Full HTA Report

Transcutaneous Bilirubinometry for the Screening of Hyperbilirubinemia in Neonates ≥35 Weeks' Gestation

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Declared Competing Interest of Authors

Competing interest is considered to be financial or non-financial interest, either direct or indirect, that would be affected by the research contained in this report or the creation of a situation in which a person's judgment could be unduly influenced by a secondary interest, such as personal advancement.

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EXECUTIVE SUMMARY

Background and Project Context

Background

Hyperbilirubinemia, an elevated level of bilirubin in the blood, and the jaundice, or yellowing of the skin, that almost always accompanies it, are common in the first week of life, occurring in almost 60% of term newborns. Left unchecked, elevated bilirubin levels can progress to critical hyperbilirubinemia, a condition that, though uncommon, can cause long-term, irreversible, debilitating, and sometimes devastating, neurological impairment and, in rare cases, death. The incidence of severe hyperbilirubinemia is one in 2480 live births (assuming about 320,000 live births per year) and the incidence of chronic encephalopathy has been estimated to be one in 100,000. Based on an annual birthrate in Canada of 330,000, the expected number of new cases of kernicterus, or bilirubin-induced neurologic dysfunction, per year is 15 to 30. Although still rare, instances of kernicterus have increased contemporaneously with significant changes in maternal breastfeeding habits and early discharge practices. Studies on the safety of early discharge policies for healthy mothers and newborns indicate that hyperbilirubinemia is the first cause for return to hospital within one week of birth and accounts for up to 50% of hospital admissions in this period.

Screening of Hyperbilirubinemia

The goal of screening for hyperbilirubinemia is to promote earlier identification and treatment to avoid severe or critical hyperbilirubinemia and kernicterus, while at the same time preventing the overtreatment of newborns whose bilirubin levels will never reach a critical level and will resolve without treatment. Three methods are used to estimate or measure directly the bilirubin levels in neonates: visual assessment, transcutaneous measurement of bilirubin, and analysis of blood serum.

Visual assessment of jaundice has been the mainstay of screening for neonatal jaundice. Visual assessment is performed by blanching the skin with slight finger pressure and noting the underlying colour of the skin and subcutaneous tissue and its progression from the head to the trunk and the extremities. Although visual assessment is commonly used, estimating the risk of hyperbilirubinemia using this method has been shown to be unreliable.

Transcutaneous bilirubinometry provides a non-invasive method for the estimation of serum bilirubin using a hand-held electronic device that measures the amount of bilirubin in the skin and subcutaneous tissues. The transcutaneous bilirubin (TcB) measurements and gestational age are used by the physician or nurse to assign a risk of clinically significant hyperbilirubinemia and to determine the need for a confirmatory serum bilirubin test.

Total serum bilirubin (TSB) measurement, the gold standard for detecting hyperbilirubinemia in newborns, requires drawing blood from the neonate, analyzing it, and estimating a risk of increasing hyperbilirubinemia by plotting the TSB measurement on an hour-specific nomogram. Using the TSB measure and gestational age, the physician or nurse can determine a risk of clinically significant hyperbilirubinemia and assess the potential benefit of further testing and follow-up.

Treatment of Hyperbilirubinemia

Phototherapy is the most common treatment for hyperbilirubinemia and is used to prevent TSB levels from reaching a level at which exchange transfusion may be required.

Exchange transfusion was the only treatment for hyperbilirubinemia prior to the development of phototherapy, but it is now an unusual occurrence even in neonatal intensive care units. During an exchange transfusion, twice the infant's blood volume is replaced with donor blood.

Clinical Practice Guidelines

The 2004 guideline of the American Pediatric Association Subcommittee on Hyperbilirubinemia and the 2007 position statement of the Fetus and Newborn Committee of the Canadian Pediatric Society both provide recommendations regarding the use of TcB in the detection, management, and prevention of hyperbilirubinemia in newborns >35 weeks' gestation. Among the recommendations are the following:

- All newborns who are visibly jaundiced within the first 24 hours of life should have their bilirubin level determined.
- TcB measurement is considered an acceptable method, either as a routine procedure or in infants with visible jaundice. The result should be summed with the 95% CI of the device to estimate the maximum probable TSB concentration.
- Universal screening requires a systematic approach to the risk assessment of all infants before discharge and the implementation of follow-up care if the infant develops jaundice.

Project Context

A 2010 environmental scan of Alberta Health Services zonal practices regarding neonatal jaundice and hyperbilirubinemia with late preterm and term (>35 weeks) infants indicated that public health nurses in all zones conducted physical assessments of newborns, typically within 48 hours of discharge, but the assessment can be as late as 7 days after discharge (mean 40.2 hours). Public health nurses tend to screen for jaundice via visual inspection and through newborn feeding/weight/elimination/behaviour history. TSB testing was not offered by public health nursing services in the South and Central zones.

TcB testing occurred in 20 of the 40 acute care sites surveyed, primarily in Calgary, Edmonton, and Central Zones. Limited TcB testing occurred in the South and North Zones. Of the two major urban zones (Calgary and Edmonton), only the Edmonton Zone indicated that TcB testing and protocols for both urban and rural settings were in place. In the Calgary Zone, TcB testing takes place in the city of Calgary only. In the South Zone, public health nurses provided TcB measurement in Medicine Hat and Brooks, and in the North Zone, TcB was provided only in Fort McMurray. In 2007, the Calgary Zone implemented a comprehensive TcB screening program for all newborn infants at 35 weeks' gestational age or older.

Incorporating TcB into regular clinical practice and community health visits holds the promise of reducing the number of invasive blood tests and hospital readmissions due to suspected hyperbilirubinemia and the need for invasive methods of testing. Ultimately, it is hoped that the use of TcB would reduce the incidence and costs of severe hyperbilirubinemia and its associated long-term health outcomes.

Technology Effects and Effectiveness

Objectives

The objectives of this systematic review and critical appraisal are:

1) to examine scientific evidence about the safety of TcB in screening neonates of ≥35 weeks' gestation for significant hyperbilirubinemia in both acute care and community settings
2) to examine scientific evidence about the accuracy of TcB in screening neonates of ≥35 weeks' gestation for significant hyperbilirubinemia in both acute care and community settings
3) to examine scientific evidence about the impact on changing patient management and clinical outcomes of implementing universal TcB screening programs
4) to identify barriers to and requirements of implementing a universal TcB screening program

Method

An experienced research librarian conducted a comprehensive literature search to identify relevant studies published between 2000 and January 2012.

Two researchers conducted study selection using pre-specified inclusion and exclusion criteria, and appraised the methodological quality of the included screening accuracy studies using a widely accepted quality assessment tool for diagnostic accuracy studies.

Results

Thirty-nine primary studies that met the pre-specified inclusion criteria were included for analysis. Thirty-four studies examined the correlation/agreement between TcB and TSB values and the accuracy of TcB tests in predicting clinically significant hyperbilirubinemia. The other five studies reported the clinical outcomes of implementing TcB in screening programs for neonatal hyperbilirubinemia.

Quality appraisal for the 34 screening accuracy studies indicated that, except for the reference standard domain, less than one third of the studies demonstrated low risk of bias in patient selection, index test, and patient flow and timing domains.

Both BiliCheck and JM-103 devices appear to be safe; very few procedure-related adverse events were reported.

Evidence from 34 screening accuracy studies indicates a strong correlation between TcB and TSB measurements, with a correlation coefficient ranging from 0.75 to 0.95. Results on the agreement between TcB and TSB values varied across the included studies. TcB did not agree well with TSB at high TSB values, for example, TSB >15 mg/dL (>250 μmol/L). TcB could underestimate (particularly at high TSB values) and overestimate TSB levels in the magnitude of more than 3 mg/dL (50 μmol/L).

Using appropriate cut-off values, mostly derived from the receiver operating characteristic (ROC) curve, TcB can accurately detect infants with clinically significant hyperbilirubinemia (defined as the bilirubin level requiring phototherapy) or predict which infants will subsequently develop clinically significant hyperbilirubinemia during the first week of their lives. The reported TcB cut-off values varied across the studies, and lower TcB cut-offs for the corresponding TSB targets must be chosen to reach 100% sensitivity (a mandate for screening hyperbilirubinemia); the resulting high false

positives limit the ability of TcB in reducing TSB testing. Limited evidence suggested that a TcB cut-off of >75th percentile may be a good predictor of TSB of >95th percentile at 48 to 72 hours of age (pre-discharge). For detecting neonates with clinically significant hyperbilirubinemia, limited evidence also suggested significantly improved screening accuracy when using TcB or the combination of TcB and visual assessment, than when using visual assessment alone.

Of the five clinical outcome studies (one conducted in Canada), four found that implementing systematic TcB screening was associated with a reduction in unnecessary TSB testing without an increase in the incidence of neonatal hyperbilirubinemia. The other study found that TcB testing did not decrease the number of TSB tests but did result in a reduction of the number of readmissions for hyperbilirubinemia; which may have contributed to improved detection of hyperbilirubinemia before hospital discharge. The Canadian study also demonstrated reductions in the incidence of clinically significant hyperbilirubinemia, the need for phototherapy, and the delay in readmission for phototherapy, but no change in the length of readmission for phototherapy.

No direct evidence is available with respect to the change in incidence of acute or chronic encephalopathy (including kernicterus—a very rare condition).

Conclusions

Early hospital discharge policies have resulted in increased hospital readmission rates of healthy term or late preterm neonates for phototherapy and in a resurgence of kernicterus—a serious neurological damage. Timely identification of neonates at high risk for severe neonatal hyperbilirubinemia is encouraged as a preventive strategy.

TcB, a rapid, non-invasive, point-of-care test for predicting neonatal hyperbilirubinemia, has undergone clinical investigation in different countries and clinical settings for its reliability and accuracy. Performance of TcB in predicting hyperbilirubinemia, as measured by BiliCheck or JM-103 devices, has been examined in term or late-preterm neonates from various ethnic origins.

Research findings suggested that TcB is a safe procedure. TcB cannot replace TSB but can be considered a valid screening tool to determine the need for a confirmatory TSB test. A TcB cut-off of ≥75th percentile at 48 to 72 hours of age (pre-discharge) is a good predictor of TSB of ≥95th percentile. TcB appears to be a promising technology and may be a useful addition to clinical assessment in the screening of neonatal jaundice.

Evidence from five studies (one conducted in Canada) suggested that the implementation of a TcB screening program was associated with a reduction in the number of TSB tests but without an increase in the incidence of significant neonatal hyperbilirubinemia.

Several aspects should be taken into consideration when planning to implement a universal TcB screening program, including the availability and cost of TcB devices, the need to develop a local TcB nomogram, the selection of appropriate TcB cutoff values (a balance between 100% sensitivity with low specificity and maximal screening accuracy), the appropriate quality assurance, training, and education of personnel, and the impact on the demand for community resources

Economics Analysis

Objective and Methods

The objective was to review and synthesize the economic literature regarding the cost implications or cost effectiveness of transcutaneous bilirubin (TcB) and/or total serum bilirubin (TSB) testing. A review of published economic literature was conducted.

Results

When examining only costs, compared to TSB testing referred by means of visual inspection, three studies found TSB testing referred by means of a TcB screen to be associated with a reduction in health service use but not necessarily a net cost savings.

The study conducted in Calgary found that TcB screening resulted in reducing the incidence of hyperbilirubinemia, TSB testing and phototherapy while also lowering the age of the child at readmission for phototherapy. However, the study found that there were earlier and more frequent contacts with public health nurses. It is uncertain whether net savings or efficiencies would be realized, particularly when factoring in not only the costs related to additional quality assurance protocols, including the development and periodic refinement of the nomograms that are required components for TcB testing, but also the cost of purchasing the required number of meters to provide TcB testing in a programmatic fashion.

When examining both costs and health outcomes, the single study on cost effectiveness estimated that the cost per case of kernicterus prevented was more costly when testing with TcB pre-discharge, compared to when testing with TSB. This suggests that testing with TcB pre-discharge is not cost effective compared to testing with TSB.

