

Transcutaneous bilirubin screening for hyperbilirubinemia in African newborns

by
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Declaration

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the sole author thereof (save to the extent explicitly otherwise stated), that reproduction and publication thereof by Stellenbosch University will not infringe any third party rights and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

This dissertation includes 5 original papers of unpublished manuscripts and 2 original published systematic review protocols. The development and writing of the papers (published and unpublished) were the principal responsibility of myself and, for each of the cases where this is not the case, a declaration is included in the dissertation indicating the nature and extent of the contributions of co-authors.

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Abstract

Background

In many parts of the world, including African countries, apparently healthy newborns are usually discharged home early. Serum bilirubin levels usually peaks on postnatal days 3 to 5, by when many newborns have already been discharged home. Severe neonatal hyperbilirubinemia constitutes an important cause of neonatal mortality and morbidity in Africa. There is a need for ways of identifying newborns at risk of severe jaundice before hospital discharge especially in developing countries with poor health systems and inadequate follow-up procedures after discharge from hospital.

Objectives

The objective of this combination of studies is to provide evidence for the use of transcutaneous bilirubin (TcB) screening in a population of indigenous African newborns.

Methods

We summarized the available evidence on the accuracy and effectiveness of TcB screening in two Cochrane systematic reviews. In the first systematic review, we summarized the evidence on the effectiveness of TcB screening in newborns. The second review summarized the evidence on the accuracy of TcB measurement compared to total serum bilirubin (TsB) measurement. We also conducted research on the effects of TcB screening and on the accuracy of the TcB measurement in a population of South African newborns

Results

For our first systematic review, we did not identify any randomized controlled trial that assessed the effect of TcB screening on readmission for jaundice or on the incidence of severe hyperbilirubinemia in newborns. Findings from included observational studies from North America suggest that universal pre-discharge TcB screening in newborns reduces readmission for hyperbilirubinemia and also reduces the incidence of severe hyperbilirubinemia.

We conducted a randomized controlled trial of TcB screening in an indigenous population of African newborns from South Africa. Findings from our trial confirmed that TcB screening reliably identified newborns at risk of severe hyperbilirubinemia and led to a 75% reduction in the readmission rate for hyperbilirubinemia and up to 73% decrease in the incidence of severe hyperbilirubinemia. However, the effect of TcB screening on kernicterus and bilirubin induced neurology dysfunction is not known. Findings from our second systematic review of accuracy of TcB measurement compared to TsB measurement in the laboratory, suggest a significant correlation coefficient of up to 0.98 between these two measurements. However, there are mixed findings from the included studies on the effect of various factors including: gestational age, race, postnatal age, TsB concentration, on the correlation. Also, there are limited studies in indigenous African newborns.

Our cross-sectional study on the accuracy of the TcB measurement in a population of South African newborns showed a good correlation between TcB measurement and TsB measured in the laboratory.

Conclusion

The TcB tool can be used to reliably estimate TsB in African newborns and can help identify newborns who need phototherapy before hospital discharge. We recommend that every newborn should be assessed for hyperbilirubinemia using objective means of measuring or estimating serum bilirubin measurement such as the TcB or TsB before discharge from hospital. This could go a long way in reducing hyperbilirubinemia related readmissions and incidence of severe hyperbilirubinemia. Pre-discharge TcB screening in newborns can therefore be used to identify newborns in need of phototherapy or those who are at risk of readmission for hyperbilirubinemia after discharge.

Abstrak

Agtergrond

In baie dele van die wêreld, insluitende Afrikalande, word oënskynlike gesonde pasgebore babas vroeg uit die hospitaal ontslaan. Serum bilirubienvlakke bereik gewoonlik 'n hoogtepunt drie tot vyf dae na geboorte, teen die tyd wanneer baie babas alreeds ontslaan en by die huis is. Ernstige hiperbilirubinemie onder pasgeborenes is 'n belangrike oorsaak van neonatale sterftes en morbiditeit in Afrika. Daar is behoefte aan maniere om pasgebore babas wat 'n risiko vir ernstige geelsug het te identifiseer nog voordat hul uit die hospitaal ontslaan word, veral in ontwikkelende lande met swak gesondheidstelsels en onvoldoende opvolgprosedures na hospitaalontslag.

Doelwitte

Die doelwit van hierdie kombinasie van studies is om navorsingsbewyse te verskaf vir die gebruik van bilirubien ("TcB") sifting deur skandering van die vel, in 'n bevolking van inheemse pasgebore babas in Afrika.

Metodes

Ons het die beskikbare navorsingsbewyse met betrekking tot die akkuraatheid en effektiwiteit van TcB sifting opgesom in twee Cochrane stelselmatige oorsigte. In die eerste stelselmatige oorsig het ons die navorsingsbewyse rakende die effektiwiteit van TcB sifting in pasgeborenes opgesom. In die tweede oorsig het ons die navorsingsbewys rakende die akkuraatheid van TcB metings vergelyk met die totale serum bilirubien ("TsB") meting. Ons het ook navorsing gedoen rakende die effek van TcB sifting asook die akkuraatheid van die TcB meting in 'n bevolking van Suid-Afrikaanse pasgeborenes.

Resultate

Vir ons eerste stelselmatige oorsig het ons nie enige ewekansige steekproewe geïdentifiseer wat die effek van heropname in die hospitaal vir hiperbilirubinemie ondersoek het nie, of wat die insidensie van pasgeborenes met ernstige hiperbilirubinemie wat TcB sifting ondergaan het, ondersoek het nie.

Bevindinge van ingesluite waarnemingstudies van Noord-Amerika suggereer dat universele TcB sifting in pasgeborenes voor hospitaalontslag die heropname vir hiperbilirubinemie, asook die insidensie van ernstige hiperbilirubinemie, verlaag. Ons het 'n ewekansige gekontroleerde proef uitgevoer van TcB sifting in 'n inheemse Suid-Afrikaanse bevolking van pasgebore babas. Bevindinge van ons proef het bevestig dat TcB sifting van pasgebore babas wat 'n risiko het vir ernstige hiperbilirubinemie betroubaar is, en tot 'n 75% afname in die heropnamekoers vir hiperbilirubinemie gelei het, asook tot en met 'n 73% afname in die insidensie van hiperbilirubinemie. Die effek van TcB sifting op kernikterus en bilirubien-geïnduseerde neurologie is egter nie bekend nie. Bevindinge van ons tweede stelselmatige oorsig oor die akkuraatheid van die TcB meting teenoor die TsB meting in die laboratorium suggereer 'n beduidende korrelasie van tot 0.98 tussen hierdie twee metings. Die ingesluite studies het egter gemengde bevindinge getoon in terme van faktore soos swangerskapsouderdom, ras, postnatale ouderdom en TsB konsentrasie wat die effek op korrelasie kan beïnvloed. Daar is ook 'n beperkte aantal studies oor inheemse pasgeborenes in Afrika. Ons deursnitstudie oor die TcB meting se akkuraatheid in 'n Suid-Afrikaanse bevolking van pasgebore babas het 'n goeie korrelasie getoon tussen TcB meting en TsB meting in die laboratorium.

Gevolgtrekkings

Die TcB hulpmiddel is betroubaar en kan gebruik word om TsB in pasgebore babas in Afrika te skat. Dit kan ook pasgeborenes identifiseer wat fototerapie voor hospitaalontslag benodig. Ons beveel aan dat elke pasgebore baba getoets moet word vir hiperbilirubinemie deur middel van 'n objektiewe meting of skatting van serum bilirubien, byvoorbeeld TcB of TsB. Dit kan hiperbilirubinemie-verwante hertoelatings in hospitale en die insidensie van ernstige hiperbilirubinemie verlaag. TcB sifting in pasgeborenes voor ontslag uit die hospital kan dus gebruik word om babas te identifiseer wat fototerapie benodig, of wat 'n risiko het vir heropname vir hiperbilirubinemie na hospitaalontslag.

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Cochrane systematic review on transcutaneous bilirubin versus total serum bilirubin measurement in newborns.	

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Abbreviations

AAP	American Academy of Pediatrics
ABE	Acute Bilirubin Encephalopathy
ABO	Blood groups A, B and O
APGAR	Appearance, Pulse, Grimace, Activity and Respiration
BIND	Bilirubin-Induced Neurologic Dysfunction
CI	Confidence Interval
CPS	Canadian Pediatric Society
G6PD	Glucose-6-Phosphate Dehydrogenase
HPLC	High Performance Liquid Chromatography
IQR	Interquartile Range
IUGR	Intrauterine Growth Restriction
LBW	Low Birth Weight
LMIC	Low- and Middle-Income Country
NNT	Number Needed to Treat
Rh-D	Rhesus D
RR	Relative Risk
SD	Standard Deviation
TcB	Transcutaneous Bilirubin
TsB	Total Serum Bilirubin
VLBW	Very Low Birth Weight

Definitions

Acute bilirubin encephalopathy: A clinical syndrome, in the presence of severe hyperbilirubinemia, of lethargy, hypotonia and poor suck, which may progress to hypertonia with a high-pitched cry and fever, and eventually to seizures and coma.

Extreme hyperbilirubinemia: A total serum bilirubin concentration greater than ≥ 428 $\mu\text{mol/L}$ at any time during the first 28 days of life.

Kernicterus: The pathological finding of deep-yellow staining of neurons and neuronal necrosis of the basal ganglia and brainstem nuclei.

Neonate: An infant from birth to 28 days of age.

Neonatal jaundice: Yellow discoloration of the skin of a neonate.

Preterm Neonate: Neonate delivered before 37 completed weeks of gestation.

Severe hyperbilirubinemia: a total serum bilirubin (TsB) concentration greater than 340 $\mu\text{mol/L}$ at any time during the first 28 days of life.

Transcutaneous Bilirubin: Bilirubin level determined by transcutaneous bilirubinometer.

TcB screening for hyperbilirubinemia: The measurement of bilirubin levels in the skin with the use of a transcutaneous bilirubinometer to identify apparently healthy newborns at risk for hyperbilirubinemia.

Total Serum Bilirubin: Bilirubin level determined by performing a blood test

Chapter 1

Introduction and scope of work

Neonatal jaundice is one of the most common clinical signs encountered among newborns and occurs in approximately two thirds of all newborns in the first week after birth. Jaundice results from bilirubin deposition in the skin and mucous membranes. For most newborns, this is a benign condition and does not require any form of treatment. However, up to 5 percent of newborns will develop severe hyperbilirubinemia requiring medical intervention. If left untreated, extreme levels of bilirubin can be toxic to the brain of the newborn and cause neurological impairment [1]. Bilirubin results primarily from the breakdown of red blood cells in the reticuloendothelial system. Bilirubin is transported to the liver where it is conjugated to a water-soluble product that is easily excreted. Immaturity of the liver enzyme system in the newborn is the main factor placing them at risk of developing jaundice [2].

Hyperbilirubinemia is a major cause of readmission in the neonatal period [1,3–5]. Peak serum bilirubin levels usually occur on postnatal days 3 to 5, when many infants have already been discharged from the hospital. This places the infant at increased risk of severe hyperbilirubinemia due to delayed treatment and unduly burdens the family. In some cases, babies could have levels that can lead to acute bilirubin encephalopathy (ABE) or subsequent brain damage. In many resource-limited countries, severe or clinically significant neonatal hyperbilirubinemia is not only a leading cause for hospital readmission in the first week of life, but also constitutes an important cause of neonatal morbidity and mortality [6]. For example, in Nigeria, neonatal hyperbilirubinemia is the most common neonatal emergency, contributing 29% and 23% to 36% of morbidity and mortality, respectively, among newborns referred to the emergency [7,8]. Similarly, a study in Egypt found that severe neonatal hyperbilirubinemia accounted for 33% of total admission diagnoses to the outborn neonatal intensive care unit often with signs of ABE [9]. In Kenya, hyperbilirubinemia is the third-leading cause of both newborn admissions and deaths [10].

Why is severe neonatal hyperbilirubinemia still a problem in resource poor countries?

- In most resource-constrained settings, newborns are discharged early from nurseries without continued medical supervision or follow-up in the first week of life [9].
- Severe hyperbilirubinemia is often unpredictable and treatment is usually delayed [9].
- The main burden of preterm births remains in developing countries [11,12]. The greatest etiological factor for preterm births worldwide is infection, mainly due to bacterial infection, malaria and HIV [12]. Late preterm infants (born between 34 and 36 week gestation) are at increased risk due to extreme hepatic immaturity and feeding difficulties [13,14].

- There are no objective screening strategies to identify newborns who are at high risk of extreme hyperbilirubinemia in many resource-limited settings.
- Many mothers are often unregistered with inadequate prenatal care; thus, maternal blood type and newborn risk of hemolytic disease is usually not known.
- There is a high prevalence of glucose-6-phosphate dehydrogenase (G6PD) deficiency in some settings and screening for G6PD is not available and not routinely done [15].
- Facilities for total serum bilirubin measurements are often not available in many resource-constrained settings.

In addition to the problems listed above, the logistics of services required by the American Academy of Pediatrics (AAP) Guideline may not be relevant for bilirubin testing or follow-up of all neonates based on the postnatal age at discharge. The guideline also requires sufficiently-trained healthcare personnel. Paucity of resources and healthcare personnel to follow-up all newborns could be alleviated by selective follow-up of high-risk newborns that could be identified through a good screening strategy.

The clinical evaluation of hyperbilirubinemia involves visual assessment of jaundice. However, this method can be affected by skin color (especially in dark skin babies) and does not provide a quantification of the total serum bilirubin (TsB) level. Current more objective methods of assessing hyperbilirubinemia include the use of total serum bilirubin measurement from blood sampling and non-invasive methods like the transcutaneous bilirubin (TcB) measurement with a handheld bilirubinometer. TcB measurement is a non-invasive method for estimating TsB level and helps to reduce the risk of anaemia and trauma associated with blood sampling for TsB measurement. Transcutaneous bilirubinometry works by directing light into the skin and measuring the intensity of the wavelength of light that is returned. The measurement is usually taken by gently pressing the meter against the sternum or forehead. TcB measurement provides an immediate (within a minute) result of bilirubin level. Using this point-of-care device saves time compared to measuring a total serum bilirubin and may reduce costs associated with measuring bilirubin in newborns. There are a few TcB devices available in the market including the Bilicheck (SpectRx, Inc, Norcross [GA], US), JM 103 (Draeger Medical Systems Inc, Telford, US) and JM 105 devices (Draeger Medical Systems Inc, Telford, US). TcB screening for hyperbilirubinemia could lead to a reduction in the number of newborns with severe hyperbilirubinemia and a reduction in the number readmitted to the hospital with the diagnosis of hyperbilirubinemia through early detection. TcB screening for hyperbilirubinemia is the measurement of bilirubin levels in the skin with the use of a non-invasive device with the aim of identifying apparently healthy newborns at risk for hyperbilirubinemia.

If hyperbilirubinemia is identified early, effective interventions such as phototherapy can be initiated early to reduce the risk of ABE from very high serum bilirubin levels.

Our systematic search for relevant studies identified some observational studies that have evaluated the use of TcB screening in newborns [16–18]. However, as also noted by Sharma, there is no randomized controlled study evaluating the effects of TcB screening on readmission rate and development of severe hyperbilirubinemia [19]. The AAP recommends the use of either pre-discharge TsB or TcB measurements as appropriate screening options for identifying infants at risk for neonatal hyperbilirubinemia [20]. In contrast, according to the U.S. Preventive Services Task Force (USPSTF), "there is insufficient evidence to make a recommendation on screening infants for hyperbilirubinemia"[21]. Also, The National Institute for Health and Care Excellence (NICE) recommends "not to perform a bilirubin measurement in babies who are not visibly jaundiced" and advises visual inspection in all babies [22–25]. There are thus conflicting recommendations on the usefulness of pre-discharge bilirubin screening in newborns. There is currently no guideline in South Africa on the use of any objective method to screen newborns for hyperbilirubinemia before hospital discharge. In South Africa, apparently healthy newborns from well-baby nurseries are discharged home without any form of objective screening for hyperbilirubinemia, apart from visual inspection. However, visual inspection has been shown to be unreliable in the assessment of jaundice in newborns, especially those with dark skin. Visual assessment for jaundice can lead to an overestimation of risk, leading to unnecessary laboratory tests. Visual assessment can also lead to an underestimation of risk, which could result in a failure or delayed identification of babies needing treatment. A recent study (unpublished study) in newborns delivered at Tygerberg Hospital, in Cape Town, South Africa showed that up to 7% of newborns are readmitted to hospital within the first week of life because of jaundice requiring phototherapy or exchange transfusion [Ndayasiba 2015]. We have a unique opportunity to evaluate the effects of TcB for jaundice in a South African population of newborns and also provide evidence from a randomized controlled trial. We compared TcB screening for risk of severe hyperbilirubinemia with visual inspection for jaundice before hospital discharge. If shown to be useful in identifying newborns with severe hyperbilirubinemia, timely initiation of phototherapy could reduce the incidence of extreme hyperbilirubinemia and its potential neurotoxic consequences, such as kernicterus. Screening could also help to prevent inappropriate discharge of newborns who require treatment for hyperbilirubinemia in the initial birth hospitalization period.

Objectives

1. To summarise the available evidence on the effect of TcB screening in newborns on readmission for hyperbilirubinemia, incidence of severe hyperbilirubinemia and kernicterus.
2. To provide evidence from a randomized controlled trial in an indigenous population of African newborns on the effect of TcB screening for severe hyperbilirubinemia compared to the visual inspection for jaundice before hospital discharge.
3. To summarise the available evidence on the accuracy of TcB measurement compared to TsB measurement in the laboratory in newborns from different populations and settings.
4. To provide evidence from an indigenous population of African newborns on the accuracy of TcB measurement compared to TsB measurement.

Research questions:

- a. What is the impact of TcB screening for hyperbilirubinemia before discharge on the rate of severe hyperbilirubinemia and readmission for phototherapy?
- b. Can TcB screening in African newborns reduce the hyperbilirubinemia related readmissions and incidence of severe hyperbilirubinemia?
- c. Can TcB measurement be used to reliably estimate TsB measurement in newborns from different populations and settings?
- d. Can TcB measurement be used to reliably estimate TsB measurement in an indigenous population of African newborns?

To answer these questions, we have carried out:

1. A Cochrane Systematic review on the effectiveness of screening for hyperbilirubinemia in newborns.
2. A randomized controlled trial on the use of the TcB in a population of South African newborns.
3. A Cochrane Systematic review on the test accuracy of TcB measurement compared to TsB measurement in newborns.
4. A cross-sectional test accuracy study of TcB measurement in a population of South African newborns.

All the above listed studies have been presented in the different sections of the dissertation as listed in the table 1 below.

Table 1. Overview of chapters included in thesis.

Chapter 1	Short introduction, problem statement and rational for the project.
Chapter 2	A Cochrane systematic review summarising the evidence on TcB screening in newborns.
Chapter 3	A randomized controlled trial of pre-discharge TcB screening in a population of South African newborns.
Chapter 4	A case study highlighting the importance of TcB screening in African newborns.
Chapter 5	A Cochrane systematic review summarizing the evidence on the accuracy of TcB measurement compared to TsB measurement in the laboratory.
Chapter 6	A cross-sectional study on the accuracy of the TcB measurement (using the JM 105 device) compared to TcB measurement in a population of South African newborns.
Chapter 7	A short conclusion summarizing the findings from the different chapters and implications for practice and future research.

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Chapter 2

Transcutaneous bilirubin screening for hyperbilirubinemia in newborns: a Cochrane systematic review

Manuscript submitted to the Cochrane neonatal review group

Transcutaneous screening for hyperbilirubinemia in neonates: A Cochrane Systematic Review

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Abstract

Background

The American Academy of Pediatrics recommends universal transcutaneous bilirubin (TcB) or total serum bilirubin (TsB) screening in all newborns before hospital discharge. This practice has been implemented in the United States and Canada and has been the standard of care in these settings for many years. However, the US Preventive Task Force concluded that there is no robust evidence that universal bilirubin screening is beneficial in reducing the incidence of important outcomes such as bilirubin induced neurologic dysfunction or kernicterus. In this review, we aimed to evaluate the impact of TcB screening on various outcomes including bilirubin induced neurologic dysfunction and kernicterus.

Objectives

We evaluated the effects of TcB screening on readmission for jaundice and other secondary outcomes like incidence of severe hyperbilirubinemia.

Search methods

We used the standard search strategy of Cochrane Neonatal to search the Cochrane Central Register of Controlled Trials (CENTRAL 2017, Issue 1), MEDLINE via PubMed (1966 to 27 February 2017), EMBASE (1980 to 27 February 2017), and CINAHL (1982 to 27 February 2017). An updated search was conducted in August 2018. We also searched clinical trials databases, conference proceedings, and the reference lists of retrieved articles for randomized controlled trials and quasi-randomized trials.

Selection criteria

We aimed to include any randomized controlled trial or prospective cohort study with control arm that evaluated the use of TcB screening for risk of hyperbilirubinemia in newborns before hospital discharge. Also, the studies need to have reported important outcomes such as incidence of readmission for hyperbilirubinemia, incidence of severe hyperbilirubinemia, bilirubin encephalopathy and kernicterus.

Data collection and analysis

Two authors independently screened through the titles and abstracts from the search output to identify any relevant study. There was no study identified that met our inclusion criteria.

The answer to the question of whether TcB screening can help to reduce readmission rate for jaundice and reduce the rate of severe hyperbilirubinemia can be best provided by a well-designed randomized

controlled trial (RCT). However, findings from our literature search did not identify any published RCT that evaluated this question. The current available evidence is from observational studies. Also, TcB or TsB screening is already standard of care in many developed countries and it will not be ethically feasible to conduct any randomized controlled studies in these settings. There might be an opportunity to evaluate the impact of TcB screening in an RCT in other settings where screening for hyperbilirubinemia before hospital discharge is not standard of care. At most any RCT evaluating the use of TcB or TsB screening in newborns might be able to evaluate surrogate outcomes such as readmission for jaundice and incidence of severe hyperbilirubinemia. Also, the impact of TcB or TsB screening on bilirubin encephalopathy or kernicterus might never be known because this will require a very large sample size including thousands of newborns because of the low incidence of kernicterus. A well designed randomized controlled trial is needed to evaluate the impact of TcB or TsB screening in newborns before hospital discharge.

Main results

We identified four observational studies and did not identify any randomized controlled trial.

Authors' conclusions

Evidence of low quality from observational studies suggest that TcB screening is associated with decreased hospital readmission rate for jaundice and decrease in the incidence of severe hyperbilirubinemia.

Plain language summary

Transcutaneous screening for hyperbilirubinemia in neonates: A Cochrane Systematic Review

Jaundice refers to yellowish discoloration of the skin and the white of the eye. It occurs because of an increase in a pigment in the blood called bilirubin. When bilirubin levels in the blood increases, it gets deposited in the skin and eyes and cause them to become yellow. Jaundice is a very common condition in newborns and affects up to 60 to 80% of newborns. In most cases, the condition is benign and does not require any treatment. However, in some instances, the newborns would require treatment in the form of phototherapy or exchange blood transfusion. Also, very high levels of bilirubin in the blood can find its way into the brain and cause damage to the newborn's brain resulting in permanent neurologic damage such as cerebral palsy. Early identification of jaundice is important to help prevent the potential adverse consequences. In this review we evaluated the use of a noninvasive transcutaneous device on readmission for jaundice and reduction in the incidence of severe hyperbilirubinemia. We did not identify any studies that met our inclusion criteria. However, evidence from a few observational studies suggest that TcB screening of newborns before hospital discharge is associated with a reduction in hospital readmission rate and results in a decrease in the incidence of severe hyperbilirubinemia. Further, well-designed studies are needed to confirm these findings from the two observational studies before widespread implementation of universal bilirubin screening.

Background

Description of the condition

Hyperbilirubinemia is a term used to describe elevated levels of bilirubin in the blood. In newborns, hyperbilirubinemia becomes clinically apparent as jaundice, a yellow coloration of the skin and the sclera, at total serum bilirubin (TsB) levels > 5 mg/dl ([Porter 2002](#)). Hyperbilirubinemia is very common in both term and preterm newborn infants (occurring in around 60% of newborns) and results from a predisposition to produce bilirubin and the newborn's limited ability to excrete it ([Lauer 2011](#)). Jaundice or hyperbilirubinemia is the most common cause of hospital readmission in the neonatal period ([Soskolne 1996](#); [Maisels 1998](#); [Escobar 2005](#)). Most cases of newborn jaundice are mild and self-limited. However, in rare cases, infants can have very high levels of bilirubin that can lead to bilirubin encephalopathy and kernicterus ([Newman 2006](#)). Acute bilirubin encephalopathy is a clinical syndrome, in the presence of severe hyperbilirubinemia, of lethargy, hypotonia and poor suck, which may progress to hypertonia with a high-pitched cry and fever, and eventually to seizures and coma. Kernicterus refers to the pathological finding of deep-yellow staining of neurons and neuronal necrosis of the basal ganglia and brainstem nuclei.

The threshold concentration of bilirubin and/or the duration of hyperbilirubinemia responsible for causing kernicterus injury in newborn infants is not known ([Dennery 2004](#)). Low concentrations of bilirubin may have some antioxidant benefits, suggesting that bilirubin should not be eliminated.

Studies from developed countries estimate the incidence of kernicterus to range from about 0.4 to 2 per 100,000 ([Sgro 2006](#); [Manning 2007](#); [Burke 2009](#)). However, studies from developing countries suggest that the incidence may be much higher ([Nair 2003](#); [Owa 2009](#)).

The acute phase signs of kernicterus are poor feeding, lethargy, high-pitched cry, hypertonia or hypotonia, opisthotonos and seizures. The chronic manifestations include athetoid cerebral palsy, motor delay, gaze palsy, dental dysplasia, mental retardation and sensorineural hearing loss ([AAP 2004](#)). Current treatments for hyperbilirubinemia include phototherapy and exchange transfusion (usually reserved for severe cases of hyperbilirubinemia) ([NICE 2010](#)).

Description of the intervention

Transcutaneous bilirubin (TcB) measurement devices are used for the rapid and noninvasive measurement of bilirubin levels in the skin. Transcutaneous bilirubinometry works by directing light into the skin of the neonate and measuring the intensity of the specific wavelength of light returned. The measurement is usually taken by gently pressing the meter against the sternum. Findings from many studies suggest that the accuracy and precision of TcB measurements correlate with standard

laboratory TsB ([Rubaltelli 2001](#); [Engle 2002](#); [Maisels 2004](#); [Slusher 2004](#); [Jangaard 2006](#)). Other studies suggest that TcB measurements do not correlate with TsB measurements in preterm newborns ([Knupfer 2001](#); [Karoly 2004](#)). TcB screening involves the measurement of bilirubin in every newborn in whom clinical jaundice is not present or observed, prior to discharge.

How the intervention might work

The practice of early discharge (< 72 hours of age) of healthy term newborns is growing worldwide. Because peak serum bilirubin levels usually occur on postnatal day three to five, an effective means of screening for the onset of hyperbilirubinemia could enhance the safety of the early discharge of newborns.

The clinical evaluation of hyperbilirubinemia involves the visual assessment of jaundice. However, this method can be affected by the newborn's skin color and does not provide a quantification of the TsB level. Current, more-objective methods of assessing hyperbilirubinemia include the use of TsB measurements from blood sampling and noninvasive methods, such as TcB measurement with a handheld bilirubinometer. To aid in identifying newborns with a significant risk of hyperbilirubinemia and its consequences, TcB and other screening strategies for hyperbilirubinemia prior to the discharge of newborns have been advocated ([Bhutani 1999](#); [Alpay 2000](#); [Newman 2000](#); [Stevenson 2001](#)). TcB screening for hyperbilirubinemia is used to identify newborns with bilirubin levels greater than the 75th percentile for age in hours and to track those with rapid rates of bilirubin rise (> 0.2 mg/dl per hour). [Bhutani 1999](#) proposed an on-the-hour-specific bilirubin nomogram as an approach to pre-discharge screening for hyperbilirubinemia. However, [Fay 2009](#) have highlighted multiple methodologic flaws in the methods used to create the hour-specific total bilirubin nomogram.

TcB screening for hyperbilirubinemia, the characterization of bilirubin levels by risk, with selective follow up of at-risk infants and timely intervention in infants at risk of hyperbilirubinemia, could lead to a reduction in the number of newborns with severe hyperbilirubinemia and a reduction in the number of newborns readmitted to the hospital for phototherapy or exchange transfusion. If hyperbilirubinemia is identified early, effective interventions such as phototherapy can be initiated to reduce the risk of bilirubin encephalopathy. However, TcB screening could also lead to unnecessary readmissions, prolonged hospitalization, excess laboratory tests and increased costs.

Why it is important to do this review

The American Academy of Pediatrics (AAP) and the Canadian Pediatric Society (CPS) both recommend the use of either pre-discharge TsB or TcB measurements as appropriate screening options for identifying infants at risk of neonatal hyperbilirubinemia ([AAP 2004](#); [CPS 2007](#)). In contrast, however, according to the US Preventive Services Task Force, "there is insufficient evidence to make a recommendation on screening infants for hyperbilirubinemia to prevent chronic bilirubin encephalopathy" ([USPSTF 2009](#)). There is conflicting evidence for, and recommendations on, the usefulness of pre-discharge bilirubin screening in newborns. Without proof of efficacy, universal screening of newborns for hyperbilirubinemia can result in the waste of healthcare resources and the unnecessary testing of many newborns.

We aim to evaluate all the relevant available evidence to assess the effects of TcB screening for hyperbilirubinemia in newborn infants before discharge from hospital.

Objectives

To evaluate to the effects of TcB screening for hyperbilirubinemia to prevent the readmission of neonates for phototherapy.

Methods

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials, quasi-randomized controlled trials, cluster randomized trials and other prospective study designs (e.g. cohort studies).

We excluded the following types of studies:

- Retrospectives cohort studies and all studies without any control.
- Studies that assessed the agreement or accuracy of TcB measurement compared to TsB measurement
- Studies that evaluated the predictive ability of TcB screening and the percentile bilirubin nomogram for subsequent hyperbilirubinemia

Types of participants

- Well newborns, of gestational age 35 weeks or more and weighing 1800 g or more, being discharged from the newborn nursery (in the first week of life)

We will not include infants admitted to, or being discharged from, the neonatal intensive care unit.

