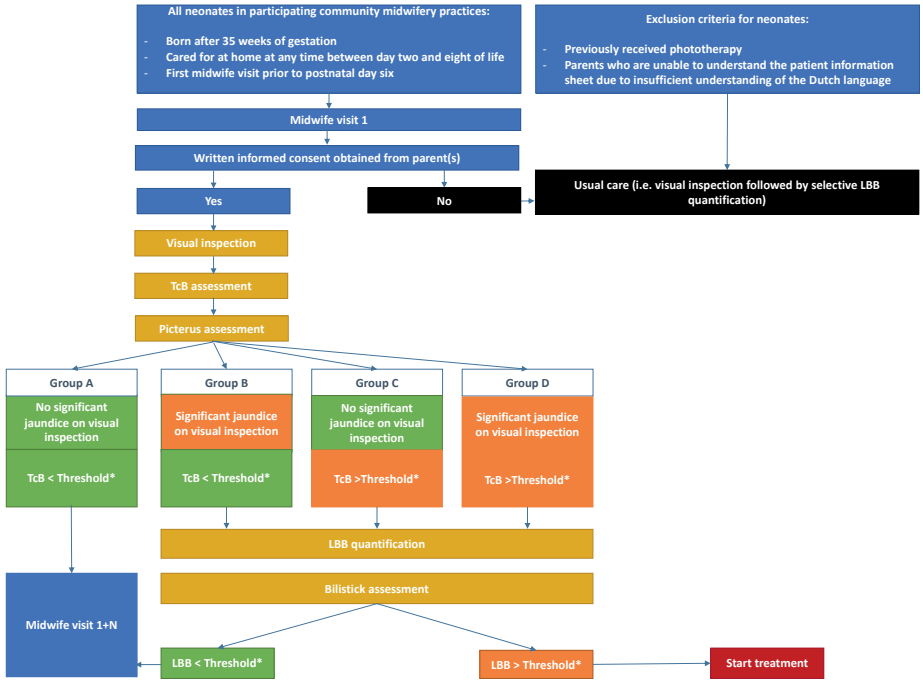

Figure 1. Flowchart of individual participant care
LBB, laboratory-based bilirubin; TcB, transcutaneous bilirubin.
*Picterus® reading will be blinded, *threshold according to national nomogram*[7]

Transcutaneous bilirubinometer (TcB screening)

Dräger JM-105 is a CE certified transcutaneous bilirubinometer and will be applied at every midwife visit at home. Three measurements will be taken on the neonate's sternum. The highest of the three TcB readings will be plotted on a customised version of the Dutch bilirubin nomogram (Figure 2). The original nomogram (Figure 3) consists of three different curves indicating the need for phototherapy based on LBB level, postnatal age, and a set of risk factors for hyperbilirubinaemia and neurotoxicity.[7] If the TcB reading is above the phototherapy threshold or higher than the phototherapy threshold minus 50 µmol/L, blood will be taken to quantify LBB. This adaptation is needed to account for the inaccuracy of TcB measurements of up to 50 µmol/L as compared to LBB.[19] As such, the original TSB-based treatment nomogram was customised by uniformly lowering the LBB thresholds by 50 µmol/L, resulting in so-called TcB nomograms. In the context of our study it is thus recommended to have LBB quantified whenever a TcB reading is higher than the corresponding TcB level on this TcB nomogram.[7,15,20] Participating midwives have experience in using the original LBB nomograms in everyday practice in the Netherlands and will be trained to use the customised TcB nomograms.

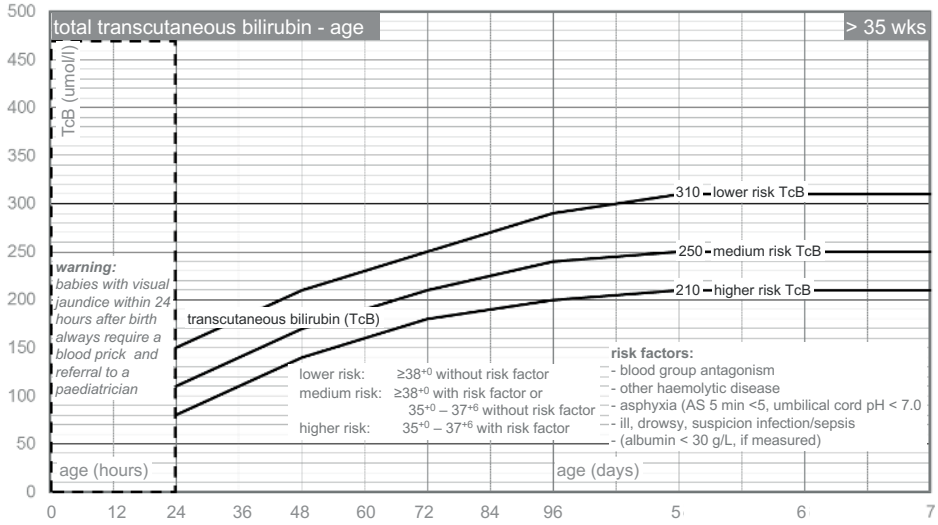

Figure 2. Customised TcB nomogram[7,15]
TcB, transcutaneous bilirubin.

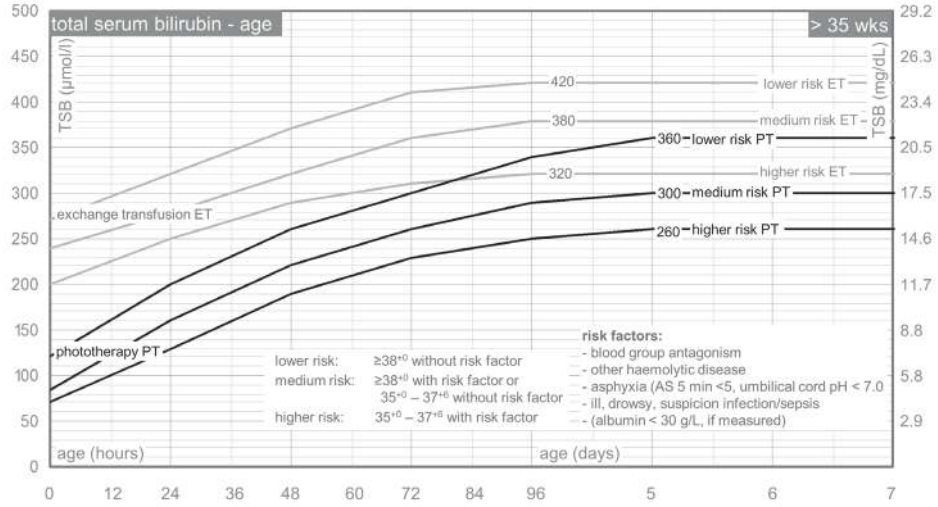

Figure 3. Bilirubin nomogram[7,15]
ET, exchange transfusion; PT, phototherapy; TSB, total serum bilirubin.

Smartphone-based mobile health application (Picterus® app)

The Picterus® reading involves three components: (1) Samsung S7 smartphone with the Picterus® app, (2) a unique colour calibration card, and (3) the Picterus® server. A Picterus® reading will also be taken at each midwife visit at home. For this purpose, the colour calibration card is placed on the neonate's sternum and a collection of six photographs (three with and three without flash) is automatically taken of the card on the sternum (Figure 4). Only the colour calibration card and a small part of the skin of the neonate's sternum will be visible on the photographs.[17] The role of the colour calibration card is to have a fixed colour reference for the digital images and to calibrate the images from variations in illumination and optical variations between different smartphones. Images taken with the Picterus® app are sent to the Picterus® server, checked for quality and colour-calibrated. Thereafter, a bilirubin level estimation will be provided based on a large database of simulated colours of neonate's skin. The simulation with the best matching colour will be automatically identified through an algorithm. Bilirubin estimates are calculated for each image and an average value of the six images is calculated to get a final result. The Picterus® app is currently under development and is expected to be CE certified and become commercially available in 2021. One clinical study has been published so far, mainly in neonates with lighter skin types.[17] This study will be the first to evaluate Picterus® in the home setting. To avoid treatment decisions being made based on the Picterus® reading, community midwives will be blinded to its reading. Picterus® diagnostic accuracy and user convenience will be analysed and determined in retrospect upon finalisation of the project.

Figure 4. Picterus® app reading*

**Rights to this illustration belong to Picterus® app, Trondheim, Norway. We have permission of Picterus® app to use this illustration*

Hand-held point-of-care device for quantifying total bilirubin in whole blood (Bilistick®)
Bilistick® is a CE certified POC test for total bilirubin quantification in 35 µl of whole blood that has recently become commercially available. The Bilistick® will be used by the community midwife in neonates requiring bilirubin quantification in blood, as indicated by visual inspection and/or elevated TcB reading (see Figure 1). First, approximately 500 µl blood will be taken and sent to a nearby lab for LBB quantification according to standard practice. Second, 35 µl (i.e. one or two drops) of blood from the same heel prick is used to additionally quantify total bilirubin in whole blood using the Bilistick® device.[16,21] The result of the conventional LBB quantification will be used to determine the need for treatment, according to the current guidelines. From a safety point of view however, if the Bilistick® bilirubin level - which will be available earlier than the LBB - exceeds the exchange transfusion threshold, the neonate will immediately be referred to a paediatrician at a nearby hospital pending the LBB result, in order to avoid delay in instituting treatment. No other decisions will be made based on the Bilistick® reading. Bilistick® might facilitate earlier treatment initiation. The device provides results rapidly and requires a smaller blood volume as compared to LBB.

Outcome measures

Primary outcome
The primary objective is to evaluate the effectiveness of universal TcB screening to increase the detection of neonates with hyperbilirubinaemia necessitating treatment compared to visual inspection, and at the same time decrease the number of heel pricks performed to quantify total bilirubin in blood, if TcB would replace visual inspection as a screening method. As such, there are two primary endpoints assessed at each time point for each neonate: (1) having a LBB above the treatment threshold, and (2) requiring a heel prick to determine LBB.

Secondary outcomes
Secondary outcomes are described in Table 1 and mainly relate to diagnostic accuracy parameters of the applied methods.

Table 1. Secondary outcomes

Secondary outcomes	
Assessed in	*Outcomes*
All participating neonates	**Diagnostic accuracy of TcB**
	Correlation between TcB and LBB
	Bland-Altman plots of TcB versus LBB
	(including mean difference with standard deviation and 95% CI of limits of agreement)
	Diagnostic accuracy of Picterus®
	Correlation between Picterus® and LBB
	The proportion of failed readings using Picterus®
	Added value of Picterus® app compared to only visual inspection in picking up neonates with hyperbilirubinaemia requiring treatment, while reducing the need for heel pricks to quantify bilirubin in blood
	Bland-Altman plots of Picterus® versus LBB
	(including mean difference with standard deviation and 95% CI of limits of agreement)
	Picterus® versus TcB
	Correlation between Picterus® and TcB
	Bland-Altman plots of Picterus® versus TcB
	(including mean difference with standard deviation and 95% CI of limits of agreement)
	Number of true positives
	Number of true negatives
	Number of false positives
	Number of false negatives
	Sensitivity
	Specificity
	Positive predictive value
	Negative predictive value
Neonates requiring LBB	**Diagnostic accuracy of Bilistick®**
	Correlation between Bilistick® and LBB
	Bland-Altman plots of Bilistick® versus LBB (including mean difference with standard deviation and 95% CI of limits of agreement)
	Number of true positives
	Number of true negatives
	Number of false negatives
	Number of false positives
	Sensitivity
	Specificity
	Positive predictive value
	Negative predictive value
	The proportion of failed readings using Bilistick®
	Difference in time-to-test result between LBB and Bilistick® (in minutes).