Conclusion

Limited published evidence is available to inform the economic implications of alternative screening strategies for severe hyperbilirubinemia. Current literature suggests that, compared to visual inspection and clinical history, screening with TcB to assess the need of TSB testing may be associated with a reduction of specific healthcare resources such as TSB testing and phototherapy, but may not result in net cost savings when including costs associated with quality assurance and equipment. Consequently, it is uncertain whether TcB screening is cost effective, as it remains undetermined whether TcB results in a net cost savings to the health system and produces equivalent or significantly better health outcomes.

ABBREVIATIONS

All abbreviations that have been used in this report are listed below unless the abbreviation is well known, has been used only once, or is a nonstandard abbreviation used only in figures, tables, or appendices, in which case the abbreviation is defined in the figure legend or below the table.

AAP	American Academy of Pediatrics
AHS	Alberta Health Services
AUC	area under ROC curve
BC	BiliCheck
CI	confidence interval
CPS	Canadian Pediatric Society
DPD	2,5-dichlorophenyldiazonium
G6PD	glucose-6-phosphate dehydrogenase deficiency
HPLC	high-performance liquid chromatography
LOS	length of stay
LR	likelihood ratio
NA	not available
NH	neonatal hyperbilirubinemia
NICU	neonatal intensive care unit
NLR	negative likelihood ratio
NPV	negative predictive value
PHN	public health nurse
PLR	positive likelihood ratio
PPV	positive predictive value
RD	risk difference
ROC curve	receiver operating characteristic curve
SNH	significant neonatal hyperbilirubinemia
SROC	summary receiver operating characteristic curve
TcB	transcutaneous bilirubin
TSB	total serum bilirubin
VA	visual assessment

GLOSSARY

Acute bilirubin encephalopathy: The term used to describe acute manifestations of bilirubin toxicity seen in the first few weeks of life.

Area under ROC curve (AUC): The area under ROC curve provides a measure of the overall accuracy of the test. Values for AUC can range from 0 to 1. If the sensitivity and specificity of the test is 100% at each threshold, then the AUC is 1.0 and the test is perfect. If the AUC is 0.5, the test does not discriminate between the presence and the absence of the disease.

Change-in-management study: Also known as a therapeutic impact study or a diagnostic before-after-study, it measures the amount of starting, stopping, or modifying treatment before and after the incorporation of the new diagnostic technology in the management pathway.

Diagnostic accuracy: The amount of agreement between the information from the test under evaluation (for example, the index test) and the reference standard. Diagnostic accuracy can be expressed in many ways, including as sensitivity, specificity, likelihood ratios, diagnostic odds ratios, and the area under ROC curve.

Differential verification: Patients receive different reference tests.

False negative: Negative test results in a person who *does* have the condition being tested for.

False negative rate: Can be calculated as the number of false negatives divided by all those who have disease (that is, the number of true positives plus the false negatives). False Negative rate = number of false negatives/(number of true positives + false negatives) which is equal to 1 – Sensitivity.

False positive: Positive test results in a person who *does not* have the condition being tested for.

False positive rate: Can be calculated as the number of false positives divided by all those who do not have disease (that is, the number of true negatives plus the false positives). False positive rate = number of false positives/(number of false positives + true negatives) which is equal to 1– Specificity.

Index test: Test under evaluation.

Kernicterus: The term used to describe chronic or permanent clinical sequelae of bilirubin toxicity. The term "kernicterus" is reserved for the chronic form of bilirubin encephalopathy. Kernicterus is a rare condition characterized by athetoid spasticity, gaze and visual abnormalities, and sensorineural hearing loss in survivors. It may also be associated with mental retardation.

Late preterm infants: Infants with a gestational age of 34, 35, and 36 completed weeks (or from 238 to 258 days, inclusive).

Likelihood ratios (LR): State how many times more likely particular test results are in patients with disease than in those without disease. Positive likelihood ratio (PLR) = Sensitivity/(1–Specificity) and negative likelihood ratio (NLR) = (1–Sensitivity)/Specificity. LR is an overall measure of the discrimination of test results. The test is useless if LR = 1. NLR <0.1 and PLR >10 have been noted as providing convincing diagnostic evidence, whereas NLR <0.2 and PLR >5 give strong diagnostic evidence.

Negative predictive value (NPV): This is the probability that a patient does not have the target disease, given that the test result is negative. NPV = number of true negatives/(number of true

negatives + false negatives). NPV is known to depend on the prevalence of disease in the patient population being examined.

Partial verification: Not all patients receive the reference test.

Photometric analysis: Photometric analysis includes measurements in the visible, ultraviolet, and infrared regions of the spectrum. It generally involves comparison of the intensity of radiation passing through a sample of the material being analyzed with the initial intensity or the intensity of a reference sample. The method of photometric analysis that uses visible light is called colorimetry. Photometric analysis in which the intensities of the monochromatic components of transmitted radiation are scanned is called spectrophotometry.

Point of care: Refers to any tests performed by clinical personnel outside of the laboratory and close to the patient-care site.

Positive predictive value (PPV): This is the probability that a patient has a target disease, given that the test result is positive. PPV = number of true positives/(number of true positives + false positives). PPV is known to depend on the prevalence of disease in the patient population being examined.

Reference standard: The best available method for establishing the presence or absence of the condition of interest.

Receiver operating characteristic (ROC) curve: A graph illustration of the inverse relationship between sensitivity and specificity, where pairs of sensitivity and specificity are plotted for different thresholds. The ROC curve displays the true positive rate (sensitivity) on the vertical axis verses the false positive rate (1–specificity) on the horizontal axis. The ROC curve demonstrates the trade-off between the sensitivity and the specificity of the test. The point in the curve that is closest to the upper left corner gives the test threshold the best accuracy.

Safety: An umbrella term for any unwanted or harmful effects caused by using a healthcare technology.

Screening: The application of a test to detect a potential disease or condition in a person who has no known signs or symptoms of that disease or condition.

Sensitivity: This is the probability of a positive test result in people with a disease. It is the capacity of a diagnostic test to make a correct (positive) diagnosis in patients who have the target disease. Sensitivity = number of true positives/(number of true positives + false negatives).

Specificity: This is the probability of a negative test result in people without a disease. It is the capacity of a diagnostic test to make a correct (negative) diagnosis in patients who do not have the target disease. Specificity = number of true negatives/(number of true negatives + false positives).

Term infants: Infants with a gestational age of 37 to 42 completed weeks.

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Table of Contents

BACKGROUND AND PROJECT CONTEXT

Ken Bond BAH, BEd, MA; Bing Guo, MD, MSc

The objective of the Background and Project Context section is to provide a brief summary of the information on the health-related issue that has motivated the request; the population and condition involved; the technology under consideration; and the current state of treatment and health service capacity in Alberta.

To identify relevant information to address the objectives of this section, several information sources were used. Electronic searches of the scientific literature published from the year 2000 onwards were conducted in the following databases: MEDLINE (including in-process), EMBASE, CINAHL, and the Cochrane Database of Systematic Reviews. In addition, reference lists of reviews and retrieved articles were checked for relevant studies. A Google search for relevant information was also conducted. Searches were limited to English language articles. The following key words and related terms were used in the searches: neonatal, newborn, jaundice, hyperbilirubinemia, kernicterus, encephalopathy, screening, diagnosis, treatment, phototherapy, transcutaneous, bilirubinometry. Systematic reviews, narrative reviews, health technology assessment reports, clinical practice guidelines, government technical reports, population-based cohort studies, and population surveys were considered potential sources of information. As this information is used for describing the background and context only, no quality assessment was performed.

Information was also obtained from the AHS environmental scan report produced in June 2011 that describes the current state of services within AHS related to neonatal jaundice and hyperbilirubinemia. In addition, the Project Working Group members were contacted for information regarding the Alberta context.

BACKGROUND

Hyperbilirubinemia refers to an elevated level of bilirubin in the blood, which is a common occurrence in the first week of life.[1] Elevated bilirubin levels can progress to critical hyperbilirubinemia, a condition which, though uncommon, can cause long-term, irreversible, debilitating, and sometimes devastating, neurological impairment and, in rare cases, death.[1,2] Although serious events arising from severe hyperbilirubinemia, such as bilirubin encephalopathy, and kernicterus, are largely preventable, Canadian researchers believe that there has been a resurgence of kernicterus in healthy late preterm and term infants.[3] Total serum bilirubin (TSB) measurement is considered the gold standard for diagnosing hyperbilirubinemia in newborns and is one of the most commonly performed laboratory tests for patients in this age group.[1] TSB requires drawing blood from the neonate and the analysis of the serum requires laboratory resources and time.

The transcutaneous bilirubin (TcB) test, a non-invasive method for the estimation of serum bilirubin using a hand-held electronic device, measures the yellow colouration of the skin and subcutaneous tissues and can be used both in hospital and community settings. Hence, incorporating TcB into regular clinical practice and community health visits holds the promise of reducing the number of hospital readmissions due to suspected hyperbilirubinemia, and the need for TSB, lowering pain inflicted on infants, reducing stress on parents, reducing travel time and cost for those in rural and remote areas, and providing better patient satisfaction and experience. Ultimately, it is hoped that the use of TcB would reduce the incidence of and costs associated with severe hyperbilirubinemia and its associated long-term health outcomes.

As part of a larger project on developing an appropriate continuum of neonatal care (screening, diagnosis, and treatment) for the management of newborn jaundice, the Neonatal Jaundice and Hyperbilirubinemia Working Group in Alberta Health Services (AHS) requested this review of the current literature on the safety, effectiveness, and cost-effectiveness of the use of TcB, in both hospital and community settings, as a screening test for neonatal hyperbilirubinemia.

Context of Early Discharge for Term Births

A 2010 survey of acute obstetric sites in Alberta[4] indicated that, for most sites, the average length of stay for an uncomplicated vaginal delivery was less than 48 hours, while the average length of stay for uncomplicated Caesarean section delivery for most sites was less than 72 hours. Studies on the safety of early discharge policies for healthy mothers and newborns indicate that hyperbilirubinemia is the first cause for return to hospital within one week of birth and accounts for up to 50% of hospital admissions in this period.[5] Canadian researchers have estimated that almost three-quarters of those neonates readmitted for severe hyperbilirubinemia were from home.[3] Although the Canadian Pediatric Society (CPS) recommends that all newborns who are visibly jaundiced within the first 24 hours of life have their bilirubin level determined,[2] it has been shown that visual inspection of newborns is not an accurate means of assessing the presence or severity of hyperbilirubinemia.[6] There is also concern that under-recognition and inadequate investigation of severe hyperbilirubinemia in otherwise healthy infants contribute to early readmission and possibly long-term consequences, including bilirubin-induced encephalopathy and kernicterus.[3,7] Researchers[3,5] have reported that early discharge and jaundice management are strongly linked, and that no discharge protocol could be both efficient and safe without an appropriate jaundice screening and management policy.

Condition

Bilirubin, which is orange-yellow, fat soluble, and not readily excreted in the bile or urine, is produced by the breakdown of heme-containing proteins in the blood.[1] Jaundice is the common name given to the clinical condition of hyperbilirubinemia, the yellow colouration of the skin and sclera.[4] Newborns produce more than twice the amount of bilirubin as do adults, mainly because of their higher red blood cell volume per kilogram and shorter red blood cell lifespan and lower levels of albumin.[1,8] At some point during the first week after birth almost every newborn has a TSB level that exceeds 1 mg/dL (17 μmol/L), the upper limit of normal for an adult, and approximately two of every three newborns are jaundiced upon visual inspection by the clinician. Traditionally, this normal, transient bilirubinemia has been called "physiologic jaundice".[9] When TSB levels exceed a certain value, the infant is described as having "pathologic jaundice". However, because average bilirubin levels vary greatly across populations, the definition of a "normal" bilirubin level is problematic and these associated terms have been abandoned in favour of the more precise "neonatal bilirubinemia" and "hyperbilirubinemia".[9]

The cause for the higher-than-normal accumulation of bilirubin is multifactorial and includes low hepatic conjugation due to delayed enzymatic maturation and increased bilirubin uptake into the entero-hepatic circulation until gut flora is created with feeding.[10] At birth, fetal bilirubin has been cleared by the mother, so TSB levels are relatively normal. Once the newborn must conjugate and excrete bilirubin on his/her own, bilirubin levels increase, peaking at around 3 to 5 days of life and usually resolving by 2 weeks of age.[8] Asian, Native American, and other populations of primarily breastfed infants have higher peak levels, which are reached later and last longer.[1]

"Severe hyperbilirubinemia" is defined by the Canadian Pediatric Society as a TSB concentration greater than 20 mg/dL (340 μmol/L) at any time during the first 28 days of life and "critical hyperbilirubinemia" as a TSB concentration greater than 25 mg/dL (425 μmol/L) at any time during the first 28 days of life.[2] Severe and critical hyperbilirubinemia refer to the subsequent risk of encephalopathy that may follow from untreated hyperbilirubinemia.