Types of interventions

1. TcB screening (alone or combined with any other method, e.g. visual assessment) compared to no screening or visual inspection for hyperbilirubinemia before discharge from hospital
2. TcB screening versus TsB screening before discharge from hospital
3. Closer follow up or home nursing visits based on TcB screening results versus post-discharge follow up or treatment decisions based on visual inspection

Types of outcome measures

Primary outcomes

- Readmission for phototherapy or home phototherapy for hyperbilirubinemia
- Exchange transfusion

Secondary outcomes

- Phototherapy before hospital discharge
- Peak bilirubin levels
- Acute bilirubin encephalopathy
- Chronic bilirubin encephalopathy
- Hearing loss
- Length of stay (days)
- Cost of care

Search methods for identification of studies

We used the standard search strategy of the Cochrane Neonatal Review Group to identify all relevant studies regardless of language or publication status (published, unpublished, in press and in progress).

Electronic searches

We used the criteria and standard methods of Cochrane and Cochrane Neonatal (see [the Cochrane Neonatal search strategy for specialized register](#)).

We conducted a comprehensive search including: Cochrane Central Register of Controlled Trials (CENTRAL 2017, Issue 1) in The Cochrane Library; MEDLINE via PubMed (1966 to 27 February 2017); EMBASE (1980 to 27 February 2017); and CINAHL (1982 to 27 February 2017) using the following search terms: (transcutaneous OR screening) AND (hyperbilirubinaemia OR hyperbilirubinemia OR jaundice), plus database-specific limiters for RCTs and neonates (see [Appendix 1](#) for the full search strategies for each database). We did not apply language restrictions. We searched clinical trials registries for ongoing or recently completed trials (clinicaltrials.gov; the

World Health Organization's International Trials Registry and Platform (www.who.int/ictrp/search/en/, and [the ISRCTN Registry](http://www.isrctn.com/)).

Searching other resources

We contacted experts and organizations or manufacturers of bilirubinometers for information on any relevant study. We scanned through the reference lists of all relevant studies. We searched conference and symposia proceedings of the Perinatal Society of Australia and New Zealand and the Paediatric Academic Societies (American Pediatric Society, Society for Pediatric Research and European Society for Paediatric Research).

Data collection and analysis

We used the standard methods of the Cochrane Neonatal Review Group.

Selection of studies

The first two review authors independently scanned through the titles and abstracts of the search output to identify potentially eligible studies. Discrepancies were resolved through discussion. We obtained full text articles of all selected abstracts to formally assess eligibility using the prespecified eligibility criteria. We summarized the reasons for exclusion of any potentially eligible study in the 'Characteristics of excluded studies' table.

Data extraction and management

We designed a data extraction form for the extraction of data. Two review authors independently extracted data from all included studies using the data extraction form. We resolved discrepancies through discussion. We entered data into the latest version of Review Manager (RevMan 2014) and checked them for accuracy.

Study information to be extracted includes:

- study details: citation, start and end dates, location and study design;
- participant details: study population eligibility (inclusion and exclusion) criteria, gestational age, sex, sample size and attrition rate;
- details about the interventions: type of TcB meter used, and any other method used for screening for hyperbilirubinemia
- outcome details: readmission rates for phototherapy, exchange transfusion, acute bilirubin encephalopathy, chronic bilirubin encephalopathy and adverse effects.

For each dichotomous outcome, we aimed to extract information on the number of participants experiencing the event and the number of participants randomized to each treatment group. For each continuous outcome we planned to extract the means or geometric means and standard deviations (or information to estimate the standard deviations) for each treatment group, together with the numbers of participants in each group. We planned to extract medians and ranges if these are reported in place of means and standard deviations.

Assessment of risk of bias in included studies

We planned to assess the risk of bias (low, high, or unclear) of all included trials using the Cochrane ‘Risk of bias’ tool (Higgins 2011) for the following domains:

- Sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Any other bias

Any disagreements were resolved by discussion or by a third assessor.

Measures of treatment effect

We planned to present results for dichotomous outcomes as summary risk ratios (RRs) with 95% confidence intervals (CIs) and absolute risk differences with 95% CIs. Also, we planned to present continuous outcomes using the mean difference (MD), if outcomes are measured using the same scale in trials or using the standardized mean difference when the outcome is measured using different scales. We planned to present the summary effect measures with 95% CIs. If the RR is statistically significant, the number needed to treat to for an additional beneficial outcome or an additional harmful outcome were to be calculated.

Unit of analysis issues

We will note the unit of analysis at the level of randomization (individual or group) and analyze the data accordingly. We will include cluster randomized trials in the analyses along with individually randomized trials. For cluster randomized trials, we will adjust the sample sizes using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions*, Section 16.3.4 or 16.3.6 ([Higgins 2011](#)) using an estimate of the intra-cluster correlation coefficient (ICC) derived from the trial (if possible) or from another source.

Dealing with missing data

We planned to contact authors if there are missing or unclear data. We also planned to note levels of attrition in each of the included studies. For all outcomes we planned to carry out an intention-to-treat analysis. For outcomes in which the results have been pooled in meta-analysis, we planned to explore the impact of including studies with significant loss to follow up in the overall assessment of treatment effect by using sensitivity analyses.

Assessment of heterogeneity

We planned to assess statistical heterogeneity by visually inspecting the forest plots to detect overlapping CIs, applying the Chi² test (P value < 0.10 considered statistically significant) and also using the I² statistic, where an I² of less than 25% will be considered as unimportant, 25% to 49% will be considered to suggest low heterogeneity, 50% to 74% will be considered to suggest moderate heterogeneity, and 75% or greater will be considered to indicate high heterogeneity.

Assessment of reporting biases

If we have 10 or more studies, we planned to explore the likelihood of reporting bias or publication bias for each outcome using funnel plots.

Data synthesis

Quality of evidence

We planned to use the GRADE approach, as outlined in the GRADE Handbook ([Schünemann 2013](#)), to assess the quality of evidence for the following (clinically relevant) outcomes.

Two authors were to independently assess the quality of the evidence for each of the outcomes above. We considered evidence from randomized controlled trials as high quality but downgraded the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates and presence of publication bias. We planned to use the [GRADEpro GDT](#) Guideline Development Tool to create a ‘Summary of findings’ table to report the quality of the evidence.

The GRADE approach results in an assessment of the quality of a body of evidence in one of four grades:

1. High: We are very confident that the true effect lies close to that of the estimate of the effect.
2. Moderate: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
3. Low: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
4. Very low: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Subgroup analysis and investigation of heterogeneity

We planned to carry out subgroup analyses based on gestation age (preterm versus term newborns); the presence of jaundice (versus no jaundice) in newborns; birth weight (<2500 g versus > 2500 g); and the presence of any comorbid conditions (e.g. hemolytic disease or other conditions known to exacerbate jaundice); mode of delivery (spontaneous vertex delivery or delivery by caesarean section).

Sensitivity analysis

Depending on the number of included studies, we planned to conduct sensitivity analyses on the robustness of the methods used regarding allocation concealment and losses to follow up in the analysis, and we will report the impact of the sensitivity analyses on the quantitative results from the meta-analysis.

Results

Description of studies

In this review we planned to include randomized controlled trials, quasi-randomized controlled trials, cluster randomized trials and other prospective study designs (e.g. cohort studies).

We identified 113 studies after deduplication of studies from the different databases in our original search in August 2017 and updated search in August 2018 did not yield any new studies. We did not identify any studies that met our inclusion criteria. A few observational studies that evaluated the use of either TcB or TsB screening are summarized in the table 1 below.

Table 1.1: Summary of observational studies that evaluated the use of TcB screening.

Study ID	Country	Period	Type of study	Setting and participants	Sample size	Outcomes
Darling 2014	Canada	July 2007 to June 2010	This was a before and after study. Canada.	This study was conducted in 42 hospitals across Ontario, Canada.	The study included a total of 534,103 infants >35 weeks gestation.	In this study, universal bilirubin screening did not find any change in jaundice related readmissions. However, there was an increase in phototherapy during hospitalization at birth (RR, 1.32; 95% CI, 1.09– 1.59) and a decrease in jaundice related emergency department visits (RR, 0.79; 95% CI, 0.64–0.96) but no statistically significant difference in phototherapy after discharge.
Eggert 2006	USA	March 2001 to Dec 2002 & Jan 2003 to Dec 2004	This was a retrospective cohort study.	This study was conducted in 18 hospitals in the US.	A total of 101,272 newborns of > 35-week gestational age, 52483 after implementing pre-discharge bilirubin screening program compared with 48789 delivered before (total 101 272) >35-week gestational age.	The study demonstrated a reduction in the proportion of newborns with bilirubin level >25mg/dl from 1 in 1572 to 1 in 4037 (p<0.005). The rate of readmission for hyperbilirubinemia was decreased from 0.55% to 0.43% after implementation of bilirubin screening (p<0.005)
Kuzniewicz 2009	USA	Jan 1995 to June 2007.	This was a retrospective cohort study.	This study was conducted in 11 hospitals in the US	A total of 38,182 born > 35-week gestational age born in 9 hospitals after implementation of	Universal bilirubin screening was associated with a significantly lower incidence of severe

			Bilirubin screening was with either TcB or TsB.		universal bilirubin screening with 319 904 born before implementation of the screening.	hyperbilirubinemia but also with increased phototherapy use.
Mah 2010	USA	May 2004 to Dec 2008	This was a prospective cohort study.	This study was conducted in 116 hospitals in the USA.	A total of 129345 births before implementation of universal bilirubin screening and 899472 after the implementation.	There was a 65% reduction in proportion of infants with TsB >30mg/dl. The rate of phototherapy use increased from 4.4% in 2004 to 5.1% in 2008.
Petersen 2005	USA	August 2002 to March 2003 (before TcB) and from May 2003 to December 2003 (after TcB)	This was a retrospective cohort study.	This study was conducted in a single hospital in the USA.	A total of 6933 healthy newborns were included.	There was a significant decrease in number of readmissions for hyperbilirubinemia per 1000 newborns per month from 4.5 to 1.8 (Wilcoxon rank sums two sample test, p=0.044). There was no significant difference in the blood sampling for TsB, length of hospital stay and duration of phototherapy prior to discharge.

Results of the search

Included studies

There was no study that met our inclusion criteria.

Excluded studies

We excluded many potentially eligible studies. Most of the studies on TcB screening evaluated the predictive ability on subsequent hyperbilirubinemia. Other studies were retrospective and did not provide any prospective data even though the authors reported on relevant outcomes. See table of excluded studies.

Risk of bias in included studies

We did not identify any studies that met our inclusion criteria.

Allocation (selection bias)

There was no study that met our inclusion criteria.

Blinding (performance bias and detection bias)

There was no study that met our inclusion criteria.

Incomplete outcome data (attrition bias)

There was no study that met our inclusion criteria.

Selective reporting (reporting bias)

There was no study that met our inclusion criteria.

Other potential sources of bias

Effects of interventions

Primary outcomes

- *Readmission for phototherapy or home phototherapy for hyperbilirubinemia*

No RCT or prospective cohort study has evaluated this outcome with the use of TcB screening.

- *Exchange transfusion*

No RCT or prospective cohort study has evaluated this outcome with the use of TcB screening.

Secondary outcomes

- *Phototherapy before hospital discharge*

No RCT or prospective cohort study has evaluated this outcome with the use of TcB screening.

- *Peak bilirubin levels*

No RCT or prospective cohort study has evaluated this outcome with the use of TcB screening.

- *Acute bilirubin encephalopathy*

No RCT or prospective cohort study has evaluated this outcome with the use of TcB screening.

- *Chronic bilirubin encephalopathy*

No RCT or prospective cohort study has evaluated this outcome with the use of TcB screening.

- *Hearing loss*

No RCT or prospective cohort study has evaluated this outcome with the use of TcB screening.

- *Length of stay (days)*

No RCT or prospective cohort study has evaluated this outcome with the use of TcB screening.

- *Cost of care*

No RCT or prospective cohort study has evaluated this outcome with the use of TcB screening.

Discussion

The AAP recommends universal pre-discharge TcB or TsB screening in all newborns for identifying infants at risk for neonatal hyperbilirubinemia [AAP 2004](#). However, the U.S. Preventive Services Task Force USPSTF, "there is insufficient evidence to make a recommendation on screening infants for hyperbilirubinemia" [USPSTF 2009](#). This systematic review aimed to evaluate the impact of TcB screening in newborns on the outcomes of readmission for hyperbilirubinemia, rates of exchange transfusion, acute and chronic bilirubin encephalopathy amongst other outcomes. We conducted a comprehensive search of all relevant databases to identify potentially eligible studies. Our search for relevant studies did not identify any randomized controlled trial or any other prospective study with control arm that evaluated the use of TcB screening in newborns. Similarly, the systematic review by Bhardwaj, did not identify any randomized controlled study evaluating the effects of TcB screening on readmission rate and development of severe hyperbilirubinemia [Bhardwaj 2017](#). We identified a few observational studies that evaluated the use of TcB screening in newborns. We did not identify any studies of TcB for jaundice in African newborns with varying skin pigmentation. This systematic review did not identify any evidence from randomized controlled trials for the use of TcB screening newborns. However, a few observational studies from the US and Canada have demonstrated that universal TcB or TsB reduced jaundice readmissions and led to a reduction in the incidence of severe hyperbilirubinemia [Alkalay 2010](#); [Darling 2014](#); [Eggert 2006](#); [Kuzniewicz 2009](#); [Mah 2010](#); [Petersen 2005](#); [Wainer 2012](#). These findings are yet to be confirmed in any randomized controlled trials. All these studies reported on surrogate outcomes and non-reported on the incidence of bilirubin induced neurologic dysfunction of kernicterus.

Summary of main results

A limited number of observational studies have evaluated the effects of pre-discharge TcB screening on readmission for jaundice and incidence of severe hyperbilirubinemia. We did not identify any randomized controlled trial or any prospective study with control arm that met our inclusion criteria. Findings from these observational studies suggest that TcB screening could lead to reduction in jaundice related readmissions and reduction in the incidence of severe hyperbilirubinemia. There is currently no randomized controlled trial that has evaluated the use of universal TcB screening for hyperbilirubinemia in newborns.

Overall completeness and applicability of evidence

We conducted a comprehensive search of the literature. We are confident that all the currently available evidence has been summarized in this review.

Quality of the evidence

The evidence presented in this review is evidence from observational studies. We did not identify any completed randomized controlled trial that evaluated the impact of TcB screening on jaundice readmission, severe hyperbilirubinemia and bilirubin encephalopathy. Low quality evidence suggest that TcB screening is associated with decreased hospital readmission rate for jaundice and decrease in the incidence of severe hyperbilirubinemia.

Potential biases in the review process

We conducted a comprehensive search in attempt to identify all relevant studies. Two authors independently screening studies for eligibility and did data extraction from the included studies.

Agreements and disagreements with other studies or reviews

A previous review by concluded that the effects of screening on the rates of bilirubin encephalopathy are unknown and that screening is not associated with any favorable clinical outcomes.

Authors' conclusions

Implications for practice

Low quality evidence suggests a beneficial effect of transcutaneous bilirubin screening. The use of TcB or TsB screening is already implemented and currently standard of care in the USA and Canada. The use of TcB screening in newborns is not associated with any harm. Therefore, depending on availability of the resources and TcB meters, clinicians caring for newborns can consider implementing this practice which shows some promising benefit.

Implications for research

The answer to the question of whether TcB screening can help to reduce readmission rate for jaundice and reduce the rate of severe hyperbilirubinemia can be best provided by a well-designed randomized controlled trial. However, findings from our literature search did not identify any published RCT that evaluated this question. The current available evidence is from observational studies. Also, TcB or TsB screening is already standard of care in many developed countries and it will not be ethically feasible to conduct any randomized controlled studies in these settings. There might be an opportunity to evaluate the impact of TcB screening in an RCT in other settings where bilirubin screening is not standard of care. At most any RCT evaluating the use of TcB or TsB screening in newborns might be able to evaluate surrogate outcomes such as readmission for jaundice and incidence of severe hyperbilirubinemia. Also, the impact of TcB or TsB screening on bilirubin encephalopathy or kernicterus might never be known because this will require a very large sample size including

thousands of newborns because of the low incidence of kernicterus. A well designed randomized controlled trial is needed to evaluate the impact of TcB or TsB screening in newborns before hospital discharge.

Contributions of authors

Charles Okwundu conceptualized and wrote the draft protocol and review. Olalekan A Uthman, Johan Smith, Vinod Bhutani and Charles Wiysonge contributed to various sections of the protocol and review.

Declarations of interest

None

Differences between protocol and review

Characteristics of excluded studies

Alkalay 2010

Reason for exclusion	This study used a historical cohort as control.
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Allen 2010

Reason for exclusion	This study evaluated the impact of TcB measurement on blood sampling for TsB. No outcome relevant to this review was reported
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Alpay 2000

Reason for exclusion	This study evaluated the value of first-day bilirubin measurement in predicting the development of significant hyperbilirubinemia in healthy term newborns. No outcome relevant to this review was reported.
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Bhutani 1999

Reason for exclusion	The study evaluated the use of a TcB nomogram for prediction of subsequent hyperbilirubinemia. No outcome relevant to this review was assessed.
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Bhutani 2000

Reason for exclusion	The study evaluated the accuracy of TcB measurement and the use of a TcB nomogram for prediction of subsequent hyperbilirubinemia. No outcome relevant to this review was assessed.
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Bhutani 2013

Reason for exclusion	Uncontrolled cohort study. The authors used TsB and clinical risk factor to predict hyperbilirubinemia
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Dalal 2009

Reason for exclusion	The study evaluated the use of a TcB nomogram for prediction of subsequent hyperbilirubinemia. No outcome relevant to this review was assessed.
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Darling 2014

Reason for exclusion	This was a population based retrospective cohort study.
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De Luca 2008

Reason for exclusion	This study compared the accuracy of two different TcB devices compared to TsB measurement. No outcome relevant to this review was reported.
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De Luca 2008a

Reason for exclusion	This study evaluated the use of visual inspection and TcB measurement for detection of hyperbilirubinemia. No outcome relevant to this review was reported.
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Eggert 2006

Reason for exclusion	This was a retrospective cohort study. Also, in this study, the authors evaluated both the use of TsB and TcB screening in the same population
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Hartshorn 2010

Reason for exclusion	This was a retrospective before-and-after study
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Ho 2006

Reason for exclusion	This was a diagnostic test accuracy study comparing TcB measurement and TsB.
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Kaplan 2008

Reason for exclusion	No outcomes relevant to this review were reported
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Karon 2008

Reason for exclusion	The study evaluated the use of a TcB nomogram for prediction of subsequent hyperbilirubinemia. No outcome relevant to this review was assessed.
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Kurokawa 2016

Reason for exclusion	This was a diagnostic test accuracy study comparing TcB and TsB measurement in very low birth weight infants.
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Kuzniewicz 2009

Reason for exclusion	This was a retrospective cohort study
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Lodha 2000

Reason for exclusion	This was a diagnostic test accuracy study comparing TcB measurement and TsB.
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Mah 2010

Reason for exclusion	This was a before and after study.
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Maisels 2009

Reason for exclusion	The study evaluated the use of a TcB nomogram and clinical risk factors for prediction of subsequent hyperbilirubinemia. No outcome relevant to this review was assessed.
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Mishra 2009

Reason for exclusion	
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Mishra 2010

Reason for exclusion	The study evaluated the use of a TcB nomogram for prediction of subsequent hyperbilirubinemia. No outcome relevant to this review was assessed.
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Morgan 2015

Reason for exclusion	This was a before and after study.
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Petersen 2005

Reason for exclusion	This was a retrospective study
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Romagnoli 2012

Reason for exclusion	This study evaluated the use of TcB and TsB measurement for prediction of subsequent hyperbilirubinemia. No outcome relevant to this review was assessed.
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Sanpavat 2005

Reason for exclusion	The study evaluated the use of a TcB nomogram for prediction of subsequent hyperbilirubinemia. No outcome relevant to this review was assessed.
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Seidman 1999

Reason for exclusion	This study evaluated a model for predicting neonatal jaundice based on several risk factors. No outcome relevant to this review was reported.
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Szabo 2004

Reason for exclusion	This study evaluated the use of the Kramer scale for the assessment of hyperbilirubinemia. No outcome relevant to this review was reported.
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van den 2016

Reason for exclusion	This study visual inspection for jaundice and TcB measurement for hyperbilirubinemia. No outcome relevant to this review was reported.
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Varvarigou 2009

Reason for exclusion	The study evaluated the use of a TcB nomogram for prediction of subsequent hyperbilirubinemia. No outcome relevant to this review was assessed.
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Wainer 2012

Reason for exclusion	This study used a historical cohort as control group.
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Wickremasinghe 2012

Reason for exclusion	This was a retrospective study.
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Yu 2011

Reason for exclusion	The study evaluated the use of a TcB nomogram for prediction of subsequent hyperbilirubinemia. No outcome relevant to this review was assessed.
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Yu 2014

Reason for exclusion	There was no control group in this study.
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Footnotes

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Chapter 3

Pre-discharge transcutaneous bilirubin screening reduces readmission rate for hyperbilirubinemia in diverse African Newborns: a randomized controlled trial

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Pre-discharge transcutaneous bilirubin screening reduces readmission rate for hyperbilirubinemia in diverse African newborns: a randomized controlled trial

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Abbreviations: TcB (transcutaneous bilirubin), TsB (Total serum bilirubin), RR (risk ratio), CI (confidence interval), NNT (number needed to treat), Rh-D (rhesus D)

Summary: We evaluated the impact on jaundice related readmissions and incidence of severe hyperbilirubinemia of pre-discharge transcutaneous bilirubin screening in an African population of newborns.

What's known on This Subject: Transcutaneous bilirubin (TcB) measurement seem to correlate with total serum bilirubin measurement (TsB) in newborns. Observational studies conducted in North America suggest that universal TcB or TsB screening reduces readmission for jaundice, incidence of severe hyperbilirubinemia and predicts need for phototherapy.

What This Study Adds: Our study provides evidence from indigenous African newborns with varying skin pigmentation on the impact of pre-discharge TcB screening on jaundice related readmissions. To our knowledge this is the first randomized controlled trial that has evaluated the effect of pre-discharge TcB screening in newborns before hospital discharge.

Contributors' Statements:

Charles Okwundu conceptualized and designed the study, designed the data collection tools, coordinated and supervised data collection at the study site, drafted the initial manuscript, and approved the final manuscript as submitted.

Vinod Bhutani, Charles Wiysonge and Johan Smith provided input into the methods and content knowledge, critically reviewed the manuscript, and approved the final manuscript as submitted.

Tonya Esterhuizen conducted the statistical analysis, reviewed the manuscript, and approved the final manuscript as submitted

Abstract

Background

South African, healthy term newborns are usually discharged less than 72 hours after delivery. If hyperbilirubinemia is not identified early, discharged babies remain at risk for severe hyperbilirubinemia, an important cause of readmission, neonatal mortality and morbidity. Use of transcutaneous bilirubin (TcB) screening before hospital discharge has been controversial especially among babies with varying skin pigmentation.

Objective

We tested the clinical benefits of TcB screening of healthy newborns before discharge for the outcomes of readmission for jaundice and severe hyperbilirubinemia in a randomized controlled trial.

Methods

This was a randomized controlled trial. We compared pre-discharge TcB with visual assessment (alone) for jaundice in apparently healthy newborns at a public tertiary hospital in Cape Town, South Africa.

Results

Of the 1858 infants, 63% were black, 35% of mixed race and 1% white. There was a significant reduction in the rate of readmission for jaundice (RR 0.25, 95% CI 0.14 to 0.46. $p < 0.0001$) and in the incidence of severe hyperbilirubinemia (RR 0.27, 95% CI 0.08- 0.97. $p = 0.05$) with the use of TcB screening compared to visual inspection.

Conclusion

Pre-discharge TcB screening is superior in identifying newborns at risk of severe hyperbilirubinemia compared to visual inspection. We recommend that every newborn regardless of skin pigmentation should receive objective bilirubin screening before hospital discharge. Universal bilirubin screening in newborns could potentially reduce hyperbilirubinemia related morbidity and mortality.

Background

Hyperbilirubinemia is the most common reason for readmission of newborns in the first week after birth [1,2]. Neonatal jaundice is usually benign and does not require any intervention in most instances. However, up to 10% of term newborns (≥ 37 week gestational age) will develop severe hyperbilirubinemia that require treatment, usually in the form of phototherapy and possibly exchange blood transfusion [30]. “Severe hyperbilirubinemia” is defined as a total serum bilirubin (TsB) concentration greater than 340 $\mu\text{mol/l}$ (20 mg/dl), and “critical hyperbilirubinemia” as a TsB concentration greater than 425 $\mu\text{mol/l}$ (25 mg/dl) at any time during the first 28 days of life for late preterm (between 34 and 37 weeks gestational age) and term newborns[4]. Failure to identify newborns at risk of developing severe hyperbilirubinemia can lead to severe post-icteric neurologic consequences, including athetoid cerebral palsy and a variety of life-long manifestations of kernicterus [5,6].

In many settings, term newborns are discharged from hospitals within 1–2 days after delivery, before hyperbilirubinemia usually becomes clinically evident. Peak serum bilirubin levels usually occur on postnatal days 3 to 5, when many newborns have already been discharged. The inability to identify and manage at-risk infants prior to hospital discharge in a timely manner has been cited as the major root cause of adverse outcomes of hyperbilirubinemia [7 ,8].

The burden of severe hyperbilirubinemia continues to be high in low- and middle-income countries (LMICs). In many LMICs, severe or clinically significant neonatal hyperbilirubinemia is not only a leading cause for hospital readmission in the first week of life, but also constitutes an important cause of neonatal mortality and morbidity [9-11]. A report on the global burden of hyperbilirubinemia suggests that sub-Saharan Africa and South Asia are the leading contributors to an estimated 1.1 million babies who develop severe hyperbilirubinemia worldwide every year [12]. In some cases, babies could have levels that can lead to subsequent brain damage from kernicterus [12-16].

Studies from countries in Africa suggest that kernicterus is still a leading cause of cerebral palsy [13-15,17,18]. In South Africa, a retrospective study of exchange transfusion for hyperbilirubinemia in newborns over a period of 5 years showed that six out of 26 (23.0%) babies requiring exchange transfusion had signs of kernicterus [19]. Findings from various observational studies conducted in North America suggest that universal bilirubin screening in newborns before discharge reduces readmission rate for jaundice and incidence of severe hyperbilirubinemia [20-23]. However, these findings have not been confirmed in any randomized controlled trial [24]. Furthermore, there is no universal consensus on the routine screening for jaundice of all newborns either using non-invasive transcutaneous bilirubin (TcB) or total serum bilirubin (TsB) measurement [25-29].

The current South African guideline on the management of jaundice in the newborn does not make any recommendation on universal screening of all newborns with either TcB or TsB before hospital discharge [30]. Similarly, in other African countries, there are no guidelines on universal screening of all newborns for risk of hyperbilirubinemia. In many LMICs, newborns are assessed for jaundice by visual inspection and serum bilirubin is measured only in newborns who look jaundiced and in some cases in newborns of rhesus D antigen (Rh-D) negative mothers [31].

In this randomized controlled trial (RCT), we compared the use of a transcutaneous device to visual inspection to screen for hyperbilirubinemia before hospital discharge in apparently healthy term and late preterm newborns (≥ 35 week gestational age).

Objective:

To evaluate the impact of TcB screening before hospital discharge as compared to visual inspection for jaundice, on readmission for hyperbilirubinemia and the incidence of severe hyperbilirubinemia in a South African population of newborns.

Methods

Study Design and setting

This was a randomized, controlled, unblinded trial that evaluated the effect of TcB screening in term newborns before hospital discharge. This study was conducted at the well-baby nurseries at Tygerberg Hospital, Cape Town, South Africa. Tygerberg Hospital is the biggest tertiary healthcare institution in the Western Cape Province and has 308 pediatric beds, with approximately 7500 deliveries per annum. According to the current policy, well babies born at ≥ 35 weeks gestation and birth weight ≥ 1800 grams (g) are discharged home after 6 hours for vaginal deliveries and 48 hours for Caesarean sections.

We obtained approval from the Health Research Ethics Committee of the Faculty of Medicine and Health Sciences, Stellenbosch University. Informed consent was obtained from the mother for each infant.

Study Procedures

We screened all infants at the time of discharge for potential eligibility into the study using the predetermined inclusion and exclusion criteria. Those who were ≤ 72 hours of life, with a gestational age of at least of 35 weeks and birth weight of at least 1800g were eligible for participation. The gestational age was determined by antenatal ultrasound scan, last menstrual period or postnatal foot length measured with a plastic Vernier's caliper for infants whose mothers were un-booked and did not have any prenatal dating scan [32].

Randomization and blinding

Infants who met all inclusion criteria were randomly assigned to either TcB screening for hyperbilirubinemia or visual inspection for jaundice. A random allocation sequence was generated using a computer random sequence generator. Allocation assignments were recorded on sequentially numbered sheets of papers and placed in sealed opaque envelopes, maintained in a secure location and accessible only by the Principal Investigator. The envelopes were opened sequentially for assignment by the research assistant after informed consent was obtained and the infants allocated to the group assigned in the envelope. The study group allocation was not blinded as it is not possible to blind clinicians or parents to the type of screening provided due to the obvious nature of the intervention. The outcome assessors and statistician were blinded to the group allocation.

Interventions:

TcB screening group:

In this group we measured TcB levels once using the JM 105 Jaundice Meter (Drager Medical UK Ltd. Hemel, Hempstead) a portable, handheld, non-invasive TcB measuring device at the time of enrollment [33]. An average of 3 readings was plotted on Bhutani's hour-specific nomogram (Figure 1) to determine the risk zone for hyperbilirubinemia. Infants in this group were classified into high-risk, high-intermediate, low-intermediate risk and low-risk groups. For all newborns in the high-risk zone, we obtained a TsB. The need for phototherapy was determined based on the TsB measurement. Infants who met the threshold for phototherapy were kept in hospital for phototherapy. Babies in the high-intermediate, low-intermediate risk and low-risk groups were asked to follow up at a primary healthcare center closest to their home at 24, 48 and 72 hours, respectively, after discharge home. We did not assess the timeliness of follow-up after discharge or assess the proportion of babies who went for follow-up.