Table 1. Secondary outcomes (*continued*)

Secondary outcomes	
All participating neonates	Proportion of neonates having a LBB level above the phototherapy threshold
	Proportion of neonates who actually received phototherapy
	Proportion of neonates having a LBB level above the exchange transfusion threshold
	Proportion of neonates who actually received an exchange transfusion
	Potential cost-effectiveness of implementation of the novel methods in daily practice

CI, confidence interval; LBB, laboratory-based bilirubin; TcB, transcutaneous bilirubin.

Study procedures

Community midwives visit the new family a number of times (usually three times) at home during the first week after delivery. The frequency of these home visits can also depend on the advice of the maternity care assistants.[6] At each visit, the midwife will, according to usual practice, first assess and record whether or not the neonate is visually jaundiced. The duration of jaundice evaluation depends on the last home visit made by the midwife (which can be beyond day 8). Accordingly, the midwife will decide, based on the visual inspection, whether LBB quantification in blood is required. Within the current project, the midwife will subsequently quantify TcB, and apply the Picterus® app in every participant. LBB quantification is then performed in any neonate who is either visually jaundiced, has a TcB above the threshold, or both. When blood is taken to quantify LBB, total bilirubin is also measured using the Bilistick®. Importantly, the midwife may never revert her initial decision to have LBB quantified in a visually jaundiced neonate based on a 'negative' TcB (i.e. TcB reading below the threshold) reading to ensure safety of the participants, which is in accordance with the current Dutch guidelines.[7]

Midwives of all participating practices will be trained in the study procedures, data collection, and use of the Dräger JM-105, the Picterus® app, and the Bilistick® device prior to the start of the inclusion to ensure safety and adequate use. The researchers will be available 24/7 by phone to address any issues that the midwives may come across while performing study procedures.

Data collection

Data collection will be performed digitally by the community midwives. After written informed consent has been given by the parent(s), every neonate will receive a coded study number. The community midwife will fill in the first standardised case report form (CRF) containing the baseline characteristics of neonate and parent(s) (Table 2). Subsequently, the community midwife will record multiple measurements during each home visit. These are displayed in Table 3. Again, all the data will be reported in a standardised

CRF. Only the study team, study monitor, and national authorities will have access to the dataset. Depending on the last home visit, the community midwife will fill out a final CRF, which will include information on several outcomes (displayed in Table 4). In the event of hospital admission, relevant hospital data will be extracted from the electronic patient record by the study team.

Table 2. Baseline characteristics

Baseline characteristics	
Characteristics of (biologic) parents	Ethnicity (Caucasian, Asian, North African, African, Latin American, Hindu, Turkish, mixed)[22]*
	Fitzpatrick scale (I, II, III, IV, V or VI)[23]*
	Maternal blood group
	Maternal Rh D factor
Characteristics of pregnancy and birth	Gestational age at birth (weeks, days)
	Parity
	Gravidity
	Type of delivery (vaginal, caesarean section, instrumental)
	Presence of irregular antibodies during pregnancy
	Presence of risk factors for neonatal hyperbilirubinaemia (blood group antagonism, presence of other haemolytic disease, presence of birth asphyxia)
	Umbilical cord pH (if known)
Characteristics of neonate	Date of birth
	Time of birth
	Sex
	Birth weight (in grams)
	Blood group (if known)
	Rh D factor (if known)
	Apgar score <5 at 5 min
Characteristics of family members	Sibling having received phototherapy or exchange transfusion for severe neonatal hyperbilirubinaemia
	Presence of haemolytic disease

**At discretion of community midwives.*

Table 3. Data collection during home visits

Data collection during home visits	
Assessed in	*Collected data items*
All participating neonates	Date and time of screening assessment
	Severity of jaundice based on visual inspection at the discretion of the community midwife and noted as either pink, slightly yellow, yellow (indicating reason for blood prick)
	TcB reading: highest of three measurements
	Comments/inconveniences TcB assessment
	Encrypted code Picterus® app reading
	Comments/inconveniences Picterus® app assessment
	Decision made by community midwife - no extra measures taken; LBB and Bilistick® quantification; contact with paediatrician
Neonates with an indication for LBB quantification	Decision for LBB quantification was based on - visual inspection; elevated TcB measurement; visual inspection and elevated TcB measurement; other
	Date and time of Bilistick® measurement
	Result Bilistick® (in µmol/L)
	Comments/inconveniences/haemolytic Bilistick® assessment
	Person responsible for the blood transportation to the laboratory for LBB (partner; family member other than partner/friend; community midwife; other)
	(Hospital) laboratory responsible for the LBB quantification
	Date and time LBB quantification result communicated to midwife
	Result LBB (in µmol/L)

LBB, laboratory-based bilirubin; TcB, transcutaneous bilirubin.

Study size

For the sample size calculation, we estimated the proportion of participants at each assessment time point in four groups based on the combination of visual inspection and TcB quantification. The four groups are as follows: (A) no significant jaundice on visual inspection, and TcB below threshold; (B) significant jaundice on visual inspection, but TcB below threshold; (C) no significant jaundice on visual inspection, but TcB equal to or higher than threshold; and (D) significant jaundice on visual inspection, and TcB equal to or higher than threshold (Figure 1). For this purpose, 'significant jaundice' is any degree of jaundice considered to be sufficiently severe to indicate the need for LBB quantification as per the midwife's assessment. The probability matrix of neonates belonging to each of the four groups at various time points across the study period is based on published literature and preliminary data from the STARSHIP Trial.[15] We estimated the proportions of neonates falling in each of the four groups across the observations as follows: A: 83%; B: 10.5%; C: 2%; D: 4.5%.[15] These proportions take into account the fact that multiple assessments may be performed for individual neonates, and as such, a neonate may be categorised in a different group at different time points.

Table 4. Follow-up data collection

Follow-up data collection	
All participating neonates	Hospital admission (yes/no)
	Reason for hospital admission
	Type of feeding of the neonate
	More than 10% loss of birth weight within the first week of life (yes/no)
	Number of (heel) pricks to determine bilirubin levels
	Coombs test result (if known)
Neonates admitted to the hospital	Duration of hospitalisation
	Indication for hospital admission
	Phototherapy treatment (yes/no)
	Characteristics of phototherapy (age of neonate at start of treatment, duration, number of lamps/blankets, intensity)
	Exchange transfusion (yes/no)
	Complications due to blood transfusion treatment (thrombocytopaenia, hypercalcaemia, other electrolyte imbalance, necrotising enterocolitis)
	Number of (heel) pricks to determine bilirubin levels
	Maximum level of bilirubin measured (if known)
	Result MRI cerebrum (if applicable)
	Result AABR (if performed)
	More than 10% loss of birth weight within the first week of life (yes/no)
	Proportion of neonates diagnosed with acute bilirubin encephalopathy
	Proportion of neonates diagnosed with kernicterus spectrum disorder

AABR, automated auditory brainstem response; MRI, magnetic resonance imaging.

To address the primary objective of assessing whether universal TcB screening can increase the timely detection of neonates with hyperbilirubinaemia necessitating treatment compared to using only visual inspection, and at the same time decrease the number of heel pricks performed to quantify total bilirubin in blood, we will test the following hypotheses:

1. Whether the absolute number of neonates with hyperbilirubinaemia necessitating treatment is higher in group C than group B, i.e. more neonates with hyperbilirubinaemia necessitating treatment are detected with TcB screening than with visual inspection; and
2. Whether the absolute number of neonates without hyperbilirubinaemia necessitating treatment is higher in group B than group C, i.e. fewer neonates without hyperbilirubinaemia necessitating treatment get a heel prick if TcB screening would replace visual inspection as the standard screening approach.

To test these hypotheses, we will use two McNemar tests, conditional on hyperbilirubinaemia necessitating treatment. Assuming a distribution of participants over the groups as indicated above we expect 20% of the neonates who test negative on visual inspection and positive on the TcB test (i.e. those in group C) to require phototherapy. Similarly, we expect 0% of the neonates who test positive on visual inspection and negative on the TcB test (i.e. those in group B) to require phototherapy; that is: TcB screening can effectively rule out hyperbilirubinaemia above the phototherapy threshold among participants with visual jaundice. Using a p-value of 0.05, the sample size calculation for the exact McNemar test indicates that, for the first hypothesis, 38 neonates with hyperbilirubinaemia requiring treatment are required to obtain a power of 80%.[24] With an anticipated event rate of hyperbilirubinaemia requiring treatment across all time points of 1.8% (20% of group C and 30% of group D combined) this would require 2100 neonates in total. The power is not affected by the repeated measures per subject since, by definition, there will be at most one measurement per neonate indicating the requirement for treatment: at this point, the neonate will be admitted to hospital and started on phototherapy and therefore will no longer contribute data points to the study.

For the second hypothesis, each neonate can have multiple outcome events (i.e. require a heel prick at more than one time point). Assuming the distributions over the four groups and event rates indicated as above, group C is expected to contain 42 neonates (i.e. 2% of 2100) of which we assume that 80% (i.e. n=34) do not require phototherapy (Figure 5). We would expect that 1.6% (34/2100*100=1.6%) of neonates not requiring phototherapy would have a negative visual inspection and a positive TcB test (group C). Similarly, group B is expected to contain 220 neonates (i.e. 10.5% of 2100; Figure 5). We would expect that 10.5% (220/2100x100=10.5%) of neonates not requiring phototherapy have a positive visual inspection and a negative TcB test (group B).

An analysis without repeated measures would require 125 neonates to obtain 80% power at a significance level of 0.05. Taking into account the expected median of 3 repeated measures per neonate and an intraclass correlation of 0.05, we obtain a variance inflation factor (VIF) of

$$VIF = 1 + (m - 1)\,\rho = 1 + (3 - 1) \times 0.05 = 2,$$

leading to a total of 250 neonates who do not necessitate treatment.[25] With an event rate of neonates requiring phototherapy of 1.8%, this would lead to sample size of 260 neonates to address the second hypothesis.