Acute bilirubin encephalopathy usually progresses through three phases of increasing severity.[1] The first phase occurs in the first few days and is characterized by lethargy, sleepiness, hypotonia, decreased movement, and poor suck.[1,2] If this first phase is not managed effectively within the first week, early signs appear of the second phase, which includes marked stupor, irritability, backward posturing of the neck and trunk, high-pitched cry, and fever.[1,2] The third phase is characterized by deep stupor or coma, pronounced backward arching of the neck and trunk, no feeding, and a shrill cry.[1]

Chronic bilirubin encephalopathy, or kernicterus, refers to the pathological finding of deep-yellow staining of neurons and neuronal necrosis of the basal ganglia and brainstem nuclei.[2] Kernicterus is the chronic, permanent clinical sequelae of bilirubin toxicity, characterized by severe athetoid cerebral palsy, paralysis of upward gaze, hearing loss, intellectual impairment, and dental dysplasia.[2,11,12] Although TSB is an important risk factor, bilirubin-induced brain damage and kernicterus cannot be defined on the basis of TSB alone. Factors such as the albumin binding of bilirubin, hemolysis, gestational age, and genetic vulnerability modify the risk of kernicterus in an individual newborn.[13]

Many concurrent risk factors may influence the development of severe hyperbilirubinemia in the newborn, including visible jaundice at less than 24 hours and before discharge at any age, gestation less than 38 weeks, a sibling with severe hyperbilirubinemia, Asian or European background, dehydration, and exclusive or partial breastfeeding. Nevertheless, acute bilirubin encephalopathy does occur in otherwise healthy infants without identifiable risk factors.[2] In their investigation of severe hyperbilirubinemia in a Canadian cohort, Sgro and colleagues[3] found the main causes of severe hyperbilirubinemia to be ABO blood incompatibility followed by glucose-6-phosphate dehydrogenase deficiency.

Incidence of Neonatal Hyperbilirubinemia

Although the advent of exchange transfusion and phototherapy add to the difficulty of establishing the natural history of neonatal bilirubinemia,[1] it is estimated that 60% of term newborns develop jaundice and 2% reach a TSB concentration above the cut-off for severe hyperbilirubinemia.[14] Canadian researchers believe a conservative estimate of the incidence of severe hyperbilirubinemia for the period 2002 to 2004 was one in 2480 live births (assuming about 320,000 live births per year).[3] If it is assumed that 20% of those infants with critical hyperbilirubinemia and neurological findings have acute bilirubin encephalopathy, the incidence of this condition would be one in 10,000, approximately the same as that of phenylketonuria (PKU).[2] The incidence of chronic encephalopathy has been estimated at one in 100,000.[2] Based on an annual birthrate in Canada of 330,000 the expected number of new cases of kernicterus or bilirubin-induced neurologic dysfunction per year is 15 to 30.[15] Although still rare, kernicterus has increased in occurrence over the last two decades. This increase has occurred contemporaneously with significant changes in maternal breastfeeding habits and early discharge practices.[1,3]

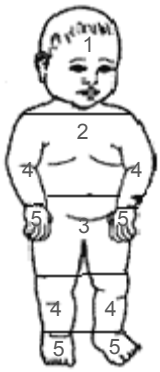
Screening for Neonatal Hyperbilirubinemia

The goal of screening for neonatal jaundice is to promote earlier identification and treatment to avoid severe or critical hyperbilirubinemia and kernicterus, while at the same time preventing the overtreatment of newborns with bilirubin levels that will never reach a critical level and will resolve without treatment. Because jaundice is a common and usually benign neonatal condition, it is difficult to tell which newborns may have a serious underlying disorder resulting in or manifesting as jaundice, as well as which newborns are at risk of developing potentially harmful levels of bilirubin. Three methods are used to estimate or measure bilirubin levels in neonates: visual assessment, transcutaneous measurement of bilirubin, and analysis of blood serum

Visual assessment

Visual assessment of jaundice is based on the yellow pigment of the skin, which has been the mainstay of screening for neonatal jaundice.[16] The visual assessment of jaundice is performed by blanching the skin with slight finger pressure and noting the underlying colour of the skin and subcutaneous tissue. Jaundice is usually visible when bilirubin levels are about 5 to 7 mg/dL (85 to 120 μmol/L)[1] and progresses from head to toe as the level of bilirubin rises. Kramer's dermal zones[17] (see Figure B.1) describe the relationship between serum bilirubin levels and the progression of skin discolouration.

Figure B.1: Estimation of serum bilirubin levels by cephalo-pedal progression of dermal icterus[17]



Dermal zone	Affected skin area	Range of serum bilirubin (mg/dL)
1	Head and neck	4 – 8
2	Truck to umbilicus	5 – 12
3	Lower body and thighs	8 –16
4	Arms and legs below knees	11 – 18
5	Hands and feet	> 15

Visual assessment relies on the association between bilirubin levels and the progression of jaundice; estimating the degree of hyperbilirubinemia by visual inspection has been generally considered unreliable.[18,19]

Analysis of blood serum

The best available method for predicting severe hyperbilirubinemia is the use of a timed TSB measurement analyzed in the context of the infant's gestational age.[2] TSB levels can be measured using high performance liquid chromatography (HPLC), Diazo-based methods, or other methods such as direct spectrophotometric methods.[20] HPLC is considered the gold standard as it is not subject to interference from hemoglobin or lipemia.[21] However, this method is usually used only in research laboratories because it is labour intensive and has a high capital cost. The most frequent TSB measurement uses a Diazo-based method, but it is subject to interference from hemoglobin and other intracellular compounds.[8]

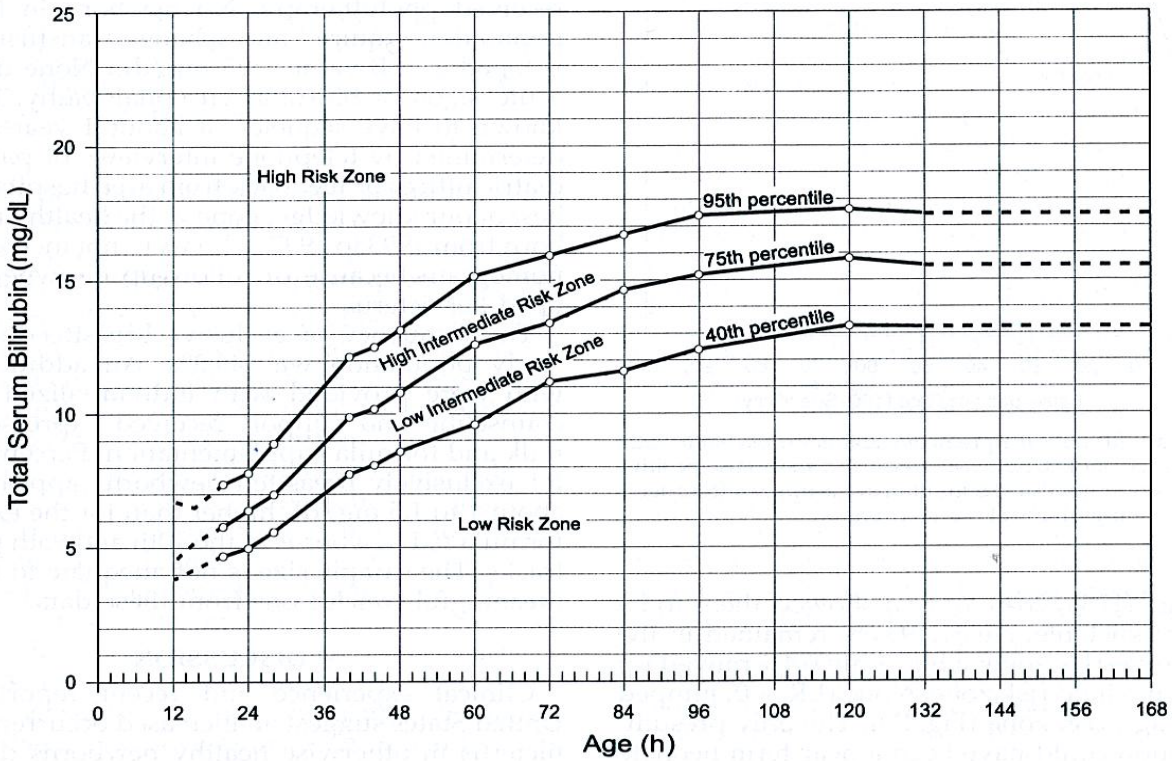
Measurements for bilirubin report the total and direct bilirubin values where "direct bilirubin" and "indirect bilirubin" refer to the way bilirubin has reacted to different fractions of the dye.[1,22] Indirect

bilirubin values are calculated as the difference between total and direct bilirubin measures. TSB measurements may use capillary or venous blood samples.

TSB nomogram

Pre-discharge risk assessment is performed using two methods, used individually or in combination.Bilirubin levels may be measured using TSB and the values plotted on an hour-specific nomogram, such as that developed by Bhutani et al.[23] (see Figure B.2). Using the TSB measure and gestational age the physician or nurse can assign a risk of clinically significant hyperbilirubinemia and assess the potential benefit of further testing and follow-up.[9]Alternatively, or in combination, the clinician or nurse can evaluate the infant for the presence of risk factors such as those listed previously.[1]

Figure B.2: TSB Nomogram for risk designation of term and late preterm neonates (from Bhutani et al.,1999[23])



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The Bhutani hour-specific TSB nomogram provides a simple and accurate method of locating a TSB value on a percentile-based frequency chart that defines risk-tracking for subsequent hyperbilirubinemia of increasing or decreasing severity. The measured level of neonate bilirubinemia is due to the net balance between bilirubin production and its elimination.[24] Because bilirubin elimination usually remains below bilirubin production during the first 72 hours after birth, an hour-based assessment of the net balance is shown by the ensuing changes in the percentile-based risk tract ("jumping of tracks") or by maintenance of the original risk tract.[24] A neonate who has a greater rate of rise is at increased risk of subsequent hyperbilirubinemia, while a neonate who is following the same percentile curve is less likely to develop severe hyperbilirubinemia.[25]

If a bilirubin value is above the 95th percentile for age curve, the nomogram predicts that the infant is in the "high-risk zone" for developing clinically significant hyperbilirubinemia. Similarly, bilirubin

levels between the 75th and 95th percentile curves predict the infant is in the "high–intermediate risk zone."[26]

According to the AAP guidelines that used the Bhutani nomogram to determine the need for phototherapy, neonates with gestational age of ≥35 weeks require phototherapy if they have TSB levels as shown in Table B.1.

Table B.1: Approximate TSB levels for initiating phototherapy for healthy neonates with gestational age ≥ 35 weeks*

Age (hour)	TSB levels	
	mg/dL	µmol/L
24	≥10	≥171
48	≥13	≥221
72	≥15	≥255
96	≥17	≥289
120	≥18	≥306
144	≥18	≥306
168	≥18	≥306

*Data were obtained from Figure 3 in the AAP guidelines[27]

Although used widely in the literature, the Bhutani TSB nomogram suffers from several limitations. First, it does not represent the natural history of bilirubinemia in newborns.[9] Second, less than 25% of infants who had pre-discharge TSB levels measured returned for follow-up after discharge. It is likely that some of those who were not clinically jaundiced or who had low pre-discharge TSB levels were not seen in follow-up visits.[9] Therefore, the TSB values obtained after 48 to 72 hours likely represent a biased sample of more-jaundiced infants. Third, The TSB levels reported for the 40th percentile after 48 hours are much higher than the mean TSB levels reported in any previous study.