Visual inspection group:

Babies in this group were managed routinely according to the current standard of care. The infants were assessed for jaundice visually for the presence of tissue yellowness by blanching the skin over the glabella and sternum. The infants were assessed by the admitting physician at the time of enrollment. Venous blood sample for TsB measurement was only collected in infants who were clinically jaundiced or in infants of Rh-D negative mothers according to the hospital protocol. The need for phototherapy was determined based on the TsB result. Babies whose TsB value met the threshold for phototherapy according to the South African phototherapy guideline were kept for phototherapy before discharge home [30]. Babies who did not meet threshold for phototherapy and

who were not visibly jaundiced at the time of discharge were managed routinely. The mothers were asked to return with their newborns for follow-up assessments at the primary healthcare facility closest to their home within 2 days of hospital discharge.

Sample Size

We did not find any published study that assessed the rate of readmission for hyperbilirubinemia in South African newborns. Therefore, we assumed a baseline readmission rate for phototherapy of 4.8% from the literature and an unpublished local study at Tygerberg Hospital, Cape Town on newborn readmission for hyperbilirubinemia [34-37]. We estimated that a minimum of 1858 participants would give us 80% power to detect a 50% reduction in the rate of readmission with the use of TcB screening at 5% level of significance. The baseline readmission rate was estimated from a study we conducted the previous year at Tygerberg Hospital on the rate of readmission for neonatal hyperbilirubinemia after discharge. The readmission rate in the study was estimated to be about 4.8%.

Study Outcomes

The primary end point was readmission for jaundice that required phototherapy or exchange transfusion. For the primary outcome, we compared the proportion of readmissions for hyperbilirubinemia, requiring phototherapy or exchange transfusion, in the TcB to the visual inspection group. For every infant that was readmitted, we ascertained whether the infant met the threshold for either phototherapy or exchange transfusion according to the South African phototherapy guideline based on the TsB result at the time of readmission [30].

The secondary end points were: phototherapy before hospital discharge, incidence of severe hyperbilirubinemia, critical hyperbilirubinemia or exchange transfusions and duration of hospital stay for those that were readmitted. The rate of phototherapy pre-discharge was measured during the birth hospitalization. Other outcomes (readmission for phototherapy, incidence of severe hyperbilirubinemia and duration of hospital stay) were determined electronically through the database and also by obtaining the infants' files and the electronic patient record transcripts from the hospital or primary healthcare Centre where the baby was readmitted. We obtained all TsB values during the first month of life for newborns who were readmitted. For each readmission, we confirmed the name of the hospital or primary healthcare centre where the baby was readmitted, length of hospital stay, treatment received (phototherapy or exchange transfusion) and highest TsB level during the readmission period.

Statistical Analysis

We collected study data using paper-based data collection forms and then transferred to the Redcap database. Statistical analyses was done with the use of STATA 14 statistical software (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

We performed an intention to treat analysis. Differences according to the group allocation for continuous variables were tested with the use of unpaired t-tests with equal variances and Wilcoxon rank-sum tests. The Pearson chi-square test was used to test for differences between the two groups for categorical variables. Fisher's exact test was used to compare the rate of phototherapy before hospital discharge, readmission for hyperbilirubinemia and incidence of severe hyperbilirubinemia. Effect sizes were reported as relative risks (RR) with 95% confidence intervals (CIs). We also adjusted for any plausible baseline confounding variable (e.g. history of jaundice in a previous sibling) by performing Mantel-Haentzel stratification.

Results

Subject recruitment and follow-up

We enrolled a cohort of 1858 late preterm and term infants born between August 2015 and October 2016. We approached a total of 1910 mothers and their infants for participation. Two mothers declined participation and 50 were excluded because they did not meet our inclusion criteria (Figure 2). A total of 929 infants were enrolled to each arm. All infants were screened according to the study arm to which they were allocated.

Participant characteristics

The baseline characteristics and demographics of enrolled infants and their mothers are shown in Table 1. There were no significant differences between the TcB screening arm and the visual inspection arm, except for the history of jaundice in a previous sibling which was significantly higher in the TcB group.

Outcome measures

Readmission for jaundice

There were a total of 65 jaundice-related readmissions (3.5%). We obtained the TsB results for these infants to determine if they met the threshold for phototherapy on readmission. We could not obtain the TsB results of 5 (3 in the visual inspection arm and 2 in the TcB arm) infants who were readmitted after discharge and could not determine the appropriateness of their readmission.

Thirteen out of 929 (1.4%) infants were readmitted in the TcB arm compared to 52 out of 929 (5.6%) infants in the visual inspection arm (RR 0.25, 95% CI 0.14 to 0.46. $p < 0.0001$). Number needed to treat (NNT) = 24, 95% CI 17 to 40]. Among all readmitted infants, there were 12 appropriate readmissions in the TcB group and 48 appropriate readmissions in the visual inspection group. Since there was a randomization imbalance in the groups regarding a previous baby with jaundice, adjustment was done by stratified analysis. The Mantel-Haentzel adjusted RR was 0.25 with 95% CI 0.14 to 0.46, indicating that after adjustment for having a previous baby with jaundice, there was still a significantly protective effect of TcB screening on readmission for jaundice.

Phototherapy before discharge

The rate of phototherapy before hospital discharge was significantly higher in the TcB group compared to the visual inspections group. A total of 48 (5.2%) infants received phototherapy before hospital discharge compared to 18 (1.9%) in the visual inspection group (RR 2.66, 95% CI 1.56 to 4.54, $p = 0.0002$). In the TcB arm, 83 (9%) of babies had predischarge TcB values in the high-risk zone (≥ 95 th percentile); of these, 39 (47%) had TsB levels at which phototherapy was recommended according the South African phototherapy guideline. A total of 131 (14%), 173 (19%) and 542 (58%) of infants had pre-discharge TcB measurements in the high-intermediate, low-intermediate and low risk zones, respectively.

Incidence of severe hyperbilirubinemia:

A total of 14 (0.75%) infants had severe hyperbilirubinemia at the time of readmission, 3 infants in the TcB arm and 11 in the visual inspection arm. The rate of severe hyperbilirubinemia was significantly lower with the use of TcB screening (RR 0.27, 95% CI 0.08 to 0.970. $p = 0.05$).

Rate of Exchange transfusion

Among those who were readmitted, all the infants in the TcB group required phototherapy and none met the threshold for exchange transfusion. Two infants who were readmitted in the visual inspection group required exchange transfusions. This difference was not statistically significant.

Bilirubin induced neurologic dysfunction

One infant in the visual inspection was identified that had clinical signs that could suggest bilirubin induced neurologic dysfunction. The baby was born at 36-week gestational age with a birth weight of 2440g, discharged home at 72 hours after delivery, and readmitted 2 weeks later for prolonged neonatal jaundice. On readmission, the baby was noted to have lost about 18% of the birth weight and had a high-pitched cry and a TsB of 459 mmol/l. No magnetic resonance imaging of the brain

was done and the long-term neurologic outcome for this infant is unknown. There was no documented case of infants showing neurologic dysfunction in TcB arm.

TsB before discharge

A total of 87 (9%) infants required TsB before discharge in the TcB group compared to 70 (7.5%) infants in the visual inspection group (RR 1.24, 95% CI 0.91 to 1.68, $p=0.156$). The difference was not statistically significant.

Duration of hospital stay

The median duration of hospital stay during the readmission period was similar in both groups. Median duration of hospital stay in the visual inspection group was 3 [interquartile range (IQR) 2-4] days compared to 3 (IQR 2-3) days in the TcB group. The Wilcoxon rank-sum (Mann-Whitney) test did not demonstrate any statistically significant difference between arms ($p = 0.216$)

Discussion

In this RCT involving indigenous African newborns recruited from a tertiary hospital in South Africa, we provide evidence for the effect of pre-discharge TcB screening on readmission for jaundice and incidence of severe hyperbilirubinemia. To our knowledge, this RCT is the first to evaluate the impact of TcB screening in an African population of newborns. We demonstrated that TcB screening for hyperbilirubinemia was superior in identifying apparently healthy newborns requiring phototherapy before hospital discharge compared to visual inspection. Earlier identification of hyperbilirubinemia combined with treatment with phototherapy during the initial birth hospitalization led to a reduction in readmission rate with the use of TcB screening.

Unexpected readmission of a newborn after discharge from the newborn nursery is an indicator of inadequate assessment of the newborn's readiness for discharge. For our study, we selected the readmission rate as a primary outcome. Though this index is often viewed from healthcare cost, epidemiological burden, societal burden of trust between healthcare provider and the family, it can have a direct personal disruption in the maternal and newborn experience [37-40].

In 2004, the American Academy of Pediatrics (AAP) recommended a patient-friendly systems approach that every newborn be assessed for the risk of developing severe hyperbilirubinemia, by using pre-discharge TsB or TcB measurements, a policy also endorsed by the Canadian Paediatric Society (CPS) [4,25,41]. After implementation of the AAP and CPS guideline, many studies in the USA and Canada have demonstrated that universal TcB or TsB reduced jaundice readmissions and led to a reduction in the incidence of severe hyperbilirubinemia [21-23,35,42,43]. Our study not only validates the finding from these studies, but also provides evidence that earlier identification of

hyperbilirubinemia with TcB screening and treatment with phototherapy is associated with a reduction in hospital readmission rate for hyperbilirubinemia and in the incidence of severe hyperbilirubinemia in an indigenous population of African newborns.

Other studies from LMICs have evaluated the correlation of TcB compared to TsB measurement in newborns with different skin pigmentation. These studies have shown good correlation between TcB and TsB measurement in newborns with varying skin pigmentation. The studies have also shown that implementation of TcB screening is feasible in LMICs [44-52]. However, because of varying access to healthcare and differential risk in the polycultural community of LMICs, there are limited if any national policy outcome studies. Thus, we could not identify any studies from LMICs that evaluated the impact of TcB screening on readmission rate or incidence of severe hyperbilirubinemia.

Our study has some important limitations. This study did not evaluate the impact of TcB screening on reducing the incidence of kernicterus. This would require a very large study and longer follow-up period. In our study, only one infant in the visual inspection arm was identified that had a clinical sign of probable kernicterus. Blood group type and the direct Coombs test for blood group incompatibility are not routinely done on all newborns in our study population. Therefore, we could not assess whether there was any difference in the rate of blood group incompatibility between the two study arms. It was difficult to determine if the highest TsB that was recorded was prior to phototherapy initiation. In some facilities where the babies were readmitted, phototherapy was initiated before blood sample for TsB was collected. Therefore, the incidence of severe hyperbilirubinemia in the study population could be higher than reported in this study. Blood draw for TsB was also ordered at the discretion of the admitting physicians. This outcome is likely to be different if we limited blood sampling only to infants whose TcB value were >95th centile for their age. This study was conducted in a tertiary facility where some mothers were kept longer in hospital for other medical reasons and consequently the babies were kept longer with the mothers. This increased the length of stay for some babies, which could lead to a reduction in readmission because of the delayed discharge from the initial birth hospitalization. Therefore, the readmission rates reported are likely to be higher in the primary healthcare setting in South Africa where mothers without any complications after delivery are typically discharged within 12 hours of delivery. However, despite these limitations, we are confident in the findings from this study because of the unique design of the study compared to other non-randomized studies that have evaluated the similar outcomes [21-23,35,42,43]. We have provided evidence from a randomized controlled study. We used a proper method of randomization and allocation concealment using sealed opaque envelopes. Though this method of concealment of allocation is prone to deliberate tampering, the investigators ensured that the envelopes were only opened at the time of enrollment. The study participants were

similar in the baseline characteristics. Even though the study personnel and participants were not blinded to the treatment allocation, the outcome assessors and statistician were blinded. Therefore, we are confident that reduction in hospital readmission rate and reduction in the incidence of severe hyperbilirubinemia was as a result of the TcB screening strategy in the treatment group.

In conclusion, TcB screening with risk stratification using the Bhutani nomogram in newborn infants at risk of severe hyperbilirubinemia can help to reduce readmissions for jaundice and incidence of severe hyperbilirubinemia. Our study further confirms that visual inspection for jaundice is not a reliable way to assess for the presence or absence of hyperbilirubinemia in newborns. Universal TcB screening in all newborns before hospital discharge in South Africa and other African countries will be an important step towards reducing the burden and consequences of severe hyperbilirubinemia. However, the high cost of the current TcB devices could be a barrier to implementation of universal TcB screening in many LMICs. Each transcutaneous device cost between \$4,000 and \$7000 [53,53]. Therefore, nationally driven public-private solutions are warranted such that healthcare during the first week after a normal pregnancy is equitable. Industry and TcB manufacturers now have the moral responsibility to make over-priced transcutaneous devices safe, affordable and accessible. Reductions in the cost of readmission, cost of more intensive treatment and family integrity are real and need to be realized for all newborns worldwide.

Abbreviations

AAP: American Academy of Pediatrics; ABE: Acute Bilirubin Encephalopathy; ABO: Blood groups A, B and O; APGAR: Appearance, Pulse, Grimace, Activity and Respiration; CI: Confidence Interval; CPS: Canadian Pediatric Society; IUGR: Intrauterine Growth Restriction; LBW: Low Birth Weight; LMIC: Low- and Middle-Income Country; NNT: Number Needed to Treat; Rh-D: Rhesus D; RR: Relative Risk; SD: Standard Deviation; TcB: Transcutaneous Bilirubin; TsB: Total Serum Bilirubin; VLBW: Very Low Birth Weight.

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Availability of data and materials

The datasets used and/or analyzed during the study are available upon reasonable request.

Contribution of authors

Charles Okwundu conceptualized and designed the study. Vinod Bhutani, Johan Smith and Charles Wiysonge and provided input into the methods and content knowledge.

Tonya Esterhuizen conducted the statistical analysis.

Ethics approval and consent to participate

Ethical approval was obtained from the Stellenbosch University Health Research Ethics Committee prior to commencement of the study (N14/03/025). Written informed consent was obtained from the mothers for all participants before enrollment into the study.

Trial registration

The trial was registered on clinicaltrials.gov.

<https://clinicaltrials.gov/ct2/show/NCT02613676>

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Figures and tables

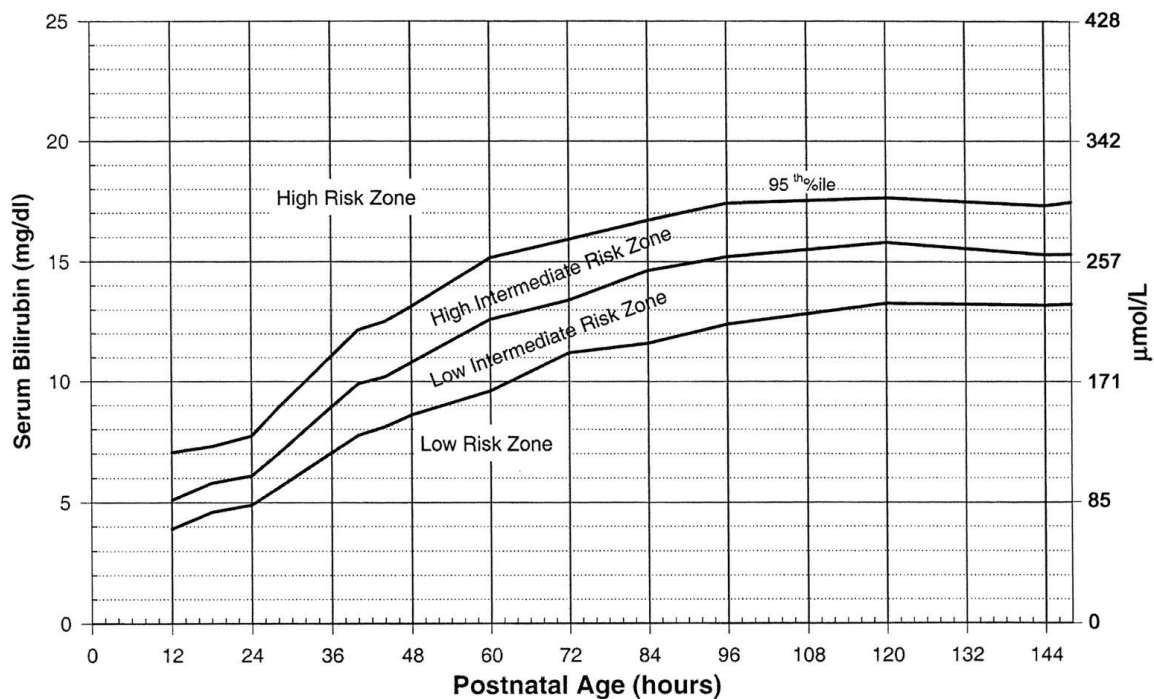


Figure 1. Bhutani nomogram: Bhutani VK, Johnson L, Sivieri EM. Pediatrics. 1999;103 :6 –14

Figure 2: Participant study flow diagram

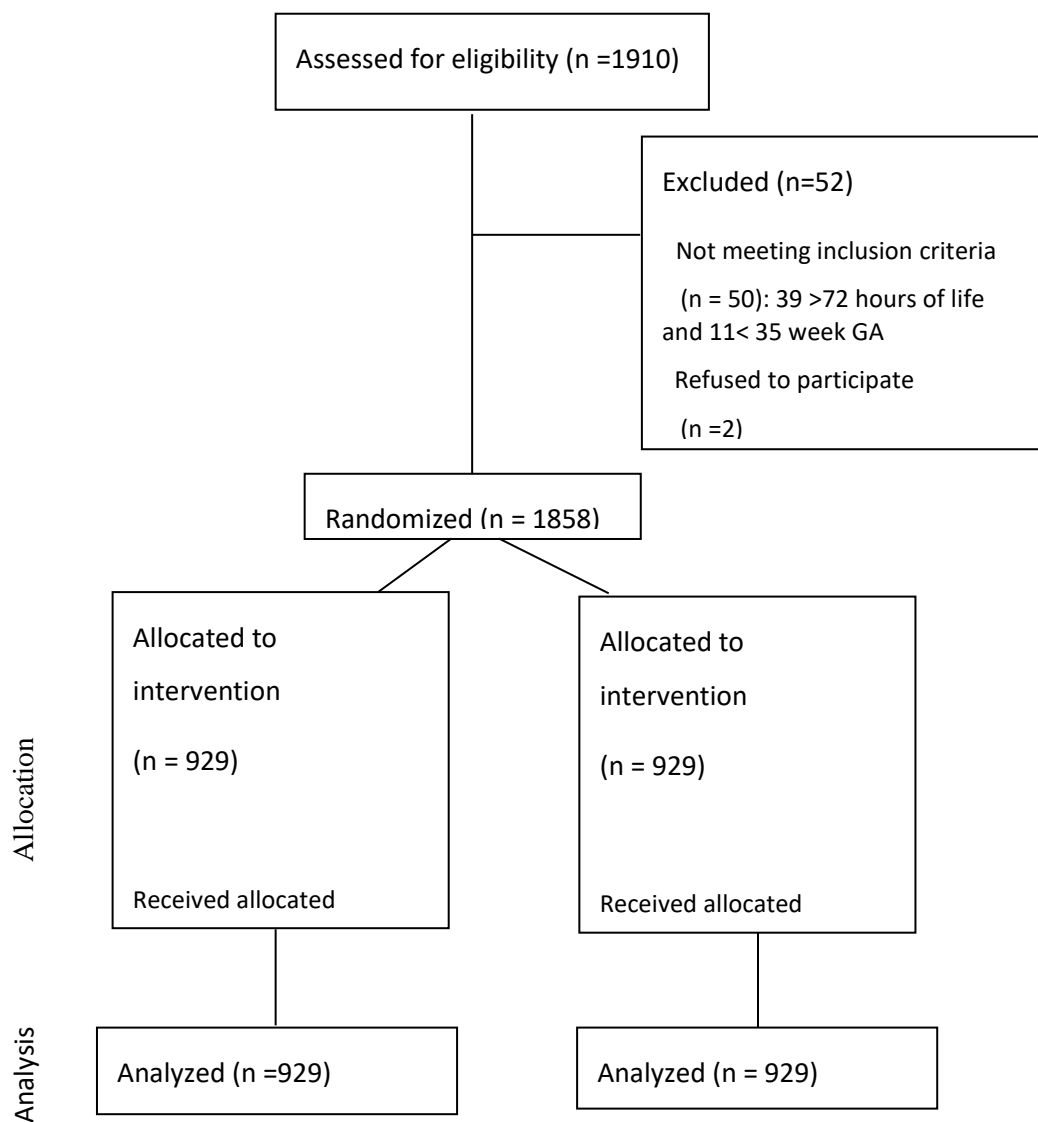


Table 1: Baseline characteristics:

Variable	TcB screening (N=929)	Visual inspection (N=929)	P value
Gestational age (mean, SD)	38.4 weeks (1.60)	38.3 weeks (1.60)	0.332
< 37 weeks gestation	123 (13.2)	144 (15.5)	0.232
≥37 weeks gestation	806 (86.8)	785 (84.5)	0.212
Birth weight (mean, SD)	3128 g (575)	3118 g (566)	0.709
IUGR	106 (12.70)	118 (11.41)	0.393
Male	485 (52.2)	480 (51.67)	0.816
Race			
Black	590 (63.5)	585 (63.0)	0.320
Mixed race	319 (34.3)	334 (36.0)	0.320
White	15 (1.3)	8 (0.9)	0.320
Others	3 (0.3)	2 (0.2)	0.320
Breastfeeding	870 (93.65)	893 (96.12)	0.052
Cephalohematoma	1 (0.11)	2 (0.22)	0.056
Previous sibling with jaundice	72 (7.75)	50 (5.38)	0.039
Age at time of assessment (hours)	31.1	31.9	0.283
Mode of delivery			
NVD	492 (52.96)	510 (54.90)	0.287
C/S	425 (45.75)	413 (44.46)	0.287
Vacuum	12 (1.29)	6 (0.65)	0.287
Mothers Rh status			
Rh negative	16 (1.72)	14 (1.51)	0.927
Rh positive	871 (93.76)	874 (94.08)	0.927
Unknown	42 (4.52)	41 (4.41)	0.927
Mother's blood group			
Group A	31 (3.34)	25 (2.69)	0.666
AB	7 (0.75)	3 (0.32)	0.666
B	16 (1.72)	16 (1.72)	0.666
O	37 (3.98)	35 (3.77)	0.666

NOTE: Data are no. (%) unless otherwise indicated.

SD= Standard deviation. NVD= Normal vertex delivery, Rh= Rhesus

IUGR: This was determined using the WHO published international growth standards for children younger than 5 years.

Chapter 4

When race trumps visual assessment. a case study

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When race trumps visual assessment: a case study

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Abbreviations: TcB (transcutaneous bilirubin), TsB (Total serum bilirubin), RR (risk ratio), CI (confidence interval), NNT (number needed to treat), Rh-D (rhesus D)

Table of Contents Summary: We present a case of a newborn in whom visual significant hyperbilirubinemia was missed by visual assessment for jaundice.

Contributors' Statements:

Charles Okwundu drafted the initial manuscript, and approved the final manuscript as submitted.

Vinod Bhutani, Charles Wiysonge and Johan smith provided input into the methods and content knowledge, critically reviewed the manuscript, and approved the final manuscript as submitted.

Abstract

Neonatal jaundice is very common in the first two weeks after birth, with up to 60 percent of term infants manifesting jaundice. Not identifying hyperbilirubinemia requiring treatment in newborns prior to hospital discharge in a timely manner is a major cause of adverse outcomes of hyperbilirubinemia. In many developing countries, there is no routine universal screening for hyperbilirubinemia using total serum bilirubin (TsB) or transcutaneous bilirubin (TcB) measurement. In these settings, jaundice in the newborns is assessed only by visual inspection before hospital discharge.

We present the case of a black male baby who was born at term gestation and who was assessed to be ready for discharge from the well-baby nursery. Visual inspection revealed no evidence of jaundice. However, the infant was enrolled in a clinical trial on TcB screening and was identified to have high risk for hyperbilirubinemia on the Bhutani nomogram and met threshold for phototherapy as confirmed by the TsB. Based on visual inspection, this infant would have been discharged home inappropriately, highlighting the difficulty experienced by clinicians to assess for hyperbilirubinemia in dark skin infants in settings where there is no universal screening for hyperbilirubinemia in all newborns. The case also highlights that visual assessment for jaundice should not be relied upon to make assessment of hyperbilirubinemia in newborns before hospital discharge.

Introduction

Jaundice is a traditional established clinical sign of hyperbilirubinemia and neonatal jaundice, mostly due to unconjugated hyperbilirubinemia is frequent in the first two weeks after birth, with up to 60 percent of term and 80% of preterm infants manifesting jaundice. Serum unconjugated bilirubin levels peaks between ages 3 to 5 days, often in a home-setting. Thus, it is not unusual that one of the common reasons for hospital readmission in the first week of life is neonatal hyperbilirubinemia. The inability to identify and manage at-risk infants prior to hospital discharge in a timely manner has been cited as the major root cause of adverse outcomes of hyperbilirubinemia (1, 2).

We present a case study of a 28-hour old infant in whom the predischarge visual assessment for jaundice completely underestimated and missed the presence of jaundice.

Birth History

The infant was born via spontaneous vaginal delivery to a 35-year-old primigravid mother at 41-week gestational age with a birth weight of 3.6 kg and APGAR scores were 9 and 10 at 1 and 5 minutes, respectively. The mother had an uneventful pregnancy and antenatal care with normal laboratory tests. She was Rh-D positive, her ABO blood type was unknown and her serology for syphilis and HIV were negative. There was no significant family medical history. After a one day (28 hours) stay in the well-baby nursery, he was presumably ready for discharge. Breastfeeding was appropriate at the time of discharge.

Physical Examination

On examination, the neonate was alert and active. He was afebrile with a heart rate of 140 bpm and respiratory rate of 48 breaths/min. He had no clinical signs of jaundice or dehydration or obvious infection. He had normal tone, symmetric Moro-, sucking and rooting reflexes. The anterior fontanelle was soft and there was no cephalohematoma. The cardiovascular, respiratory and abdominal examination were normal. There was no hepatosplenomegaly. The infant was assessed by the medical team prior to discharge. In the meantime, the mother was approached by our research team and she consented to enroll in an ongoing randomized transcutaneous bilirubin (TcB) screening trial that was evaluating the effect of pre-discharge TcB screening compared to visual inspection in newborn infants (3). By random allocation, the infant was allocated into the TcB screening arm.

At this time, there was no clinical sign of jaundice (see image in Figure 1). The TcB measurement was 299 $\mu\text{mol/L}$ taken at age 28 hours. Concurrent TsB data was available about 2 hours later and was 229 $\mu\text{mol/L}$. Both the TcB and TsB data plotted in high-risk zone on the Bhutani nomogram

(figure 2). In addition, the infant met the threshold for phototherapy (5, Figure 3). Despite receiving phototherapy, the baby's TsB continued to rise and had a peak bilirubin level of 352 $\mu\text{mol/L}$ on the third day of life and decreased to 247 $\mu\text{mol/L}$ by day five of life.



Figure 1. Baby's photo at the time of discharge. (Photo taken with consent from the mother)

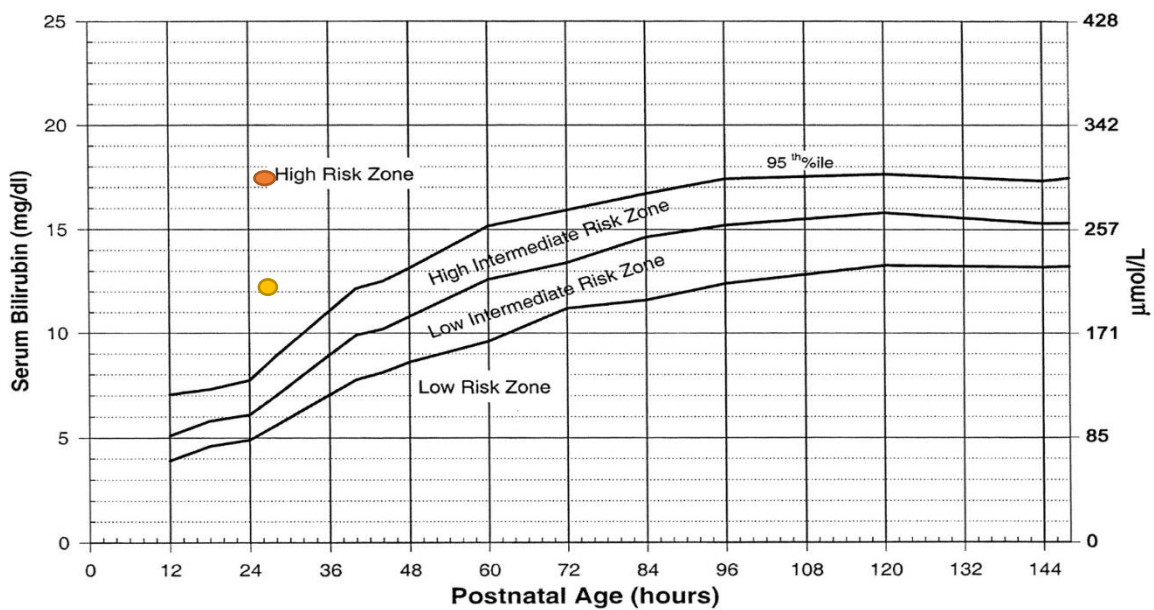


Figure 2. Bhutani nomogram: Bhutani VK, Johnson L, Sivieri EM. Pediatrics. 1999;103 :6 –14

The baby was discharged home after 5 days of phototherapy and did not meet threshold criteria for an exchange transfusion. Investigations for a cause of the hyperbilirubinemia was not initiated. The baby did not show any signs of acute bilirubin or post-icteric encephalopathy.