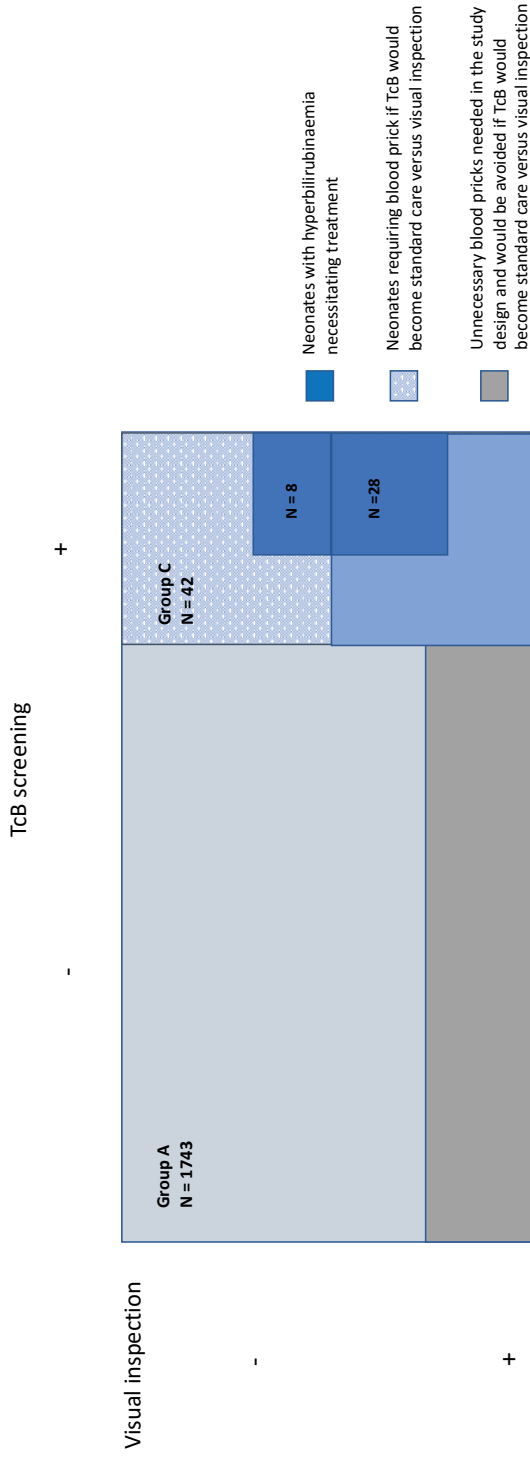

Figure 5. Probability matrix distribution of participants
TcB, transcutaneous bilirubin.

We expect a loss to follow-up of maximum 10%. To account for this expected loss to follow-up, we aim to include 2310 neonates for the first hypothesis.

Statistical analysis

The primary analysis will involve two separate McNemar tests, conditional on LBB being above the phototherapy threshold or not. These tests will provide p-values for testing the following two H_0 hypotheses: (1) there is no difference in the detection of neonates with hyperbilirubinaemia necessitating treatment between TcB screening and visual inspection, and (2) there is no difference in the number of heel pricks needed to quantify total bilirubin in blood if TcB would replace visual inspection as standard care.

For the first hypothesis we test whether, conditional on having hyperbilirubinaemia, the probability of a 'positive' TcB test (i.e. TcB reading above the threshold) is different than that of a 'positive' visual inspection (i.e. visual inspection indicating the need for LBB quantification at the discretion of the community midwife). As both tests are performed in the same neonate and hence are paired we only need to test whether the probabilities of having discordant test results are different: P(TcB + , Visual −|hyperbilirubinaemia) > P(TcB − , Visual +|hyperbilirubinaemia). In which + and – are displayed as positive and negative tests respectively. Similarly, for the second hypothesis, we will perform an adjusted McNemar test, taking into account the repeated measurements in neonates, to test if the probability of having a positive TcB test is different than the probability of having a positive visual inspection, conditional on not having hyperbilirubinaemia: (P(TcB +, Visual −|no hyperbilirubinaemia) < P(TcB − , Visual +|no hyperbilirubinaemia).

Sensitivity of the TcB and visual inspection is estimated by the proportion of positive tests divided by the number of babies requiring phototherapy. Agresti-Coulli 95% confidence intervals will be estimated for the sensitivities.[26] If, as expected, the sensitivity of TcB is indeed 100% we will use the 'rule of three' to derive the 95% confidence interval for the first hypothesis.[27] To quantify the specificity of TcB and visual inspection at the population level we will use generalised estimating equations (GEE) models for both tests separately.

Furthermore, we will use 2x2 tables and Bland-Altman plots to assess the diagnostic accuracy of each novel screening method to obtain a first impression at each time point, without taking correlation between repeated measurements into account. The primary diagnostic comparison will involve TcB versus visual inspection. Other relevant diagnostic comparisons are displayed in Table 1.

We will perform subgroup analyses to determine effectiveness of TcB screening and the diagnostic accuracy of the tools across different and gestational age strata. Ethnicities will be defined according to the guideline of the Royal Dutch Organisation of Midwives.[22]

Cost-effectiveness analysis

Following established methodologies,[28-31] a model-based cost-effectiveness analysis (CEA) will be performed to analyse the cost-effectiveness of the three screening and diagnostic tools compared with standard care, as described above. A decision tree model will be built, because screening for neonatal hyperbilirubinaemia can be represented by a relatively simple sequence of decisions. The decision tree will be constructed such that a hypothetical neonate would either receive screening by one of the novel tools or standard care. The model will consider the accuracy of the different screening tools. The analysis will be performed from a healthcare perspective, using a time horizon of the 8-14-day observation period of the study. The probabilities used in the model will be based on the current study.

All relevant healthcare use will be considered in the model, including screening for hyperbilirubinaemia by TcB and by the Picterus® app, total bilirubin quantification using Bilistick®, LBB testing, frequency of community midwife visits (including telephone calls), visits of a specialised laboratory home service that performs the heel prick (if relevant), transport costs for LBB samples to the local laboratory, consultations with a paediatrician, hospital admission days, and treatments for hyperbilirubinaemia (phototherapy, exchange transfusion). To arrive at costs, resources used will be multiplied by integral cost prices. The effectiveness measure of the CEA will be the number of correctly diagnosed cases of hyperbilirubinaemia necessitating treatment and the number of heel pricks avoided.

For each of the three tools, the mean expected costs and effects will be calculated and compared with standard care. To this aim, incremental cost-effectiveness ratios (ICERs) will be calculated, expressed as incremental costs per additional correctly diagnosed case of hyperbilirubinaemia necessitating treatment (regarding TcB and Picterus® app) or incremental costs per heel prick avoided (regarding TcB and, Picterus® app). Sensitivity analysis will be carried out to assess the robustness of the results to realistic variations in the levels of the underlying parameter values and key assumptions.

Safety

All adverse events reported spontaneously by the parents of the participant or observed by the study personnel, starting from the first application of the novel approaches until 24 hours after the last application of the novel approaches, will be recorded. Serious

adverse events (SAEs) will be reported by the community midwives and communicated to the principal investigator within one week after identification of the event. The principal investigator, in collaboration with the study team, will record these events and report them to the sponsor and Medical Research Ethics Committee of the Erasmus MC Rotterdam. The SAEs are defined *a priori* and communicated with the study team. SAEs consisted of bilirubin levels above exchange transfusion threshold, exchange transfusion, disabilities related to severe hyperbilirubinaemia, hospital admission or death.

Monitoring will be conducted according to the Guideline for Good Clinical Practice by an independent, professional monitor once a year per community midwifery practice.[32]

Patient and public involvement

The study protocol and procedures were discussed with the patient panels of the Regional Consortia Pregnancy & Childbirth South-West and North Netherlands. Parents and student midwives from the Rotterdam University of Applied Sciences were involved to give feedback on the study design and recruitment into the study. Moreover, the Regional Consortia Pregnancy & Childbirth South-West and North Netherlands, multidisciplinary organisations that provide a platform for healthcare professionals to share and obtain knowledge regarding childbirth at the regional level, were actively involved in developing the study protocol. Prior to start of the inclusion, participating community midwives were invited to give feedback and discuss the study protocol and procedures thoroughly with the study team. Their input is incorporated to optimise study procedures.

Ethics and dissemination

The study has received ethical approval from the Medical Research Ethics Committee of the Erasmus MC Rotterdam, the Netherlands (MEC-2020-0618), and was registered at the Netherlands Trial Register (NL9545; now available via the International Clinical Trials Registry Platform). Parents will provide written informed consent. Any protocol modifications will be reported to the Medical Research Ethics Committee and, if relevant, to the participating community midwifery practices.

Data will be pseudonymised. The identification list will only be accessible by the investigators and the study monitor. The data provided to Picterus® will only be used for providing bilirubin level estimates. Data of participants will not be used for any other purpose (e.g. commercial purposes).

The results of this study will be published in peer-reviewed journals and presented at national and international scientific meetings. The results will be reported using the

guideline for diagnostic studies of the EQUATOR Network.[33] The statistical code will be published alongside the manuscript. We intend to provide an anonymised version of the study data upon reasonable request after publication. The International Committee of Medical Journal Editors guideline will be used to determine authorship.[34]

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9.

General discussion

Severe neonatal hyperbilirubinaemia and its devastating consequences are entirely preventable by timely recognition and adequate treatment. However, severe hyperbilirubinaemia and its potential consequences still occur. This is not solely an issue in low- and middle-income countries with limited access to healthcare, but also in high-income countries.[1]

In the Netherlands, ten to twenty neonates are admitted to neonatal intensive care units for exchange transfusions and have symptoms of acute bilirubin encephalopathy each year.[2,3] These neonates are at risk of developing kernicterus spectrum disorder (KSD), a spectrum of neurological sequelae with lifelong impairments at the extreme end.[4] An additional challenge in care for jaundiced neonates in the Netherlands is the unique perinatal care system in which postpartum care to mothers and neonates is mainly provided in primary care by a maternity care assistant (MCA) under supervision of a community midwife. As mothers and neonates cared for in primary care are mostly healthy, maternity care professionals in primary care are more used to physiology rather than pathology. This may carry the risk that pathology, for example potentially severe hyperbilirubinaemia, is not always recognised in time or that the clinical problem is downplayed.

The Screening and TreAtment to Reduce Severe Hyperbilirubinaemia in Infants in Primary care (STARSHIP) Trial was designed to evaluate whether or not non-invasive, universal screening of bilirubin levels in primary care could improve the recognition of potentially severe neonatal hyperbilirubinaemia. Also, phototherapy in primary care was evaluated in the STARSHIP Trial. Potential advantages of implementing phototherapy in primary care may be avoiding hospital admissions and healthcare associated costs.

In this thesis, the problem of recognition and management of unconjugated hyperbilirubinaemia is described along with a new strategy for screening and treatment as proposed in the STARSHIP Trial, the first results of this trial, and a further improvement of the screening strategy based on the first experiences of the STARSHIP Trial.

REFLECTION ON THE OBTAINED RESULTS

Assessment and management of neonatal hyperbilirubinaemia

As visible jaundice occurs in 60-90% of neonates,[5-7] it is important to study its assessment and management. In most high-income countries, near term and term neonates are cared for in a hospital during the first days after birth and incidence of visible jaundice is evaluated in such settings. This evaluation commonly includes assessment

of total serum bilirubin (TSB) levels or screening via transcutaneous bilirubinometry.[8,9] In the Netherlands – where perinatal care for healthy neonates is mainly primary care based – visible jaundice is present in approximately 70% of neonates cared for in primary care (**Chapter 6**). Although visible jaundice is a physiologic phenomenon, a small, but substantial proportion of these neonates necessitate treatment to reduce TSB levels and avoid progression to acute bilirubin encephalopathy. Hyperbilirubinaemia is one of the commonest reasons for (re)admission to the hospital in the neonatal period.[10] As discussed in **Chapter 6**, hyperbilirubinaemia and its potentially devastating consequences are not only an issue in neonates cared for in a hospital, but neonates cared for in primary care are also at risk for developing pathological TSB levels.

Previous studies showed that severe hyperbilirubinaemia constitutes a substantial global health burden, not only in low- and middle-income countries, but also in high income countries.[1,2,11,12] In **Chapter 2**, we showed the results of three years of a nationwide perinatal audit programme regarding severe hyperbilirubinaemia in the Netherlands. Although it was not an official registry study and thus carried a risk of underreporting, the incidence of severe hyperbilirubinaemia was comparable to other studies in high income countries.[2,13-15] The improvable factors revealed during the audit meetings, emphasise the need for more awareness regarding the burden of hyperbilirubinaemia in terms of hospital admissions for treatment and the potentially severe consequences of (too) late recognition and treatment.