Clinical issues with TSB measurements

A clinical challenge in the management of newborn jaundice has been the widespread reports of high variability in the laboratory measurement of bilirubin.[28] Errors in the laboratory measurement of TSB have been a perennial problem because of difficulties with bilirubin standards, protein matrix effects, and a variety of different methods used for measurement.[29] Furthermore, significant differences have been reported in TSB levels from capillary blood obtained by the heel-stick method compared with blood obtained from a vein.[28] This observation adds additional uncertainty to the interpretation of TSB measurements.

The determination of TSB levels remains an invasive, painful, stressful, and time consuming procedure.[30] Repeated blood sampling is associated with risk of infection and scar formation.[31] Depending on the location of laboratory services, there may be delay before TSB results are available for initiating treatment.[31]

Transcutaneous bilirubin test

Transcutaneous bilirubinometry, which uses a handheld, noninvasive, point-of-care testing technology, allows the estimation of serum bilirubin concentration via the spectral reflectance of an infant's skin. A detailed description of this technology is provided in T section.

Other tests may be used to assess the risk of hyperbilirubinemia, including umbilical cord blood TSB, cord blood hemoglobin or hematocrit measurement, blood group and Coombs testing, glucose-6-phosphate dehydrogenase deficiency (G6PD), and end-tidal monoxide. Although all these tests may be useful in establishing a diagnosis, most of them are considered unsuitable for screening in the absence of other risk factors.[2,32]

Treatment of Hyperbilirubinemia

Phototherapy

Phototherapy is the most common treatment for hyperbilirubinemia and is used to prevent TSB from reaching a level at which an exchange transfusion may be required. Phototherapy uses light energy directed at the skin to change the shape and structure of bilirubin molecules residing in the skin and subcutaneous tissue into molecules that can be excreted without undergoing conjugation by the liver. The rate of reduction of serum bilirubin concentrations depends on the rate of bilirubin photoalteration, the transport of these products, and their elimination.[1] The light used must match the bilirubin absorption spectrum (violet, blue, or green light); light sources for this spectrum include fluorescent, tungsten, halogen, light-emitting diode, and fiberoptic lights. Serious side effects of phototherapy are rare and include injury to the retina (if the eyes are not properly covered), loose bowel movements, temporary lactose intolerance, decreased platelet count, and potential interference with circadian rhythm and with parent-infant bonding.[1]

Exchange transfusion

Prior to the development of phototherapy, exchange transfusion was the only treatment for hyperbilirubinemia, but it is now an unusual occurrence even in neonatal intensive care units.[1] During an exchange transfusion, twice the infant's blood volume is exchanged in small aliquots and replaced with equal aliquots of donor blood. The procedure is usually performed through two central catheters. The double volume exchange transfusion replaces approximately 85% of the infant's blood volume and reduces bilirubin levels by approximately 40%, although serum bilirubin levels can rise to 70% to 80% of pre-exchange levels within 30 minutes of the procedure. Potential complications of exchange transfusion include thrombocytopenia, hypocalcemia, hypomagnesemia, arrhythmia, cardiac arrest, respiratory or metabolic acidosis, rebound metabolic alkalosis, and complications associated with blood transfusion and umbilical vessel catheterization.[1]

Clinical Practice Guidelines

Three clinical practice guidelines were selected to provide background about the recommended role that serum and transcutaneous bilirubin measures play for the management and treatment of hyperbilirubinemia in newborns >35 weeks' gestation: United States' clinical practice guideline,[27] Canadian position statement,[2] and National Collaborating Centre for Women's and Children's Health (UK National Health Service).[33]

The focus of the 2004 clinical practice guideline of the American Academy of Pediatrics (AAP)[27] is to reduce the incidence of severe hyperbilirubinemia and bilirubin encephalopathy while minimizing the risks of unintended harm such as maternal anxiety, decreased breastfeeding, and unnecessary costs or treatment. The guideline provides recommendations for both primary and secondary prevention of jaundice. Primary prevention consists mainly of encouraging breastfeeding. The recommended secondary prevention includes routine monitoring for development of jaundice, and that nurseries have established protocols for the assessment of jaundice that include nursing staff assessing jaundice via visual assessment and the capacity to obtain a TcB level or order a TSB measurement in the event of suspected jaundice. The guideline recommends:

- Jaundice should be assessed (preferably by TcB) whenever the infant's vital signs are measured but no less than every 8 to 12 hours (Recommendation 2.2); however, if there is any doubt about the degree of jaundice, TcB or TSB should be measured (Recommendation 3.1).
- A TcB or TSB measurement should be performed on every infant who is jaundiced within the first 24 hours after birth.
- Assessment of risk should also be made for newborns at 36 weeks' gestational age weighing 2000 grams or more, or at 35 weeks' gestational age and weighing 2500 grams.
- TcB or TSB should be used individually or in combination with an assessment of clinical risk factors for pre-discharge assessment of risk (Recommendation 5.1.1). TSB or TcB measurement and plotting results on a nomogram is the best documented method for assessing risk of subsequent hyperbilirubinemia.
- All infants should be examined by a qualified healthcare professional within the first few days of discharge to be assessed for the presence or absence of jaundice.
- Two follow-up visits may be required: one visit within 24 to 48 hours and a second between 72 and 120 hours. In the absence of ensured appropriate follow-up for those considered at elevated risk, discharge should be delayed until appropriate follow-up is secured or the risk period has passed (Recommendation 6.1.3).
- For follow-up assessment, clinical judgment should be used to determine the need for a bilirubin measurement. If there is any doubt about the degree of jaundice, TSB or TcB levels should be measured. Visual estimation of bilirubin levels can lead to errors, particularly in darkly pigmented infants.
- With respect to a management program, there should be universal screening for jaundice among newborns that includes a systematic assessment before discharge for the risk of severe hyperbilirubinemia, early and focused follow-up based on that risk assessment, and prompt intervention when indicated, to avoid complications.

The Canadian Pediatric Society (CPS)[2] 2007 position statement for the detection, management, and prevention of hyperbilirubinemia recommends:

- All newborns who are visibly jaundiced within the first 24 hours of life should have their bilirubin level determined.
- If the TSB or TcB concentration has not been measured already because of clinical jaundice, a TSB measurement should be obtained at the same time as the metabolic screening test, or a TcB measurement should be obtained either at discharge or within the first 72 hours of life.
- Any infant discharged before 24 hours of life should be reviewed within 24 hours by an individual competent in newborn care and assessment, who can obtain a TSB or TcB measurement and arrange for treatment, if necessary.
- TcB measurement is considered an acceptable method for the estimation of serum bilirubin levels, either as a routine procedure or in infants with visible jaundice. The result should be summed with the 95% CI of the device to estimate the maximum probable TSB concentration.

- Universal screening requires a systematic approach to the risk assessment of all infants before discharge and the institution of follow-up care if the infant develops jaundice.

The 2010 practice guidelines of the UK National Collaborating Centre for Women's and Children's Health[33] were produced to address the difficulty of identifying which neonates are at risk of developing high levels of bilirubin that could become dangerous, or which neonates have a serious problem as the explanation for their physiological jaundice. The guidelines recommend:

- All neonates should be checked for factors associated with an increased likelihood of developing significant hyperbilirubinemia soon after birth. These factors include gestational age <38 weeks, having a sibling who had neonatal jaundice requiring phototherapy, the mother's intention to breastfeed exclusively, and visible jaundice within the first 24 hours of life.
- Visual assessment should be made of all neonates for jaundice at every opportunity, especially in first 72 hours of life.
- Neonates who have factors associated with an increased likelihood of developing significant hyperbilirubinemia should receive additional visual inspection by a healthcare professional during the first 48 hours of life.
- Serum bilirubin measurement should always be used to determine bilirubin level in neonates with jaundice in first 24 hours of life.
- Bilirubin levels should be used to determine management of hyperbilirubinemia in all neonates.

The guideline makes no recommendation regarding the need to determine the serum bilirubin of non-jaundiced neonates prior to discharge. The main difference between North American (that is, the United States and Canada) and UK guidelines is that the UK guidelines do not recommend the routine check of bilirubin levels in all newborn infants.

PROJECT CONTEXT

Alberta Health Services (AHS) wants to ensure that appropriate screening and diagnostic strategies are in place to identify newborns who are at high risk of developing severe or critical hyperbilirubinemia, and to avoid treatment of newborns who have physiological jaundice. In pursuit of this goal, AHS wants to know whether there is value in increasing the availability and use of TcB to test for hyperbilirubinemia across Alberta.[4] In 2010, Health Promotion and Disease Prevention conducted an environmental scan to determine the current state of practices in AHS zones as related to neonatal jaundice and hyperbilirubinemia with late preterm and term (gestation age >35 weeks) infants, the perceived strengths and areas for improvement in screening for neonatal hyperbilirubinemia, and the perceived challenges if widespread TcB testing were to be considered. Information was gathered from 40 of the 60 acute care sites having obstetrical services in Alberta. Acute care sites that did not respond to the survey were not located in large urban areas and provided service to a predominantly rural population.[4] While all but one site in each of the Edmonton and Calgary Zones and 80% of sites in the Central Zone responded, only 4/8 and 12/20 sites from the South and North Zones, respectively, responded. Hence, information on practices in large urban areas and the Central Zone is relatively complete, while that for the north and south of the province provides a less-than-complete picture.

Capacity of the current system to provide screening

All but one acute care site offers TSB testing.[4] That one site does not offer testing because of the low number of deliveries and its early discharge policy. Serum samples required for TSB testing are primarily collected by in-patient laboratory services personnel (80%), but nursing personnel (27%) also contribute to serum collection. Public health nurses in all zones conduct physical assessments of newborns, typically within 48 hours of discharge, but the assessment can be as late as 7 days after discharge (mean 40.2 hours). Public health nurses tend to screen for jaundice via visual inspection and through the history of newborn feeding, weight, elimination, and behaviour. TSB testing was not offered by public health nursing services in the South and Central Zones. In the Calgary Zone, only public health nurses working in the city of Calgary collected TSB samples in the home or clinic setting. In the Edmonton Zone, TSB testing was offered by public health nurses across the zone, in both urban and rural settings. Importantly, while TSB testing was available in a variety of settings across the province, families living in rural and remote areas were often required to travel significant distances to a hospital or laboratory for testing and follow-up if TSB testing was not offered in the home or at local clinics.[4]

TcB testing occurs in 20 of the 40 acute care sites, primarily in the Calgary, Edmonton, and Central Zones. Limited TcB testing occurs in the South and North Zones. TcB testing in the acute care sites is performed primarily by registered nurses (96%) and licenced practical nurses (74%). Of the two major urban zones (Calgary and Edmonton), only the Edmonton Zone indicated that TcB testing and protocols were in place for both urban and rural settings. Public health nurses across the Edmonton Zone offered TcB testing within the community. In the Calgary Zone, TcB testing takes place in the city of Calgary only. In the South Zone, public health nurses provided TcB measurement in Medicine Hat and Brooks; in the North Zone, TcB was provided only in Fort McMurray. The most common brand of TcB meter used in acute care sites was the Dräger JM-103™.[4] Sixty percent of acute care sites indicated that their bilirubinometers were owned rather than leased.

The Calgary Zone implemented a comprehensive TcB screening program in June 2007 using locally developed nomograms for all newborn infants of 35 week's gestational age or older (Dr. S. Wainer et al. 2010, unpublished internal document). TcB measurements are performed on all healthy infants during the first day of life and then subsequently on a daily basis while in hospital or at subsequent home or community clinic visits by public health nurses during the early neonatal period. Nursing staff decide on the need for TSB measurements based on both action lines on the nomograms and TcB trends.