AAP Phototherapy Guidelines (2004)

Neurotoxicity Risk Level	Start phototherapy?	Approximate threshold at 28 hours of age
Lower Risk (\geq 38 weeks and well)	Yes	210.33 $\mu\text{mol/L}$
Medium Risk (\geq 38 weeks + neurotoxicity risk factors OR 35 to 37 6/7 weeks and well)	Yes	179.55 $\mu\text{mol/L}$
Higher Risk (35 to 37 6/7 weeks and neurotoxicity risk factors)	Yes	145.35 $\mu\text{mol/L}$

Figure 3. Generated from bilitool.org: Based on the AAP Phototherapy Guidelines (5)

Discussion

Most nurseries in developing countries discharge babies early and depend on visual assessment for jaundice, which has repeatedly been found wanting. Visual assessment is not adequate in identifying hyperbilirubinemia in newborns. This case report is one of several African babies, who were deemed ready for early discharge from hospital and in whom visual inspection missed the presence of significant jaundice, as confirmed by transcutaneous bilirubinometry and central laboratory, as part of a randomized controlled trial. The case again highlights the difficulty experienced by clinicians to diagnose jaundice in African infants. The baby would have been discharged home inappropriately, had he not been enrolled in the clinical study, and the outcome uncertain at best, depending on whether the mother would have returned to hospital around 72 hours of age.

Severe hyperbilirubinemia continues to be the major reason for newborn readmissions in the first month of life. This could be as a result of early discharge and inappropriate identification of newborns who require phototherapy. Although kernicterus represents the worst outcome of the spectrum of hyperbilirubinemia in newborns, it is potentially preventable if jaundice is timeously diagnosed and managed. Kernicterus continues to be a cause of morbidity and mortality in many developing countries and resources constrained settings. In South Africa, a retrospective study of exchange transfusion for hyperbilirubinemia in newborns over a period of 5 years showed that six out of 26 (6/26; 23.0%) babies requiring exchange transfusion had signs of kernicterus (4).

Hyperbilirubinemia may not be clinically apparent in newborns before hospital discharge, especially in very dark-skinned babies. This will result in inappropriate home discharge of newborns who require treatment for jaundice before discharge. Visual inspection for jaundice should not be relied on to assess hyperbilirubinemia in newborns. Objective screening assessments using risk factors and TcB measurement or TsB measurement can help to identify those who need treatment before discharge. This could help to reduce readmissions for hyperbilirubinemia and potentially eliminate kernicterus. Also, cheaper and more affordable point of care bilirubin testing devices will help to make bilirubin testing in newborns more feasible more available in resource constrained settings with limited access to laboratories or the current expensive TcB meters.

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Chapter 5

Transcutaneous bilirubinometry versus total serum bilirubin measurement for newborns: a Cochrane systematic review

Transcutaneous bilirubinometry versus total serum bilirubin measurement for newborns: a Cochrane systematic review

Authors

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Abstract

Background

Jaundice is a very common condition in newborns, with up to 60% of term newborns and 80% of preterm newborns developing jaundice in the first week of life. Bilirubin measurement can be done formally by standard laboratory method which requires a blood sample to be sent to the laboratory. Noninvasive transcutaneous bilirubin (TcB) measurement devices are currently widely available and used in many settings for estimation of total serum bilirubin (TsB) levels.

Objectives

In this review we aimed to summarize the relevant available evidence on the accuracy of TcB compared to TsB measurement in newborns of various race, skin colour and settings.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL 2018, Issue 7), MEDLINE via PubMed (1966 to 22 August 2018), EMBASE (1980 to 22 August 2018), and CINAHL (1982 to 22 August 2018). We also searched clinical trials databases, conference proceedings, and the reference lists of retrieved articles for randomized controlled trials and quasi-randomized trials. Two review authors independently examined the search output to identify studies and also did the data extractions. Risk of bias assessment using the QUADAS 2 tool was also done independently by two review authors. All disagreements were resolved by discussion or by contacting a third author.

Selection criteria

We included prospective studies that evaluated the accuracy of any TcB device compared to TsB measurement in the laboratory. In addition to reporting correlation coefficients comparing TcB and TsB, the studies have to report on other measures of accuracy such as sensitivities and specificities. We excluded all studies that only reported correlation coefficients.

Data collection and analysis

Two authors independently extracted data from the included studies using a standardized data extraction form. We summarized the available results narratively and where possible we combined study data in a meta-analysis.

Main results

We included 54 studies that met our inclusion criteria. All the included studies were of acceptable methodological quality based on the QUADAS 2 tool. The studies compared the use of various TcB devices (including the Minolta Airshield JM 101, JM 102, JM 103, Bilicheck, Bilimed, Bilitest and JH2-1A), were conducted in different countries and settings, and included newborns of different gestational and postnatal age. For most of the studies, the TcB measurement was taken from the forehead or sternum. Almost all of the studies reported on correlation coefficients and all reported on some other measure of accuracy such as sensitivity and specificity. The correlation coefficients between TcB and TsB ranged from 0.45 to 0.987. The sensitivity and specificity of various TcB cut-off values to detect significant hyperbilirubinemia ranged from 74% to 100% and 18% to 89% respectively.

Authors' conclusions

TcB devices reliably estimated TsB levels in term and preterm newborns and could help in reducing the blood sampling associated with performing TsB measurements.

Plain language summary

Transcutaneous bilirubinometry versus total serum bilirubin measurement for newborns

Jaundice is a very common problem in the newborn period and results from high levels of bilirubin in the blood known as hyperbilirubinemia. It is important to detect hyperbilirubinemia early in order to prevent adverse consequences of very high bilirubin levels such as brain damage in the newborn.

We included studies that evaluated the use of any transcutaneous bilirubin (TcB) device compared to total serum bilirubin (TsB) measured in the laboratory. Findings from this review suggest that TcB measurement is a suitable alternative to TsB measurement in monitoring hyperbilirubinemia in newborn infants. This would save cost, time and invasive pricks to obtain blood from the newborn. TcB measurement is taken from the skin and does not require blood draw. Further studies may be needed to better understand the best site for TcB measurement and the reason for the difference if any in the measurement taken from the forehead and sternum. Also, further studies are needed to ascertain the impact of phototherapy on the accuracy of TcB measurement. The studies need to evaluate the optimal timing after phototherapy when the TcB reading can be compared to or becomes similar to TcB obtained in newborns without any prior exposure to phototherapy.

Background

Target condition being diagnosed

Hyperbilirubinemia is a term used to describe excess of bilirubin in the blood. In newborns, hyperbilirubinemia becomes clinically apparent as jaundice, a yellow coloration of the skin and sclera ([Woodgate 2015](#)). Hyperbilirubinemia is very common in both term and preterm newborn infants (occurring in about 60% of newborns) and results from a predisposition to the production of bilirubin and their limited ability to excrete it ([Lauer 2011](#)). Most cases of newborn jaundice are mild and resolve spontaneously ([Srgo 2006](#)). However, in rare cases babies can have very high levels of bilirubin that can lead to bilirubin encephalopathy and kernicterus ([Ebbesen 2005](#); [Srgo 2006](#)). The acute phase signs of kernicterus are poor feeding, lethargy, high-pitched cry, hypertonia or hypotonia, opisthotonos and seizures ([Johnson 2002](#)). The chronic manifestations include athetoid cerebral palsy, motor delay, gaze palsy, dental dysplasia, mental retardation and sensorineural hearing loss ([AAP 2004](#)). Studies from developed countries estimate the incidence of kernicterus to range from about 0.4 to 2 per 100,000 newborns ([Srgo 2006](#); [Mannig 2007](#); [Burke 2009](#)). However, studies from developing countries suggest that the incidence may be much higher ([Nair 2003](#); [Owa 2009](#)). Following guidelines issued by the American Academy of Pediatrics for the management of jaundice in the neonate ([AAP 2004](#)), the age-long critical cut-off value of total serum bilirubin (TsB) of 20 mg/dL (342 μ mol/L) at which therapy was required is being replaced by a plot of TsB against time (hours) for each baby. This is compared to the nomogram for the age of the baby and used to determine the line of management ([Higgins 2012](#)). Current treatments for hyperbilirubinaemia include phototherapy and exchange transfusion, which is usually used for severe cases of hyperbilirubinaemia ([Woodgate 2015](#)).

Index test(s)

Transcutaneous bilirubin (TcB) measurement is a non-invasive method for estimating total serum bilirubin (TsB) level ([Dai 1997](#)). Transcutaneous bilirubinometry works by directing light into the skin and measuring the intensity of the wavelength of light that is returned ([Boo 2007](#)). Transcutaneous bilirubinometry is based on optical spectroscopy, which relates the amount of light absorption by bilirubin to the concentration of bilirubin in the skin. The technology was first introduced in 1980 ([Yamanouchi 1980](#)). The measurement is usually taken by gently pressing the meter against the sternum or forehead. TcB measurement provides an immediate (less than a minute) result of bilirubin levels ([Dai 1997](#)). Using this point-of-care device saves time compared to measuring TsB and may reduce costs associated with measuring TsB in newborns ([Maisels 1997](#)).

However, the accuracy of TcB results may be affected by gestational age, body weight and skin color (Knüpfer 2001; Karen 2009). For example, TcB tends to underestimate TsB in light and medium skin colors and overestimates in dark skin color (Samiee-Zafarghandy 2014). There are a number of TcB devices currently available in the market (Grohmann 2006).

Clinical pathway

Newborns are routinely monitored by nursing staff and physicians for the development of jaundice in the first few hours of life and before discharge from the newborn nursery. This is usually done by visual inspection and skin blanching to assess for yellowish discoloration. Visual estimation of bilirubin level is not reliable ([Barrington 2012](#)). Therefore, bilirubin level needs to be assessed objectively by means of a TcB or TsB measurement. In some settings, TcB or TsB measurements are performed on all newborns as part of routine screening before hospital discharge or as targeted screening based on risk factors for severe hyperbilirubinemia. Some of the risk factors include breastfeeding, ABO/Rhesus incompatibility, glucose-6-phosphate dehydrogenase deficiency, use of oxytocin during delivery, vacuum-assisted delivery, prematurity, and history of jaundice in a sibling ([AAP 2004](#); [Keren 2005](#); [Bhutani 2010](#)). TcB or TsB measurement can be done as part of universal screening or only if a newborn is visibly jaundiced and the value is plotted on a nomogram to assess the need for treatment ([AAP 2004](#)). In addition, the measurements may be taken on newborns undergoing phototherapy to help in deciding on when to stop treatment. The bilirubin levels are interpreted based on the infant's gestational age and postnatal age ([AAP 2004](#)).

Role of index test(s)

The TcB assay is a non-invasive method for measuring bilirubin levels and it may help to reduce the risk of anemia and trauma associated with blood sampling for TsB measurement ([Dai 1997](#)). TcB has been shown to work well in both hospital and outpatient settings; and has been shown to be better than visual inspection for estimation of hyperbilirubinemia ([De Luca 2008](#); [Wainer 2012](#)). Additionally, the TcB measurement ensures a readily available result for immediate clinical decision-making while reducing the chances of infections associated with all invasive procedures ([Jangaard 2006](#)). The TcB meter can be used as a screening tool to estimate the TsB level in newborns who are not clinically jaundiced or as a diagnostic tool in jaundiced newborns to assess the need for treatment ([AAP 2004](#)).

Alternative test(s)

Various methods are used to determine bilirubin levels in newborns. These include visual assessment, direct spectrophotometric methods (requiring capillary blood) and use of an icterometer ([Higgins 2012](#)). Visual assessments for jaundice are common in newborn nurseries and outpatient settings, such as physicians' offices ([Harrison 1989](#)). However, studies have shown that the severity of jaundice cannot be assessed through visual estimation. The icterometer is a specialized ruler marked with different shades of yellow used to estimate the bilirubin level when pressed against a newborn's skin ([Akman 2000](#)).

Rationale

Bilirubin measurement is one of the most frequently performed tests in newborn infants ([Donzelli 2000](#); [Madsen 2000](#)). Chemical methods for TsB measurement are currently the reference standard for measuring bilirubin levels. However, this requires repeated blood sampling which can be painful to the newborn, costly and time consuming. TcB measurement has been recommended as a more cost-effective and less traumatic method of measuring bilirubin levels in newborns ([Dai 1996](#)). In order to justify routine use of TcB devices, we need to systematically review all the available evidence from well-designed studies on the accuracy of TcB measurements compared to TsB measurement in newborn infants. A clear understanding of the diagnostic test accuracy of transcutaneous bilirubinometry using a variety of instruments in a variety of populations (including preterm and term infants as well as infants with various racial backgrounds) would be invaluable for understanding the usefulness of TcB measurement in newborns.

Objectives

1. To determine the diagnostic accuracy of TcB compared with TsB as:
 - a) a diagnostic test for hyperbilirubinaemia in newborns suspected to have hyperbilirubinaemia on visual inspection;
 - b) diagnostic test for monitoring bilirubin levels in newborns receiving treatment (e.g. phototherapy) for hyperbilirubinaemia.
- 2) To determine whether the gestational age, postnatal age, body weight, race and site of TcB measurement have any influence on the accuracy of TcB measurement for hyperbilirubinaemia in newborns.

Methods

Criteria for considering studies for this review

Types of studies

We included diagnostic test accuracy studies comparing TcB and TsB measurement for hyperbilirubinemia in newborns, as follows.

- Cross-sectional studies.
- Cohort studies.

We excluded all randomized controlled trials, retrospective studies, case-control studies, case reports and any studies in which data for true positives, true negatives, false positives and false negatives could not be determined or studies that only reported correlation coefficients between TcB and TsB.

Participants

We included studies evaluating infants aged 0 to 29 days (including term or preterm newborns) who required bilirubin measurement either as a universal screening test or a test for visible jaundice or for monitoring therapy for hyperbilirubinemia. We included studies conducted in different patient settings such neonatal intensive care units, pediatric emergency units, pediatric wards and studies that recruited participants from home or in the communities.

Index tests

The index test is TcB measurement in newborns with the use of any TcB device.

Target conditions

The target condition is hyperbilirubinemia requiring treatment either by phototherapy or by exchange transfusion.

Reference standards

The reference standard is TsB measured in the laboratory, which requires blood sampling from the newborn. TsB measurement can be performed in the laboratory using various methods such as high performance liquid chromatography (HPLC), Diazo-based methods, or other methods such as direct spectrophotometric methods ([Kazmierczak 2002](#)) and capillary electrophoresis ([Higgins 2012](#)). TsB measurement by the HPLC method is not subject to interference from hemoglobin or lipemia. However, this method is costly, labor-intensive and not practical for routine use ([Kazmierczak 2004](#)). The Diazo-based methods are the most frequently used laboratory assays but may be affected by hemolysis ([el-Beshbishi 2009](#)). TsB measurement requires drawing of blood causing pain and trauma to the neonate. Repeated blood sampling for TsB measurement can cause anemia, especially in preterm neonates. Inter- and intra-laboratory variability has been reported with measurements of TsB ([Lo 2011](#)).

Search methods for identification of studies

We used the standard search strategy of the Cochrane Neonatal Review Group to identify all relevant studies without any language restriction. Methodological filters for diagnostic studies was not used, to avoid missing out on some relevant studies. We attempted to get help with translation for articles published in other languages but in the end did not include any of these articles if we could not get a translation. We recorded any article for which we could not get a translation in the section 'Characteristics of studies awaiting classification'

Electronic searches

We used the criteria and standard methods of Cochrane and Cochrane Neonatal (see [the Cochrane Neonatal search strategy for specialized register](#)).

We conducted a comprehensive search including: Cochrane Central Register of Controlled Trials (CENTRAL 2017, Issue 7) in The Cochrane Library; MEDLINE via PubMed (1966 to 22 August 2017); EMBASE (1980 to 22 August 2017); and CINAHL (1982 to 22 August 2018) using the following search terms: ((transcutaneous adj2 bilirubin) OR TcB OR bilicheck OR bilichek OR JM-103 OR JM-105 OR bilirubinomet*) AND (((blood* or serum) adj bilirubin) OR TsB OR spectrophotomet*).mp AND (human not animal), plus database-specific limiters for neonates (see [Appendix 1](#) for the full search strategies for each database). We did not apply language restrictions. We searched clinical trials registries for ongoing or recently completed trials (clinicaltrials.gov; the World Health Organization's International Trials Registry and Platform www.who.int/ictrp/search/en/, and [the ISRCTN Registry](#)).

Searching other resources

We screened the reference lists of any relevant reviews from DARE and MEDION for potentially eligible studies.

Data collection and analysis

Selection of studies

Two review authors (CO and OA) independently assessed eligible articles for inclusion from the titles and abstracts obtained in the initial search. We resolved any disagreement through discussion or, if necessary, by involving a third review author.

Data extraction and management

Two review authors (CO and OA) independently extracted data on study characteristics using a standard data extraction form. Where possible we computed 2×2 tables of true positives, false positives, true negatives and false negatives, for the index tests at the thresholds reported in the primary study. For each included study, we extracted information on the first author's last name and year of publication; study country or race; gestational age of included newborns, number of enrolled infants and number of paired TcB and TsB, type of TcB device and site of measurement, time interval between TcB and TsB measurement; prior use of phototherapy and accuracy results (including correlation coefficients and sensitivities and specificities). The information we extracted from each study is presented in [Table 1](#).

Table 1: Summary of study characteristics and results (n=54)

Study ID	Ethnicity or Race	Gestation & postnatal age	Sample size and number of paired results	TcB device and site of measurement	TsB measurement and time interval	Indication for bilirubin	Phototherapy use	Results
Ahmed 2010	Caucasians, Indian and mixed ethnicity	Preterm < 35 weeks	57 newborns and 183 paired results	Bilicheck. Forehead	Diazo method Within 30 minutes	Clinical jaundice	Both infants with and without prior phototherapy use	r = 0.8965, P, Area under ROC curve 0.8423
Akahira-Azuma 2013	Mongolia, race not described	Late preterm and term ≥ 35 weeks	53 newborns and 57 paired samples	JM 103. Sternum and Forehead	Photometric method. Within 3 hours	Clinical jaundice	No prior phototherapy use	TcBf, r= 0.888 TcBs, r=0.886 AUC from 0.909 at 0.987 for different TsB values (>10, >13 and >15 mg/dL)
Bental 2009	Mixed (Ashkenazi and Sephardic Ethiopian)	Late preterm and term ≥ 35 weeks	628 newborn and 1091 paired samples	JM 103. Sternum and Forehead	Colorimetric method. Within 90 minutes	Clinical jaundice	No prior phototherapy use	r= 0.846 AUC were 0.969, 0.971 & 0.987 for TsB values >10, >13 and >15 mg/dl respectively.
Bertini 2008	Italian/White	Preterm and term newborns > 32 weeks	241 newborns and 241 paired samples.	Bilitest BB 77. Forehead	Spectrophotometric method. Within 10 minutes.	Clinical jaundice	No prior phototherapy use	r= 0.830 AUC were 0.851, 0.63 & 0.939 for TsB values >11, >13 and >15 mg/dl respectively.
Bhutani 2000	USA/ Mixed (white, black, hispanics)	Late preterm and term ≥ 35 weeks. 12 to 98 hours	517 newborns and 1788 paired samples	Bilicheck. Forehead	HPLC. Within 30 minutes	Clinical jaundice	No prior phototherapy use	r= 0.91 white: r=0.91 Blacks: r= 0.91 Hispanics: r= 0.93 Asian and others: r=0.90
Bhutta 1991	Pakistani newborns, race not specified	Term and preterm > 34 weeks	63 newborns and 100 paired samples	JM 101. Forehead	Photometric method with 2 hours	Clinical jaundice	No prior phototherapy use	r= 0.66 TcB cut-off of 17 detects TsB > 12.5 with sensitivity and specificity of 88 & 53% respectively.

Bilgen 1998	Turkish newborns, race not specified	Term newborns \geq 37 weeks, 1 to 5 days of life	96 newborns and 96 paired samples	JM 101. Forehead	Direct spectrophotometric method within 30 minutes.	Clinical jaundice	No prior phototherapy use	r= 0.83 TcB cut-off of 13 detects TsB $>$ 12.9 with sensitivity and specificity of 100 & 56% respectively
Boo 2007	Malay, Chinese and Indian newborns	Term newborns \geq 37 weeks, 1 to 5 days of life	345 newborns and 345 paired samples	Bilichek. Forehead and sternum.	Direct spectrophotometric method within 30 minutes.	Clinical jaundice	No prior phototherapy use	TcBf, r= 0.80 TcBs, r= 0.86 TcBf cut-off of 250 μ mol/L, the Bilicheck detected TsB \geq 300 μ mol/L with a sensitivity of 100% & specificity of 39.2%, At TcBs cut-off of 200 μ mol/L, the Bilicheck detected TsB \geq 300 μ mol/L with a sensitivity of 100% and a specificity of 33.6%.
Campbell 2011	Canada, diverse population (whites, blacks, Asian, Indian, Latino)	Late preterm and term \geq 35 weeks	430 newborns and 430 paired samples.	Bilichek. Forehead	Direct spectrophotometric method within 30 minutes.	Clinical jaundice	No prior phototherapy use	To detect a TsB of 200 μ mol/L, a TcB value of 180 μ mol/L would provide 96% sensitivity and 55% specificity. To detect a TsB value of 250 μ mol/L, a TcB of 200 μ mol/L would provide 96% sensitivity and 57% specificity.
Chimhini 2018	Zimbabwe, Black	Preterm and term infants between 28 and 42 weeks, 0-10 days of life	283 newborns and 283 paired samples.	JM 103, forehead and sternum	Diazo within 30 minutes.	Clinical jaundice with no prior phototherapy	No prior phototherapy use	TcBf, r = 0.72 TcBs, r= 0.77
Christo 1988	South Indian	Term and preterm newborns	138 newborns and 138 paired samples	JM 101, forehead and sternum and average of the two readings	Spectrophotometric method within 30 minutes.	Infants from whom blood specimen was drawn for bilirubin or other reasons	Infants with and without prior phototherapy use	r= 0.90 TcB cut off of 18 mg/dl detects TsB $>$ 13 mg/dl with 95% sensitivity and 83% specificity.

De Luca 2007	Caucasian	Preterm newborns, 30 to 36 week gestation	340 newborns and 340 paired results	Bilicheck, forehead	Spectrophotometric method within 10 minutes.	Universal screening of all newborns	No prior phototherapy use	r= 0.795. TcB cut-off values were 111 umol/l for TsB > 171 Amol/l (sensitivity 100%; specificity 40%) and 171 umol/l for TsB >205 Amol/l (sensitivity 100%; specificity 72%).
De Luca 2008	Italy, Caucasian	Term and preterm newborns > 34 week gestation	686 newborns and 686 paired results	BiliMed and Bilicheck, forehead	Spectrophotometric method within 15 minutes.	Clinical jaundice	No prior phototherapy use	BiliMed, r= 0.45 Bilicheck, r= 0.75 To identify TsB levels > 205.2 mmol/l, BC cut-off values are 116.3 mmol/l (sensitivity 99%; specificity 20%) while for BM they are 85.5 mmol/l (sensitivity 99%; specificity 13%)
Donzelli 2000	Italy, Caucasian	Preterm newborns, 24-36 weeks gestation	70 newborns, number of paired samples not specified	JM 102, sternum	Spectrophotometric method within 10 minutes.	Clinical jaundice	Both patient with prior and without prior phototherapy use	r=0.84 TcB index of 18 gave a Specificity and positive predictive value were 64% and 54%, respectively.
Engle 2002	Hispanic and nonhispanic	Term and late preterm newborns ≥ 35 week gestation	304 newborns and 404 paired comparisons	Bilicheck, forehead	Diazo method within 30 minutes.	Clinical jaundice	No prior phototherapy use	r= 0.84 The authors reported different sensitivities and specificities with 6 different cut offs for TcB measurement.
Engle 2005	Hispanic	Term and late preterm newborns ≥ 35 weeks	121 newborns and 121 paired samples.	JM 103, sternum	Diazo method within 30 minutes.	clinical jaundice	No prior phototherapy use	R=0.77 The authors reported different sensitivities and specificities with 6 different cut offs for TcB measurement. For TsB >17 mg/dl and a JM cutoff value of 13 mg/dl, sensitivity was 100%, specificity of 58%.

Fok 1986	Chinese newborns	Term newborns \geq 37 week gestation	259 newborns and 705 paired comparisons	JM 101, Forehead and sternum	Spectrophotometric method within one hour.	Clinical jaundice	Both patient with prior and without prior phototherapy use	TcBs, $r = 0.91$ TcBf, $r = 0.86$ The sensitivity and specificity, the forehead TcBf index ≥ 22 has a sensitivity OF 100% and specificity 20 % to detect TsB $\geq 255 \mu\text{mol/l}$ (15 mg/dl).
Harish 1998	North Indian newborns	Term and preterm newborns $>$ 30 weeks. 2 to 20 days	145 newborns. Number of paired comparisons not mentioned.	JM 101, forehead	Not described	Clinical jaundice	Both patient with prior and without prior phototherapy use	$r = 0.71$ The sensitivity and specificity, the forehead TcBf index ≥ 18 has a sensitivity of 97.3% and specificity 50 % to detect TsB $\geq 13 \text{ mg/dl}$.
Hemmati 2013	Iranian newborns	Mostly term and late preterm ≥ 35 weeks, ≤ 35 weeks (only 5 patients)	560 newborns. Number of paired comparisons not mentioned.	Bilicheck, forehead	Spectrophotometric and Diazo method	Clinical jaundice	No prior phototherapy use	$r = 0.969$ A TcB cut-off value of 15mg/dl detected TsB $>15 \text{ mg/dl}$ with sensitivity and specificity of 96.6% and 99% respectively.
Ho 2006	Chinese newborns	Term ≥ 37 weeks and preterm $>$ 32 weeks. 2 to 9 days	83 newborns (77 term and 6 preterm), number of paired comparisons not reported.	Bilicheck, JM 102, forehead & sternum	Spectrophotometric and Diazo method	Clinical jaundice	No prior phototherapy use	JM 102, TcBf, $r = 0.718$ & TcBs, $r = 0.814$ Bilicheck, TcBf, $r = 0.757$ & TcBs, $r = 0.794$ JM 102, a cut-off point of 20 at the forehead and 21 at the sternum produced a specificity of 50% and 78%, respectively with a sensitivity of 100%. For BiliCheck, a cut-off point of 250 $\mu\text{mol/L}$ on the forehead and 260 $\mu\text{mol/L}$ on the sternum produced a specificity of 61.9% and 70.0%, respectively with a sensitivity of 100%.

Holland 2009	Race was recorded for 83.8%, consisting of 27.1% Caucasian, 54.7% Hispanic, 16.0% African American, and 2.2% other races	Term and preterm newborns > 36 weeks, 1-5 days old	343 newborns with 343 paired comparisons	Bilicheck, forehead and sternum	Diazo	Indication for bilirubin measurement not mentioned	No prior phototherapy use	The study reported multiple correlation between TcB and TsB were similar for all laboratory methods and TcB measurement sites.
Karolyi 2004	Caucasian	Preterm newborns 23 to 33 weeks	124 newborns, 124 paired comparisons	JM 102, sternum	Photometric method within 10 minutes	Routine bilirubin measurement	No prior phototherapy use or at least 6 hours after phototherapy use.	R=0.68 TcB cut-off reading of 14 detected hyperbilirubinemia \geq 150 μ mol/l with a sensitivity of 100% and a specificity of 34%
Karon 2008	146 Caucasian, 19 Asian, 9 Hispanic, and 3 African American	Term and late newborns > 32 weeks	177 newborns, 177 paired comparisons. 8 to 81 hours	Bilicheck, forehead	Diazo and Vitros method within 30 minutes.	Clinical jaundice	No prior phototherapy	R= 0.65 (Diazo) and r= 0.66 (Vitros). TcB risk was in a higher risk zone in 128 (72.3%) of 177 neonates compared with the diazo TsB, while the TcB was in a higher risk zone for 68 (51.9%) of 131 neonates compared with the Vitros TsB.
Karrar 1989	Saudi newborns	Term newborns \geq 37 week gestation and 4 to 10 days of life.	155 newborns and 155 paired comparisons	JM 101, forehead	American optical bilirubinometer, Time interval was not mentioned (but probably within 30 minutes)	Clinical jaundice	No prior phototherapy	r= 0.817 At a cut-off TcB index of 21, the device had sensitivity of 74% and specificity of 90% to detect TsB \geq 12.5 mg/dl
Kaynak-Turkmen 2011	Turkish newborns	Term and preterm \geq 30 weeks. 3 to 19 days of life.	54 newborns and 54 paired comparisons	Bilicheck, forehead	HPLC, Diazo method, BR 501 bilirubinometer	Indication for bilirubin measurement not mentioned.	No prior phototherapy	There was good correlation between TcB and HPLC-bilirubin (B) (r=0.85). The cut-off limits providing a sensitivity of 100% for TcB measurements were TcB \geq 9 mg/dl for HPLC-B >17 mg/dl and TcB \geq 8 mg/dl for HPLC-

								B >15 mg/dl and HPLC-B >13 mg/dl.
Kitsommat 2013	Asian newborns (not specified)	Term and late preterm newborns age 5-14 days of life	405 newborns and 455 paired comparisons	Konica Minolta JM-103	Diazo method within 30 minutes	Clinical jaundice	No prior phototherapy use or at least 24 hours after phototherapy use.	r=0.80 To detect a TsB level of $\geq 255 \mu\text{mol/L}$, using the TcB cutoff level of $204 \mu\text{mol/L}$ provides a sensitivity of 96 % with a specificity of 58 %.
Knupfer 2001	128 Caucasians and 7 Asians	Preterm 23-36 weeks. 2 to 6 days of life.	135 newborns and 400 paired comparisons	Bilicheck, forehead	Diazo method, time interval not mentioned	Indication for bilirubin measurement not mentioned.	Newborns without prior phototherapy and with phototherapy were included	The sensitivity and specificity of TcB to detect TsB above treatment threshold were 78.0 and 72.5 respectively
Kolman 2007	Hispanics	Term and late preterm newborns > 35 weeks gestations. 0 to 144 hours of life.	192 newborns and 192 paired comparisons	Bilicheck, forehead	Diazo within 30 minutes.	Universal bilirubin screening	No prior phototherapy	r=0.870 A TcB level above the 75th percentile detected all infants with a TsB level above the 95th percentile, sensitivity 100%, and specificity 66%.
Laeq 1993	Pakistani newborns	Term newborns ≥ 37 weeks	105 newborns, number of paired comparisons not mentioned	JM101, forehead, sternum and chest	Diazo method within 30 minutes.	Indication for bilirubin measurement not stated	No prior phototherapy use	r=0.774 TcB sensitivity was 90%, specificity 78% and positive predictive value 64% at mean TsB of 9.92 mg/dl
Lam 2008	Chinese newborns	Term and late preterm >35 weeks gestation 3 to 7 days of life.	113 newborns and 113 paired comparisons	JM 103, forehead and sternum	Spectrophotometric method within 5 minutes	Clinical jaundice	No prior phototherapy use	TcB cut-off of $230 \mu\text{mol/L}$ (13.5 mg/dl) and $298 \mu\text{mol/L}$ (17.7 mg/dl) have 100% sensitivity and specificity respectively, to predict a total TsB level of higher than $250 \mu\text{mol/L}$. The area under the curve was 0.822. JM-103 tended to overestimate the TsB; the bias was around $14 \mu\text{mol/L}$.