To avoid late recognition of potentially severe hyperbilirubinaemia, national guidelines have been developed and implemented.[8,9,16,17] These guidelines include risk assessment, and screening and treatment strategies. As previously shown in Sweden, the US, Canada, and Indonesia,[18-21] hyperbilirubinaemia guidelines are regularly not adhered to. This may be due to various reasons, including insufficient awareness, lack of knowledge, and practical issues. Previous studies that evaluated whether guidelines were adhered to or not, were mainly restricted to the hospital setting, focusing on adherence by paediatricians. A Canadian study showed that compliance to the guideline varied among different kinds of healthcare professionals. Paediatricians were most likely to use the hyperbilirubinaemia guideline when compared to family physicians and midwives.[22] In **Chapter 2**, we showed that in the Netherlands, non-compliance to the hyperbilirubinaemia guideline is often not considered as improvable factor in cases of near term and term neonates with severe hyperbilirubinaemia. In **Chapter 6**, we showed that guidelines regarding indications for TSB quantification and phototherapy treatment were not always adhered to. Severe hyperbilirubinaemia and KSD may be avoidable by adequate compliance to the hyperbilirubinaemia guidelines.[18] Unfortunately, considerations on not adhering to the guidelines remain unclear in many cases. One may speculate

that the recommendations in the guidelines are not known by the involved healthcare professionals, but also practical issues in implementing the guideline or disagreeing with its recommendations may cause deviation from the guideline. If healthcare providers are more familiar with a guideline, they tend to use it more.[23,24] A campaign to improve hyperbilirubinaemia guideline adherence in the US by increasing awareness through education showed an increase in adherence from 60% to 90%.[25] In addition, KSD seems to be considered as an event that only occurs in rare cases and as 'bad luck' too often. TSB levels above exchange transfusion threshold should be considered as a complication or critical incident and being reviewed as such. Accordingly, this review procedure, for example via formal audits, may help to increase awareness among healthcare professionals. Furthermore, nudges can be used as tool to promote guideline compliance. For example, healthcare professionals can be supported to adhere to the guideline by making the most important decisions and the consequences visual in a flowchart. Another example of a potential nudge is to remind healthcare professionals of the guideline recommendations by implementing questions, standard sentences, or reminders on these recommendations in medical records (e.g. a healthcare professional has to fill in whether or not *a priori* risk on neonatal hyperbilirubinaemia is increased). A systematic review assessing various nudging strategies to promote guideline adherence in healthcare showed success of these kind of nudging strategies.[26]

Whereas the inaccuracy of visual inspection of the neonate's skin colour to estimate TSB levels has been known for a long time and has been confirmed in **Chapter 3** and **Chapter 6**, it is still used as a first-line screening for severe hyperbilirubinaemia in many countries and settings.[8,16,17] The inaccuracy of visual inspection and the continued occurrence of KSD underline the urgent need for other, more objective screening methods for early recognition of potentially severe hyperbilirubinaemia. Several guidelines advise a single measurement of transcutaneous bilirubin (TcB) or TSB before discharge from the hospital or during standard of care dried blood spot test (i.e. metabolic screening) of neonates, to screen for hyperbilirubinaemia.[8,9,27] As healthy neonates cared for in primary care also commonly develop visible jaundice (**Chapter 6**) and are at risk for potentially severe hyperbilirubinaemia, screening methods should be accessible and cost-effective outside the hospital as well. Non-invasive point-of-care assessments, for example using TcB, may be more feasible than laboratory-based TSB quantifications outside the hospital due to practical issues (e.g. blood needs to be transported to a medical laboratory). The recommendation of management guidelines of other countries with different healthcare systems to screen routinely for hyperbilirubinaemia using a single TcB or TSB quantification is challenging: in near term and term neonates developing severe hyperbilirubinaemia based on haemolysis, TSB levels usually exceed treatment thresholds within the first 24 hours of life. However, other causes of hyperbilirubinae-

mia – such as neonatal infection or hyperbilirubinaemia related to dehydration – may cause TSB levels to exceed treatment thresholds several days later. Hence, it is difficult to determine the optimal timing of single bilirubin screening. This is also an issue when quantifying bilirubin together with blood spot test of neonates, which typically occurs between day 3 and day 7 after birth.[28] Consequently, daily screening is likely to be much more reliable, but also requires more effort from healthcare professionals.

If a neonate is judged as visibly jaundiced, many maternity care professionals tend to follow a wait-and-see approach rather than act upon their assessment (**Chapter 3**). Since many healthy neonates cared for in primary care become visibly jaundiced but only a small proportion (i.e. 3.6%) necessitates treatment, this will mostly turn out well. But as a consequence of this wait-and-see approach, neonates who are severely jaundiced are at risk of developing long-term sequelae due to being exposed to hazardous TSB levels. Therefore, more awareness regarding the potentially severe consequences of a wait-and-see approach is necessary. The primarily reactive mind-set has to be changed to a proactive mind-set in which an extra bilirubin quantification is preferred over taking the risk of missing a neonate with severe hyperbilirubinaemia. In current practice, there appears to be a high threshold to quantify bilirubin, as it necessitates an invasive blood sample. Availability of TcB or other non-invasive devices to quantify bilirubin in all primary care settings may lower this threshold.

If an otherwise healthy neonate cared for in primary care has hyperbilirubinaemia necessitating treatment, the current standard approach is to admit the neonate to a nearby hospital for treatment. Preliminary findings from the STARSHIP Trial suggest that hospital admission can be avoided in most near term and term neonates by providing phototherapy in primary care (**Chapter 7**). Comparable studies in other countries in North America, Europe, and Asia showed similar results.[29-33] By avoiding hospital admissions, phototherapy in primary care may promote mother-child bonding and may reduce healthcare associated costs on the short and the long term. Preconditions regarding practical issues and agreements on responsibility are important for the success of phototherapy in primary care. As community midwives feel they lack time to perform the extra blood samplings needed during phototherapy to evaluate its effectiveness, availability of a medical laboratory service who perform blood draws to quantify TSB may ease implementation of phototherapy in primary care. Another possibility is to teach MCAs how to perform a heel prick to quantify TSB. Additionally, support of the transition from standard application of phototherapy in a hospital setting to the primary care setting by paediatricians is needed. They should be available for consultation (by phone) by the community midwife, especially if the community midwife lacks experience regarding application of phototherapy. If phototherapy will be implemented in

primary care nationally, all community midwives and MCAs need to be educated on the topic.

As parents are the most important caregivers and are even more involved in daily care if a neonate receives phototherapy in primary care, their experience is very important. In general, parents whose neonates participated in the STARSHIP Trial were satisfied with phototherapy in primary care (**Chapter 7**). However, if a neonate had to be admitted to the hospital for intensive phototherapy after initial phototherapy in primary care, parents of two (out of three) neonates were unsatisfied with phototherapy in primary care. The underlying considerations are unknown, but the parents may have the feeling that their neonate was not treated adequately. Adequate counselling and management of parental expectations before start of phototherapy may reduce parental dissatisfaction if their neonate needs to be admitted to the hospital secondarily. A large majority of parents in whose neonate phototherapy was initiated and completed in the primary care birth centre (PCBC), would prefer phototherapy in the PCBC again. This underlines the relevance of providing phototherapy in primary care. Nevertheless, approximately half of the parents whose neonate received phototherapy in the PCBC indicated that they would not feel comfortable with phototherapy at home. Underlying considerations are unknown, but many parents mentioned minor issues. For example, the neonate cried a lot during phototherapy, the eye patches caused discomfort to the neonate or did not stay in place in multiple neonates. The latter issue scared some of the parents, as they were afraid of retinal damage or that their neonate would choke on the eye patches. Adequate counselling of parents regarding safety and issues that are frequently experienced by parents is important as well. Additionally, some of these issues may be avoided in future. In our study, the eye patches were used because the manufacturer advised to do so. However, some hospitals and manufacturers do not advise eye patches if a neonate receives phototherapy using a mattress. As the neonate on a phototherapy mattress does not look directly into the blue light (in contrast to during overhead phototherapy), it may be safe to omit the eye patches. Although advice on eye patches during phototherapy using a mattress varies, safety of omitting the eye patches in this modality of phototherapy is unknown.

Whereas some parents whose neonate received treatment in the PCBC judged the healthcare professionals as (very) incompetent regarding phototherapy, none of the parents whose neonate received phototherapy in the hospital judged the healthcare professionals (very) incompetent regarding phototherapy. PCBCs are established to make neonates and parents feel at home. It may be that some parents prefer a feeling of professionalism and close monitoring that may be inherent to the more clinical hospital setting over feeling at home if their neonate necessitates hyperbilirubinaemia treat-

ment. In addition, healthcare professionals working in a hospital usually have extensive experience with phototherapy. In the PCBCs, phototherapy was a new development and consequently healthcare professionals did not have extensive experience yet. Gaining more experience is a matter of time on the one hand, but on the other hand can be promoted by offering primary care healthcare professionals to be trained in phototherapy procedures on neonatal wards, where healthcare professionals care for neonates necessitating phototherapy more frequently than in primary care. Additionally, good information about phototherapy and its implications beforehand may decrease some of the stress and discomfort of parents. This information can be provided orally by healthcare professionals, but also information sheets or short (animation) videos may be helpful. More experienced healthcare professionals are more likely to make parents feel at ease during phototherapy of their neonate. Consequently, these recommendations may also help increase the proportion of parents that would feel comfortable with phototherapy at home.

Opportunities and challenges for large-scale research projects in primary care

The STARSHIP Trial is a factorial stepped-wedge cluster randomised controlled trial (RCT) in seven PCBCs in the Netherlands. A factorial stepped-wedge cluster RCT has some, mostly practical, advantages over a traditional RCT, but there are disadvantages as well and these should be taken into account when considering a factorial stepped-wedge cluster RCT design (**Chapter 5**). These disadvantages include challenging sample size calculations that should take intracluster correlation into account; potential confounding of time that demands simultaneous enrolment of different clusters; less flexibility if the inclusion rate is behind schedule; and the difficulty of implementing and analysing more than one intervention. An important observation of the STARSHIP Trial is that parents seemed more willing to participate if there was a direct advantage of participation for their neonate. This may have resulted in variations in demographic characteristics or in risk factors for hyperbilirubinaemia between the group exposed to (one of) the interventions and the control group and may affect the comparability of the groups. To mitigate this risk, participants should, preferably, be recruited blind to the allocation status. The feasibility of blind recruitment can be doubted: healthcare professionals who are aware of the allocation status should withhold that information from participants and still participants can find out the allocation status, for example if they know other participants. In conclusion, a factorial stepped-wedge cluster RCT is an innovative design with practical advantages, but the disadvantages should be taken into consideration and, ideally, solutions for potential issues should be formulated beforehand.