Acute care sites in large urban zones (Edmonton, Calgary, and central Alberta) are more likely to have and use formal protocols to guide the assessment of jaundice. In other zones, informal or verbal guidelines are used to direct practice.[4] Respondents reported a lack of availability of TcB meters in rural and remote areas of the province, and the environmental scan identified significant disparities between the level of services available to urban and rural populations.[4]

System supports and related services necessary for appropriate provision of TcB

Most of the acute service staff surveyed believed that service providers must have the ability to offer timely TSB testing and follow-up when TcB testing is being used. Respondents in zones using TcB devices believed that the meters assisted decision-making, were less invasive than TSB, decreased the number of blood samples drawn, decreased the number of infants presenting with critical bilirubin

levels, allowed treatment to be initiated earlier, and reduced the length of hospital stay.[4] Respondents in zones without TcB devices believed that a lack of meters reduced the amount of equipment needed for home visits, and that without reliance on a TcB meter, nurses developed strong clinical skills and parents developed increased confidence in their own assessment skills.

With respect to TcB meter maintenance, it was noted that up to 25% of TcB devices can be under repair at any given time. In addition, concern existed about the turn-around time for TcB meter validation, maintenance, and repairs and with respect to the accuracy of TcB meters in general.[4] To address this, respondents suggested establishing a province-wide maintenance and calibration contract to ensure the accuracy and validity of TcB meter readings. Respondents also suggested that TcB meter orientation be available where TcB meters are in use.

The Calgary Zone reported that a multidisciplinary and closely coordinated approach (involving community pediatrics, laboratory services, acute care and public health nursing) was essential to the success of the program there (Dr. S. Wainer et al., 2010, unpublished internal document). In addition, rigorous and ongoing clinical validation processes have been critical to ensuring that all TcB monitors used in the community perform within defined limits. Over 25% of the devices have required recalibration or repair due to unacceptable performance on the benchmarking tests. Quality control processes have included electronic quality control as per manufacturer guidelines, direct TcB-TSB correlations, and in-vitro accuracy testing using multiple colour standards (Dr. S. Wainer et al., 2010, unpublished internal document). The Calgary TcB Program Management Committee recommends that any alternative nomograms be validated relative to local laboratory methods, and that a mechanism be put in place to provide ongoing data collection regarding both device performance and patient outcomes.

TECHNOLOGY EFFECTS AND EFFECTIVENESS

Bing Guo, MD, MSc; Christa Harstall, MHSA

INTRODUCTION

This health technology assessment report has been prepared in response to a request from Alberta Health Services to perform a systematic review and critical appraisal of the scientific evidence on the performance of TcB testing in the screening of hyperbilirubinemia in healthy term or late preterm neonates (gestational age ≥35 weeks).

Objectives

The objectives of this systematic review and critical appraisal are:

1) to examine scientific evidence about the safety of TcB in screening neonates of ≥35 weeks' gestation for significant hyperbilirubinemia in both acute care and community settings
2) to examine scientific evidence about the accuracy of TcB in screening neonates of ≥35 weeks' gestation for significant hyperbilirubinemia in both acute care and community settings
3) to examine scientific evidence about the impact on changing patient management and clinical outcomes of implementing universal TcB screening programs
4) to identify barriers to and requirements of implementing a universal TcB screening program

This section will address a set of questions from Alberta Health Services with respect to the screening test, effects and effectiveness, and program context.

- Is TcB a safe measurement in terms of procedure-related adverse events?
- Can TcB accurately detect which neonates have clinically significant hyperbilirubinemia (defined as a bilirubin level requiring phototherapy) or predict which neonates will develop clinically significant hyperbilirubinemia within the first week of their lives?
- Is TcB more accurate than visual assessment in detecting which neonates have clinically significant hyperbilirubinemia or in predicting which neonates will develop clinically significant hyperbilirubinemia within the first week of their lives?
- What are the optimal TcB cut-off values in predicting clinically significant hyperbilirubinemia?
- Does the implementation of a universal TcB screening program reduce the number of TSB testing without resulting in an increase in the incidence of clinically significant hyperbilirubinemia?
- Does the implementation of a universal TcB screening program reduce the incidence of clinically significant hyperbilirubinemia and/or the need for phototherapy?
- Does the implementation of a universal TcB screening program reduce the delay in readmission for phototherapy?
- Does the implementation of a universal TcB screening program reduce the length of hospital readmission time for phototherapy?

- Does the implementation of a universal TcB screening program reduce the incidence of acute or chronic encephalopathy (including kernicterus)?
- What are the essential components of a universal TcB screening program?

Project Scope

Population: healthy term or late preterm neonates (gestational age ≥35 weeks), regardless of ethnic background.

Index test: TcB measured by BiliCheck or JM-103 jaundice meters, because these two devices have been approved by Health Canada and are currently available in Alberta.

Comparator test: visual assessment.

Reference standard: TSB measured by HPLC, 2,5-dichlorophenyldiazonium (Diazo or modified Diazo), or other standard laboratory methods. Diazo method and other standard laboratory methods are used most commonly in clinical practice for both screening and confirmation of neonatal hyperbilirubinemia, whereas the gold standard HPLC is rarely conducted in current clinical practice because of its high cost and technical difficulty. Therefore, while studies using HPLC as the reference standard are highly desired, for practical reasons, TSB measured by Diazo or other standard laboratory methods is also considered an appropriate reference standard. The comparison between different laboratory methods for TSB is beyond the scope of this report.

Outcomes of interest: adverse events associated with the use of TcB devices; test performance (correlation/agreement between TcB and TSB measurements, sensitivity, and specificity); clinical outcomes (avoidance of unnecessary blood sampling for TSB testing, incidence of clinically significant hyperbilirubinemia, rate of hospital readmission for phototherapy, number of neonates needing phototherapy or exchange transfusion, or incidence of kernicterus).

DESCRIPTION OF TECHNOLOGY

Devices

Currently, two devices are available in Canada for TcB measurement: the Philip's BiliCheck® and the Dräger JM-103™. The devices use different methods to estimate serum bilirubin levels, therefore they may differ slightly in terms of their test accuracy in different infant populations.

BiliCheck

The BiliCheck instrument consists of a light source, a microspectrophotometer, a fiberoptic probe, and a microprocessor control circuit with firmware for analysis and interpretation of bilirubin measurement.[34] BiliCheck measures TcB using the entire spectrum of visible light (380 to 760 nm) reflected from the skin.[24] The measuring probe is pressed against the forehead of the infant. White light is transmitted through the skin of the infant, and by analysis of the light reflected back from the infant's skin, an internal microprocessor calculates the amount of bilirubin present in the skin.[35] The microprocessor uses an algorithm to account for interfering factors such as hemoglobin, melanin, and dermal thickness. Therefore, theoretically the BiliCheck should be able to provide an unbiased measurement of TcB independent of an infant's race, ethnicity, gestational age, and weight.[24]

The BiliCheck device provides a digital read-out of the actual transcutaneous bilirubin concentration and requires five repeat measurements that are averaged to provide one TcB measurement. The

main limitation with BiliCheck is the need for disposable clean tips (called BiliCal) for each measurement, which increases the cost of using the BiliCheck device.[36]

JM-103

The JM-103 device was introduced in 2003.[37] The JM-103™ (manufactured by Dräger Medical Canada, Inc., Richmond Hill, ON) utilizes a dual wavelength and optical path system, which is designed to minimize the impact of melanin, hemoglobin, and subcutaneous tissue depth on device performance.[38] The measuring probe is pressed against the sternum or forehead of the infant, and bilirubin concentration is calculated by the difference between optical densities of light returning to the sensor from shallow tissue and light returning from the subcutaneous tissue. This difference allows evaluation of bilirubin levels in the subcutaneous tissue without the influence of skin pigmentation.

Regulation Status (Health Canada and US FDA)

Health Canada (Medical Devices Active License Listing, Health Canada [accessed January 10, 2012]) and the United States FDA have approved three devices for TcB measurement (Table T.1):

- the BiliCheck™ (Children's Medical Ventures; Norwell, MA)
- the JM-102 (Minolta/Hill-ROM; Rockville, MD) predecessor to the JM-103
- the JM-103 (Dräger Medical; Richmond Hill, ON)

Table T.1: Approval for TcB devices in Canada and the United States

Device	Manufacturer	Health Canada Licence Issue Date	US FDA Approval Date
BiliCheck™ System	Philips Children's Medical Ventures LLC, Munroeville, PA, USA	1998.12.04	2001.03.19
Minolta/Hill-ROM Air Shields Jaundice Meter JM-102	Air-Shields, Inc. Rockville, MD, USA	2002.12.04 (no longer available)	1998.09.22
Dräger Jaundice Meter JM-103	Dräger Medical Canada, Inc., Richmond Hill, ON	2008.05.01	2003.04.01

TcB Nomograms

Since its publication, the Bhutani TSB nomogram[23] has been used widely to plot TSB or TcB data, although it suffers from some limitations (see Background section). Recently several TcB nomograms have been developed in various countries.

The TcB nomogram plots neonates' postnatal ages in hours against their TcB levels. As the level of bilirubin normally varies with age, this nomogram helps determine whether the bilirubin level at a particular hour of life puts a neonate at risk for developing clinically significant hyperbilirubinemia.[26]

A recent systematic review[25] identified and compared four TcB nomograms developed in North American (mixed population), European, Hispanic, or Thai populations. The analysis revealed significant differences in bilirubin values across populations and substantial variability in rates of bilirubin rise. Bilirubin rates of rise tend to plateau (equilibrium between bilirubin production and elimination) at about 96 hours of life. The systematic review concluded that a bilirubin rate of rise higher than in the previous period implies that bilirubin production exceeds elimination and indicates high risk for subsequent hyperbilirubinemia in neonates.

In addition to the four studies[39-42] indentified in this systematic review[25], TcB nomograms were also developed in Canada,[7,38] Brazil,[43] Israel,[44] China,[45] and India[46] for healthy term or late preterm neonates (see Table T.2).

Table T.2: Summary of studies that developed TcB nomograms

Study	No. of neonates	Ethnicity	TcB measurement	Time frame (hours)
Wainer 2012[7,38] Canada	774	Caucasian 41%, Black 5%, Middle Eastern 9%, Aboriginal 3%, Asian 41%, unknown 2%	Device: JM-103 TcB performer: study nurse or device-trained PHN	12 to 168
Maisels & Kring 2006[41] United States	3984	Caucasian 73%, Black 11%, Middle Eastern 7%, Indian 4%, East Asian 4%, Hispanic 1%, Native American 0.1%, unknown 0.3%	Device: JM-103 TcB performer: research nurses	First 96
Bental 2009[44] Israel	628	Ashkenazi 33%, mix of Ashkenazi and Sephardic 24%, Sephardic 41%, Ethiopian 2%	Device: JM-103 TcB performer: NA	12 to 168
Draque 2011[43] Brazil	223	Caucasian 46%, mixed race 34%, Black 20%,none of Asian ethnicity	Device: BiliCheck TcB performer: NA	24 to 288
Luca 2008[40] Italy	2198	Caucasian 100%	Device: BiliCheck TcB performer: a single fellow-neonatologist	First 96
Fouzas 2010[47] Greece	2646	Caucasian 100%	Device: BiliCheck TcB performer: trained physicians	12 to 120
Engle 2009[39] USA	2005	Hispanic 100%	Device: JM-103 TcB performer: nursing personnel	First 72
Yu 2011[45] China	6035	Chinese 100%	Device: JM-103 TcB performer: trained physician	0 to 168
Mishra 2010[46] India	625	Indian 100%	Device: BiliCheck TcB performer: a single fellow-neonatologist	First 72
Sanpavat 2005[42] Thailand	248	Thai 100%	Device: BiliCheck TcB performer: NA	First 96

Abbreviations: h – hour; NA – not available; TcB – transcutaneous bilirubin.

Summary of studies that developed TcB nomograms

As shown in Table T.2, five studies, conducted in the United States,[39,41] Italy,[40] Greece,[47] or China,[45] enrolled more than 2000 neonates. Four studies[7,41,43,44] included neonates from diverse ethnic origins,

while other studies included exclusively Caucasian,[40,47] Hispanic,[39] Chinese,[45] Indian,[46] or Thai[42] newborn populations.

Characteristics of included neonates varied across the studies. All neonates included in the Thailand study[42] were exclusively born by cesarean section. The Israel study[44] included only clinically jaundiced neonates. The Brazil study[43] included exclusively breastfed, term neonates. Except for two studies,[40,44] neonates who required phototherapy were excluded for the construction of TcB nomograms.