Leite 2007	White (66.5%), mixed race (23.5%) and black (10%)	Term and preterm newborns < 36 weeks, postnatal age < 3 days and ≥ 3 days	200 newborns and 200 paired comparisons	Bilicheck,	Spectrophotometric method within 30 minutes	Indication for bilirubin measurement not stated	37.5% were on phototherapy and 62.5% had no prior phototherapy use.	r= 0.92 TcB cut-off 14 mg/dL had sensitivity of 88.2% and specificity 97.8%.
Lin 1993	Chinese newborns	Term newborns ≥ 37 weeks	305 newborns and 444 paired comparisons	Minolta Airshield, forehead and sternum	Spectrophotometric method within 30 minutes	Indication for bilirubin measurement not stated	No prior phototherapy use	TcBf, r= 0.82 TcBs, r= 0.86 The sensitivity and specificity of TcBf to detect TsB > 12.9mg/dl were 68% and 80 % respectively. The sensitivity and specificity of TcBs to detect TsB > 12.9mg/dl were 84% and 84% respectively.
Maisels 1982	White newborns	Term newborns ≥ 37 weeks	157 newborns and 292 paired comparisons	JM 101, forehead and sternum	Diazo method within 30 minutes	Bilirubin measurement was obtained routinely on all infants except 11 infants where it was obtained on clinical grounds	No prior phototherapy use	TcBf and TcBs, r= 0.93 The authors report different sensitivities and specificities for different TcB cut-offs. TcBf index of 24 had sensitivity and specificity of 100% and 97% respectively to detect TsB> 12.9 mg/dl. TcBs index of 23 had sensitivity and specificity of 100% and 96% respectively to detect TsB> 12.9mg/dl.
Maisels 2004	White (59.2%), black (29.8%), East Asian (4.5%), Middle Eastern (3.8%), Indian/Pakistani (1.6%), and 1.1% Hispanic.	Term and late preterm newborns >35 weeks	849 newborns and 849 paired comparisons	JM 103 and Bilicheck, forehead and sternum	Not specified.	Clinical jaundice	No prior phototherapy use	TcBf, r=0.914 TcBs, r=0.953 The areas under the ROC for different JM-103 cutoff values when TsB > 10 mg/dL, >13 mg/dL, and >15 mg/dL were 0.962, 0.963, 0.975, respectively.

Maisels 2011	Mixed-race population (primarily Caucasian and Hispanic, followed by Asian and African American infants)	Term and late preterm newborns >35 weeks	120 newborns and 120 paired comparisons	JM 103, sternum	Diazo within 30 minutes	Clinical jaundice	No prior phototherapy use	r=0.78 Different sensitivities and specificities for different TcB cut of values and TcB cut-off of 13 detected TsB 15 mg/dl with 99% sensitivity and 44%.
Neocleous 2014	White newborns	Term newborns ≥ 37 weeks. 24 to 96 hours	222 newborns and 368 paired samples.	Bilicheck, forehead	Direct spectrophotometric method within 20 minutes	Clinical jaundice	Prior use of phototherapy was not mentioned	r=0.439 To detect a TsB value of 205 μmol/l, a TcB value of 207 μmol/l would provide 95.4% sensitivity and 18.6% specificity (positive predictive value would be 79.4% and negative predictive value 55.2%). Similarly, to detect a TsB value of 240 μmol/l, a TcB of 265 μmol/l would provide 22.5% sensitivity and 94.2% specificity
Panburana 2010	Thailand (specific race not mentioned)	Term and late preterm ≥ 35 weeks. 24 to 130 hours	74 newborns and 224 paired comparisons	JM 103, forehead	Method for TsB measurement was not reported	Clinical jaundice	Newborns without prior phototherapy and with phototherapy were included	r= 0.81 The authors reported different sensitivities and specificities for before and during phototherapy use. TcB accurately predicted different levels of TsB before phototherapy use.
Qualter 2011	Ireland (97.7% Caucasian)	Term and late preterm ≥ 35 weeks. 18 to 124 hours	84 newborns and 84 paired comparisons	Bilicheck and JM 103, forehead	Diazo method within 30 minutes	Clinical jaundice	No prior phototherapy use	Bilicheck, r= 0.88 JM 103, r= 0.70 100% sensitivity was achieved using the 75 th percentile on Bhutani nomogram for BiliCheck and the 40 th percentile for JM 103

Raimondi 2012	Caucasian and black newborns.	Term and late preterm \geq 35 weeks	289 newborns and 343 paired comparisons	JM 103, Bilicheck and Bilimed, forehead	Direct spectrophotometric method, within 20 minutes	Clinical jaundice	Phototherapy use was not mentioned	Correlations coefficients, r, were 0.85, 0.86 and 0.70 for JM 103, Bilicheck and Bilimed respectively. The corresponding area under the ROC curves when TsB > 14 mg/dl were 0.92, 0.95 and 0.75 respectively. All devices showed tendency to overestimate at higher levels of TsB.
Rodríguez-Capote 2009	Caucasian and non-Caucasian	Term and late preterm \geq 35 weeks	154 newborns and 154 paired comparisons	JM 103 and Bilicheck, forehead	Diazo method, within 30 minutes	Routine bilirubin measurement	No prior phototherapy use	Correlations coefficients, r, were 0.85 and 0.86 for JM 103 and Bilicheck respectively. Applying the risk classification using the 40th, 75th, and 95th percentile of the Bhutani nomogram a 6%, 0%, and 1% false negative rate was found for BiliCheck and 62%, 74% and 81% for the Minolta Air-Shields JM-103. Both devices showed tendency to underestimate TsB.
Rubaltelli 2001	white, Asian, Hispanic, African, and other races.	Term and preterm > 30 weeks and 0 to 28 days of life	210 newborns, number of paired comparisons not reported	Bilicheck, forehead and sternum	HPLC, within 30 minutes	Routine bilirubin measurement	No prior phototherapy use	TcBf, r = 0.890 TcBs, r = 0.881 With the use of a cutoff point for HPLC-B of 13 mg/dL (222 mmol/L) and a cutoff of 11 mg/dL on the TcBf and TsB, similar sensitivity/specificity (93%/73% for TcBf, 95%/76% for TsB) were observed. The use of a cutoff point for HPLC-B of 17 mg/dL (290 mmol/L) and 14

								mg/dL (240 mmol/L) for TcBf and TsB also produced Similar sensitivity/specificity (90%/87% for Bilicheck and 87%/83% for TsB).
Rylance 2014	Black African	Preterm (mostly > 32 weeks) and term newborns > 37 weeks. 0 to 14 days of life.	128 newborns and 296 paired comparisons	JM 103, forehead and sternum	Diazo method, near simultaneous measurements with TcB	Clinical jaundice	Newborns without prior phototherapy and with phototherapy were included	For infants not under phototherapy, the lowest TcB reading (from forehead or sternum) gave the strongest correlation with TsB: $r=0.83$ for term infants and $r=0.71$ for premature infants. For infants undergoing phototherapy, the highest TcB reading gave the strongest correlation with TsB: $r=0.66$ for term infants and $r=0.71$ for premature infants.
Sajjadian 2012	Iranian newborns	Preterm 25 to 37 week gestation. 1 to 14 days of life.	126 newborns and 126 paired comparisons	JH2-1A, forehead and sternum	Diazo method, within 30 minutes	Clinical jaundice	Newborns without prior phototherapy and with phototherapy were included	There was significant correlation coefficients of TcBf and TsBs vs TsB TcB for infants under phototherapy ($r=0.67$ and $r=0.69$, $P<0.001$) and in neonates without phototherapy ($r=0.69$ and $r=0.64$). The authors reported different sensitivities and specificities for different cut-offs of TsB.
Samanta 2004	The race/population was not reported	Preterm ≥ 33 week and Term ≥ 37 weeks gestation. 1 to 11 days of life.	300 newborns and 300 paired comparisons	Bilicheck, site of measurement was not reported	Diazo method, near simultaneous measurements with TcB	Clinical jaundice	No prior phototherapy use	$r = 0.77$ Bilicheck identified significant jaundice (TsB above 250 mol/l) with a sensitivity of 91% and specificity of 66%.

Samiee-Zafarghandy 2014	Multi-racial with different skin color	Term and preterm \geq 35 weeks	451 newborns and 598 pairs comparisons	JM 103, sternum	Direct spectrophotometric method, within 30 minutes	Clinical jaundice and during routine newborn screening	No prior use of phototherapy for at least 12 hours	For light skin color. TcB cut-off of 145 $\mu\text{mol/L}$ detected TsB $>$ 170 $\mu\text{mol/L}$ with sensitivity and specificity of 100 & 95 respectively. Medium skin color: TcB cut-off of 130 $\mu\text{mol/L}$ detected TsB $>$ 170 $\mu\text{mol/L}$ with sensitivity and specificity of 95.9 & 75.1 respectively. Dark skin color: TcB cut-off of 170 $\mu\text{mol/L}$ detected TsB $>$ 170 $\mu\text{mol/L}$ with sensitivity and specificity of 100 & 89.3 respectively.
Sampavat 2004	Thailand/Asian	Term and preterm \geq 36 weeks	388 newborns and 460 paired comparisons	JM 103, sternum	Direct spectrophotometric method, within 15 minutes	Clinical jaundice	No prior use of phototherapy	$r=0.8$ TcB levels of more than 8, 9, 10, and 12 mg/dl, which were used as cut-off points to indicate blood sampling were chosen as demarcations in predicting TsB levels of 10, 12, 13 and 15 mg/dl, respectively. The sensitivity and specificity for different TcB cut-offs ranged from 92-96% and 50-83% respectively. TcB showed a tendency to underestimate TsB levels.
Sampavat 2005	Thailand/Asian	Term and preterm \geq 36 weeks	134 newborns and 154 paired comparisons	JM 103 and Bilicheck, forehead	Direct spectrophotometric method, within 15 minutes	Clinical jaundice	No prior use of phototherapy	The correlation coefficients between TcB (JM and BC) and TsB were r 0.80 and 0.82, respectively. TcB levels of more than 8, 9, 10, and 12 mg/dl,

								which were used as cut-off points to indicate blood sampling were chosen as demarcations in predicting TsB levels of 10, 12, 13 and 15 mg/dl, respectively. The sensitivity of BC was higher, but specificity was lower, than JM in corresponding to different TsB levels, except at a TsB level of 15 mg/dl when both instruments yielded 100% sensitivity.
Sanpavat 2007	Thailand/Asian	Preterm newborns < 36 weeks	196 newborns and 249 paired comparisons	JM 103, forehead	Direct spectrophotometric method, within 1 hour.	Clinical jaundice	No prior use of phototherapy	r=0.79 The sensitivity and specificity of TcB of different cut-off values to detect significant hyperbilirubinemia ranged from 53.1% to 97.8% and 40% to 88.9% respectively.
Schmidt 2009	Hispanic	Preterm newborns ≤ 34 weeks	90 newborns, number of paired comparisons not clear from the article.	JM 103, sternum	Diazo method within 45 minutes	Routine bilirubin measurement	No prior use of phototherapy	The correlation coefficient, r ranged from 0.79 to 0.92. The sensitivity and specificity of TcB of different cut-off values to detect significant hyperbilirubinemia ranged from 88% to 100% and 21% to 81% respectively.
Schumacher 1985	Caucasian	Newborns > 36 weeks, postnatal age 1 to 5 days.	106 newborns and 106 paired comparisons	JM 101, sternum	Direct spectrophotometric method within 30 minutes	Clinical jaundice	No prior use of phototherapy	r = 0.74= The TcB device classified hyperbilirubinemia with a sensitivity of 94% and specificity of 77.5%.

Szabo 2004	White, Asian, Indian and African	Preterm newborns 34 to 36 weeks gestation	69 newborns and 107 paired comparisons.	JM 102 & Bilicheck, forehead and sternum.	Direct spectrophotometric method, near simultaneous measurements.	Clinical jaundice	No prior use of phototherapy	The correlation coefficients, r, for JM 102 and Bilicheck from the sternum where: 0.90 and 0.89 respectively. TsB > 190 umol/l can be detected with 95% sensitivity with Minolta JM 102 >19 units, with Bilicheck >145 umol/l over the sternum and >165 umol/l over the forehead
Taha 1984	Saudi newborns	Term newborns > 37 week gestation. 3 to 12 days	68 newborns and 120 paired comparisons	JM 101, forehead	Direct spectrophotometric method, near simultaneous measurements.	Clinical jaundice	No prior use of phototherapy	r=0.878 TcB index of 22 has a sensitivity and specificity of 69% and 92% respectively to detect TsB > 12.9 mg/dl
Wong 2002	Mostly white, 6 non-white	Term and preterm > 31 to gestation	64 newborns and 64 paired comparisons	JM 102 and Bilicheck, forehead	Photometric method, within 30 minutes.	Clinical jaundice	No prior use of phototherapy	r= 0.94 to 0.99 TcB with JM 105 cut-off > 170 umol/L detected a TsB > 250 umol/L with 100% sensitivity and 31.9% specificity. TcB with Bilicheck cut-off > 150 umol/L detected a TsB > 250 umol/L with 100% sensitivity and 21.3% specificity.

Yaser 2014	South African newborns	Preterm 24 to 34 weeks	122 newborns and 122 paired comparisons	JM 103, forehead, sternum and interscapular area.	Method for TsB measurement was not reported.	Clinical jaundice	No prior use of phototherapy	The correlation coefficients for TcBf, TcBs and TcBi were 0.904, 0.929 and 0.859 respectively. The interscapular site had the highest sensitivity of 94% and lowest false negative rate of 6%.
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Assessment of methodological quality

Two of the review authors (CO and OA) independently assessed the methodological quality of each included study using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool ([Whiting 2011](#)), which consists of four domains. We developed a rating guideline for assessment of the domains in order to ensure consistency. We assessed each of the four domains with respect to the risk of bias. Additionally, we assessed the first three domains in terms of applicability. We conducted a pilot test of our review-specific QUADAS-2 tool against five primary studies in order to identify possible areas of discrepancies between authors. We resolved discrepancies in assessments by consensus. The items of the QUADAS-2 tool and our scoring interpretations for each item are presented in [Appendix 2](#).

Statistical analysis and data synthesis

We planned to perform statistical analysis according to Cochrane guidelines for diagnostic test accuracy (DTA) reviews ([Macaskill 2010](#)). We planned to include studies that reported on correlation between TcB and TsB and also reported sufficient data that allows for the construction of a 2×2 table. However, during the review process we made the decision to broaden the inclusion criteria and include studies that did not have sufficient data for 2×2 table but reported on other measures of accuracy apart from the correlation coefficient. Studies that only reported the Pearson correlation coefficients to describe the relationship between TcB and TsB measurements were excluded.

We had planned to use the 2×2 tables to calculate sensitivity and specificity for each study and also meta-analysis of sensitivities and specificities where appropriate using the bivariate model if the same threshold for positivity was used. According to the bivariate method we planned to calculate overall sensitivity and specificity and their 95% confidence intervals (CIs), based on the binomial distributions of the true positives and true negatives ([Reitsma 2005](#)). However, because the studies were very clinically heterogeneous, we presented most of the findings narratively. We were able to combine the results for some of the studies that evaluated the accuracy of the JM 101 device.

Investigations of heterogeneity

We had planned to investigate heterogeneity by visual examination of both the ROC plot of raw data and the forest plots of sensitivities and specificities. However, this was not done because we could not perform a meta-analysis.

Sensitivity analyses

We did not perform any sensitivity analysis because data from none of the studies was combined in a meta-analysis.

Assessment of reporting bias

We are not planning to use funnel plots to evaluate the impact of publication bias or other biases associated with small studies.

Results

Results of the search

We identified a total of 495 studies from the various databases. After de-duplication, we screened 315 titles and abstracts for eligibility. Of these, we obtained full text articles of 146 studies for full assessment. We included 54 studies that met our inclusion criteria and 91 studies were excluded for various reasons as described in the [Characteristics of excluded studies](#) section ([Figure 1](#)).

Methodological quality of included studies

Risk of bias assessment for each included study was done using the QUADAS-2 tool. The majority of the studies were assessed as low risk for bias across the different domains; patient selection, index test, reference standard, and flow and timing ([Figure 2](#) & [Figure 3](#)). The detailed assessment of the risk of bias and the judgement for each domain are described in the [Characteristics of included studies](#). The majority of the included studies were assessed as low risk for bias with respect to patient selection, index test, reference standard, flow timing and applicability.

Findings

The 54 included studies have a total sample size of 12,254 newborns. The total number of paired comparisons of TcB and TsB could not be ascertained because in many of the studies, the number of paired measurements was more than the number of included participants (because some participants had measurements at more than one occasion) and not all the studies mentioned the number of paired measurements.

The characteristics of the included studies are presented in [Characteristics of included studies](#) and table 1 . The studies were published between 1982 and 2018 and varied in terms of population characteristics/ethnicity, gestational age and postnatal age of the included infants, sample size and number of paired measurements of TcB and TsB, the TcB device used, site of TcB measurement, type of method used for TsB assay in the laboratory, time interval between TcB and TsB measurement, indication for measurement of bilirubin and whether the participants received phototherapy or not prior to measurement of TcB and TsB.

Most of the included studies were carried out in the neonatal intensive care units or the regular well baby nurseries. A few of the studies were conducted in outpatient settings of emergency departments

([Engle 2005](#); [Kitsommart 2013](#); [Lam 2008](#); [Maisels 1982](#)). Different race groups were represented across the different studies. Some studies included a mixture of infants from different ethnic backgrounds while others focused on newborns from a specific race group. Amongst others, the different ethnic groups/race include: White ([Bertini 2008](#), [De Luca 2007](#), [De Luca 2008](#); [Donzelli 2000](#); [Maisels 1982](#); [Schumacher 1985](#)); Chinese infants ([Fok 1986](#), [Ho 2006](#), [Lam 2008](#), [Lin 1993](#)); Indigenous African infants ([Chimhini 2018](#); [Rylance 2014](#)); and Hispanic ([Engle 2002](#); [Kolman 2007](#); [Schmidt 2009](#)). The gestational age of the newborns included also differed across the included studies. Most of the studies included late preterm ≥ 35 -week gestational age and term newborns ≥ 37 weeks gestational age (18 studies), while others included preterm infants < 35 weeks gestation (9 studies), only term newborns ≥ 37 weeks gestation (8 studies), and the rest of the studies included newborns of any gestational age > 23 weeks.

The postnatal age varied significantly across the studies and ranged from 0 to 29 days of life. Some studies did not report the postnatal age of the included participants. The sample size ranged from 57 infants ([Ahmed 2010](#)) to 849 infants ([Maisels 2004](#)) and the number of paired measurements of TcB and TsB ranged from 57 ([Akahira-Azuma 2013](#)) to 1091 ([Bental 2009](#)). Some studies included multiple paired measurements of TcB and TsB from the same participant. The number of paired TcB and TsB corresponded to the number of newborns included in the study in the following studies ([Bertini 2008](#); [Bilgen 1998](#); [Boo 2007](#); [Campbell 2011](#); [Chimhini 2018](#); [Christo 1988](#); [De Luca 2007](#); [De Luca 2008](#); [Holland 2009](#); [Karolyi 2004](#); [Karon 2008](#); [Karrar 1989](#); [Kaynak-Turkmen 2011](#); [Kolman 2007](#); [Lam 2008](#); [Leite 2007](#); [Maisels 2004](#); [Qualter 2011](#); [Sajjadian 2012](#); [Schumacher 1985](#)). The number of paired samples not reported in [Donzelli 2000](#); [Harish 1998](#); [Hemmati 2013](#); [Ho 2006](#); and [Rubaltelli 2001](#).

The studies assessed the measurement of TcB using various TcB devices (Minolta-Air Shields JM 101, JM 102, JM 103, Bilicheck) compared with TsB measurement in the laboratory by different methods (including HPLC, direct spectrophotometric, and diazo method). All the included studies reported on the correlation between TcB and TsB using the Pearson correlation coefficient and also reported on some other measure of accuracy such as sensitivity or specificity using for a specific TsB threshold as diagnostic for hyperbilirubinemia. Overall, there were good correlations between TcB and TsB in the included studies. The studies reported different sensitivity and specificity for different thresholds.

JM 101 transcutaneous device

TcB measurement with the JM 101 jaundice meter was assessed in a number of studies ([Bhutta 1991](#); [Bilgen 1998](#); [Christo 1988](#); [Fok 1986](#); [Harish 1998](#); [Karrar 1989](#); [Laeq 1993](#); [Maisels 1982](#); [Schumacher 1985](#); [Taha 1984](#)). All these studies showed a significant correlation between TcB measured with the JM 101 device and the TsB measured in the laboratory. The Pearson correlation coefficient, r , ranged from 0.66 ([Bhutta 1991](#)) to 0.93 ([Maisels 1982](#)). TcB measured with the JM 101 device also showed a high sensitivity in detecting significant hyperbilirubinemia. The studies used different thresholds to define hyperbilirubinemia and also different TcB cut-off values. The Sensitivity ranged from 74% to 100% and specificity ranged from 53 to 88%. [Data table 1](#); [Data and analyses](#). [Figure 4](#); [Figure 5](#).

JM 102 transcutaneous device

JM 102 ([Donzelli 2000](#); [Harish 1998](#); [Ho 2006](#); [Karolyi 2004](#); [Lin 1993](#); [Szabo 2004a](#); [Wong 2002](#)). All the studies reported a significant correlation between TcB measured with the JM 102 device and the TsB measured in the laboratory. The Pearson correlation coefficient, r , ranged from 0.68 ([Karolyi 2004](#)) to 0.99 ([Wong 2002](#)). TcB measured with the JM 102 device also showed a high sensitivity in detecting significant hyperbilirubinemia. The studies used different thresholds to define hyperbilirubinemia and also different TcB cut-off values. The Sensitivity ranged from 68% to 100% and specificity ranged from 21 to 88%.

JM 103 transcutaneous device

The JM 103 device has been evaluated in multiple studies ([Akahira-Azuma 2013](#); [Bental 2009](#); [Chimhini 2018](#); [Engle 2005](#); [Kitsommart 2013](#); [Lam 2008](#); [Maisels 2004](#); [Maisels 2011](#); [Panburana 2010](#); [Qualter 2011](#); [Raimondi 2012](#); [Rodriguez-Capote 2009](#); [Rylance 2014](#); [Samiee-Zafarghandy 2014](#); [Sanpavat 2004](#); [Sanpavat 2005](#); [Sanpavat 2007](#); [Schmidt 2009](#); [Yaser 2014](#)). Findings from these studies showed a good correlation (with correlation coefficient, r , ranging from 0.70 to 0.95) between TcB measured with the JM 103 device and TsB measured in the laboratory.

Bilicheck transcutaneous device

The Bilicheck has been evaluated in numerous studies ([Ahmed 2010](#); [Bhutani 2000](#); [Boo 2007](#); [Campbell 2011](#); [De Luca 2007](#); [De Luca 2008](#); [Engle 2002](#); [Hemmati 2013](#); [Ho 2006](#); [Holland 2009](#); [Karon 2008](#); [Kaynak-Turkmen 2011](#); [Knutper 2001](#); [Kolman 2007](#); [Leite 2007](#); [Maisels 2004](#); [Neocleous 2014](#); [Qualter 2011](#); [Raimondi 2012](#); [Rodriguez-Capote 2009](#); [Rubaltelli 2001](#); [Samanta 2004](#)). Findings from these studies showed a good correlation (with correlation coefficient, r , ranging

from 0.75 to 0.96)) between TcB measured with the Bilicheck device and TsB measured in the laboratory.

Bilimed transcutaneous device

De Luca 2008; Raimondi 2012 evaluated the use of Bilimed for TcB measurement and found a correlation coefficient, r of 0.45 and 0.70 respectively with TsB.

Factors affecting TcB measurement:

1) Site of measurement.

Maisel 2004 reported a better correlation between TcB and TsB when the measurement is taken from the sternum ($r=0.953$) compared to the forehead ($r=0.914$). Other studies also report better correlation when the measurement is taken from the sternum compared to the forehead (Engle 2002; Fok 1986; Holland 2009). In Engle 2002 among a Hispanic population, BiliCheck measurements from the forehead underestimated TsB, particularly when the TsB exceeded 10 mg/dl. For neonates under 28 weeks of age, TcB measurement over sternum with the JH2-1A device had better correlation than TcB over forehead (Sajjadian 2012).

2) Race/Ethnicity

The findings on the effect of ethnicity or skin color was mixed across the included studies. Maisels 2004 showed a better correlation between TcB and TsB among white newborns with light or medium skin color compared to black newborns with dark skin color, with correlation coefficients, r or 0.95 and 0.82 respectively. Samiee-Zafarghandy and Wainer 2009 observed that TcB underestimated TsB in light and medium skin color and overestimated it in dark skin color with wide limits of agreement. In contrast, ethnicity did not significantly affect the correlation between TcB and TsB measurements (Bental 2009; Bhutani 2000; Campbell 2011; Karon 2008; Rodriguez-Capote 2009). Holland 2009 and Szabo 2004a found that TcB measurement on the forehead was affected by race with a 1.3 to 1.7 mg/dL negative bias for non-Caucasian compared with Caucasian neonates. However, ethnicity may not be a surrogate for skin color (Samiee-Zafarghandy 2014). Engle 2002 and Neocleous 2014; found a poor correlation among Hispanic and Greek newborns respectively. This could be because their study included a large proportion of newborns with TsB level > 13 mg/dl.

3) Gestational age

The effect of gestational age on the correlation between TcB and TsB was evaluated in a number of studies. The correlation among preterm infants ranged from 0.68 to 0.96 (De Luca 2007; Donzelli 2000; Sanpavat 2007; Knupfer 2001; Szabo 2004a; Rubaltelli 2001; Rylance 2014). In Knupfer 2001 Rubaltelli 2001; Rylance 2014 found that the TcB correlation in the preterm is less compared to term newborns, with more overestimation of TsB in preterm newborns. However, Hemmati 2013; Karolyi 2004; Karon 2008; Sanpavat 2004 did not find any difference with change in gestational age in preterm newborns. In these studies, the correlation between TcB and TsB was almost similar to that in term newborns. In Sanpavat 2004; Sanpavat 2005; Sanpavat 2007 it was also reported that TcB might tend to overestimate TsB in preterm infants and underestimate TsB in term infants. It is not

clear whether TcB over- or underestimates TsB in preterm infants as the included studies report different findings.

4) Postnatal age

Postnatal age is an important variable that seem to affect the correlation of TcB and TsB. There are also conflicting results from across the studies. Some studies report no difference in the correlation with advancing postnatal age while others report poorer correlation with advancing postnatal age ([Karolyi 2004](#); [Knupfer 2001](#); [Knudsen 1996](#); [Szabo 2004](#)). The effect of postnatal age could be the effect of maturation and thickening of the skin ([Knudsen 1996](#)). [Karon 2008](#) and [Samanta 2004](#) did not find any effect of postnatal age on the accuracy of TcB measurement. It is important to note that many of the reported studies did not report the postnatal age of the included participants.

5) Type of TcB device

Some of the included studies evaluated the use 2 of more TcB devices ([De Luca 2008](#); [Ho 2006](#); [Maisels 2004](#); [Neocleous 2014](#); [Raimondi 2012](#); [Rodriguez-Capote 2009](#); [Sanpavat 2005](#)). [De Luca 2008](#) compared the use of the Bilimed device and Bilicheck with TsB. The linear regression analysis showed a better correlation between BiliCheck and TsB ($r=0.75$) than between BiliMed and TsB ($r=0.45$). Similarly, in the study by [Raimondi 2012](#), correlation analysis using Pearson coefficients showed good results for Bilicheck ($r = 0.86$) and JM-103 ($r = 0.85$) but poor for BiliMed ($r = 0,70$) regardless of the skin pigmentation. In [Sanpavat 2005](#), the correlation coefficients between TcB measured with the JM 103 and Bilicheck device and TsB were similar ($r= 0.80$ and 0.82 , respectively). However, TcB using the JM 103 device had a tendency to underestimate TsB levels, and TcB using the Bilicheck device had a tendency to overestimate TsB levels ([Sanpavat 2005](#)). [Holland 2009](#) found that the performance of the BiliCheck is influenced by the site of the measurement. [Rodriguez-Capote 2009](#) showed that both the Bilicheck and the JM 103 device showed a good correlation with TsB (BiliCheck, $r=0.86$; JM-103, $r=0.85$), with both devices showing a tendency to underestimate the TsB. Similarly, [Maisels 2004](#) found no difference in the performance of the JM 103 and Bilicheck device (Bilicheck: $r = 0.973$, JM: $r = 0.971$). Also, the study by [Samanta 2004](#) showed no difference between Bilicheck and JM 103 ($r = 0.82$ and $r = 0.80$, respectively). In contrast, in a mostly Caucasian population of newborns, [Qualter 2011](#) found that Bilicheck was more accurate than JM 103 having a slightly stronger correlation with the TsB.

Discussion

We conducted a comprehensive systematic review to evaluate the use of TcB measurement compared to TsB measurement in newborns of various gestational and postnatal age and from different ethnic background and race. Findings from our review supports the AAP guideline that states TcB is a suitable alternative to measure TsB in newborns ([AAP 2004](#)). Unlike previous reviews, we did not restrict our review to newborns of any particular gestational age or newborns from any specific ethnic background or race ([Moey 2016](#); [Nagar 2016](#); [Nagar 2013](#)).