The innovation of the STARSHIP Trial was not only the design, but also the primary care setting in which the trial was conducted (**Chapter 5**). In the Netherlands, perinatal care, and consequently recognition of hyperbilirubinaemia, is mainly primary care based. Conducting research in the primary care setting reflects the daily reality of management of neonatal jaundice and offers the opportunity to draw conclusions adapted to this unique setting. Currently, there is a trend towards providing healthcare at home as much as possible ('Juiste Zorg op de Juiste Plek') in order to improve the quality of healthcare, and to reduce workload in the hospital and associated costs.[34] This development is in line with the increasing appreciation of the relevance of value-based healthcare, i.e. the concept that treatment costs should be adequately balanced against value for patients. Accordingly, there is a need for more research in primary care. However, in general, primary care healthcare providers in perinatal care occurred to be unfamiliar to conducting research. Making research one of the subjects during education of all kind of healthcare professionals and at all levels of education has the potential to increase the engagement of these professionals in conducting research. As long as conducting research is not common for primary care healthcare professionals, extra study personnel is needed to support them.

New assessment strategies in primary care

The STARSHIP Trial has shown that neonatal jaundice is an issue that healthcare professionals in perinatal primary care are facing daily. This emphasises the importance of improving neonatal jaundice management strategies for primary care and promoting its implementation. The STARSHIP Trial was conducted in PCBCs rather than the home setting. The transition from the hospital setting to the PCBCs was smaller than directly to the home setting. This was due to several reasons. First, a PCBC is generally closer to a hospital and hospital facilities are more easily available than in the home setting. Second, MCAs are 24/7 available in the PCBCs. Lastly, less transcutaneous bilirubinometers and phototherapy mattresses were needed due to clustering of the neonates in a limited number of locations. The availability of PCBCs in the Netherlands is limited and differs per region. Consequently, not all neonates will have access to transcutaneous bilirubinometry and phototherapy if it is only provided in PCBCs. Hence, transition of screening and treatment to the home setting is needed in order to promote availability of the interventions to all healthy neonates cared for in primary care. Neonates in the PCBCs are comparable to neonates in the home setting in terms of health status. However, the organisation of perinatal care at home is different from perinatal care in a PCBC. Thus, additional research regarding implementation and feasibility of screening and treatment of hyperbilirubinaemia at home is needed.

As most near term and term neonates in the Netherlands are cared for at home, screening for and diagnosis of potentially severe neonatal hyperbilirubinaemia at home is needed. As described in **Chapter 8**, the BEAT jaundice@home study evaluates screening for neonatal hyperbilirubinaemia using TcB in the home setting. Additionally, screening for and diagnosis of neonatal hyperbilirubinaemia using a smartphone application (Picterus®) and a point-of-care device for bilirubin quantification in whole blood (Bilistick®) is evaluated in the home setting as well. The effectiveness of TcB quantification in the hospital setting has been shown,[35-37] and is currently being evaluated in the STARSHIP Trial.[38] However, the effectiveness of TcB screening at home in the unique Dutch perinatal care system has not been evaluated yet. In addition to improving the recognition, it is useful to assess whether or not less heel pricks for TSB quantification are needed.

Currently, approximately half of the world population owns a smartphone,[39] a smartphone app that screens for neonatal hyperbilirubinaemia is likely to be more accessible than a transcutaneous bilirubinometer, in particular in low- and middle-income countries. Also, the Picterus® smartphone app is likely to be cheaper than the expensive transcutaneous bilirubinometer. However, the diagnostic properties of Picterus® for recognition of hyperbilirubinaemia have to be established before evaluating it as primary screening method. Hence, the effectiveness of the transcutaneous bilirubinometer was the primary outcome of the BEAT jaundice@home study and the evaluation of the Picterus® application was performed secondarily.

FUTURE DIRECTIONS

Implications for practice and policy

Early recognition of potentially severe neonatal hyperbilirubinaemia remains an important challenge in which all kind of perinatal healthcare professionals are involved. The first and most important recommendation is that more awareness regarding neonatal hyperbilirubinaemia and its potentially devastating consequences is needed. The awareness can be increased by education of all involved healthcare professionals. Neonatal hyperbilirubinaemia should not only be a topic at the initial training for healthcare professionals, but should also be a topic in continuing training programs. As described in **Chapter 3**, these training programs can also be provided as an e-learning module. Attending education regarding neonatal hyperbilirubinaemia could be made compulsory for re-registration as healthcare professional. Involved healthcare professionals should obtain a better understanding of the extreme consequences of neonatal hyperbilirubinaemia. Experiences of paediatricians who treat neonates and older children suffering from the lifelong consequences of severe hyperbilirubinaemia and of parents of these

children may further increase awareness. Better awareness of these consequences may increase compliance to the hyperbilirubinaemia guideline. A Canadian prospective cohort study among near term and term neonates showed that the introduction of a guideline on the management of neonatal hyperbilirubinaemia and better awareness among physicians likely contributed to a reduction in the incidence of severe hyperbilirubinaemia from 1 in 2480 to 1 in 8352 neonates.[13] In the Netherlands, an updated version of the hyperbilirubinaemia guideline is currently being developed. To promote compliance to the guidelines, identification of barriers for guideline adherence would be useful. Focus groups among different kinds of healthcare professionals involved in postpartum care can be held. These findings can then be used to adapt the guideline and develop an implementation strategy. In any case, emphasising the importance of adhering to the hyperbilirubinaemia guidelines is important. However, to achieve better compliance, only emphasising the importance will probably be insufficient. First, educating all involved healthcare professionals regarding the recommendations of the guidelines and their responsibility is key. This education should be adapted to the kind of involved healthcare professional, their responsibilities, and their educational level. The guideline can be summarised in a short factsheet that visualises the most important recommendations. Short (animation) videos may help to improve knowledge regarding the guideline as well. Additionally, nudges to promote guideline compliance can be used as well.

If a neonate necessitates an exchange transfusion or has symptoms of KSD, this seems generally to be considered as 'bad luck'. This mind-set should change to 'every neonate necessitating an exchange transfusion or showing symptoms of KSD is one neonate too many'. Accordingly, the case of every neonate having a TSB level above exchange transfusion threshold or showing symptoms of KSD should be reviewed as a complication or critical incident. Lessons for future can be learnt from these reviews and, as a positive side effect, it may also raise awareness. As paediatricians treat neonates in this stage of hyperbilirubinaemia, they should be responsible for this review. In order to increase the awareness, the lessons learnt can be shared regionally or nationally via associations of involved healthcare professionals. Awareness can also be increased by adequate registration of the extent of the problem. Only few countries have such a registration or can extract data on neonatal hyperbilirubinaemia from medical records systematically. Registering all neonates with TSB levels that exceed exchange transfusion threshold and their follow-up would offer the opportunity to reveal the burden of severe hyperbilirubinaemia on the short and on the long term.

Knowledge gaps and future research directions

More and more, healthcare will be moved from the hospital to primary care. The Dutch Coalition Agreement 2017 described that the Right Care should be in the Right Place ('Juiste Zorg op de Juiste Plek').[40] This is particularly relevant for screening and treatment of neonatal hyperbilirubinaemia, as many neonates at risk for the potentially severe consequences are cared for in a PCBC or at the home. Neonatal hyperbilirubinaemia is even more a problem in low- and middle-income countries and screening and treatment can be challenging in areas with limited resources (**Appendix A**). Therefore, point-of-care quantification of bilirubin (either in blood, or using transcutaneous bilirubinometry or a smartphone app) in the home situation can also be part of the solution there. This also complies with the third Sustainable Development Goal, which states that healthy lives should be ensured.[41]

First results of the effectiveness of daily screening for neonatal hyperbilirubinaemia using transcutaneous bilirubinometry from the STARSHIP study are not available yet, but other studies have shown a reduction in severe hyperbilirubinaemia following implementation of single routine screening using TcB or TSB.[13,35,36,42] In contrast to these previous studies, in the STARSHIP Trial routine screening takes place daily instead of a single bilirubin quantification. If effectiveness of daily screening in primary care has been proven, it should be implemented. Daily screening will be more feasible if non-invasive methods are used for bilirubin quantification rather than bilirubin quantification in blood. Up to date, transcutaneous bilirubinometers are the preferred non-invasive method, because they correlate well to TSB levels.[30,43-47] However, transcutaneous bilirubinometers are expensive, making them less accessible in several healthcare settings. First results of different smartphone applications using a photograph of the neonate's sternum with a calibration card and combined with some information regarding the neonate (e.g. gestational age, postnatal age, birth weight) are promising. Further development of such smartphone applications are the future. These smartphone applications may be further optimised by machine learning, which has been shown to provide adequate early prediction models of clinically relevant hyperbilirubinaemia.[48] Diagnosis of neonatal hyperbilirubinaemia is still based on bilirubin quantification in blood. In primary care, the blood draws are performed by the community midwife or a medical laboratory. Subsequently, the blood sample has to be transported to the medical laboratory and the quantification has to be performed. The whole process from taking the blood to obtaining the result may take several hours and a large effort of involved healthcare professionals. Point-of-care bilirubin quantification in blood would quicken the diagnostic process and thus the start of phototherapy, if needed. Currently, diagnosis of neonatal hyperbilirubinaemia in primary care using point-of-care bilirubin quantification in blood is being investigated in the BEAT jaundice@home study (**Chapter 8**). The accuracy of this point-of-care quan-

tification during phototherapy should be of interest as well. If phototherapy is applied at home, such point-of-care quantification would ease the follow-up and the treatment decisions. Continuous monitoring of bilirubin levels during phototherapy would even more ease the process of follow-up. Inamori *et al*. developed a wearable device placed on the neonate's forehead using transcutaneous bilirubin quantification for continuous monitoring.[49] First results show a good correlation of the TcB levels quantified by the wearable device and TcB levels quantified by a commercially available handheld device. Additionally, the error between the wearable device and a single TSB measurement during phototherapy was within approximately 51 µmol/L (3 mg/dL). Further enhancement of such continuous, non-invasive monitoring of bilirubin levels is preferable to improve follow-up before, during, and after phototherapy while reducing the number of heel pricks to quantify TSB. In neonates receiving phototherapy at home, these devices may be connected to the electronic medical records of the community midwives and the hospital by telemetry.

Following diagnosis of neonatal hyperbilirubinaemia necessitating phototherapy, phototherapy in otherwise healthy neonates has the potential to be implemented in primary care soon. PCBCs can continue providing phototherapy, but if safety and feasibility has been proven, it is most likely that phototherapy in primary care will mainly take place at home. In the Netherlands, there are few early adopter hospitals that have already implemented phototherapy at home. Lessons from these hospitals and from the PCBCs can be learnt for nationwide implementation of phototherapy in primary care. The TowaRds implEmentATion of phototherapy for neonatal jaundice at home (TREAT jaundice@home) study will explore these lessons learnt and develop a nationwide implementation strategy within the next years. One of the most important challenges is an adequate selection of neonates (and their parents) eligible for phototherapy at home. Research focussing on patient and parent characteristics that can predict the success rate of phototherapy at home or in a PCBC would provide the opportunity of a personalised approach regarding the location of phototherapy. Additionally, instructions for parents should be available in different languages and should be adapted to the level of parents. These instructions should be available in written form, but also visually using images or videos. Given the observations that the eye patches caused discomfort for neonates and their parents, safety of omitting the eye patches should be investigated. Not all parents are satisfied with the phototherapy mattresses or 'sleeping bags' that are currently used for phototherapy in primary care. Other types of phototherapy devices may be implemented in future as well. A wearable jaundice device (Bilihome) is currently being developed. A wearable device offers the opportunity to provide care to the neonate in the most natural way possible, as a neonate can be breastfed, cared for, and carried around to its own needs.