Five studies (including the three studies conducted in North America) used JM-103 devices and the other five studies used BiliCheck devices. TcB was measured during the first 72 hours in two studies,[39,46] during the first 96 hours (4 days) after birth in three studies,[40-42] up to 168 hours (7 days) in three studies,[7,44,45] and up to 228 hours (12 days) in one study.[43]

The major limitations associated with these studies are that they are not population-based and they represent the data of a single clinical centre only.

Limited data are available with respect to the natural course of TcB levels during the first days of life. The Brazil study[43] followed 223 neonates for 12 days, and measured TcB on each neonate on days 1, 2, 3, 4, 5, 6, 8, 10, and 12. The two European studies[40,47] provided normative data for TcB levels during the natural history of neonatal hyperbilirubinemia. The Greece study[47] took at least five TcB measurements for each neonate, at between 12 and 120 hours, with a large number of TcB measurements performed at 96 hours (1257 TcB measurements) and 120 hours (778 TcB measurements).

In the Italy study,[40] TcB levels recorded after the first 48 hours of birth came equally from neonates born both by Caesarean section and vaginally. In the United States, healthy neonates born from vaginal delivery are usually discharged at 48 hours of life. Therefore, data after 48 hours was obtained predominantly from neonates delivered by cesarean section (for example, from 60 to 96 hours, 86% of the study infants were delivered by cesarean section). In addition, one of the US studies[41] included neonates with a positive Coombs test who did not require phototherapy. Their inclusion could interfere with a correct description of the real natural course of neonatal hyperbilirubinemia.

Description of TcB nomograms

TcB nomograms presented in these studies are either based on TcB measurements obtained from the whole population,[39,42,43,45,46] or separately according to neonates' gestational age; for example, one for gestational age ≥37 weeks and another one for gestational age <37 weeks.[7,40] Some studies also presented a basic nomogram based on TcB measurements from the whole population, plus two or three separate TcB nomograms according to gestational age.[41,47]

All nomograms are similar in that the most rapid increase of TcB values occurred during the first 24 to 48 hours, and the rates of increase in TcB values then declined. Peak TcB values were reached at between 75 to 108 hours of age for 95th percentile. One study with a 12-day (228-hour) follow-up showed that the 95th percentile TcB level was 8.2 mg/dL at 24 hours, reached the peak of 12.2 mg/dL on the fourth day, and declined to 8.5 mg/dL on the 12th day of life.[43]

Yu et al.[45] developed a TcB nomogram using data obtained from 6035 Chinese neonates at 0 to 168 hours of age. The TcB level of most neonates remained in the pre-discharge TcB percentile-based risk zone and subsequently decreased to lower risk zones. Of neonates in the intermediate-to-high risk zone prior to discharge, 27% moved to the high risk zone after discharge. Of neonates in the

low-to-intermediate risk zone prior to discharge, 5.5% jumped to the high risk zone after discharge. None of the neonates in the low risk zone prior to discharge moved into the high-risk zone after discharge.

One of the US studies[41] found that breastfeeding and decreasing gestational age were associated with significantly higher TcB levels, but did not find any significant difference in TcB values at 48 to 96 hours between neonates born by vaginal delivery or cesarean section.

The two US nomograms[39,41] showed small but consistent differences in TcB values. Compared to a predominantly White, non-Hispanic population,[41] the Hispanic population showed significantly higher TcB values at the majority of time points studied.[39]

When compared to the Bhutani TSB nomogram, TcB nomograms[39,41,47] showed lower 95th percentile, particularly after 24 hours. At higher TSB levels, TcB seems to underestimate serum bilirubin. Some authors suggest that clinicians perform a serum bilirubin measurement when TcB values are approaching the threshold for starting phototherapy, or when the TcB rate of increase is higher than expected.[40]

METHODS

Literature Search

An experienced research librarian conducted a comprehensive literature search to identify all relevant studies published between January 2000 and January 2012. A broad search strategy was developed by using the search term not limited to any specific areas, to capture all relevant studies that examined various outcomes including safety, accuracy, or clinical outcomes of the use of TcB. No language limitation was applied. See Appendix T.A for details of the literature search strategy, including information sources, search terms used, and dates searched.

Study Selection

Study selection was conducted in two phases (Appendix T.A: Methodology/Study Selection).

First, two researchers (BG and KB) screened titles and abstracts; articles that appeared to be relevant were retrieved. Second, the same two researchers piloted and modified study selection criteria and assessed all retrieved studies for their eligibility. Disagreement was resolved by consensus. Appendix T.A: Methodology/Study Selection outlines the inclusion and exclusion criteria. Appendix T.B lists excluded studies and presents the reasons for their exclusion.

Quality Assessment

Two independent researchers (BG and KB) appraised the methodological quality of the included screening accuracy studies using the QUADAS–2 quality appraisal tool (see Table T.C.1). Appendix T.C presents the modified QUADAS–2, the guidance developed and piloted by the two researchers (BG and KB), and the quality assessment results.

The quality assessment results are incorporated into the review by investigating whether a relationship exists between quality concerns and study findings.[48]

A preliminary literature search indicated a paucity of studies that specifically examine the safety and clinical outcomes of the use of TcB. Methodological issues of such studies were identified and discussed in the report but no formal quality assessment was conducted.

Data Extraction

According to a pre-developed data extraction form, one researcher (BG) extracted information about the population, index test, reference standard, source of nomograms, target condition, outcomes of interest, and research funding sources (see Appendix T.A: Methodology/Data Extraction). A second reviewer (CH) cross-checked the extracted data for accuracy and consistency. Appendix T.D and Appendix T.E present the data extracted from each study.

Data Analysis and Synthesis

TcB measures subcutaneous (tissue) bilirubin concentrations, and TSB measures serum bilirubin concentrations, which are not the same. Furthermore, the transfer of bilirubin from blood to tissue is a complex process. Exploration of the relationship and agreement between TcB and TSB values would help determine whether TcB should be used to avoid unnecessary TSB sampling or whether it can replace TSB measurement. Within this context, outcomes of interest for this report include safety, test performance (correlation and agreement, and accuracy), and clinical outcomes.

Outcomes of interest

Safety

Safety is an umbrella term for any unwanted or harmful effects caused by using a healthcare technology.[49] For this report, safety outcomes were defined as any adverse events associated with the use of TcB devices, including direct harm (for example, infection of the measurement site caused by skin contact with uncleaned TcB devices) or indirect harm (for example, TcB reading errors caused by insufficient training or experience of TcB performers or technical failure of the devices).

Correlation between TcB and TSB values

Correlation quantifies the degree to which two variables are related. Correlation coefficients express the extent to which, when one variable goes up, the other variable goes up as well, and vice versa.[50]

For this report, the Pearson's correlation coefficient (r) is used to demonstrate the strength of the linear relationship between TcB and TSB values. The Pearson's correlation coefficient (r) ranges from −1 to 1.[50] An r value of 1 implies a perfect positive relationship and an r value of −1 implies a perfect negative relationship between the two variables. An r value of 0 implies no linear correlation between the variables. An r value between 0.7 and 0.9 indicates a strong (high) correlation, and an r value between 0.9 and 1.0 indicates a very strong correlation.

Agreement between TcB and TSB values

One of the shortcomings of the Pearson's correlation coefficient is that it cannot detect situations in which one set of readings is systematically higher or lower than the other.[50] The Pearson's correlation coefficient measures the strength of a relationship between two measurements, but not the agreement between them.[51] Data that show poor agreement between the two measurements can still produce high correlations.

In 1986, Bland and Altman suggested a more appropriate measure of the agreement between two measurements.[51] Their method is to plot the difference between the two measurements against their mean, assuming that the average of the two measurements represents the best estimate of the true value.[51] Measuring how much two measurements differ can help determine whether the new test can replace the old one, or whether the two tests can be used interchangeably.

For this report, the mean difference (d) between TcB and TSB values and 95% limits of agreement (d−1.96 standard deviation, d+1.96 standard deviation) are used to demonstrate the agreement between TcB and TSB values.

Screening accuracy

Screening for clinically significant hyperbilirubinemia in otherwise healthy term or late preterm neonates requires 100% sensitivity (that is, no false negatives). Therefore, TcB cut-off values are presented that yield 100% sensitivity with the best specificity.

The target TSB levels can be expressed as hour-specific percentiles or pre-specified single TSB values. For pre-discharge (≤72 hours of life), TSB levels of ≥200 μmol/L (12 mg/dL) and ≥250 μmol/L (15 mg/dL) are of particular interest because these two values are clinically significant at 48 hours and 72 hours of age, respectively, for healthy term infants ready for discharge (see Table B.1). For post-discharge (72 hours to 168 hours of life), TSB levels of ≥250 μmol/L (15 mg/dL) and ≥300 μmol/L (18 mg/dL) are of particular interest because these two values are clinically significant at 72 hours and from 120 to 168 hours of age, respectively, for healthy term infants discharged from the hospital (see Table B.1).

Clinical outcomes

Clinical outcomes include reduction in number of TSB tests, incidence of clinically significant hyperbilirubinemia, length of hospital stay upon readmission for phototherapy treatment, or incidence of kernicterus.

Approaches for data analysis and synthesis

Data extracted from the studies were described and integrated using a narrative approach. Sensitivity and specificity data are presented graphically in a forest plot, and in summary receiver operating characteristic (ROC) curves, if appropriate.

Although meta-analysis of the individual study results was planned, no formal meta-analysis could be conducted because:

1) the assumptions of the minimum number of studies[52] could not be satisfied to conduct a bivariate analysis
2) when limited to studies using a common TcB threshold, the studies were considered too heterogeneous with respect to other relevant clinical variables to be meaningfully combined in a univariate analysis

In addition, too few studies were available to make it possible to assess, formally or informally, the strength of a possible threshold effect. No formal assessment of heterogeneity was conducted as none of the meta-analytic models were appropriate based on the results of exploratory analysis.[52]

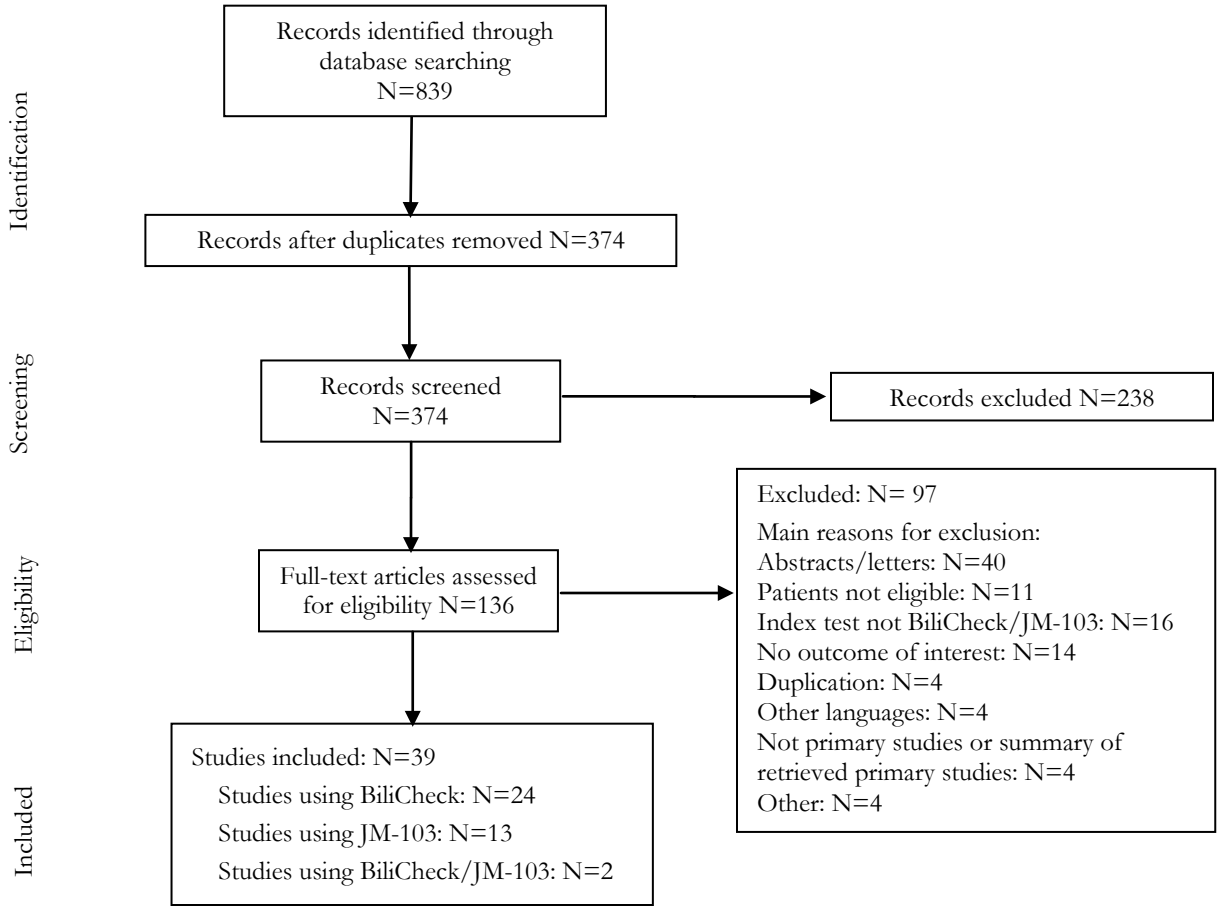
Neonate bilirubin levels change quickly during the first week of birth, increase most rapidly in the first 72 hours, and peak at 96 to 120 hours, and then decline. Early discharge policies (neonates by normal vaginal delivery are discharged by 48 hours, and neonates by C-section are discharged by 72 hours in Canada or by 96 hours in some countries) do not allow for the complete follow-up of neonates before bilirubin levels peak. To make evidence more relevant to clinical practice, TcB/TSB data are analyzed and presented separately for different time intervals, that is, pre-discharge (≤72 hours, or ≤96 hours), post-discharge (>72 h), or during the first week of life when studies measured TcB/TSB during an entire hospital stay.