Summary of main results

Findings from this review demonstrate that the various TcB devices have been extensively evaluated in newborns from different ethnic groups and settings. The findings show acceptable correlation between TcB measured with these devices and TsB measured in the laboratory. The JM-101 (Draeger Medical Systems Inc, Telford, US), JM-102 (Draeger Medical Systems Inc, Telford, US), JM 103 (Draeger Medical Systems Inc, Telford, US) and JM 105 devices (Draeger Medical Systems Inc, Telford, US) and BiliChek (Bilicheck (SpectRx, Inc, Norcross [GA], US), all showed very good correlation coefficients when compared with the different methods for TsB measurement in the laboratory. However, the BiliMed in general performed quite poorly compared to other devices. TcB measurement also has a high sensitivity in detecting clinically significant hyperbilirubinemia in newborns and has been shown in the included studies to be an acceptable screening tool for hyperbilirubinemia in newborns.

There are conflicting results on the effects of various variable or factors on the accuracy of the TcB measurement. The findings are mixed on the impact of factors such as gestational age, postnatal age, race or ethnic background, site of TcB measurement (e.g. forehead vs sternum), type of TcB device and use of phototherapy. [Maisels 2006](#) concluded that both the BiliCheck and the JM-103 are less reliable in predicting TsB in more preterm infants, particularly those younger than 30 weeks' gestation. Some studies suggest that TcB measurement shows better correlation in Caucasian or light skinned newborns compared to black newborn while other have found no effect of race or ethnic group on TcB measurement. Also, many studies have shown a better correlation of TcB with TsB when the measurement is taken from the sternum compared to the forehead. The evidence from the included studies is also conflicting in terms of other factors (such as gestational age, skin colour and type of TcB device) that could affect the accuracy of TcB measurement.

Strengths and weaknesses of the review

We conducted a comprehensive search of the literature to identify all potentially eligible studies. We included studies of newborns from different ethnic background and race, and also newborns of various gestational age and race. We narrowed our inclusion criteria to exclude studies published in languages other than English and studies that did not report any other measure of accuracy apart from the correlation coefficient. Many of the included studies did not report blinding of the observers. However, we do not think this is likely to affect the outcome both TcB and TsB are objective measurement and very unlikely to be influenced by lack of blinding.

Applicability of findings to the review question

Authors' conclusions

Implications for practice

Guidelines published by both the AAP and the Canadian Pediatric Society suggest that the TcB value may be used as a substitute for TsB in evaluating the risk of significant neonatal hyperbilirubinemia in the healthy newborn ([AAP 2004](#); [CPS 2007](#)). Currently various TcB devices are being used in many countries and settings. TcB method of measuring bilirubin has several advantages. It is a non-invasive and non-painful way to measure bilirubin compared to TsB which requires blood draw through heel sticks or venipuncture. TcB results are obtained almost instantaneously. Though previous guidelines ([Kazmierczak 2006](#)) suggested that there insufficient evidence to recommend one device over another, more recent studies have shown advantage of some devices and better correlation of some of the TcB devices compared to others. For example, TcB measured with the Bilicheck and JM 103 device have been shown in more recent studies to have better correlation with TsB than with TcB measured with the Bilimed. The Bilimed device has been shown to have poor correlation with TsB ([De Luca 2008](#) and [Raimondi 2012](#)).

Implications for research

Several studies of the JM device suggest that measurement taken from the sternum correlates better with TsB compared to measurement taken from the forehead ([Fok 1986](#); [Holland 2009](#); [Maisels 2004](#); [Yamauchi 1991](#)). However, the manufacturer of the device suggests that both sternum and forehead can be used. Further studies may be needed to better understand the best site for TcB measurement and the reason for the difference if any in the measurement take from the forehead and sternum. Also, further studies are needed to ascertain the impact of phototherapy on the accuracy of TcB measurement. The studies need to evaluate the optimal timing after phototherapy when the TcB reading can be compared to or becomes similar to TcB obtained in newborns without any prior exposure to phototherapy.

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Contributions of authors

Charles Okwundu conceptualized and wrote the draft protocol. Olalekan Uthman, Gautham Suresh, Johan Smith, Charles Wiysonge and Vinod Bhutani contributed to various sections of the protocol.

Declarations of interest

None known

Differences between protocol and review

We intended to include only studies that had sufficient information for us to extract data for 2x2 tables to enable us calculate sensitivities and specificities. However, in order not to lose valuable information we also included studies that reported on any other measure of accuracy in addition to the correlation coefficient. There was no language restriction in the search for studies. However, we excluded studies published in languages other than English for which we could not get a translation.

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Classification pending references

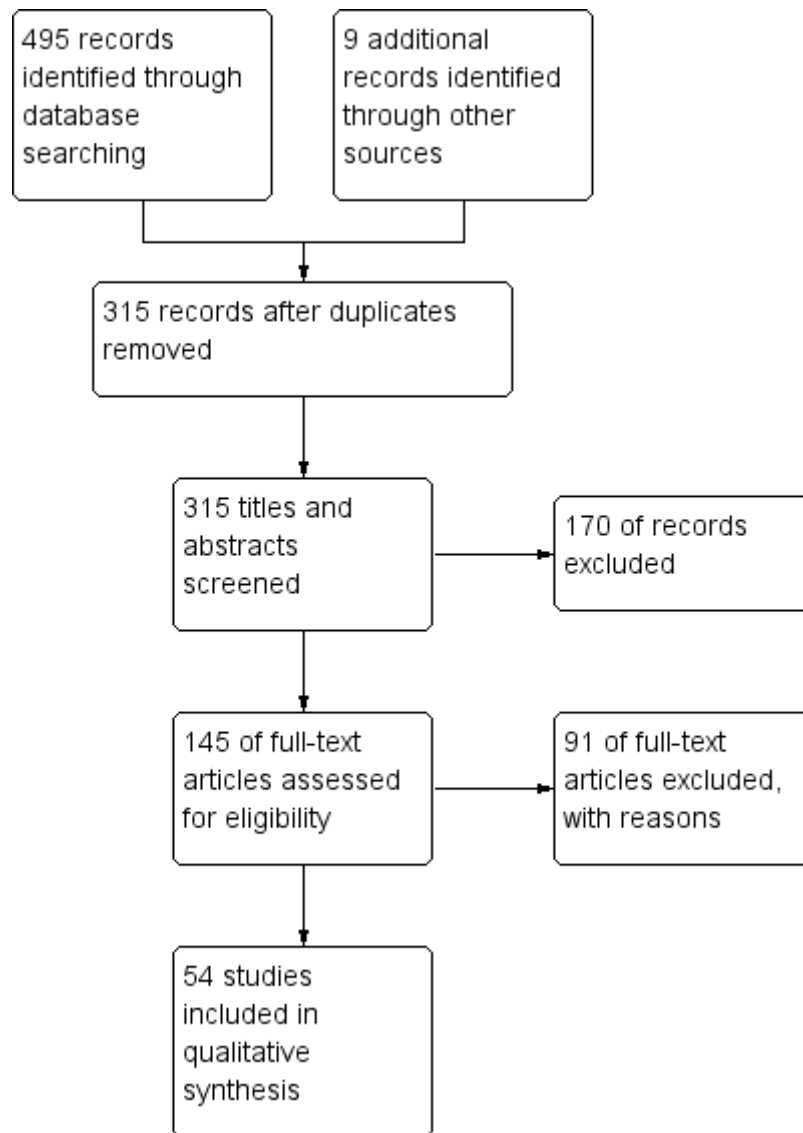


Figure 1: Study flow diagram.

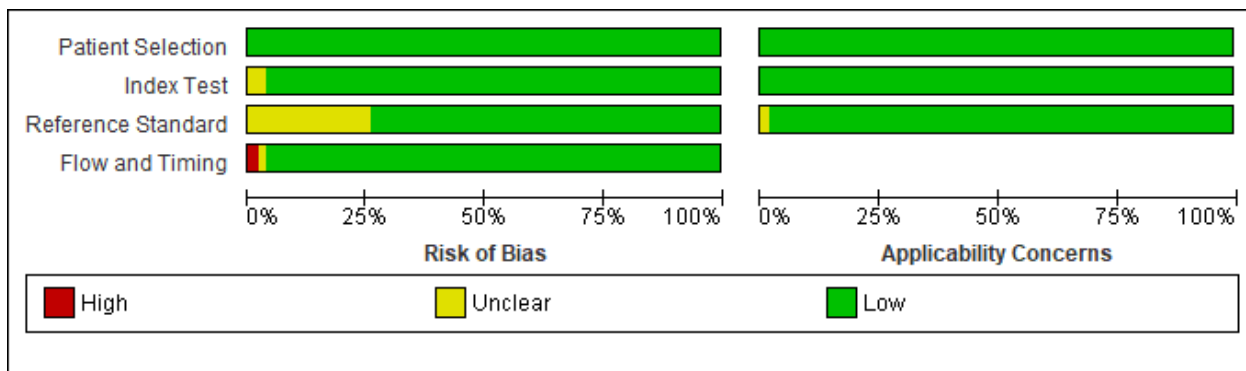


Figure 2: Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies

	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Ahmed 2010	Low	Low	Low	Low	Low	Low	Low
Akahira-Azuma 2013	Low	Low	Low	High	Low	Low	Low
Bental 2009	Low	Low	Low	Low	Low	Low	Low
Bertini 2008	Low	Low	Low	Low	Low	Low	Low
Bhutani 2000	Low	Low	Low	Low	Low	Low	Low
Bhutta 1991	Low	Low	Low	Low	Low	Low	Low
Bilgen 1998	Low	Low	Low	Low	Low	Low	Low
Boo 2007	Low	Low	Low	Low	Low	Low	Low
Campbell 2011	Low	Low	Low	Low	Low	Low	Low
Chimhini 2018	Unclear	Low	Low	Low	Low	Low	Low
Christo 1988	Low	Low	Low	Low	Low	Low	Low
De Luca 2007	Low	Low	Low	Low	Low	Low	Low
De Luca 2008	Low	Low	Low	Low	Low	Low	Low
Donzelli 2000	Low	Low	Low	Low	Low	Low	Low
Engle 2002	Low	Low	Low	Low	Low	Low	Low
Engle 2005	Low	Low	Low	Low	Low	Low	Low
Fok 1986	Low	Low	Low	Low	Low	Low	Low
Harish 1998	Low	Low	Low	Low	Low	Low	Low
Hemmati 2013	Low	Low	Low	Low	Low	Low	Low
Ho 2006	Low	Low	Low	Low	Low	Low	Low
Holland 2009	Low	Low	Low	Low	Low	Low	Low
Karolyi 2004	Low	Low	Low	Low	Low	Low	Low
Karon 2008	Low	Low	Low	Low	Low	Low	Low
Karrar 1989	Low	Low	Low	Low	Low	Low	Low
Kaynak-Turkmen 2011	Low	Low	Low	Low	Low	Low	Low
Kitsomart 2013	Low	Low	Low	Low	Low	Low	Low
Knupfer 2001	Low	Low	Low	Low	Low	Low	Low
Kolman 2007	Low	Low	Low	Low	Low	Low	Low
Laeq 1993	Low	Low	Low	Low	Low	Low	Low
Lam 2008	Low	Low	Low	Low	Low	Low	Low
Leite 2007	Low	Low	Low	Low	Low	Low	Low
Lin 1993	Low	Unclear	Unclear	Unclear	Low	Low	Low
Maisels 1982	Low	Low	Low	Low	Low	Low	Low
Maisels 2004	Low	Low	Low	Low	Low	Low	Low
Maisels 2011	Low	Low	Low	Low	Low	Low	Low
Neocleous 2014	Low	Low	Unclear	Low	Low	Low	Low
Panburana 2010	Low	Low	Unclear	Low	Low	Low	Low
Quatter 2011	Low	Low	Unclear	Low	Low	Low	Low
Raimondi 2012	Low	Low	Unclear	Low	Low	Low	Low
Rodriguez-Capote 2009	Low	Unclear	Low	Low	Low	Low	Low
Rubattelli 2001	Low	Low	Low	Low	Low	Low	Low
Rylance 2014	Low	Low	Unclear	Low	Low	Low	Low
Sajjadian 2012	Low	Low	Low	Low	Low	Low	Unclear
Samanta 2004	Low	Low	Low	Low	Low	Low	Low
Samiee-Zafarghandy 2014	Low	Low	Unclear	Low	Low	Low	Low
Sanpavat 2004	Low	Low	Unclear	Low	Low	Low	Low
Sanpavat 2005	Low	Low	Unclear	Low	Low	Low	Low
Sanpavat 2007	Low	Low	Unclear	Low	Low	Low	Low
Schmidt 2009	Low	Low	Low	Low	Low	Low	Low
Schumacher 1985	Low	Low	Unclear	Low	Low	Low	Low
Szabo 2004a	Low	Low	Unclear	Low	Low	Low	Low
Taha 1984	Low	Low	Unclear	Low	Low	Low	Low
Wong 2002	Low	Low	Unclear	Low	Low	Low	Low
Yaser 2014	Low	Low	Low	Low	Low	Low	Low

● High ● Unclear ● Low

Figure 3: Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Bhutta 1991	35	28	5	32	0.88 [0.73, 0.96]	0.53 [0.40, 0.66]		
Karrar 1989	36	11	13	95	0.73 [0.59, 0.85]	0.90 [0.82, 0.95]		
Maisels 1982	5	5	0	126	1.00 [0.48, 1.00]	0.96 [0.91, 0.99]		
Schumacher 1985	16	20	1	69	0.94 [0.71, 1.00]	0.78 [0.67, 0.86]		
Taha 1984	11	8	5	104	0.69 [0.41, 0.89]	0.93 [0.86, 0.97]		

Figure 4: (Analysis 1)

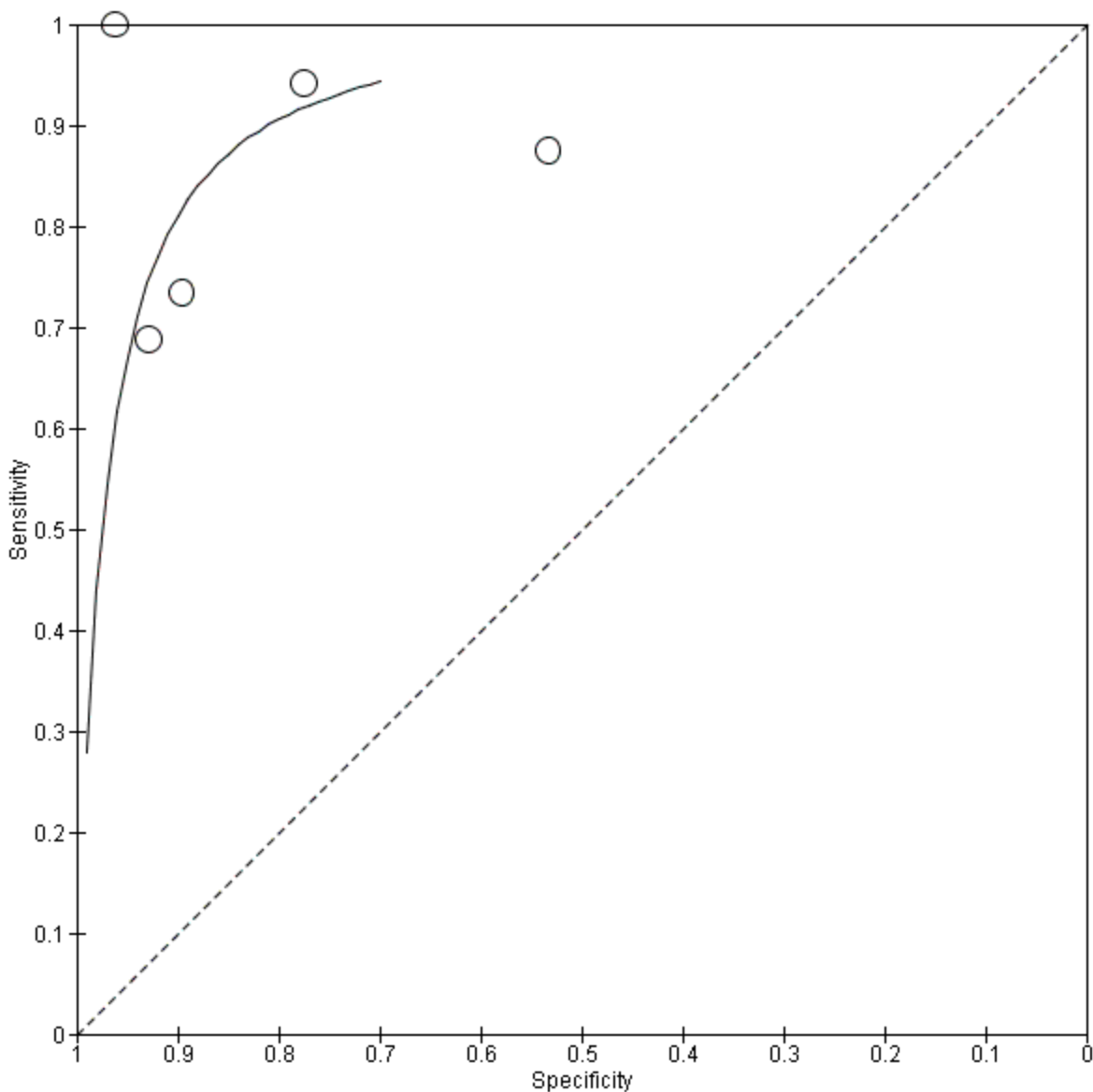


Figure 5: Summary ROC Plot of 1 TcB (JM 101)

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Chapter 6

Accuracy of the JM-105 transcutaneous bilirubin measurement in a population of South African newborns

Manuscript submitted to BMC Pediatrics

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Accuracy of the JM-105 transcutaneous bilirubin measurement in a population of South African newborns

Manuscript submitted to BMC Pediatrics

Accuracy of the JM-105 transcutaneous bilirubin measurement in a population of South African newborns: a cross-sectional study

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Short title: Transcutaneous bilirubin screening in African newborns

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Conflict of Interest: None of the other authors have any conflict of interest to disclose.

Abbreviations: TcB (transcutaneous bilirubin), TsB (Total serum bilirubin), RR (risk ratio), CI (confidence interval), NNT (number needed to treat), Rh-D (rhesus D)

What's known on This Subject: TcB measurement has been shown to correlate with TsB in preterm and newborns in many different settings.

What This Study Adds: Our study provides evidence from indigenous African newborns with varying skin pigmentation on the accuracy of TcB measurement using the JM 105 device in a population of South African late preterm and term newborns. To our knowledge at the time of this study there was no published studies that assessed the performance of the JM 105 transcutaneous device in newborns.

Keywords: Jaundice, Hyperbilirubinemia, Transcutaneous bilirubin, Newborn

Abstract

Background:

Transcutaneous bilirubin (TcB) measurement in newborns has been studied extensively in many countries and settings. However, there are no reported studies on TcB measurements among late preterm and term South African newborns. Also, there are currently no published studies that evaluated the new Draeger JM 105 transcutaneous device in newborns.

In this study we compared the performance of the JM 105 device for measurement of TcB compared with total serum bilirubin (TsB) measurements in South African late preterm and term newborns.

Methods:

TcB measurements were obtained using the JM 105 TcB device from the sternum at postnatal age 6 to 72 hours in a population of late preterm and term South African newborns. TcB measurements were performed within 15 minutes of obtaining blood sample for TsB measurement. The Pearson correlation coefficient (r) and the Bland-Altman plot were used to estimate the relationship between the TcB and TsB measurement.

Results:

An indigenous population of 132 African newborns were enrolled. The gestational age ranged from 35 to 42 weeks; birth weight from 2010 to 5030 grams; and postnatal age 11 to 72 hours of life. The TsB ranged from 11 to 311 $\mu\text{mol/l}$ while the TcB ranged from 9 to 308 $\mu\text{mol/l}$. Overall, the correlation analysis using Pearson coefficient, r , showed a good correlation with $r = 0.902$ (95% CI 0.83 to 0.98) between TcB and TsB. The Bland Altman analysis showed that the TsB can be overestimated by TcB measured with the JM 105 device with a bias of up to 16.7 $\mu\text{mol/L}$ with 95% limits of agreement of $(1.96 \times 23.5 \mu\text{mol/l} = 46.1)$, lower limit = -29.4; upper limit = 62.8).

Conclusions:

TcB measurement using the JM 105 transcutaneous device showed a good correlation with TsB measurement in an indigenous population of South African late preterm and term newborns and can be used as a reliable screening tool to identify hyperbilirubinemia.

Keywords

Hyperbilirubinemia, transcutaneous bilirubin, serum bilirubin, newborn

Background

Jaundice is a very common condition in the newborn during the first week of life with up to 60 percent of term newborns developing jaundice during the first week of life [1,2]. Jaundice is the discoloration of skin and sclera color to yellowish in a newborn by bilirubin [3].

Hyperbilirubinemia can be defined as total serum bilirubin (TsB) above the 95th percentile for age during the first week of life [4,5]. The types or causes of hyperbilirubinemia in the newborn can be classified into physiological jaundice, pathological jaundice, breastfeeding or breast milk jaundice [6]. In many settings, with the current practice of early discharge of newborns, usually within 2 days for normal vaginal deliveries and within 3 days for caesarean section deliveries, hyperbilirubinemia is the most common reason for readmission in the first week of life.

Assessment of hyperbilirubinemia can be done by visual inspection, TsB measurement, or by transcutaneous bilirubin (TcB) measurement. TsB measurement in the laboratory requires blood draw which is painful to the newborn and results are not available immediately. TcB measurement is noninvasive, does not require blood draw and provides immediate result. The American Academy of Pediatrics (AAP) recommends the use of either a TsB or a TcB measurement to screen and identify newborns at risk of severe hyperbilirubinemia [7]. Visual assessment for hyperbilirubinemia has been shown to be inaccurate and not recommended [8,9].

TcB measurement was introduced more than 30 years ago [10]. Since its first introduction, various transcutaneous point of care devices have been developed that can give instantaneous bilirubin measurements. The accuracy of various TcB devices has been extensively studied in many countries and settings. The accuracy of the JM 103 (Draeger Medical Systems Inc, Telford, US) device was studied in a population of preterm infants in South Africa [11]. However, there are no published studies on the reliability or accuracy of TcB measurement in late preterm and term South African newborns with varying skin pigmentation. Furthermore, there are limited studies of the new JM-105 (Draeger Medical Systems Inc, Telford, US) device. The Draeger JM-105 jaundice meter is portable, handheld, non-invasive TcB measuring device, which measures the yellowness of subcutaneous tissue by using two optical paths to measure the optical density difference at two wavelengths in the newborn and provides a visual digital measurement. The JM-105 is a modification of the JM-103 jaundice meter. The basic functionality, including the measuring probe, hardware, and software used to process the measurements, are identical to the JM-103 [12].

In this study, we assessed the correlation of TcB measurement using the JM 105 TcB device with TsB measurement in a population of South African late preterm (≥ 35 week gestational age) and term newborns.

Methods:

Study setting and participant selection

This study was carried out in the postnatal ward of Tygerberg Hospital, a teaching hospital in Cape Town, South Africa between August 2015 and October 2016. Tygerberg Hospital is a tertiary hospital with about 7500 deliveries per annum. The study was approved by the Health Research Ethics Committee of Stellenbosch University and written informed consent was obtained from all parents before participation. During a clinical trial on TcB screening for hyperbilirubinemia, we obtained TsB samples on all infants whose TcB measurement was $>95^{\text{th}}$ centile for age on the Bhutani's nomogram [13–15]. We also simultaneously obtained TcB readings on all infants who required blood draw for TsB measurement based on clinical evidence of jaundice. We included newborn infants with gestational age ≥ 35 weeks and birth weight of 1800g with postnatal age 6 to 72 hours of life. Infants with previous phototherapy use or who were currently undergoing phototherapy were excluded.

For each infant, the following demographic information were collected from the medical records: gestational age, birth weight, postnatal age at time of assessment, sex, and race.

TcB measurement

The TcB measurements were done with the Draeger JM 105 TcB meter by the principal investigator who was trained in the use of the device. A single device was used during the study and the device was used according to the manufacturer's instructions. The device was calibrated each day before use and was set to take the average of 3 different readings. The measurements were taken within 15 minutes of blood sampling for TsB. The TcB measurements were taken by pressing the device probe against the infants' skin on the mid sternum. The bilirubinometer was cleaned with an alcohol wipe between patients.

TsB measurement

Venous blood samples were used to measure the TsB levels by means of Diazo method at the Tygerberg Hospital NHLS laboratory. After blood samples were taken, the samples were protected from light exposure by sending them through to the Hospital laboratory through the pneumatic tube system. The laboratory technicians were not aware of the TcB results.

Data collection and analysis

The data was collected on a paper data collection form and registered in a Database using Microsoft Excel 2016 and analysed using STATA 12 statistical software. The correlation between TcB and TsB was assessed using the Pearson correlation coefficient. The Bland-Altman analysis which plots the differences between two assays against the mean of the two compared methods was used. The bias was calculated as a mean of the differences between the paired TsB and TcB values [16]. A p-value of < 0.05 was considered to be statistically significant.

Results:

A total of 132 newborns were enrolled from whom 132 pairs of TcB and TsB measurements were obtained. The baseline characteristics of the newborns are summarized in Table 1. TsB was requested on the infants for the following reasons; 82 (62%) infants were classified as high-risk zone of the Bhutani nomogram based on TcB screening; 46 (35%) infants had clinical evidence of jaundice by visual inspection; 4 (0.03%) infants had mothers who were Rh negative.

The TsB levels ranged from 11 to 311 $\mu\text{mol/l}$ (mean 176 $\mu\text{mol/l}$) while the TcB readings ranged from 9 to 308 $\mu\text{mol/l}$ (193 $\mu\text{mol/l}$). The linear regression correlations between TcB and TsB measurements are shown in Figure 1. The correlation coefficient between TcB and TsB in all 132 participants was; $r=0.907$ 95% CI 0.83 to 0.98, $p< 0.001$. The correlation between TcB and TsB varied between the two major race groups (Blacks and mixed race) in the study sample. The correlation coefficient among the blacks was 0.94 compared to 0.92 among the mixed race. However, this difference between the two groups was not statistically significant. A Bland–Altman plot of all 132 comparisons is shown in Figure 2. The average of TcB measured with the JM 105 device and TsB values is shown on the x-axis, and the difference is displayed on the y-axis. The analysis showed that the agreement between TcB and the TsB can be overestimated with a bias of up to 16.7 $\mu\text{mol/L}$ with 95% limits of agreement of (1.96 x 23.5 $\mu\text{mol/l}=46.1$), lower limit = -29.4; upper limit = 62.8). The TcB measured by the JM 105 device in our study showed a tendency to overestimate the TsB. The tendency for TcB to overestimate TsB was uniform throughout the range of bilirubin values studied. A linear regression analysis showed that bias was uniform and did not show any particular pattern with increasing or decreasing levels of TsB.

Table 1: Demographics of the study population (n=132)

Gestational age, weeks (mean \pm SD)	38.4 \pm 1.57
Birth weight, g (mean \pm SD)	3152 \pm 588
Male sex	79 (60%)
Race	
Blacks	69 (52%)
Mixed race	58 (44%)
Indians	1 (1%)
White	4 (3%)
Postnatal age at time of assessment, hours (mean \pm SD).	37.7 \pm 17.6

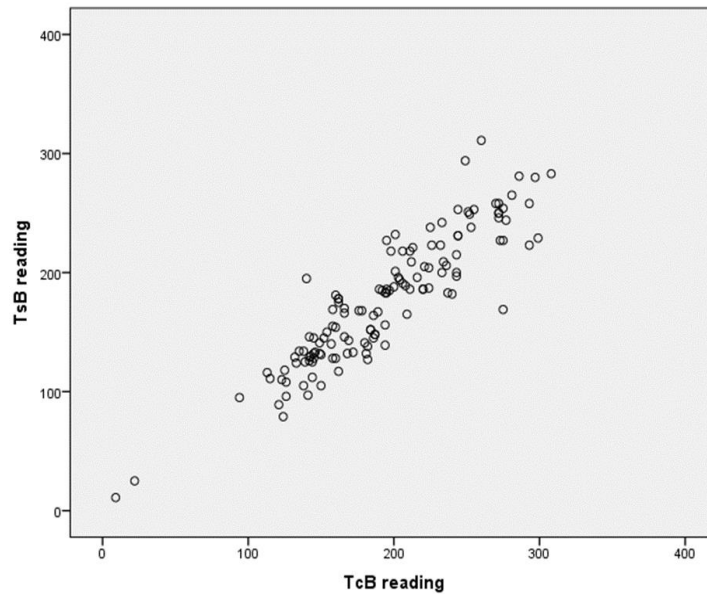


Fig. 1. Graphical depiction of TsB versus TcB measurements (taken with the Draeger JM 105 device). TsB and TcB values presented in $\mu\text{mol/L}$.

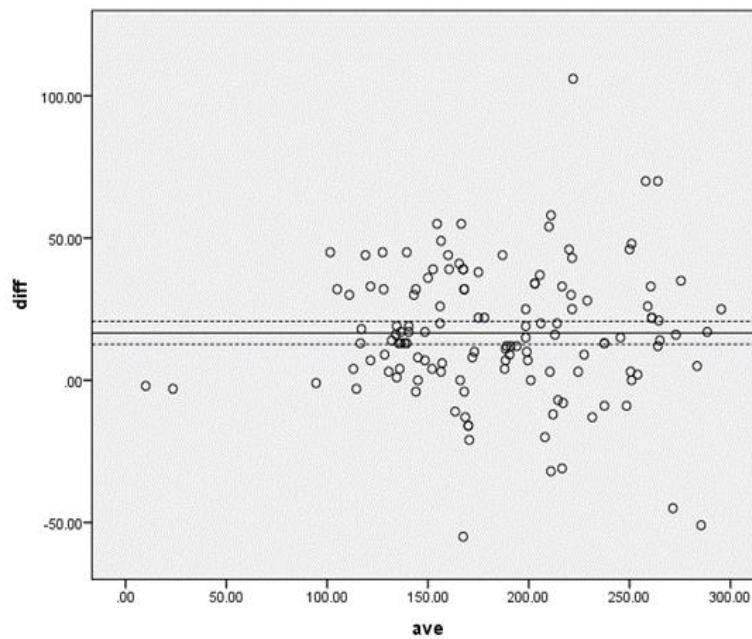


Fig. 2 Bland–Altman plot depicting difference between TcB and TsB measured at sternum, on Y-axis against mean of TcB and TsB on X-axis.