Screening, diagnosis, and treatment of neonatal hyperbilirubinaemia can be implemented in primary care, but this transition needs to be supported by research funding organisations and healthcare insurance companies. Research funding organisations should acknowledge the unfamiliarity of primary care healthcare providers in perinatal care with conducting research and make more funds available for research in primary care (and in other settings in which research is important but uncommon). Furthermore, replacing healthcare from the hospital to primary care is more demanding for the primary care healthcare professionals and they should receive reimbursement for their work. To this end, a cost-effectiveness analysis is needed. A cost-effectiveness analysis for screening and treatment of neonatal hyperbilirubinaemia in PCBCs is embedded in the STARSHIP Trial. Results of this analysis are not available yet. Cost-effectiveness of implementing the STARSHIP interventions to the home setting rather than the PCBC setting will be different. Hence, an extra cost-effectiveness analysis will be needed if screening and treatment at home has been proven safe and feasible. In the STARSHIP Trial, only cost-effectiveness on the short term will be analysed. However, screening and treatment of neonatal hyperbilirubinaemia in primary care may also prevent long-term costs. Therefore, expanding the cost-effectiveness analysis in the STARSHIP Trial with long-term costs such as healthcare expenses for children with KSD and costs for the society of lifelong support of these children will likely change the balance towards higher cost-effectiveness. Important to consider is that some of the potential advantages of screening and treatment for hyperbilirubinaemia in primary care cannot be expressed in costs: for example, success of breastfeeding, bilateral bonding, and comfort of neonate and parents.

CONCLUSION

KSD should be a 'never-event'. Results from this thesis show that neonatal hyperbilirubinaemia remains a problem. Recognition of potentially severe hyperbilirubinaemia and the attitude of healthcare professionals towards jaundiced neonates in primary care can and should be improved. We recommend better awareness, education, and objective screening methods using TcB. Additionally, our preliminary results suggest that phototherapy in primary care is safe, can avoid hospital admissions, and parents are satisfied with it. Further research should focus on the added value of novel objective screening methods; safety, feasibility, and implementation of phototherapy in the home setting; and cost-effectiveness of the interventions on the short and the long term, and in different primary care settings.

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10.

Summary
Samenvatting

SUMMARY

Neonatal hyperbilirubinaemia is common during the first days after birth. Total serum bilirubin (TSB) levels usually decrease spontaneously, but phototherapy or exchange transfusions may be needed if TSB levels are high. If neonatal hyperbilirubinaemia is not timely recognised and treated, a neonate may develop acute bilirubin encephalopathy and eventually kernicterus spectrum disorder. Currently, screening for neonatal hyperbilirubinaemia in the Netherlands is based on visual jaundice assessment and selective TSB quantification. If phototherapy is needed, this is generally applied in-hospital.

In the Netherlands, postpartum care is mainly primary care-based. A maternity care assistant (MCA) provides postpartum care to a healthy mother and her neonate at home or in a primary care birth centre (PCBC) under supervision of a community midwife. Hence, timely recognition of neonatal hyperbilirubinaemia in primary care is essential to prevent the potentially devastating consequences of severe neonatal hyperbilirubinaemia. Additionally, implementation of phototherapy in primary care has the potential to reduce hospital admissions.

In **Chapter 1**, the general background on neonatal hyperbilirubinaemia and the Dutch perinatal care system is provided.

Part one describes the size and severity of the problem of neonatal hyperbilirubinaemia in the Netherlands and explores room for improvement. In **Chapter 2**, characteristics of neonates with severe neonatal hyperbilirubinaemia in the Netherlands were evaluated and improvable factors were identified. In total, 109 neonates with severe neonatal hyperbilirubinaemia were registered in the perinatal audit database during the three-year audit period. All neonates received phototherapy and 30 neonates (28%) also received an exchange transfusion. Improvable factors were mainly related to knowledge deficits and insufficient communication among healthcare professionals, and to poor adherence to the national hyperbilirubinaemia management guideline. Whereas *a priori* risk assessment of neonatal hyperbilirubinaemia, which is recommended for all neonates in the national guideline, was lacking in at least 90 neonates (83%), this was considered as an improvable factor by (involved) healthcare professionals during perinatal audit meetings in only 24 neonates. This study indicates that severe neonatal hyperbilirubinaemia remains a problem in the Netherlands and that adherence to the national guideline needs to be improved.

As MCAs provide daily postpartum care for neonates in primary care, they have a first-line role in the recognition of potentially severe hyperbilirubinaemia. In **Chapter 3**, the cur-

rent state of their knowledge and skills regarding neonatal hyperbilirubinaemia using an online questionnaire was assessed. Out of all Dutch MCAs (n=9065), 1465 MCAs (16.2%) completed the questionnaire. The median number of correctly answered knowledge questions was 5 (out of 6). An in-service training on neonatal hyperbilirubinaemia in the previous year was significantly associated with better knowledge. The large majority of MCAs felt that they were highly skilled or skilled to assess visual jaundice. However, estimation of TSB levels based on skin colour assessment was generally poor; MCAs tend to underestimate TSB levels. Additionally, a large proportion of MCAs (63%) did not feel that a blood sample needed to be collected for TSB quantification despite them assessing the neonate as 'quite yellow' or 'very yellow'. This study shows that knowledge of MCAs regarding neonatal hyperbilirubinaemia was good but that their assessment of skin colour to estimate TSB levels was prone to inaccuracy. This emphasises that other approaches to identify neonates with potentially severe hyperbilirubinaemia are needed.

Part two focuses on the Screening and TreAtment to Reduce Severe Hyperbilirubinaemia in Infants in Primary care (STARSHIP) Trial. The rationale and design of the STARSHIP Trial are described in **Chapter 4**. STARSHIP is a factorial stepped-wedge cluster randomised controlled trial (RCT). It evaluates two interventions regarding hyperbilirubinaemia in seven PCBCs in the Netherlands. The first intervention is universal, non-invasive screening of bilirubin levels using a transcutaneous bilirubinometer. The second intervention is implementation of phototherapy in PCBCs rather than in the hospital, when hyperbilirubinaemia is present. The aim of the STARSHIP Trial is to test whether universal transcutaneous bilirubin screening can reduce the number of neonates having severe neonatal hyperbilirubinaemia, and whether phototherapy in the PCBC reduces hospital admissions for phototherapy.

The lessons learnt from conducting this factorial stepped-wedge cluster RCT in primary care are outlined in **Chapter 5**. The stepped-wedge design allowed us to implement the interventions in a stepwise manner during the study. The factorial design offers the opportunity to evaluate two interventions in one trial and is therefore time- and cost-efficient. At the end of the trial, all clusters (i.e. PCBCs) will have implemented both interventions. This provides the study team with lessons regarding implementation of the interventions during the study. Also, the participating PCBCs have already implemented both interventions if they have the intention to continue with the interventions. As all clusters started with a control phase, neonates included in this phase of the study did not experience any benefit of participation in the STARSHIP Trial. This may have affected parental willingness to participate during the control phase. Another drawback of the stepped-wedge design is that it is less flexible in handling delay in inclusion rate due to

the pre-set timelines of the clusters. Perinatal healthcare providers in primary care, in particular MCAs, are relatively unfamiliar with conducting research. Consequently, more support is needed to assist them in their research tasks. This evaluation of the design and the setting of the STARSHIP Trial shows the pros and cons of a factorial stepped-wedge cluster RCT in primary care and the need of timely detection of challenges.

The control phase of the STARSHIP Trial offered a unique opportunity to evaluate standard care regarding neonatal hyperbilirubinaemia in primary care in the Netherlands. In **Chapter 6**, we prospectively evaluated the assessment and management of neonatal jaundice in healthy neonates cared for in primary care. Of the 860 neonates included during the control phase of STARSHIP, 608 (71.9%) were visibly jaundiced at some point during admission in the PCBC. Although 20 neonates were considered 'very yellow', 4 (20%) of them did not receive TSB quantification. There was no association between the degree of visible jaundice and the TSB level in neonates in whom TSB was quantified (p=0.416). Thirty-one neonates (3.6%) received phototherapy. Notably, an additional five neonates had a TSB level above phototherapy threshold, but did not receive phototherapy. This study demonstrates that neonatal jaundice and the need for phototherapy is common in primary care. Visual estimation of TSB levels is unreliable and not all neonates cared for in primary care receive phototherapy when indicated.

One of the interventions of the STARSHIP Trial is phototherapy in primary care. Final results of the STARSHIP Trial are not available yet, because the analyses are still ongoing. In **Chapter 7**, we undertook preliminary analyses on phototherapy in primary care on data from a single PCBC using a before-after design. In total, 468 neonates were included: 186 neonates before and 282 after implementation of phototherapy in primary care. Following implementation of phototherapy in primary care, hospital admission was avoided in 27 out of 32 neonates necessitating phototherapy (84.4%). Two neonates were admitted to the hospital after initial phototherapy in the PCBC and three neonates were admitted to the hospital primarily. In general, parents were satisfied with phototherapy in primary care. These preliminary results of phototherapy in primary care suggest that phototherapy can be safely and effectively applied in primary care and that hospital admission can be avoided in the majority of patients.

Part three describes the future steps to further improve screening for neonatal hyperbilirubinaemia in the home setting. To this end, the BEtter AssesmenT of neonatal jaundice at home (BEAT jaundice@home) study was designed. In **Chapter 8** the rationale and design of the BEAT jaundice@home study is presented. The BEAT jaundice@home study is a multicentre prospective cohort study in nine community midwifery practices in the Netherlands. It evaluates the effectiveness of universal transcutaneous bilirubin screen-

ing at home to enhance timely recognition of neonates with potentially severe hyperbilirubinaemia at home and reduce the need for heel pricks to quantify TSB. In parallel to transcutaneous bilirubin screening, diagnostic properties of Picterus®, a smartphone application that estimates bilirubin levels in blood based on a picture of the neonate's sternum, will be evaluated. If TSB quantification is needed based on visual inspection and/or transcutaneous bilirubin quantification, one extra drop of blood will be taken to evaluate Bilistick®, a point-of-care device to quantify bilirubin in whole blood. Bilistick® has the potential to reduce the time to test result and the amount of blood required to quantify bilirubin levels. The BEAT jaundice@home study is currently recruiting and first results are expected within the next years.

In conclusion, this thesis aimed to evaluate the current status of recognition and treatment of neonatal hyperbilirubinaemia. Additionally, novel screening and treatment strategies for neonatal hyperbilirubinaemia in primary care were explored. To this end, the STARSHIP Trial was designed and conducted in seven PCBCs in the Netherlands. The first results of the STARSHIP Trial are presented in this thesis. Also, the next steps towards improved recognition and diagnosis of neonatal hyperbilirubinaemia at home have been outlined. The findings presented in this thesis may contribute to making severe hyperbilirubinaemia and its potentially devastating consequences a ‘never-event’.