RESULTS

Literature Search Results

A comprehensive literature search identified 839 citations from electronic databases. Full-text articles were retrieved for 136 citations that appeared to be relevant. On close examination of the full-text articles, 39 primary studies met the inclusion criteria and were included in this review. Ninety-seven studies were excluded for various reasons (see Appendix T.B). The process used for study selection is illustrated in Figure T.1.

Figure T.1: Flow diagram of study selection



Characteristics of Included Studies

The study characteristics with respect to study design, neonate characteristics, index test, and reference standard are summarized in Tables T.D 1–4 (Appendix T.D) for screening accuracy studies, and in Table T.E.1 (Appendix T.E) for clinical outcome studies.

Study design

Of the 39 included primary studies, 34 were screening accuracy studies that reported correlation and/or agreement between TcB and TSB measurements and sensitivity and specificity outcomes.

The other five studies reported the clinical outcomes of using TcB as a screening test for neonatal hyperbilirubinemia. These include one randomized controlled trial (RCT),[53] one non-randomized comparative study,[54] and three before-and-after studies.[7,55,56]

None of the 39 studies specifically examined the safety outcomes of using TcB; however, five studies reported adverse events associated with the use of TcB devices.

Data were collected prospectively in 21 studies[7,30,31,34,36,38,44-46,53,57-67] and retrospectively in four studies.[37,54,56,68] In the other 14 studies, however, no information was provided about the timing of data collection.

Location and setting

Of the 39 included studies, four studies[7,38,60,66] were conducted in Canada (two of them[7,38] in Calgary, Alberta). Nine studies[26,34,56,57,61,63,65,68,69] were conducted in the United States and one study[67] was conducted in Argentina. Twelve studies[16,28,30,36,44,54,59,64,70-73] were conducted in European countries and one[55] was conducted in Australia. Twelve studies[31,37,42,45,46,53,58,62,74-77] were conducted in Asian countries such as China, India, Thailand, or Malaysia.

The majority of studies were conducted at university hospitals; a few were conducted in community or regional hospitals. No study was found that was conducted in a rural setting.

Study population

The majority of the neonates enrolled in the 34 screening accuracy studies were healthy, full term or late preterm (gestational age ≥35 weeks). Generally, neonates were excluded from these studies if they had Rh isoimmunization, had been admitted to neonatal intensive care unit, had major congenital malformation, or were receiving or had received phototherapy.

While some accuracy studies included neonates having a diverse ethnic background, other studies included neonates mainly from a single ethnic origin, such as Caucasian,[30,36,59,64,70,71] Hispanic,[26,68] Chinese,[37,45,62,77] Thai,[42,74,75] or Indian.[46,58,76] All three Canadian studies[38,60,66] included neonates of diverse ethnic origins. Fifteen studies included only neonates with visible jaundice (see Tables T.D.1–4 in Appendix T.D).

Of the five studies that reported clinical outcomes, neonate populations were predominantly Caucasian in two studies,[54,55] Hispanic in one study,[56] and Indian in one study.[53] The one Canadian study[7] did not provide information about the population composition.

Index test

To measure TcB, 24 studies used BiliCheck, 13 studies used JM-103, and two studies[60,74] used BiliCheck and/or JM-103. Three of the four Canadian studies[7,38,60] used JM-103 devices.

As shown in Tables T.D.1–3, TcB was measured before hospital discharge in 11 studies, post-discharge in four studies[57,69,70,78] and during the first week of life in 14 studies; however, there was an overlap in the measurement times. Five studies[42,45,46,58,59] measured TcB during the first 72 or 96 hours after birth to construct a TcB nomogram and then followed neonates for subsequent hyperbilirubinemia; these studies were referred to as follow-up studies (Appendix T.D: Table T.D.4).

TcB was usually measured on the neonate's forehead using BiliCheck or JM-103 devices. The point of measurement was distanced from the hairline and free of any bruising, nevus, hemangioma or other skin anomalies. Some studies also measured TcB on the neonates' mid-sternum.

The BliliCheck devices were calibrated with a disposable tip before each measurement in all but one[76] study, whereas the JM-103 devices were calibrated once daily.

While information about who performed the measurement was not available in some studies, TcB was usually performed by a single investigator or trained nurses. One Canadian study[66] examined the results of TcB measured by several healthcare professionals, which tends to represent common clinical practice.

Comparator test (visual assessment)

Of the 34 screening accuracy studies, four studies[16,71,72,76] compared visual assessment with TcB measured by BiliCheck or JM-103 devices.

The five clinical outcome studies compared the results of adding TcB to visual assessment with visual assessment alone; however, only the RCT[53] provided details about the procedure for performing visual assessment.

Reference standard

While the majority of studies measured TSB using the Diazo or other standard laboratory methods, four studies, conducted in the United States,[34] Europe,[28] Turkey,[70] and Argentina[67] used TSB measured by HPLC (gold standard) as the reference standard; in all of these four studies, TcB was measured by BiliCheck.

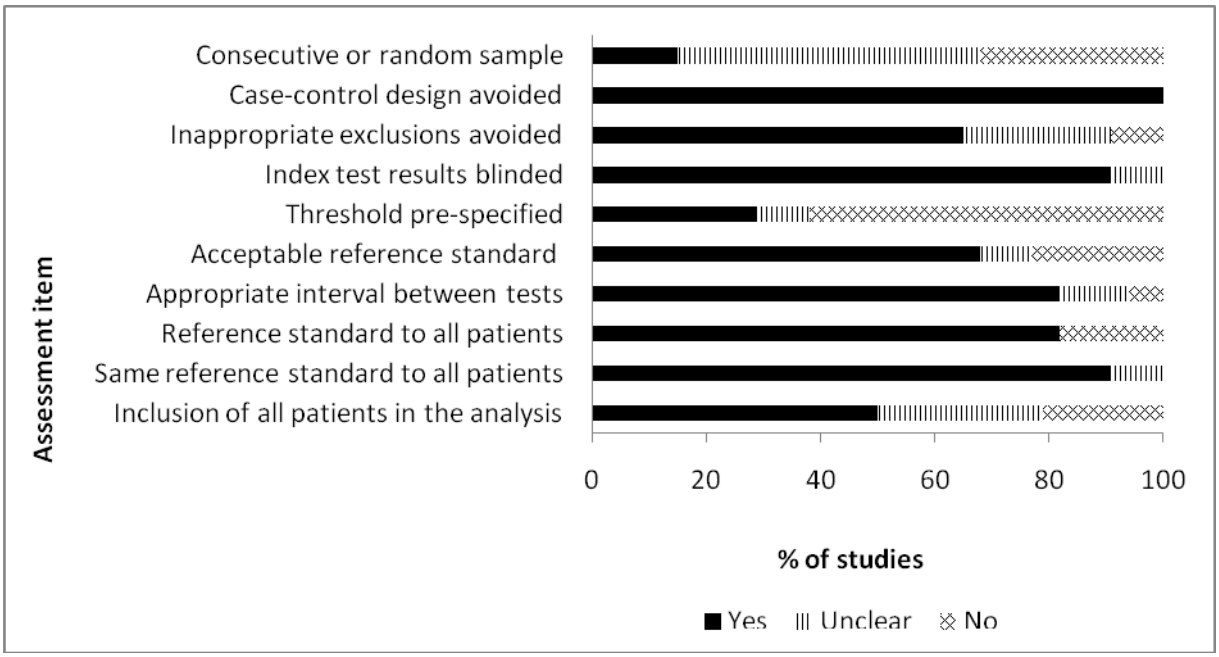
Outcomes

Only five studies reported safety related outcomes. In addition to accuracy outcomes such as sensitivity and specificity, the majority of the 34 screening accuracy studies also reported correlation/agreement between TcB and TSB measurements. The other five studies[7,53-56] reported clinical outcomes, such as the reduction in the number of confirmatory TSB testing, incidence of significant neonatal hyperbilirubinemia.

Methodological Quality of the Screening Accuracy Studies

Ratings for the 10 quality questions for each individual study are summarized in Figure T.2. A 'Yes' response indicates where the specific quality item in the signaling question was met and the study was deemed to have been conducted in such a way as to minimize the bias associated with the particular domain. The methodological quality (risk of bias) results for each individual study are presented in Appendix T.C (Table T.C.2–4).

Figure T.2: Methodological quality of screening accuracy studies



Within the 34 studies, none received 'Yes' responses to all 10 signaling questions contained in the QUADAS-2 assessment tool, suggesting that all of the studies were subject to at least one source of potential bias. No overall quality score was used, given that various shortcomings may generate different magnitudes of bias, even in opposing directions, making it difficult to assign sensible weights to each quality item.[79,80]

As shown in Figure T.2, of the ten signaling questions, questions 3, 4, 6, 7, 8, and 9 received 'Yes' responses in more than half of the studies. Question 2 ('Was a case control design avoided?') received a 'Yes' response from all 34 studies, as none of the studies enrolled neonates with the condition and a control group without the condition. In some studies, TSB (reference standard) was performed before TcB measurement (index test); however, simply reversing the order in which the index test and reference standard are performed will not change estimates of test accuracy.[81]

Only a small number of studies clearly enrolled a consecutive or random sample of neonates, indicating the potential presence of selection bias in the majority of studies, which may lead to overestimation of test accuracy.

Question 5 ('If a threshold was used, was it pre-specified?') received 'No' responses in the majority of studies, reflecting the fact that these studies used receiver operating characteristic (ROC) curves to identify the optimal TcB cut-off values. The test performance determined by this approach will be overestimated compared to when measuring performance using a previously derived cut-off point.[82,83]

Disease progression bias (question 7) seems not to have been an issue in most studies because the time intervals between TcB and TSB measurements were usually less than 30 minutes and bilirubin levels may not change significantly within an hour.

In some studies, TSB was performed only in the neonates whose TcB levels were above a certain levels, (for example, TcB >40th percentile or TcB >150 μmol/L); no information was provided for neonates whose initial TcB levels were below the pre-defined values. This partial verification bias

(question 8), one of the most problematic biases in primary test accuracy studies, can bias the accuracy estimates.