Discussion

In this study, we evaluated the use of the JM 105 device in an indigenous population of African newborns. All the TcB measurements in our study was taken from the sternum. A previous study in South Africa evaluated the use of the JM 103 device in preterm newborns less than 35-week gestational age [11]. At the time of our study in 2015, there was no known published study that evaluated the use of the JM 105 jaundice device. This is the first study to our knowledge to assess the correlation between TcB and TsB in South African late preterm and term newborns. Our study demonstrated a good correlation between TcB measurement taken from the sternum and TsB measured in the laboratory. Similarly, other studies among indigenous African newborns showed good correlation between TcB and TsB measurement with correlation coefficient ranging from 0.77 to 0.90 [17–19]. In our study, TcB had tendency to overestimate TsB in almost all the measurements. Again, this finding is similar to that from other studies of indigenous African newborns in Malawi and Nigeria that showed that TcB values overestimated TsB for both premature and term infants [17,20].

A number of studies have evaluated the correlation and accuracy between various TcB devices and TsB in late preterm and term newborns from diverse populations and settings [21–31]. To our knowledge, our study is the first to address the accuracy of the JM-105 device during the late first week of life in a South African population of late preterm and term newborns.

The study by Yamana et al published in 2017 evaluated the use of JM 105 TcB device among Japanese newborns with measurements taken from the scaphoid fossa [32].

Findings from other studies from different race groups have been mixed. Some studies have also reported a tendency for TcB to overestimate TsB [21,22,33–36]. In contrast, other studies have reported a tendency for TcB to underestimate TsB [23,37–40]. In our study, the Bland Altman analysis showed a uniform bias for all the range of TsB measurements. Similarly, Maisels et al did not find any significant difference between the deviations from the regression line when comparing lower and higher concentrations of TsB concentration [41].

Many factor can affect the accuracy of the TcB meter. These include race, ethnicity or skin colour. There has been mixed findings from other studies on the impact of race or skin colour on the accuracy of TcB compared with TsB measurement. Maisel et al showed a better correlation between TcB and TsB among white newborns with light or medium skin colour compared to black newborns with dark skin colour, with correlation coefficients, r or 0.95 and 0.82 [42]. Also, other studies among Hispanic newborns found a poor correlation among Hispanic and Greek newborns respectively [29,43]. In contrast, race or skin did not

significantly affect the correlation between TcB and TsB measurements in some other reports [14,39,40,44,45]. In our study, the correlation between TcB and TsB was not significantly different in dark skinned newborns compared with that in the mixed-race population.

Our study has a few limitations. We did not compare the measurements of TcB taken from different sites of the body. TcB measurements were obtained by only one person, the principal investigator after training. In clinical practice the device will be used by different persons with varying level of training, this could affect the performance of the device. However, the device is very user-friendly and requires minimal training to use.

This study provided evidence on the validity of the Draeger JM 105 transcutaneous bilirubinometer in a population of indigenous African newborns in South Africa. We have evidence of good correlation and reliability between TcB and TsB measurement among late preterm and term South African newborns. In our setting, TcB measurement may be considered as a screening tool for babies who require blood sampling for TsB and possible decision to commence phototherapy. Further studies are needed to evaluate the effect of TcB measurement among South African infants undergoing phototherapy and evaluate if TcB measurement can be used to decide when to stop phototherapy. The number of blood samples obtained for TsB could be reduced with the use of TcB measurement as a screening tool for newborns who might need phototherapy for hyperbilirubinemia.

Abbreviations

AAP: American Academy of Pediatrics; CI: Confidence Interval; CPS: Canadian Pediatric Society; HPLC: High Performance Liquid Chromatography; TcB: Transcutaneous Bilirubin; TsB: Total Serum Bilirubin.

Acknowledgements:

Draeger South Africa donated the TcB device used in the study.

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Availability of data and materials

The datasets used and/or analyzed during the study are available upon reasonable request.

Contribution of authors

Charles Okwundu conceptualized and designed the study. Vinod Bhutani, Johan Smith and Charles Wiysonge and provided input into the methods and content knowledge.

Tonya Esterhuizen conducted the statistical analysis.

Ethics approval and consent to participate

Ethical approval was obtained from the Stellenbosch University Health Research Ethics Committee prior to commencement of the study (N14/03/025). Written informed consent was obtained from the mothers for all participants before enrollment into the study.

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Chapter 7

Conclusion

Hyperbilirubinemia is a common problem in the newborn period with up to 60% of term newborns and 80% of preterm newborns having some degree of hyperbilirubinemia. Severe hyperbilirubinemia with TsB exceeding 20mg/dl or extreme hyperbilirubinemia with bilirubin level > 25mg/dl puts the newborn at risk of adverse neurologic consequences such as kernicterus. Kernicterus is very rare in developed countries with adequate resources and health care infrastructure. However, in many resource constrained settings, kernicterus is still an important cause of morbidity and mortality in the newborn.

In this project we have sought to provide evidence on the usefulness of transcutaneous bilirubin (TcB) screening in an African population of newborns.

We aimed to provide answers the following questions:

- a. What is the evidence for the use of TcB screening for hyperbilirubinemia in newborns before discharge?
- b. What is the effect of TcB screening on readmissions for hyperbilirubinemia and on the incidence of severe hyperbilirubinemia in an indigenous population of African newborns?
- c. Can TcB measurement be used to reliably estimate TsB measurement in newborns from different populations and settings and what factors effect the accuracy of TcB measurement?
- d. What is the accuracy of TcB measurement using the JM 105 device compared to TsB measurement in an indigenous population of African newborns?

These questions have been addressed by a mix of different study designs. We started by reviewing the currently available evidence on the of TcB screening on readmissions for hyperbilirubinemia and incidence of severe hyperbilirubinemia in newborns. We conducted a comprehensive search of the literature to identify all relevant studies that evaluated the use of TcB screening for the aforementioned outcomes. We identified 5 observational studies conducted in the United States and Canada. We did not identify any randomized controlled trial (RCT) that evaluated the effect of TcB screening on readmissions for jaundice and incidence of severe hyperbilirubinemia. Findings from the observational studies suggest that TcB screening for hyperbilirubinemia in newborns is associated with reduction in hyperbilirubinemia related readmissions and incidence of severe hyperbilirubinemia. Currently, universal TcB or TsB screening for hyperbilirubinemia has been implemented in the United States and Canada following recommendations from the American Academy of Pediatrics and the Canadian Pediatric Society. However, universal screening for hyperbilirubinemia is not standard of care in many other countries, including South Africa. In these

settings, TcB or TsB measurements are only obtained for diagnosis of hyperbilirubinemia in newborns when jaundice is present.

The answer to the question on the impact of TcB screening for hyperbilirubinemia in newborns can best be provided by a well-designed RCT. However, our systematic review of TcB screening did not identify any RCT. Therefore, we designed and implemented an RCT to assess the impact on readmission and incidence of severe hyperbilirubinemia in a population of indigenous African. To our knowledge, this is the first RCT that has evaluated the use of TcB screening for hyperbilirubinemia in newborns. We were able to demonstrate in this RCT that TcB screening in South African newborn infants led to a reduction in the incidence of hyperbilirubinemia related readmissions and the incidence of severe hyperbilirubinemia. Our findings further confirmed the findings from previous observational studies conducted in the United States and Canada. Our trial on TcB screening for hyperbilirubinemia and previous observational studies were not able to provide evidence on the impact of TcB screening on other clinically relevant outcomes such as kernicterus. The impact of universal bilirubin screening of newborns on kernicterus has not been demonstrated in any study. This is because of the rare incidence of kernicterus. Any randomized trial to evaluating this question will require recruitment of millions of newborns to be able to detect a difference. Therefore, a clinical trial to answer this question might never be feasible, especially in developed countries where universal bilirubin screening in all newborn infants before hospital discharge is already standard of care. We have contributed to the currently available body of evidence by providing the first evidence from a RCT that TcB screening in newborns can lead to a reduction in jaundice related readmissions and also a reduction in the incidence of severe hyperbilirubinemia in newborns. Furthermore, our study is the first to evaluate the impact of TcB screening in a population of indigenous African newborns with varying skin pigmentation.

In this project we also conducted a Cochrane systematic review on the currently available evidence on the accuracy of TcB measurement compared to TsB in newborns. Our search of the literature identified numerous studies of TcB accuracy compared with TsB. These studies were conducted in many different countries and settings and included newborns of various gestational age. The included studies evaluated the use of various TcB devices, including the Bilicheck (SpectRx, Inc, Norcross [GA], US), JM 103 (Draeger Medical Systems Inc, Telford, US) and JM 105 devices (Draeger Medical Systems Inc, Telford, US).

Finding from the review suggests that TcB devices can be used to reliably estimate TsB. However, many studies report the tendency of TcB to overestimate TsB. Also, many factors or variables have been shown to affect the accuracy of TcB measurements. These factors include; gestational age, postnatal age, race, skin colour or ethnicity, type of TcB device, previous exposure to phototherapy

and site of TcB measurement (e.g. forehead vs. sternum). The findings from the included studies on how these factors could affect TcB measurement are not consistent.

Our systematic review of the literature did not find any studies evaluating the accuracy of TcB measurement in late preterm or term South African newborns. Also, there are very limited number of studies that evaluated the new Draeger JM 105 TcB device. Therefore, we conducted a cross-sectional study to evaluate the usefulness of the Draeger JM 105 device to estimate TcB compared to TsB measured in the laboratory. We recruited a total of 132 late preterm and term newborns in the study. Findings from the study showed a good correlation between TcB measured with the JM 105 device and TsB measured in the laboratory, with correlation coefficient, r , of up to 0.97. Suggesting that TcB measurement can reliably estimate TsB in an indigenous population of South African newborns.

In summary, findings from the studies presented in this dissertation suggest that:

- TcB measurement can be used to reliably estimate TsB in indigenous African newborns.
- TcB screening of newborns for hyperbilirubinemia before hospital discharge can lead to a reduction hyperbilirubinemia related readmissions and also reduction in the incidence of severe hyperbilirubinemia.
- TcB measurement can be affected by factors such as gestational age, postnatal age, skin colour/ethnicity and prior use of phototherapy.

Based on these findings, we make the following recommendations:

1. We recommend a policy and practice change to start implementation of routine screening of newborns for hyperbilirubinemia before hospital discharge in South Africa and other African countries. As recommended by the AAP, hyperbilirubinemia screening should be with the use of either TcB or TsB measurement before hospital discharge of apparently healthy newborns.
2. We recommend implementation studies to identify potential barriers to the implementation of TcB or TsB screening in newborns especially in resource-limited settings.
3. Further studies are needed to determine the optimal timing for TcB screening for hyperbilirubinemia in newborns before discharge, especially in settings where newborns are discharged home as early as 6 hours after delivery.
4. There is a need for studies to evaluate the cost effectiveness of the various options for screening for hyperbilirubinemia in newborns (e.g. cost effectiveness of TcB vs TsB screening).
5. We recommend further studies to evaluate the best methods for screening of hyperbilirubinemia in preterm newborns who are < 35 weeks gestation and require longer stay in the hospital.

6. Further studies are needed to further evaluate the impact of various factors such as gestational age, postnatal age, skin colour/ethnicity and prior phototherapy use.
7. TcB device manufacturers now have the moral responsibility to make over-priced transcutaneous devices safe, affordable and accessible. If not, the high cost of the current TcB devices could be a barrier to implementation of universal TcB screening in many low- and middle-income countries.

Appendices

Search strategy for TcB screening systematic review

PubMed: ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh]))

Embase: (infant, newborn or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW or Newborn or infan* or neonat*) AND (human not animal) AND (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial)

CINAHL: (infant, newborn OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or Newborn or infan* or neonat*) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)

Cochrane Library: (infant or newborn or neonate or neonatal or premature or preterm or very low birth weight or low birth weight or VLBW or LBW)

Risk of bias tool

We used the standard methods of Cochrane and Cochrane Neonatal to assess the methodological quality (to meet the validity criteria) of the trials. For each trial, we sought information regarding the method of randomization, and the blinding and reporting of all outcomes of all the infants enrolled in the trial. We assessed each criterion as low, high, or unclear risk. Two review authors separately assessed each study. We resolved any disagreement by discussion. We added this information to the table Characteristics of included studies. We evaluated the following issues and entered the findings into the risk of bias table:

1. Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?

For each included study, we categorized the method used to generate the allocation sequence as:

- a. Low risk (any truly random process e.g. random number table; computer random number generator);
- b. High risk (any non-random process e.g. odd or even date of birth; hospital or clinic record number);
- c. Unclear risk.

2. Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?

For each included study, we categorized the method used to conceal the allocation sequence as:

- a. Low risk (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes);
- b. High risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- c. Unclear risk

3. Blinding of participants and personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?

For each included study, we categorized the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding was assessed separately for different outcomes or class of outcomes. We categorized the methods as:

- a. Low risk, high risk or unclear risk for participants;
- b. Low risk, high risk or unclear risk for personnel;

4. Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?

For each included study, we categorized the methods used to blind outcome assessment. Blinding was assessed separately for different outcomes or class of outcomes. We categorized the methods as:

a. Low risk for outcome assessors.

b. High risk for outcome assessors.

c. Unclear risk for outcome assessors.

5. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?

For each included study and for each outcome, we described the completeness of data including attrition and exclusions from the analysis. We noted whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomized participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we re-included missing data in the analyses. We categorized the methods as:

a. Low risk (< 20% missing data);

b. High risk (\geq 20% missing data);

c. Unclear risk.

6. Selective reporting bias. Are reports of the study free of suggestion of selective outcome reporting?

For each included study, we described how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

a. Low risk (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);

b. High risk (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified outcomes of interest and are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);

c. Unclear risk.

7. Other sources of bias. Was the study apparently free of other problems that could put it at a high risk of bias?

For each included study, we described any important concerns we had about other possible sources of bias (for example, whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We assessed whether each study was free of other problems that could put it at risk of bias as:

- a. Low risk;
- b. High risk;
- c. Unclear risk

If needed, we explored the impact of the level of bias through undertaking sensitivity analyses.

Search strategy for TcB accuracy review.

PubMed:

((transcutaneous n2 bilirubin) OR TcB OR bilicheck OR bilichek OR JM-103 OR JM-105 OR bilirubinomet*) AND (((blood* or serum) n1 bilirubin) OR TsB OR spectrophotomet*) AND ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) NOT (animals [mh] NOT humans [mh]))

CINAHL:

((transcutaneous N2 bilirubin) OR TcB OR bilicheck OR bilichek OR JM-103 OR JM-105 OR bilirubinomet*) AND (((blood* or serum) N bilirubin) OR TsB OR spectrophotomet*) AND (infant, newborn OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or Newborn or infan* or neonat*)

Embase:

(infant, newborn or neonat* or premature or very low birth weight or low birth weight or VLBW or LBW or infan*) AND ((transcutaneous adj2 bilirubin) OR TcB OR bilicheck OR bilichek OR JM-103 OR JM-105 OR bilirubinomet*) AND (((blood* or serum) adj bilirubin) OR TsB OR spectrophotomet*).mp AND (human not animal)

CRS:

((transcutaneous NEAR2 bilirubin) OR TcB OR bilicheck OR bilichek OR JM-103 OR JM-105 OR bilirubinomet*) AND (((blood* or serum) NEXT bilirubin) OR TsB OR spectrophotomet*) AND (infant* or newborn or neonat* or premature or preterm or very low birth weight or low birth weight or VLBW or LBW)

QUADAS-2 tool

QUADAS-2 tool: Risk of bias and applicability judgements

Domain 1: Patient selection	
A. Risk of bias	
1. Was a consecutive or random sample of patients enrolled?	<p>Yes/No/Unclear</p> <p>"Yes" if it is clearly stated in the paper that a consecutive or a random sample of patients was enrolled.</p> <p>"No" if the patients were not recruited consecutively or the sample was not random.</p> <p>"Unclear" if there is insufficient information to answer "yes" or "no".</p>
2. Was a case-control design avoided?	<p>Yes/No/Unclear</p> <p>The answer will always be "yes" since the review will exclude case-control studies.</p>
3. Did the study avoid inappropriate exclusions?	<p>Yes/No/Unclear</p> <p>"Yes" if the stated inclusion and exclusion criteria are clear and appropriate.</p> <p>"No" if the stated inclusion and exclusion criteria include inappropriate subjects.</p> <p>"Unclear" if insufficient information is available to answer "yes" or "no".</p>
4. Could the selection of patients have introduced bias?	<p>RISK: Yes/No/Unclear</p> <p>"No" if questions 1 and 3 are answered "yes" (Low risk).</p> <p>"Yes" if questions 1 or 3 is answered "no" (High risk).</p> <p>"Unclear" if insufficient information is available to answer questions 1 or 3.</p>
B. Concerns regarding applicability	
Describe included patients (prior testing, presentation, intended use of index test and setting):	
1. Is there concern that the included patients do not match the review question?	<p>CONCERN: Yes/No/Unclear</p> <p>"No" when the study population represents an unselected sample of newborns expected to receive TcB assessment for hyperbilirubinaemia (Low).</p> <p>"Yes" if included patients are inherently different from those expected to receive TcB assessment for hyperbilirubinaemia (High).</p> <p>"Unclear" if there is insufficient information to make a judgement on the patient inclusion (Unclear).</p>
Domain 2: Index test(s) (if more than 1 index test was used, please complete for each test)	
A. Risk of bias	

Describe the index test and how it was conducted and interpreted:	
1. Were the index test results interpreted without knowledge of the results of the reference standard?	<p>Yes/No/Unclear</p> <p>“Yes” if the paper states that the index test is interpreted by individual(s) who were unaware of the results of the reference test(s).</p> <p>“No” if the results of the index test were known by the individuals performing the reference test, or if the same individual performed both tests.</p> <p>"Unclear" if there is insufficient information to answer "yes" or "no".</p>
2. If a threshold was used, was it pre-specified?	<p>Yes/No/Unclear</p> <p>"Yes" if a pre-specified positivity threshold was stated.</p> <p>"No" if a threshold was not pre-specified.</p> <p>"Unclear" if there is insufficient information to answer "yes" or "no".</p>
3. Could the conduct or interpretation of the index test have introduced bias?	<p>RISK: Low/High/Unclear</p> <p>“No” if questions 1 and 2 are answered "yes" (Low risk).</p> <p>“Yes” if questions 1 or 2 is answered "no" (High risk).</p> <p>“Unclear" if there is insufficient information available to answer "yes" or "no" (Unclear risk).</p>
B. Concerns regarding applicability	
Is there concern that the index test, its conduct, or interpretation differ from the review question?	<p>CONCERN: Low/High/Unclear</p> <p>“No” if there are no concerns based on the information available (Low).</p> <p>“Yes” if the index test is not TcB measurement for hyperbilirubinaemia in newborns or if the conduct of the test or its interpretation is not applicable to the review question (High).</p> <p>"Unclear" if there is insufficient information to answer "yes" or "no".</p>
Domain 3: Reference standard	
A. Risk of bias	
Describe the reference standard and how it was conducted and interpreted:	
1 Is the reference standard likely to correctly classify the target condition?	<p>Yes/No/Unclear</p> <p>"Yes" if the reference standard is TsB measured by one of the laboratory methods mentioned in this protocol.</p> <p>"No" if the above condition is not met.</p> <p>"Unclear" if there is insufficient information to answer "yes" or "no".</p>

2 Were the reference standard results interpreted without knowledge of the results of the index test?	<p>Yes/No/Unclear</p> <p>"Yes" if it is stated that the individual performing/interpreting the results of the reference standard was kept unaware of the results of the index test.</p> <p>"No" if the results of the TcB measurement were known to the individual performing/interpreting the reference standard.</p> <p>"Unclear" if there is insufficient information to answer "yes" or "no".</p>
Could the reference standard, its conduct, or its interpretation have introduced bias?	<p>RISK: Low/High/Unclear</p> <p>"No" if questions 1 and 2 are answered "yes" (Low risk).</p> <p>"Yes" if question 1 or 2 is answered "no" (High risk).</p> <p>"Unclear" if there is insufficient information to answer "yes" or "no".</p>
B. Concerns regarding applicability	
Is there concern that the target condition as defined by the reference standard does not match the review question?	<p>CONCERN: Low/High/Unclear</p> <p>"No" if the target condition is hyperbilirubinaemia in newborns (Low).</p> <p>"Yes" if the target condition is not hyperbilirubinaemia in newborns or it is not clearly stated (High).</p> <p>"Unclear" if there is insufficient information available to answer "yes" or "no" (Unclear).</p>
Domain 4: Flow and timing	
A. Risk of bias	
<p>Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram):</p> <p>Describe the time interval and any interventions between index test(s) and reference standard:</p>	
1. Was there an appropriate interval between index test(s) and reference standard?	<p>Yes/No/Unclear</p> <p>"Yes" if the time between the index test and the reference standard is less than 30 minutes.</p> <p>"No" if the time between the index test and the reference standard is longer than 30 minutes for a significant proportion of the patients.</p> <p>"Unclear" if insufficient information is available to answer "yes" or "no".</p>
2. Did all patients receive a reference standard?	<p>Yes/No/Unclear</p> <p>"Yes" if all the patients who received the index test received a reference standard.</p> <p>"No" if not all the patients who received the index test received a reference standard.</p> <p>"Unclear" if there is insufficient information to answer "yes" or "no".</p>

3. Did patients receive the same reference standard?	<p>Yes/No/Unclear</p> <p>“Yes” if the same reference standard was used for all patients.</p> <p>“No” if different reference standards were used.</p> <p>“Unclear” if there is insufficient information to answer "yes" or "no".</p>
4. Were all patients included in the analysis?	<p>Yes/No/Unclear</p> <p>“Yes” if all patients were included in the analysis, or if any withdrawals or exclusions are adequately explained with a flow chart.</p> <p>“No” if withdrawals or exclusions are not explained or accounted for. “Unclear” there is insufficient information to answer "yes" or "no".</p>
Could the patient flow have introduced bias?	<p>RISK: Low/High/Unclear</p> <p>"No" if questions 1, 2, 3 and 4 are answered "yes" (Low risk).</p> <p>"Yes" if any of the four questions is answered "no" (High risk).</p> <p>"Unclear" if there is insufficient information to answer "yes" or "no" (Unclear risk).</p>

TcB: Transcutaneous bilirubin

TsB: Total serum bilirubin



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Transcutaneous screening for hyperbilirubinemia in neonates (Protocol)

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Transcutaneous screening for hyperbilirubinemia in neonates.

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Transcutaneous screening for hyperbilirubinemia in neonates

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To evaluate to the effects of transcutaneous screening for hyperbilirubinemia to prevent the readmission of neonates for phototherapy.

BACKGROUND

Description of the condition

Hyperbilirubinemia is a term used to describe elevated levels of bilirubin in the blood. In newborns, hyperbilirubinemia becomes clinically apparent as jaundice, a yellow coloration of the skin and the sclera, at serum bilirubin levels > 5 mg/dL (Porter 2002). Hyperbilirubinemia is very common in both term and preterm newborn infants (occurring in around 60% of newborns) and results from a predisposition to produce bilirubin and the newborn's limited ability to excrete it (Lauer 2011). Jaundice or hyperbilirubinemia is the most common cause of hospital readmission in the neonatal period (Soskolne 1996; Maisels 1998; Escobar 2005). Most cases of newborn jaundice are mild and self limited. However, in rare cases, infants can have very high levels of bilirubin that can lead to bilirubin encephalopathy and kernicterus (Newman 2006). The threshold concentration of bilirubin and/or the duration of hyperbilirubinemia responsible for causing kernicterus in-

jury in newborn infants is not known (Dennerly 2004). Low concentrations of bilirubin may have some antioxidant benefits, suggesting that bilirubin should not be completely eliminated. Studies from developed countries estimate the incidence of kernicterus to range from about 0.4 to 2 per 100,000 (Sgro 2006; Manning 2007; Burke 2009). However, studies from developing countries suggest that the incidence may be much higher (Nair 2003; Owa 2009).

The acute phase signs of kernicterus are poor feeding, lethargy, high-pitched cry, hypertonia or hypotonia, opisthotonos and seizures. The chronic manifestations include athetoid cerebral palsy, motor delay, gaze palsy, dental dysplasia, mental retardation and sensorineural hearing loss (AAP 2004). Current treatments for hyperbilirubinemia include phototherapy and exchange transfusion (usually reserved for severe cases of hyperbilirubinemia) (NICE 2010).

Description of the intervention

Transcutaneous bilirubin (TcB) measurement devices are used for the rapid and noninvasive measurement of bilirubin levels in the skin. Transcutaneous bilirubinometry works by directing light into the skin of the neonate and measuring the intensity of the specific wavelength of light returned. The measurement is usually taken by gently pressing the meter against the sternum. Findings from many studies suggest that the accuracy and precision of TcB measurements are correlated with standard laboratory total serum bilirubin (T_sB) (Rubaltelli 2001; Engle 2002; Maisels 2004; Slusher 2004; Jangaard 2006). Other studies suggest that TcB measurements do not correlate with T_sB measurements in preterm newborn (Knupfer 2001; Karoly 2004). TcB screening involves the measurement of bilirubin in every newborn in whom clinical jaundice is not present or observed, prior to discharge.

How the intervention might work

The practice of early discharge (< 72 hours of age) of healthy term newborns is growing worldwide. Because peak serum bilirubin levels usually occur on postnatal days three to five, an effective means of screening for the onset of hyperbilirubinemia could enhance the safety of the early discharge of newborns.

The clinical evaluation of hyperbilirubinemia involves the visual assessment of jaundice. However, this method can be affected by the newborn's skin color and does not provide a quantification of the T_sB level. Current, more-objective methods of assessing hyperbilirubinemia include the use of T_sB measurements from blood sampling and noninvasive methods, such as TcB measurement with a handheld bilirubinometer. To aid in identifying newborns with a significant risk of hyperbilirubinemia and its consequences, TcB and other screening strategies for hyperbilirubinemia prior to the discharge of newborns have been advocated (Bhutani 1999; Alpay 2000; Newman 2000; Stevenson 2001). Transcutaneous screening for hyperbilirubinemia is used to identify newborns with bilirubin levels greater than the 75th percentile for age in hours and to track those with rapid rates of bilirubin rise (> 0.2 mg per 100 mL per hour). Bhutani 1999 proposed an on-the-hour-specific bilirubin nomogram as an approach to pre-discharge screening for hyperbilirubinemia. However, Fay 2009 have highlighted multiple methodologic flaws in the methods used to create the hour-specific total bilirubin nomogram.

Transcutaneous screening for hyperbilirubinemia, the characterization of bilirubin levels by risk, with selective follow up of at-risk infants and timely intervention in infants at risk of hyperbilirubinemia, could lead to a reduction in the number of newborns with severe hyperbilirubinemia and a reduction in the number of newborns readmitted to the hospital for phototherapy or exchange transfusion. If hyperbilirubinemia is identified early, effective interventions such as phototherapy can be initiated to reduce the risk bilirubin encephalopathy. However, TcB screening could also

lead to unnecessary readmissions, prolonged hospitalization, excess laboratory tests and increased costs.

Why it is important to do this review

The American Academy of Pediatrics (AAP) and the Canadian Pediatric Society both recommend the use of either pre-discharge serum bilirubin or TcB measurements as appropriate screening options for identifying infants at risk of neonatal hyperbilirubinemia (AAP 2004; CPS 2007). In contrast, however, according to the US Preventive Services Task Force, "there is insufficient evidence to make a recommendation on screening infants for hyperbilirubinemia to prevent chronic bilirubin encephalopathy" (USPSTF 2009). There is conflicting evidence for, and recommendations on, the usefulness of pre-discharge bilirubin screening in newborns. Without proof of efficacy, universal screening of newborns for hyperbilirubinemia can result in the waste of healthcare resources and the unnecessary testing of many newborns.

We aim to evaluate all the relevant available evidence to assess the effects of transcutaneous screening for hyperbilirubinemia in newborn infants before discharge from hospital.

OBJECTIVES

To evaluate the effects of transcutaneous screening for hyperbilirubinemia to prevent the readmission of neonates for phototherapy.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials, quasirandomized controlled trials, cluster randomized trials and other prospective study designs (e.g. cohort studies).

Types of participants

- Well newborns, of gestational age 35 weeks or more and weighing 1800 g or more, being discharged from the newborn nursery (in the first week of life)

We will not include infants admitted to, or being discharged from, the neonatal intensive care unit.

Types of interventions

1. TcB screening (alone or combined with any other method, e.g. visual assessment) compared to no screening or visual inspection for hyperbilirubinemia before discharge from hospital
2. TcB screening versus serum bilirubin screening before discharge from hospital
3. Closer follow up or home nursing visits based on TcB screening results versus postdischarge follow up or treatment decisions based on visual inspection

Types of outcome measures

Primary outcomes

- Readmission for phototherapy or home phototherapy for hyperbilirubinemia
- Exchange transfusion

Secondary outcomes

- Phototherapy before hospital discharge
- Peak bilirubin levels
- Acute bilirubin encephalopathy
- Chronic bilirubin encephalopathy
- Hearing loss
- Length of stay (days)
- Cost of care

Search methods for identification of studies

We will use the standard search strategy of the Cochrane Neonatal Review Group to identify all relevant studies regardless of language or publication status (published, unpublished, in press and in progress).

Electronic searches

We will search the following electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library* - current), MEDLINE (1950 to current), EMBASE (1980 to current) and CINAHL (1982 to current). We will search MEDLINE, EMBASE and CINAHL for relevant articles using the search terms: [Infant OR Newborn (explode) [MeSH heading] AND transcutaneous (explode) [MeSH heading] OR screening AND [hyperbilirubinaemia OR hyperbilirubinemia OR jaundice (explode) [MeSH heading]]. We will search clinical trial registries for any ongoing trials (www.clinicaltrials.gov; www.controlled-trials.com/ and www.who.int/ictrp).