SAMENVATTING

De meeste pasgeboren baby's krijgen in de eerste dagen van het leven een gele verkleuring van de huid. Dit komt door een stijging van concentratie van de gele stof bilirubine in het bloed. Een verhoogde waarde van het bilirubine in het bloed bij baby's wordt ook wel neonatale hyperbilirubinemie genoemd. Meestal daalt de bilirubinewaarde vanzelf, maar soms is behandeling nodig als de bilirubinewaarden erg hoog zijn. Als neonatale hyperbilirubinemie niet op tijd herkend en behandeld wordt, kan een baby hersenschade met uiteindelijk levenslange handicaps oplopen. De behandeling gebeurt meestal met fototherapie. Hierbij wordt de huid beschenen met blauw licht, waardoor bilirubine wordt omgezet in ongevaarlijke afbraakproducten die gemakkelijk door het lichaam uitgescheiden kunnen worden. Als fototherapie onvoldoende helpt, kan een wisseltransfusie nodig zijn. Tijdens een wisseltransfusie wordt een deel van het bloed van de baby met daarin veel bilirubine vervangen ('gewisseld') door donorbloed met daarin weinig bilirubine. Hierdoor wordt de hoeveelheid bilirubine in de baby in korte tijd veel minder. Op dit moment wordt neonatale hyperbilirubinemie herkend door visuele inspectie van de gele kleur van de huid van de baby ('met het blote oog'). Als een zorgverlener een baby te geel vindt, moet er bloed worden geprikt om de bilirubinewaarde te bepalen.

In Nederland wordt de zorg voor een gezonde moeder en gezonde baby na de geboorte voornamelijk in de eerste lijn gegeven. Een kraamverzorgende zorgt na de geboorte voor de moeder en haar baby, thuis of in een geboortecentrum. Deze zorg vindt plaats onder supervisie van een eerstelijns verloskundige. Veel baby's krijgen dus zorg van een kraamverzorgende en een verloskundige op het moment dat ze geel gaan zien. De kraamverzorgende en de verloskundige spelen dan ook een belangrijke rol in de tijdige herkenning van neonatale hyperbilirubinemie. Door neonatale hyperbilirubinemie op tijd te herkennen en te behandelen, kunnen de mogelijk zeer ernstige gevolgen van een extreem hoge bilirubinewaarde voorkomen worden. Als via de bloedprik neonatale hyperbilirubinemie wordt vastgesteld, moet een baby in het algemeen in het ziekenhuis worden opgenomen voor fototherapie. Zeer beperkte ervaringen laten zien dat fototherapie ook in de eerste lijn zou kunnen plaatsvinden.

In **Hoofdstuk 1** wordt de algemene achtergrond van neonatale hyperbilirubinemie en de herkenning en behandeling ervan binnen het Nederlandse geboortezorg systeem beschreven.

Deel één beschrijft de omvang en de ernst van het probleem van neonatale hyperbilirubinemie in Nederland en onderzoekt waar ruimte is voor verbetering. Van 2017 tot

en met 2019 is neonatale hyperbilirubinemie een van de thema's van de perinatale audit geweest. In de perinatale audit worden casus rondom bepaalde aandoeningen of ziektebeelden op een gestructureerde manier geanalyseerd door zorgverleners. Hierin wordt onder andere gekeken of er 'goede zorg' verleend is, of de richtlijnen nageleefd zijn en hoe de zorg verbeterd kan worden. In **Hoofdstuk 2** worden de karakteristieken van baby's met ernstige neonatale hyperbilirubinemie die van 2017 tot en met 2019 aangemeld zijn voor de perinatale audit geëvalueerd en worden verbeterpunten vastgesteld. In totaal zijn er in de driejarige auditperiode 109 baby's met ernstige hyperbilirubinemie geregistreerd in de perinatale auditdatabase. Al deze baby's werden behandeld met fototherapie en dertig baby's (28%) hadden ook een wisseltransfusie nodig. Verbeterpunten die tijdens de perinatale auditbijeenkomsten geformuleerd werden, waren voornamelijk gerelateerd aan kennishiaten, ontoereikende communicatie tussen zorgverleners en aan slechte naleving van de landelijke richtlijn neonatale hyperbilirubinemie. De landelijke richtlijn adviseert een *a priori* risico-inschatting op het ontwikkelen van neonatale hyperbilirubinemie bij elke baby. Echter, deze inschatting ontbrak bij ten minste negentig baby's met ernstige hyperbilirubinemie (83%). Ondanks dat de landelijke richtlijn door iedereen gevolgd zou moeten worden, beschouwden (betrokken) zorgverleners het niet volgen van de richtlijn tijdens de perinatale auditbijeenkomsten slechts bij 24 baby's als een verbeterpunt. Dit onderzoek laat zien dat ernstige hyperbilirubinemie een probleem blijft in Nederland en dat navolging van de landelijke richtlijn verbeterd moet worden.

Aangezien kraamverzorgenden dagelijks voor pasgeboren baby's in de eerste lijn zorgen, hebben zij een belangrijke rol in het herkennen van mogelijk ernstige hyperbilirubinemie. In **Hoofdstuk 3** worden hun kennis en vaardigheden met betrekking tot neonatale hyperbilirubinemie geëvalueerd met behulp van een online vragenlijst. Van de ruim negenduizend kraamverzorgenden in Nederland hebben 1465 kraamverzorgenden (16.2%) de vragenlijst afgemaakt. Het mediaan aantal correct beantwoorde vragen was vijf van de zes vragen. Als de kraamverzorgende in het afgelopen jaar een bijscholing over neonatale hyperbilirubinemie had gevolgd, beantwoordde zij significant meer kennisvragen correct. Een grote meerderheid van de kraamverzorgenden voelde zich (zeer) deskundig in het beoordelen van geelzien met het blote oog. Echter, de inschatting van de bilirubinewaarde op basis van de beoordeling van de kleur van de huid was over het algemeen matig; kraamverzorgenden hadden de neiging om de bilirubinewaarden te onderschatten. Daarnaast zou een groot deel van de kraamverzorgenden (63%) geen bloed laten prikken om het bilirubine te bepalen bij een baby die ze als redelijk of zeer geel beoordeelden. Dit onderzoek laat zien dat de kennis van kraamverzorgenden met betrekking tot neonatale hyperbilirubinemie goed is, maar dat hun inschatting van de bilirubinewaarde op basis van de kleur van de huid van de baby vaak niet accuraat is.

Dit onderstreept de noodzaak om andere manieren te vinden om baby's met mogelijk ernstige hyperbilirubinemie te herkennen.

Deel twee richt zich op het onderzoek 'Screening and TreAtment to Reduce Severe Hyperbilirubinaemia in Infants in Primary care': STARSHIP. De achtergrond en de onderzoeksopzet van het STARSHIP-onderzoek is beschreven in **Hoofdstuk 4**. STARSHIP is een 'factorial stepped-wedge cluster' gerandomiseerd onderzoek in zeven eerstelijns geboortecentra in Nederland. Deze onderzoeksopzet betekent dat in het STARSHIP-onderzoek een of twee geboortecentra samen een cluster vormen. Elk cluster is via loting toegewezen aan een van de vooraf vastgestelde tijdlijnen. In deze tijdlijn staat beschreven wanneer welke interventie ingevoerd werd in het cluster. Er werden twee interventies met betrekking tot hyperbilirubinemie tegelijkertijd onderzocht ('factorial'). De timing van het invoeren van de interventie verschilde per cluster en gebeurde stapsgewijs ('stepped-wedge'). Elk cluster begon met een controleperiode, waarin de standaardzorg werd geëvalueerd. In de standaardzorg werd de kleur van de huid van de baby met het blote oog beoordeeld en kreeg de baby, als dat nodig was, fototherapie in het ziekenhuis.
Na de controleperiode werd een van de twee mogelijke interventies ingevoerd. De ene interventie was universele, niet-invasieve screening van de bilirubinewaarden door dagelijks gebruik te maken van een transcutane bilirubinemeter bij elke baby. Een transcutane bilirubinemeter is een apparaat dat tegen het borstbeen kan worden gehouden en door een lichtflits de waarde van het bilirubine vaststelt. Bij deze interventie wordt bij alle deelnemende baby's ouder dan 24 uur dagelijks de bilirubinewaarde met de transcutane bilirubinemeter bepaald. De transcutane bilirubinemeter wordt onafhankelijk van de mate van de gele kleur van de huid van de baby gebruikt.
De andere interventie is het toepassen van fototherapie in eerstelijns geboortecentra in plaats van in het ziekenhuis bij baby's met een te hoge bilirubinewaarde in bloed. Als de verloskundige en de kinderarts akkoord zijn, hoeven deze baby's dus niet meer in het ziekenhuis opgenomen te worden voor fototherapie. De helft van de clusters gebruikte in deze tweede fase van het STARSHIP-onderzoek de transcutane bilirubinemeter (interventie 1). Als er fototherapie nodig was, werd de baby daarvoor opgenomen in het ziekenhuis, conform de standaardzorg. In de andere helft van de clusters werd de mate van geelzien bij baby's met het blote oog beoordeeld (standaardzorg) en indien de bilirubinewaarde in het bloed te hoog was, konden baby's met fototherapie in het geboortecentrum behandeld worden (interventie 2). In de laatste fase werd de andere interventie toegevoegd. Hierdoor eindigden alle deelnemende eerstelijns geboortecentra uiteindelijk met een fase waarin beide interventies werden toegepast: screening met de transcutane bilirubinemeter (interventie 1) én fototherapie in het geboortecentrum (interventie 2).

In welk geboortecentrum de baby opgenomen was en het moment van opname in het geboortecentrum bepaalden welke interventie de baby kreeg. Er werd dus niet per baby geloot wat de interventies zouden worden. Dit heet ook wel clusterrandomisatie (in tegenstelling tot individuele randomisatie). Het STARSHIP-onderzoek had twee hoofddoelen. Ten eerste om te bekijken of universele screening met de transcutane bilirubinemeter het aantal baby's met ernstige hyperbilirubinemie kan verminderen. Ten tweede om te bekijken of fototherapie in eerstelijns geboortecentra het aantal ziekenhuisopnames voor neonatale hyperbilirubinemie kan verminderen.

De lessen die we geleerd hebben van het 'factorial stepped-wedge cluster' gerandomiseerd onderzoek in de eerste lijn worden geschetst in **Hoofdstuk 5**. Deze onderzoeksopzet had een aantal voordelen. De 'stepped-wedge' onderzoeksopzet maakte het mogelijk om de interventies op een stapsgewijze manier te implementeren tijdens het onderzoek. De 'factorial' onderzoeksopzet gaf de gelegenheid om twee interventies in een onderzoek te evalueren en is daardoor tijds- en kostenefficiënt. Aan het einde van het onderzoek hebben alle clusters (de eerstelijns geboortecentra) beide interventies geïmplementeerd. Hieruit heeft het onderzoeksteam lessen kunnen trekken over de implementatie van de interventies. Daarnaast hebben de deelnemende eerstelijns geboortecentra beide interventies al geïmplementeerd. Dit betekent dat ze direct door kunnen gaan met deze interventies, als ze dat zouden willen. Ook had de onderzoeksopzet nadelen. Omdat alle clusters startten met een controleperiode, hadden baby's in deze periode geen voordeel van deelname aan het STARSHIP-onderzoek. Dit kan invloed hebben gehad op de bereidheid van ouders om met hun baby mee te doen aan het onderzoek tijdens de controleperiode. De vooraf vastgestelde tijdlijnen maken het aanpassen van de planning van het onderzoek minder flexibel. Dit kan een nadeel van de 'stepped-wedge' onderzoeksopzet zijn als het aantal deelnemers achter ligt op de oorspronkelijke planning. Perinatale zorgverleners in de eerste lijn, in het bijzonder kraamverzorgenden, zijn relatief onbekend met het verrichten van onderzoek. Zodoende is er meer ondersteuning nodig om ze te helpen bij het uitvoeren van onderzoekstaken. Deze evaluatie van de onderzoeksopzet van STARSHIP laat de voor- en nadelen van een 'factorial stepped-wedge cluster' gerandomiseerd onderzoek in de eerste lijn zien en toont dat het essentieel is om uitdagingen op tijd op te merken.

De controleperiode van het STARSHIP-onderzoek gaf ons de unieke kans om de standaardzorg rondom neonatale hyperbilirubinemie in Nederland te evalueren. In **Hoofdstuk 6** wordt de inschatting en het beleid bij geelzien bij gezonde, pasgeboren baby's in de eerste lijn geëvalueerd. Van de 860 baby's die in de controleperiode deelnamen aan het STARSHIP-onderzoek, waren er 608 (71.9%) zichtbaar geel op enig moment tijdens opname in het eerstelijns geboortecentrum. Hoewel twintig baby's als 'zeer geel'

beoordeeld werden, werd er bij vier van deze baby's (20%) geen bilirubinewaarde in het bloed bepaald. Het was niet duidelijk aan te tonen dat er vaker bloed werd geprikt om de bilirubinewaarde te bepalen als baby's als geler beoordeeld werden (p=0.416). In totaal kregen 31 baby's (3.6%) fototherapie. Opvallend is dat vijf andere baby's een bilirubinewaarde boven de fototherapiegrens hadden, maar geen fototherapie kregen. Dit onderzoek laat zien dat geelzien en fototherapie gangbaar zijn bij gezonde baby's in de eerste lijn. Inschatting van de bilirubinewaarden door de kleur van de huid te beoordelen is onbetrouwbaar en niet alle baby's die in de eerste lijn verzorgd worden na de geboorte krijgen fototherapie als daar een indicatie voor is.

Eén van de interventies in het STARSHIP-onderzoek is fototherapie in de eerste lijn. Definitieve resultaten van het STARSHIP-onderzoek zijn nog niet beschikbaar, omdat de analyses van het onderzoek nog gaande zijn. In **Hoofdstuk 7** worden de gegevens van een van de zeven deelnemende eerstelijns geboortecentra gebruikt om voorlopige analyses van fototherapie in de eerste lijn te verrichten. We hebben de analyses uitgevoerd door middel van een voor- en een nameting. In totaal deden 468 baby's mee: 186 baby's voor en 282 baby's na invoering van fototherapie in de eerste lijn. Na invoering van fototherapie in de eerste lijn konden 27 van de 32 baby's die fototherapie nodig hadden in het geboortecentrum blijven (84.4%). Bij deze baby's werd dus een ziekenhuisopname voorkomen. Twee baby's werden opgenomen in het ziekenhuis nadat ze aanvankelijk fototherapie in het eerstelijns geboortecentrum hadden gekregen en drie baby's werden direct opgenomen in het ziekenhuis. Over het algemeen waren ouders tevreden met fototherapie in de eerste lijn. Deze eerste resultaten van fototherapie in de eerste lijn doen vermoeden dat fototherapie veilig en effectief toegepast kan worden in de eerste lijn en dat ziekenhuisopname voorkomen kan worden in de meerderheid van de verder gezonde patiënten die fototherapie nodig hebben.

Deel drie beschrijft de toekomstige stappen om herkenning en diagnose van neonatale hyperbilirubinemie in de thuissituatie verder te verbeteren. Hiervoor werd het 'BEtter AssessmenT of neonatal jaundice at home' (BEAT jaundice@home) onderzoek opgezet. In **Hoofdstuk 8** worden de achtergrond en de onderzoeksopzet van het BEAT jaundice@home-onderzoek gepresenteerd. Dit onderzoek is een multicenter prospectief cohortonderzoek in negen eerstelijns verloskundigenpraktijken in Nederland. In dit onderzoek zal de effectiviteit van universele screening op neonatale hyperbilirubinemie met een transcutane bilirubinemeter in de thuissituatie geëvalueerd worden. De verloskundige zal hiervoor bij elk huisbezoek eerst de kleur van de huid van de baby met het blote oog beoordelen en daarna de bilirubinewaarde bij de baby bepalen met de transcutane bilirubinemeter. Deze verschillende manieren van herkenning van geelzien zullen worden vergeleken. Het doel van het BEAT jaundice@home-onderzoek is om de tijdige

herkenning van baby's met mogelijk ernstige hyperbilirubinemie te verbeteren en tegelijkertijd in de toekomst het aantal bloedprikken om de bilirubinewaarde te bepalen te verminderen.
Parallel aan screening met de transcutane bilirubinemeter zal de Picterus® app gebruikt worden. De Picterus® app is een smartphone-applicatie die een inschatting maakt van bilirubinewaarden in het bloed gebaseerd op een foto van het borstbeen van de baby met op het borstbeen een kalibratiekaart. Omdat deze app nog in ontwikkeling is, zal de app voor de verloskundige geen resultaat van de inschatting van de bilirubinewaarde geven. De diagnostische eigenschappen van de Picterus® app zullen achteraf geëvalueerd worden.
Als er op basis van de kleur van de huid of van de transcutane bilirubinewaarde bloed geprikt moet worden om de bilirubinewaarde te bepalen, zal er één extra druppel bloed afgenomen worden om een derde apparaat, de Bilistick®, te evalueren. De Bilistick® is een sneltest die de bilirubinewaarde in volbloed meet en binnen enkele minuten een uitslag geeft. De Bilistick® heeft de potentie om de tijdsduur tot de uitslag van de bilirubinebepaling en de hoeveelheid bloed die nodig is voor de bilirubinebepaling te verminderen. Het BEAT jaundice@home-onderzoek werft momenteel deelnemers en de eerste resultaten worden verwacht in de komende jaren.

Concluderend had dit proefschrift als doel om de huidige staat van herkenning en behandeling van neonatale hyperbilirubinemie te evalueren. Daarnaast werden nieuwe methoden voor screening en behandeling van neonatale hyperbilirubinemie onderzocht. Hiervoor werd het STARSHIP-onderzoek opgezet en uitgevoerd in zeven eerstelijns geboortecentra in Nederland. De eerste resultaten van het STARSHIP-onderzoek worden gepresenteerd in dit proefschrift. Ook worden de volgende stappen richting verbeterde herkenning en diagnose van hyperbilirubinemie in de thuissituatie geschetst. De bevindingen die gepresenteerd worden in dit proefschrift zouden eraan bij kunnen dragen dat ernstige hyperbilirubinemie en de mogelijk levenslange gevolgen een 'never-event' worden.

11.

ABBREVIATIONS

aABR	(Automated) auditory brainstem response
ABE	Acute bilirubin encephalopathy
AS	Apgar score
BEAT jaundice@home	Better assessment of neonatal jaundice at home
BIND	Bilirubin-induced neurologic dysfunction
CEA	Cost-effectiveness analysis
CI	Confidence interval
CONSORT	Consolidated standards of reporting trials
CRF	Case report form
DAT	Direct antiglobulin test
EMR	Electronic medical record
EQUATOR	Enhancing the quality and transparency of health research
ET	Exchange transfusion
GA	Gestational age
GEE	Generalised estimating equation
GLMM	Generalised linear mixed model
IC	Informed consent
ICER	Incremental cost-effectiveness ratio
ICMJE	International committee of medical journal editors
IQR	Interquartile range
IVIg	Intravenous immunoglobulin
KSD	Kernicterus spectrum disorder
LBB	Laboratory-based bilirubin
LGA	Large for gestational age
MCA	Maternity care assistant
MREC	Medical research ethics committee
MRI	Magnetic resonance imaging
n/a	Not applicable
OCN	Obstetric care network
PAA	Perinatal audit assistant
PCBC	Primary care birth centre
POC	Point-of-care
PT	Phototherapy
RCT	Randomised controlled trial
SAE	Serious adverse event
SD	Standard deviation
SNH	Severe neonatal hyperbilirubinaemia

SOP	Standard operating procedure
SSF	Substandard care factor
STARSHIP	Screening and treatment to reduce hyperbilirubinaemia in infants in primary care
TB	Total bilirubin
TcB	Transcutaneous bilirubin
TREAT jaundice@home	Towards implementation of phototherapy for neonatal jaundice at home
TSB	Total serum bilirubin
UGT1A1	Uridine diphosphate glucuronosyltransferase family 1 member A1
VIF	Variance inflation factor

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Basic course Rules and Organisation for Clinical researchers (BROK®) course, EMWO	2018	1.50
Research Integrity, Erasmus MC	2018	0.30
Biomedical English Writing and Communication, Erasmus MC	2019-2020	3.00
Classical Methods in Data Analysis, UMC Utrecht	2019-2020	6.00
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Seminars, workshops and research meetings		
Attending Sophia Research Days (yearly)	2017-2019	0.90
Erasmus MC PhD day	2017, 2019	0.60
Presentation on neonatal hyperbilirubinaemia, refresher training for perinatal healthcare professionals	2018	0.25
Workshop on hyperbilirubinaemia, Dag van de Kraamzorg, Kenniscentrum Kraamzorg	2018	0.25
Presentation on novel developments regarding neonatal hyperbilirubinaemia, Mini symposium Regional Consortium Pregnancy and Childbirth Southwest Netherlands	2019	0.25
Weekly obstetric research meeting, Department of Obstetrics and Gynaecology, Erasmus MC	2017-2021	5.00
Weekly neonatal research meeting, Department of Paediatrics, Division of Neonatology, Erasmus MC	2017-2021	4.00
Annual RGOC award meeting 'Wladimiroff symposium'	2017-2019	0.30
International and national conferences		
Attending 10th World Congress on Developmental Origins of Health and Disease (DOHaD), Rotterdam, the Netherlands	2017	1.0

4th Symposium Urban Perinatal Health – *poster*	2017	0.5
European Academy for Paediatric Societies (EAPS) Congress, Paris, France - *poster*	2018	0.5

2. Teaching tasks	**Year**	**Workload (ECTS)**
Lecturing		
Lecture on hyperbilirubinaemia for Bachelor students – Erasmus MC (yearly)	2017-2019	0.75
Lecture on hyperbilirubinaemia for Bachelor students of the Minor Mystery of Creation	2019	0.25
Training		
Training maternity care professionals regarding neonatal hyperbilirubinaemia, transcutaneous bilirubin quantification, and phototherapy (within STARSHIP Trial)	2017-2020	4.25
Supervising Master's theses		
Supervising Master thesis of Imke Theeuwen, medical student, Erasmus MC Title: 'Non-invasive screening and treatment of hyperbilirubinaemia in primary perinatal care: what do caregivers know?'	2017-2018	2.0
Supervising Master thesis of Malou de Mol, medical student, Erasmus MC Title: 'Prevalence of hyperbilirubinaemia in newborns in primary care'	2018-2019	2.0
Supervising Master thesis of Ivana Barendse, medical student, Erasmus MC Title: 'Incidence of neonatal hyperbilirubinaemia necessitating treatment in healthy newborns (and associated factors)'	2020-2021	2.0

3. Other	**Year**	**Workload (ECTS)**
Sophia Education Committee, Sophia Onderzoekersvertegenwoordiging (SOV)	2018-2020	1.5
Sophia Research Day Committee, Sophia Onderzoekersvertegenwoordiging (SOV)	2019-2021	2.5