Searching other resources

We will attempt to contact experts and organizations or manufacturers of bilirubinometers for information on any relevant study. We will scan through the reference lists of all relevant studies. We will search any previous reviews, including cross-references and abstracts, and conference and symposia proceedings of the Perinatal Society of Australia and New Zealand and the Paediatric Academic Societies (American Pediatric Society, Society for Pediatric Research and European Society for Paediatric Research).

Data collection and analysis

We will use the standard methods of the Cochrane Neonatal Review Group.

Selection of studies

The first two review authors will independently scan through the titles and abstracts of the search output to identify potentially eligible studies. Discrepancies will be resolved through discussion or, if required, we will consult the third author. We will obtain full text articles of all selected abstracts to formally assess eligibility using the prespecified eligibility criteria. We will summarize the reasons for exclusion of any potentially eligible study in the 'Characteristics of excluded studies' table.

Data extraction and management

We will design a data extraction form for the extraction of data. Two review authors will independently extract data from all included studies using the data extraction form. We will resolve discrepancies through discussion or, if required, we will consult the third review author. We will enter data into the latest version of Review Manager ([RevMan 2011](#)) and check them for accuracy. We will contact authors of the studies identified via email or telephone to provide more information, if necessary.

Study information that will be extracted will include:

- study details: citation, start and end dates, location and study design;
- participant details: study population eligibility (inclusion and exclusion) criteria, gestational age, sex, sample size and attrition rate;
- details about the interventions: type of transcutaneous bilirubin meter used and any other method used for screening for hyperbilirubinemia
- outcome details: readmission rates for phototherapy, exchange transfusion, acute bilirubin encephalopathy, chronic bilirubin encephalopathy and adverse effects.

For each dichotomous outcome, we will extract information on the number of participants experiencing the event and the number of participants randomized to each treatment group. For each continuous outcome we will extract the means or geometric means and standard deviations (or information to estimate the standard deviations) for each treatment group, together with the numbers of participants in each group. Medians and ranges will also be extracted if these are reported in place of means and standard deviations.

Assessment of risk of bias in included studies

The first two review authors will independently assess the risk of bias in each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreement by discussion or by consulting the third review author.

(1) Sequence generation (checking for possible selection bias)

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. We will assess the method as:

- adequate (any truly random process, e.g. random number table; computer random number generator);
- inadequate (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear (if we do not find enough information to make a judgment).

(2) Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal the allocation sequence in sufficient detail and determine whether intervention allocation could have been foreseen in advance of or during recruitment, or changed after assignment. We will assess the methods as:

- adequate (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes);
- inadequate (open random allocation; unsealed or nonopaque envelopes; alternation; date of birth);
- unclear (if we do not find enough information to make a judgment).

(3) Blinding (checking for possible performance bias)

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will judge studies to be at low risk of bias if they were blinded, or if we judge that the lack of blinding could not have affected the results. We will assess blinding separately for different outcomes or classes of outcomes. We will assess the methods as:

- adequate, inadequate or unclear for participants;

- adequate, inadequate or unclear for personnel;
- adequate, inadequate or unclear for outcome assessors.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data, including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total numbers of randomized participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will reinstate missing data in the analyses that we undertake. We will assess methods as:

- adequate (where fewer than 20% of data are missing);
- inadequate (where more than 20% of the data are missing);
- unclear (if we do not find enough information to make a judgment).

(5) Selective reporting bias

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We will assess the methods as:

- adequate (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- inadequate (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear (if we do not find enough information to make a judgment).

(6) Other sources of bias

We will describe for each included study any important concerns we have about other possible sources of bias. We will assess whether each study was free of other problems that could put it at risk of bias as: yes, no or unclear.

Measures of treatment effect

We will present results for dichotomous outcomes as summary risk ratios (RRs) with 95% confidence intervals (CIs) and absolute risk differences with 95% CIs. Continuous outcomes will be presented using the mean difference (MD), if outcomes are measured using the same scale in trials, or using the standardized mean difference when the outcome is measured using different scales. The summary effect measures will be presented with 95% CIs. If the RR is statistically significant, the number needed to treat to for an

additional beneficial outcome (NNTB) or an additional harmful outcome (NNTH) will be calculated.

Unit of analysis issues

We will note the unit of analysis at the level of randomization (individual or group) and analyze the data accordingly. We will include cluster randomized trials in the analyses along with individually randomized trials. For cluster randomized trials, we will adjust the sample sizes using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions*, Section 16.3.4 or 16.3.6 (Higgins 2011) using an estimate of the intracluster correlation coefficient (ICC) derived from the trial (if possible) or from another source.

Dealing with missing data

We will attempt to contact authors if there are missing or unclear data. We will also note levels of attrition in each of the included studies. For all outcomes we will carry out an intention-to-treat analysis. For outcomes in which the results have been pooled in meta-analysis, we will explore the impact of including studies with significant loss to follow up in the overall assessment of treatment effect by using sensitivity analyses.

Assessment of heterogeneity

We will assess statistical heterogeneity by visually inspecting the forest plots to detect overlapping CIs, applying the χ^2 test (P value < 0.10 considered statistically significant) and also using the I^2 statistic, where an I^2 of less than 25% will be considered as unimportant, 25% to 49% will be considered to suggest low heterogeneity, 50% to 74% will be considered to suggest moderate heterogeneity, and 75% or greater will be considered to indicate high heterogeneity.

Assessment of reporting biases

If we have 10 or more studies, we will explore the likelihood of reporting bias or publication bias for each outcome using funnel plots.

Data synthesis

We will analyze the data using Review Manager 5.2.7. Where possible, we will adjust for the effect of clustering in cluster randomized trials and combine the results with results from individually randomized studies in meta-analysis. We will use a random-effect model for any meta-analyses.

Quality of evidence

The quality of evidence across each outcome measure will be assessed using the GRADE approach. GRADE defines the quality of evidence as the confidence we have in the estimate of effect for an outcome (Atkins 2004). The quality rating across studies has four levels: high, moderate, low or very low. Randomized trials are categorized as high quality, but can be downgraded. Some of the factors that would impact on the quality of evidence are the risk of bias in included studies, the presence of unexplained heterogeneity or inconsistency, the imprecision of results, indirectness of the evidence and publication bias (Balslem 2011).

Subgroup analysis and investigation of heterogeneity

We plan to carry out subgroup analyses based on gestation age (preterm versus term newborns); the presence of jaundice (versus no jaundice) in newborns; birth weight (<2500g versus > 2500g); and the presence of any comorbid conditions (e.g. hemolytic disease or other conditions known to exacerbate jaundice); mode of delivery (spontaneous vertex delivery or delivery by caesarean section).

Sensitivity analysis

Depending on the number of included studies, we plan to conduct sensitivity analyses on the robustness of the methods used regarding allocation concealment and losses to follow up in the analysis, and we will report the impact of the sensitivity analyses on the quantitative results from the meta-analysis.

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* Indicates the major publication for the study

CONTRIBUTIONS OF AUTHORS

Charles Okwundu conceptualized and wrote the draft protocol. Olalekan A Uthman and Johan Smith contributed to various sections of the protocol.

DECLARATIONS OF INTEREST

None

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Internal sources

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Transcutaneous bilirubinometry versus total serum bilirubin measurement for newborns (Protocol)

Okwundu CI, Uthman OA, Suresh G, Smith J, Wiysonge CS, Bhutani VK

Okwundu CI, Uthman OA, Suresh G, Smith J, Wiysonge CS, Bhutani VK.

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[Diagnostic Test Accuracy Protocol]

Transcutaneous bilirubinometry versus total serum bilirubin measurement for newborns

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ABSTRACT

This is a protocol for a Cochrane Review (Diagnostic test accuracy). The objectives are as follows:

- To determine the diagnostic accuracy of TcB as:
 - i) a diagnostic test for hyperbilirubinaemia in newborns suspected to have hyperbilirubinaemia on visual inspection;
 - ii) a diagnostic test for monitoring bilirubin levels in newborns receiving treatment (e.g. phototherapy) for hyperbilirubinaemia.
- 1. a diagnostic test for hyperbilirubinaemia in newborns suspected to have hyperbilirubinaemia on visual inspection;
- 2. a diagnostic test for monitoring bilirubin levels in newborns receiving treatment (e.g. phototherapy) for hyperbilirubinaemia.
- To determine whether the gestational age, postnatal age, body weight, race and site of TcB measurement have any influence on the accuracy of TcB measurement for hyperbilirubinaemia in newborns.

BACKGROUND

Target condition being diagnosed

Hyperbilirubinaemia is a term used to describe excess of bilirubin in the blood. In newborns, hyperbilirubinaemia becomes clinically apparent as jaundice, a yellow colouration of the skin and sclera (Woodgate 2015). Hyperbilirubinaemia is very common in both term and preterm newborn infants (occurring in about 60% of newborns) and results from a predisposition to the production of bilirubin and their limited ability to excrete it (Lauer 2011). Most cases of newborn jaundice are mild and resolve spontaneously (Srgo 2006). However, in rare cases babies can have very high levels of bilirubin that can lead to bilirubin encephalopathy and kernicterus (Ebbesen 2005; Srgo 2006). The acute phase signs of kernicterus are poor feeding, lethargy, high-pitched cry, hypertonia or hypotonia, opisthotonos and seizures (Johnson 2002). The chronic manifestations include athetoid cerebral palsy, motor delay, gaze palsy, dental dysplasia, mental retardation and sensorineural hearing loss (AAP 2004). Studies from developed countries estimate the incidence of kernicterus to range from about 0.4 to 2 per 100,000 (Srgo 2006; Mannig 2007; Burke 2009). However, studies from developing countries suggest that the incidence may be much higher (Nair 2003; Owa 2009). Following guidelines issued by the American Academy of Pediatrics for the management of jaundice in the neonate (AAP 2004), the age-long critical cut-off value of total serum bilirubin (T_sB) of 20 mg/dL (342 µmol/L) at which therapy was required is being replaced by a plot of T_sB against time (hours) for each baby. This is compared to the nomogram for the age of the baby and used to determine the line of management (Higgins 2012). Current treatments for hyperbilirubinaemia include phototherapy and exchange transfusion, which is usually used for severe cases of hyperbilirubinaemia (Woodgate 2015).

Index test(s)

Transcutaneous bilirubin (T_cB) measurement is a non-invasive method for measuring serum bilirubin level (Dai 1997). Transcutaneous bilirubinometry works by directing light into the skin and measuring the intensity of the wavelength of light that is returned (Boo 2007). Transcutaneous bilirubinometry is based on optical spectroscopy, which relates the amount of light absorption by bilirubin to the concentration of bilirubin in the skin. The technology was first introduced in 1980 (Yamanouchi 1980). The measurement is usually taken by gently pressing the meter against the sternum or forehead. Transcutaneous bilirubin measurement provides an immediate (less than a minute) result of bilirubin levels (Dai 1997). Using this point-of-care device saves time compared to measuring serum bilirubin and may reduce costs associated with measuring serum bilirubin in newborns (Maisels 1997).

However, the accuracy of T_cB results may be affected by gestational age, body weight and skin colour (Knüpfer 2001; Karen 2009). For example, T_cB tends to underestimate TSB in light and medium skin colours and overestimates in dark skin colour (Samiee-Zafarghandy 2014). There are a number of T_cB devices available, including the Bilicheck device, JM 103 and JM 105 devices (Grohmann 2006).

Clinical pathway

Newborns are routinely monitored by nursing staff and physicians for the development of jaundice in the first few hours of life and before discharge from the newborn nursery. This is usually done by visual inspection and skin blanching to assess for yellowish discolouration. Visual estimation of bilirubin level is not reliable (Barrington 2012). Therefore, bilirubin level needs to be assessed objectively by means of a T_cB or T_sB measurement. In some settings, T_cB or T_sB measurements are performed on all newborns as part of routine screening before hospital discharge or as targeted screening based on risk factors for severe hyperbilirubinaemia. Some of the risk factors include breastfeeding, ABO/Rhesus incompatibility, glucose-6-phosphate dehydrogenase deficiency, use of oxytocin during delivery, vacuum-assisted delivery, prematurity, and history of jaundice in a sibling (AAP 2004; Keren 2005; Bhutani 2010). T_cB or T_sB measurement can be done as part of universal screening or only if a newborn is visibly jaundiced and the value is plotted on a nomogram to assess the need for treatment (AAP 2004). In addition, the measurements may be taken on newborns undergoing phototherapy to help in making a decision on when to stop treatment. The bilirubin levels are interpreted based on the infant's gestational age and postnatal age (AAP 2004).

Role of index test(s)

The T_cB assay is a non-invasive method for measuring bilirubin levels and it may help to reduce the risk of anaemia and trauma associated with blood sampling for T_sB measurement (Dai 1997). T_cB has been shown to work well in both hospital and outpatient settings; and has been shown to be better than visual inspection for estimation of hyperbilirubinemia (De Luca 2008; Wainer 2012). Additionally, the T_cB measurement ensures a readily available result for immediate clinical decision-making while reducing the chances of infections associated with all invasive procedures (Jangaard 2006). The T_cB meter can be used as a screening tool to estimate the serum bilirubin level in newborns who are not clinically jaundiced or as a diagnostic tool in jaundiced newborns to assess the need for treatment (AAP 2004).

Alternative test(s)

Various methods are used to determine bilirubin levels in newborns. These include visual assessment, direct spectrophotometric methods (requiring capillary blood) and use of an icterometer (Higgins 2012). Visual assessments for jaundice are common in newborn nurseries and outpatient settings, such as physicians' offices (Harrison 1989). However, studies have shown that the severity of jaundice cannot be assessed through visual estimation. The icterometer is a specialized ruler marked with different shades of yellow used to estimate the bilirubin level when pressed against a newborn's skin (Akman 2000).

Rationale

Bilirubin measurement is one of the most frequently performed tests in newborn infants (Donzelli 2000; Madsen 2000). Chemical methods for serum bilirubin measurement is currently the reference standard for measuring bilirubin levels. However, this requires repeated blood sampling which can be painful to the newborn, costly and time consuming. Transcutaneous bilirubin measurement has been recommended as a more cost-effective and less traumatic method of measuring bilirubin levels in newborns (Dai 1996). In order to justify routine use of TcB devices, we need to systematically review all the available evidence from well-designed studies on the accuracy of TcB measurements in newborn infants. A clear understanding of the diagnostic test accuracy of transcutaneous bilirubinometry using a variety of instruments in a variety of populations (including preterm and term infants as well as infants with various racial backgrounds) would be invaluable for understanding the usefulness of TcB measurement in newborns.

OBJECTIVES

- To determine the diagnostic accuracy of TcB as:
 - i) a diagnostic test for hyperbilirubinaemia in newborns suspected to have hyperbilirubinaemia on visual inspection;
 - ii) a diagnostic test for monitoring bilirubin levels in newborns receiving treatment (e.g. phototherapy) for hyperbilirubinaemia.
- To determine whether the gestational age, postnatal age, body weight, race and site of TcB measurement have any influence on the accuracy of TcB measurement for hyperbilirubinaemia in newborns.

METHODS

Criteria for considering studies for this review

Types of studies

We will include diagnostic test accuracy studies comparing TcB and TsB measurement for hyperbilirubinaemia in newborns, as follows.

- Cross-sectional studies.
- Cohort studies.

We will exclude all randomised controlled trials, retrospective studies, case-control studies, case reports and any studies in which data for true positives, true negatives, false positives and false negatives cannot be determined. Retrospective studies will also be excluded.

Participants

We will include studies evaluating infants aged 0 to 29 days (including term or preterm newborns) who require bilirubin measurement either as a universal screening test or a test for visible jaundice or for monitoring therapy for hyperbilirubinaemia. We will include studies conducted in different patient settings such as neonatal intensive care units, paediatric emergency units, paediatric wards and studies that recruited participants from home or in the communities.

Index tests

We will include studies that assessed the accuracy of any TcB device in newborns.

Target conditions

The target condition is hyperbilirubinaemia requiring treatment either by phototherapy or by exchange transfusion.

Reference standards

The reference standard is TsB measured in the laboratory, which requires blood sampling from the newborn. TsB measurement can be performed in the laboratory using various methods such as high performance liquid chromatography (HPLC), Diazo-based methods, or other methods such as direct spectrophotometric methods (Kazmierczak 2002) and capillary electrophoresis (Higgins 2012). Total serum bilirubin measurement by the HPLC method is not subject to interference from haemoglobin or lipaemia. However, this method is costly, labour-intensive and not practical for routine use (Kazmierczak 2004). The Diazo-based methods are the most frequently used laboratory assays but may be affected by haemolysis (el-Beshbishi 2009). Total serum bilirubin measurement requires drawing of blood causing pain and trauma to the

neonate. Repeated blood sampling for TsB measurement can cause anaemia, especially in preterm neonates. Inter- and intralaboratory variability has been reported with measurements of TsB (Lo 2011).

Search methods for identification of studies

We will use the standard search strategy of the Cochrane Neonatal Review Group to identify all relevant studies without any language restriction. Methodological filters for diagnostic studies will not be used, to avoid missing out on some relevant studies. We will attempt to get translation for articles written in languages other than English. We will record any article for which we could not get a translation in the section 'Characteristics of studies awaiting classification'.

Electronic searches

We will search the following databases.

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library.
- MEDLINE Ovid (from 1966).
- Embase Ovid SP (from 1982).
- CINAHL (via EBSCOhost) (from 1982).

We will also search the following trial registries.

- ClinicalTrials.gov
- International Standard Randomised Controlled Trial Number (ISRCTN) registry (www.isrctn.com/)
- World Health Organization (WHO) International Clinical Trials Platform (ICTRP) Search portal (apps.who.int/trialsearch/).

There will be no date restrictions in the search of trial registries. Our search strategy for Embase was developed by discussion between the author team and the Cochrane Neonatal Group's Trials Search Co-ordinator (Appendix 1). We will adapt it for use in other databases.

We will also conduct searches based on the Embase strategy to identify other potential studies in:

- DARE (Database of Abstracts of Reviews of Effects);
- MEDION database (for Systematic Reviews of Diagnostic Studies).

We will screen the reference lists of any relevant reviews from DARE and MEDION for potentially eligible studies.

Searching other resources

We will examine the references lists of all included studies for possible additional studies.

Data collection and analysis

Selection of studies

Two review authors will independently assess eligible articles for inclusion from the titles and abstracts obtained in the initial search. They will resolve any disagreement through discussion or, if necessary, by involving a third review author.

Data extraction and management

Two review authors will independently extract data on study characteristics using a standard data extraction form. We will compute 2×2 tables of true positives, false positives, true negatives and false negatives, for the index tests at the thresholds reported. Where reported, we will exclude undetermined or indefinite results from the analyses. We will discuss differently extracted data until consensus is reached. The information we will extract from each study is presented in Table 1.

Assessment of methodological quality

Two of the authors will independently assess the methodological quality of each included study using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool (Whiting 2011), which consists of four domains. We will develop a rating guideline for assessment of the domains in order to ensure consistency. We will assess each of the four domains with respect to the risk of bias. Additionally, we will assess the first three domains in terms of applicability. We will pilot our review-specific QUADAS-2 tool against five primary studies in order to identify possible areas of discrepancies between authors. We will make modifications to the tool if possible, to ensure consistency. We will resolve discrepancies in assessments between review authors by consensus. If this is impossible, we will seek final resolution using a third-party arbitrator. The items of the QUADAS-2 tool and our scoring interpretations for each item are presented in Appendix 2.

Statistical analysis and data synthesis

We will perform statistical analysis according to Cochrane guidelines for diagnostic test accuracy (DTA) reviews (Macaskill 2010). We will include studies reporting sufficient data that allows for the construction of a 2×2 table and also studies that only reported the Pearson correlation coefficients to describe the relationship between TcB and TsB measurements. The data from the 2×2 tables will be used to calculate sensitivity and specificity for each study and also meta-analysis of sensitivities and specificities where appropriate using the bivariate model if the same threshold for positivity was used. According to the bivariate method we will calculate overall sensitivity and specificity and their 95% confidence intervals (CIs), based on the binomial distributions of the true positives and true negatives (Reitsma 2005). However,

we anticipate that studies will use multiple thresholds, both between studies and within individual studies. If data with more than one positive threshold is reported within a study, we will extract the relevant data and present the findings graphically for each threshold. We will perform meta-analysis with the most common threshold where appropriate; and fit a summary receiver operating characteristic (ROC) curve using a bivariate random-effects model (Reitsma 2005). We will use the latest version of the Review Manager (RevMan) software to graphically present coupled forest plots, showing the pairs of sensitivity and specificity (and their 95% CIs) of each study, for each threshold. We will also present coupled forest plots of the Pearson correlation coefficients across studies where relevant, to allow basic visual inspection of individual studies only. All indefinite results will be excluded from the analysis.

Investigations of heterogeneity

The investigation of heterogeneity will be performed through visual examination of both the ROC plot of raw data and the forest plots of sensitivities and specificities. We will formally investigate potential sources of heterogeneity other than threshold effect in bivariate models if we have a sufficient number of studies. By fit-

ting the covariates in a bivariate regression model, we will investigate the following sources of heterogeneity in the diagnostic performance across studies: type of TcB meter; gestational age (term versus preterm infants); race or skin colour; prior use of phototherapy; and reference standard. We will investigate the effect of these covariates by conducting subgroup analyses in the latest version of the RevMan software and by including each of these factors as covariates in the bivariate regression model. A minimum of 10 studies will be needed per covariate included in the regression model.

Sensitivity analyses

We will perform sensitivity analyses on the different domains scored on the QUADAS-2 tool, in order to explore the influence of the quality of the included studies. We will perform additional sensitivity analyses if other suitable factors are identified during the review process and any such analysis will be reported as 'post hoc' in the final review.

Assessment of reporting bias

We are not planning to use funnel plots to evaluate the impact of publication bias or other biases associated with small studies.

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* Indicates the major publication for the study

ADDITIONAL TABLES

Table 1. Data from each study

[Study ID]	First author, year of publication
Type of study	Journal article, unpublished data
Participants	Sample size Country of study Baseline characteristics (gestational age, postnatal age, race, body weight)
Study design	Retrospective/prospective design Sample (consecutive, random or unclear)
Study criteria	Inclusion criteria Exclusion criteria
Reference standard	Name of assay/manufacturer Name of instrument Cut-off values Time between reference standard performance and TcB measurement Blinding of operator to TcB result
Index test	Name of device Cut-off values Operator training site of measurement (forehead, sternum)
Target condition	Universal screening of newborns for hyperbilirubinaemia Diagnostic determination of hyperbilirubinaemia in visibly jaundiced newborns Monitoring of bilirubin in newborns on therapy for hyperbilirubinaemia

Table 1. Data from each study (Continued)

Data	Number of true positives and false positives Number of true negatives and false negatives Number of undetermined/uninterpretable results Sensitivity and specificity of index test Number of missing results for index test Number of missing results for reference standard
Notes	Source of funding (whether any author is affiliated with the manufacturer of the index test; the study was directly funded by the manufacturer; authors reported conflicts of interests related to the manufacturer or other funding sources)

APPENDICES

Appendix 1. Embase search strategy

Our search strategy for Embase OVID below was developed by discussion between the author team and the Cochrane Neonatal Group's Trials Search Co-ordinator. We will adapt it for use in other databases.

(infant, newborn or neonat* or premature or very low birth weight or low birth weight or VLBW or LBW or infan*) AND ((transcutaneous adj2 bilirubin) OR TcB OR bilicheck OR bilicheck OR JM-103 OR JM-105 OR bilirubinomet* AND ((blood* or serum) adj bilirubin) OR TsB OR spectrophotomet*).mp

Appendix 2. QUADAS-2 tool

QUADAS-2 tool: Risk of bias and applicability judgements

Domain 1: Patient selection	Domain 1: Patient selection
A. Risk of bias	
1. Was a consecutive or random sample of patients enrolled?	Yes/No/Unclear “Yes” if it is clearly stated in the paper that a consecutive or a random sample of patients was enrolled “No” if the patients were not recruited consecutively or the sample was not random “Unclear” if there is insufficient information to answer “yes” or “no”

(Continued)

2. Was a case-control design avoided?	Yes/No/Unclear The answer will always be “yes” since the review will exclude case-control studies
3. Did the study avoid inappropriate exclusions?	Yes/No/Unclear “Yes” if the stated inclusion and exclusion criteria are clear and appropriate “No” if the stated inclusion and exclusion criteria include inappropriate subjects “Unclear” if insufficient information is available to answer “yes” or “no”
4. Could the selection of patients have introduced bias?	RISK: Yes/No/Unclear “No” if questions 1 and 3 are answered “yes” (Low risk). “Yes” if questions 1 or 3 is answered “no” (High risk). “Unclear” if insufficient information is available to answer questions 1 or 3

B. Concerns regarding applicability

Describe included patients (prior testing, presentation, intended use of index test and setting):

1. Is there concern that the included patients do not match the review question?	CONCERN: Yes/No/Unclear “No” when the study population represents an unselected sample of newborns expected to receive TcB assessment for hyperbilirubinaemia (Low) “Yes” if included patients are inherently different from those expected to receive TcB assessment for hyperbilirubinaemia (High) “Unclear” if there is insufficient information to make a judgement on the patient inclusion (Unclear)
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Domain 2: Index test(s) (if more than 1 index test was used, please complete for each test)

A. Risk of bias

Describe the index test and how it was conducted and interpreted:

1. Were the index test results interpreted without knowledge of the results of the reference standard?	Yes/No/Unclear “Yes” if the paper states that the index test is interpreted by individual(s) who were unaware of the results of the reference test(s) “No” if the results of the index test were known by the individuals performing the reference test, or if the same individual performed both tests “Unclear” if there is insufficient information to answer “yes” or “no”
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(Continued)

<p>2. If a threshold was used, was it pre-specified?</p>	<p>Yes/No/Unclear “Yes” if a pre-specified positivity threshold was stated. “No” if a threshold was not pre-specified. “Unclear” if there is insufficient information to answer “yes” or “no”</p>
<p>3. Could the conduct or interpretation of the index test have introduced bias?</p>	<p>RISK: Low/High/Unclear “No” if questions 1 and 2 are answered “yes” (Low risk). “Yes” if questions 1 or 2 is answered “no” (High risk). “Unclear” if there is insufficient information available to answer “yes” or “no” (Unclear risk)</p>
<p>B. Concerns regarding applicability</p>	
<p>Is there concern that the index test, its conduct, or interpretation differ from the review question?</p>	<p>CONCERN: Low/High/Unclear “No” if there are no concerns based on the information available (Low) “Yes” if the index test is not TcB measurement for hyperbilirubinaemia in newborns or if the conduct of the test or its interpretation is not applicable to the review question (High) “Unclear” if there is insufficient information to answer “yes” or “no”</p>
<p>Domain 3: Reference standard</p>	
<p>A. Risk of bias</p>	
<p>Describe the reference standard and how it was conducted and interpreted:</p>	
<p>1 Is the reference standard likely to correctly classify the target condition?</p>	<p>Yes/No/Unclear “Yes” if the reference standard is TsB measured by one of the laboratory methods mentioned in this protocol “No” if the above condition is not met. “Unclear” if there is insufficient information to answer “yes” or “no”</p>
<p>2 Were the reference standard results interpreted without knowledge of the results of the index test?</p>	<p>Yes/No/Unclear “Yes” if it is stated that the individual performing/interpreting the results of the reference standard was kept unaware of the results of the index test “No” if the results of the TcB measurement were known to the individual performing/interpreting the reference standard “Unclear” if there is insufficient information to answer “yes” or “no”</p>
<p>Could the reference standard, its conduct, or its interpretation have introduced bias?</p>	<p>RISK: Low/High/Unclear “No” if questions 1 and 2 are answered “yes” (Low risk). “Yes” if question 1 or 2 is answered “no” (High risk).</p>

(Continued)

	“Unclear” if there is insufficient information to answer “yes” or “no”
B. Concerns regarding applicability	
Is there concern that the target condition as defined by the reference standard does not match the review question?	CONCERN: Low/High/Unclear “No” if the target condition is hyperbilirubinaemia in newborns (Low) “Yes” if the target condition is not hyperbilirubinaemia in newborns or it is not clearly stated (High) “Unclear” if there is insufficient information available to answer “yes” or “no” (Unclear)
Domain 4: Flow and timing	Domain 4: Flow and timing
A. Risk of bias	
Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:
1. Was there an appropriate interval between index test(s) and reference standard?	Yes/No/Unclear “Yes” if the time between the index test and the reference standard is less than 30 minutes “No” if the time between the index test and the reference standard is longer than 30 minutes for a significant proportion of the patients “Unclear” if insufficient information is available to answer “yes” or “no”
2. Did all patients receive a reference standard?	Yes/No/Unclear “Yes” if all the patients who received the index test received a reference standard “No” if not all the patients who received the index test received a reference standard “Unclear” if there is insufficient information to answer “yes” or “no”
3. Did patients receive the same reference standard?	Yes/No/Unclear “Yes” if the same reference standard was used for all patients “No” if different reference standards were used. “Unclear” if there is insufficient information to answer “yes” or “no”
4. Were all patients included in the analysis?	Yes/No/Unclear “Yes” if all patients were included in the analysis, or if any withdrawals or exclusions are adequately explained with a flow chart “No” if withdrawals or exclusions are not explained or accounted

(Continued)

	for. “Unclear” there is insufficient information to answer “yes” or “no”
Could the patient flow have introduced bias?	RISK: Low/High/Unclear “No” if questions 1, 2, 3 and 4 are answered “yes” (Low risk) “Yes” if any of the four questions is answered “no” (High risk) “Unclear” if there is insufficient information to answer “yes” or “no” (Unclear risk)

TcB: Transcutaneous bilirubin

TsB: Total serum bilirubin

CONTRIBUTIONS OF AUTHORS

Charles Okwundu conceptualised and wrote the draft protocol. Olalekan Uthman, Gautham Suresh, Johan Smith, Charles Wiysonge and Vinod Bhutani contributed to various sections of the protocol.

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None known

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