In some studies, sufficient information was lacking to make an informed judgment about a quality item. With incomplete reporting by study authors, the information that can be derived from a quality assessment becomes limited. It is impossible to know whether an unreported quality item reflects a true methodological flaw or just the authors' poor reporting of a study that may be methodologically sound.[84]

Table T.3 summarizes the judgments for risk of bias within the four domains. Overall, except for the reference standard domain, less than one third of studies demonstrated low risk of bias in the patient selection, index test, and patient flow and timing domains.

Table T.3: Overall risk of bias results

Domain	Judgments for risk of bias		
	Low	High	Unclear
Patient selection	4 studies	11 studies	19 studies
Index test	9 studies	21 studies	4 studies
Reference standard	24 studies	7 studies	3 studies
Patient flow and timing	12 studies	12 studies	10 studies

There are sone concerns about applicability of research findsings to the loacal context. Although the inclusion/exclusion criteria for the selection of the primary studies were pre-defined and based strictly on the population, index test, and reference standard relevant to the research questions, variations in neonate populations raised a question about the applicability to the Alberta neonate population, particularly to the Aboriginal population.

Adverse Events

The majority of studies did not report any adverse events associated with the use of the TcB devices. Of the five studies[7,30,34,36,68] that provided some information about the safety aspects, two Italian studies[30,36] that used BiliCheck did not note any device failure, and one US study[34] that used BiliCheck did not observe any adverse events or injury. However, one US study[68] reported the abrupt mechanical failure of one BiliCheck device during the study.

One Canadian study[7] reported that 25% of JM-103 devices did not perform within allowable limits of their quality control procedures at the time of purchase, in spite of having passed the manufacturer's standard wavelength calibration. More than 60% of the devices were returned for repair or recalibration during the three years of program operation, which highlights the need for routine device validation before and during clinical deployment, particularly when multiple devices are used.

Correlation and agreement between TcB and TSB measurements

Pre-discharge

Nine studies reported correlation and agreement between TcB and TSB values measured before hospital discharge. These results are summarized in Table T.E.1 (Appendix T. E).

As shown in Table T.E.1, the total number of neonates included in these studies ranged from 177 to 2167. Four studies[34,38,61,66] included neonates from diverse ethnic origins, whereas the other five studies included neonates from a single ethnic origin, such as Caucasian[26,30,36] or Chinese.[37,77]

Of the nine studies, six used BiliCheck[26,30,34,36,61,66] and three used JM-103.[37,38,77] In terms of the reference standard, while most studies used TSB measured by Diazo or other methods, only one US study[34] used TSB measured by HPLC. Another US study[61] compared the results between TcB and TSB measured by Diazo or Vitros methods.

Correlation

All these studies showed a strong correlation between TcB and TSB values, with coefficients ranging from 0.75 to 0.91 (see Table T.E.1). This information provides the degree to which TcB and TSB are related and indicates the strength of the relationship between TcB and TSB, but not the level of agreement between them.

The Italian study[30] that involved 2167 neonates found that the correlation between TcB and TSB values was independent of gestational age, gender, hour of age, TSB level except for TSB >15 mg/dL (256 μmol/L), and ethnic group except for Hispanic neonates (less than 10% of total number in this study). The study by Bhutani et al.[34] found similar correlations between TcB and TSB values obtained from neonates of different ethnic origins (r=0.91 for Caucasian, 0.91 for Black, 0.93 for Hispanic, and 0.90 for Asian and other ethnicities) and neonates with different gestational age (r=0.91 for term and 0.90 for late preterm neonates). One Canadian study[66] also found that the correlation did not vary among different ethnic groups. One US study[61] did not find any difference in correlation between TcB and TSB by the Diazo or Vitros methods (r=0.81 for both methods).

In addition to an overall correlation coefficient of 0.83, the Canadian study[66] also reported a correlation coefficient of 0.75 for TSB ≤12 mg/dL (200 μmol/L) (N=266), 0.52 for TSB >12 mg/dL (200 μmol/L) (N=164); 0.79 for TSB ≤15 mg/dL (250 μmol/L) (N=362), and 0.23 for TSB >15 mg/dL (250 μmol/L) (N= 68). These data suggest that the correlation between TcB and TSB becomes poorer with higher TSB levels, particularly when TSB values are greater than 15 mg/dL.

Agreement

As shown in Table T.E.1, the Bland-Altman plot showed different direction and magnitude in the agreements between TcB and TSB measurements. The mean difference between TcB and TSB values ranged from -12 to 34 μmol/L, indicating an overall trend of TcB underestimating TSB (mean difference is negative) or overestimating TSB (mean difference is positive). The reported 95% limits of agreement indicated that TcB either underestimated or overestimated TSB in all nine studies. TcB overestimated TSB values by up to 87 μmol/L (5.1 mg/dL),[36] but more clinically important was the indication that TcB underestimated TSB values by up to 88 μmol/L (5.1 mg/dL).[38]

In the Bhutani TSB nomogram the differences in TSB values between the 95th percentile (high risk zone) and the 40th percentile increased with age, ranging from 3 mg/dL (50 μmol/L) at 24 hours to 5 mg/dL (86 μmol/L) at 72 hours of life.[23] Therefore, the observed magnitude of the differences between TcB and TSB values could incorrectly classify neonates who are actually in the high-risk zone as being in the low-risk zone. For example, the Canadian study[66] found that in the 86 infants requiring phototherapy, the TcB overestimated the TSB in the majority of infants, but underestimated the TSB in 10 infants by more than 3 mg/dL (50 μmol/L). In those with TSB values in the high-risk zone (n=97), 19 were incorrectly categorized as being in a lower risk zone.

Post-discharge

Four studies[57,63,69,70] measured TcB and TSB in neonates older than 72 hours of age. The sample sizes in these studies are relatively small, with the total number of neonates ranging from 54 to 121. The European study[70] included only Caucasian neonates and used both HPLC and Diazo methods to measure TSB. The three US studies[57,63,69] were conducted in an outpatient setting and included neonates from diverse ethnic origins who had visible jaundice.

Two studies[63,70] reported both correlation and agreement results, one study[69] reported only correlation coefficients, and the other study[57] reported only agreement results between TcB and TSB measurements (see Table T.E.2).

Correlation

As shown in Table T.E.2, the correlation coefficients reported in the three studies ranged from 0.77 to 0.85, indicating a strong correlation between TcB and TSB measurements in an outpatient setting. The European study[70] found no significant differences in the correlation coefficients between TcB and TSB by HPLC (r=0.85) and TcB and TSB by Diazo method (r=0.83).

Agreement

As shown in Table T.E.2, the Bland-Altman plot showed different direction and magnitude in the agreements between TcB and TSB measurements in outpatient settings. The mean difference between TcB and TSB measurements ranged from -70 to +26 μmol/L, indicating an overall trend of TcB either underestimating or overestimating TSB values. The reported 95% limits of agreement indicated that TcB either underestimated or overestimated TSB in all three studies. TcB overestimated TSB by up to 98 μmol/L (5.7 mg/dL),[57] but more clinically important was the indication that TcB underestimated TSB by up to 189 μmol/L (11 mg/dL).[70] The magnitude that TcB underestimated TSB was reportedly much smaller in the two US studies (by 44 and 82 μmol/L, respectively).

One US study[57] noted that TcB screening protocols based on the observed relationship between TcB and TSB in inpatient neonates cannot be used without modification in the outpatient environment. Higher variability between TcB and TSB was observed in the outpatient than in the inpatient neonate population.

During the first week of life

Fourteen studies measured TcB in neonates during their first week of life, which may have included inpatient neonates but with extended hospital stay. Table T.E.3 (Appendix T.E) summarizes the results from these studies.

As shown in Table T.E.3, the total number of neonates included in these studies ranged from 83 to 849. Most studies included neonates of diverse ethnic origins; some studies only included neonates from a single ethnic origin such as Northern European (Caucasian),[73] Hispanic, [68] Chinese,[62] Thai,[74,75] or Indian.[76]

Of the 14 studies, nine[28,31,62,64,67,68,72,73,76] used BiliCheck and three[44,65,75] used the JM-103 for TcB measurements. Two studies[60,74] used BiliCheck and/or JM-103 devices. In terms of the reference standard, while most studies measured TSB using the Diazo or other laboratory methods, two studies[28,67] measured TSB using both HPLC (gold standard) and other laboratory methods.

Correlation

As shown in Table T.E.3, all 14 studies demonstrated a strong or very strong correlation between TcB and TSB measurements, with coefficients ranging from 0.76 to 0.95. The correlation coefficients for TcB and TSB as measured by HPLC ranged from 0.88 to 0.94. One study[44] found that the correlation between TSB and TcB measured by JM-103 was slightly improved when the average of the TcB values obtained from the mid-sternum and the forehead locations was used, compared to the TcB values from either of the two measurement sites. Another three studies[28,31,62] found that the correlation appeared to be similar between TcB measured on the forehead or on the sternum.

One study[72] that included 140 jaundiced neonates found that the correlation between TcB and TSB appeared to be similar for Caucasian neonates (66% of included neonates; r=0.95) and non-Caucasian neonates (32% of included neonates; r=0.93). Another study[44] also found that the ethnic origin of the neonates did not significantly affect the quality of the correlation between TcB and TSB values. In contrast, a US study[65] found that the correlation between TSB and TcB by JM-103 was poorer in African-American neonates (r=0.82) than in Caucasian neonates (r=0.95).

The European multi-centre study[28] found that the correlation between BiliCheck and TSB measured by HPLC (r=0.89) was slightly better than that with TSB measured by other standard laboratory methods (r=0.87), and was comparable to the correlation between TSB measured by standard laboratory methods and TSB measured by HPLC (r=0.93). In addition, TcB measurements obtained from the forehead (r=0.89) and sternum (r=0.88) generated comparable and strong correlation results.

Agreement

As shown in Table T.E.3, the five studies that measured the agreement between TcB by BiliCheck (on the forehead) and TSB showed an overall trend of TcB underestimating TSB, with mean differences ranging from -25 to -0.2 μmol/L. The reported 95% limits of agreement indicated that TcB either underestimated or overestimated TSB in all five studies. TcB overestimated TSB by up to 68 μmol/L (4.0 mg/dL),[28] but more clinically important was the indication that TcB underestimated TSB by up to 120 μmol/L (7.0 mg/dL).[73]

Of the three studies[44,65,75] that measured the agreement between TcB by JM-103 and TSB, two studies[44,75] showed an overall trend of TcB underestimation of TSB (mean difference -21 to -12 μmol/L) and one study[65] showed an overall trend of TcB overestimation of TSB with a mean difference of 9 μmol/L. TcB measured by JM-103 underestimated TSB by 65 μmol/L and overestimated TSB by 51 μmol/L.

A Canadian study[60] confronted an intrinsic difference between TSB and TcB measurements using either the BiliCheck or JM-103 devices, and suggested the use of a correction factor and the Bhutani curves, rather than developing their own nomograms.

Comparison between BiliCheck and JM-103

One study[74] measured TcB using both BiliCheck and JM-103 in 134 Thai neonates. Both BiliCheck and JM-103 devices showed a strong correlation with TSB. The correlation coefficients between BiliCheck and TSB (r=0.82) were the same as those between JM-103 and TSB (r=0.82).

The mean difference between BiliCheck and TSB was 10 μmol/L, with 95% limits of agreement from -41 to 62 μmol/L. The mean difference between JM-103 and TSB was -12 μmol/L, with 95% limits of agreement from -65 to 41 μmol/L. TcB measured by JM-103 had a tendency to

underestimate TSB levels, while TcB measured by BiliCheck had a tendency to overestimate TSB levels (see Table T.E.3).

Summary

The available evidence suggests that TcB measured by either BiliCheck or JM-103 correlated well with TSB measured either by HPLC, Diazo method or other standard laboratory methods. Research evidence indicates inconsistent findings about the impacts of ethinic origin on the correlation between TcB and TSB measurements. The correlation between TcB and TSB appeared to be poorer in neonates with higher TSB levels (for example >200 μmol/L).

TcB appears to be imprecise in predicting TSB because it can both underestimate or overestimate TSB by a magnitude of more than 50 μmol/L (3 mg/dL). Overestimation of TSB levels could lead to unnecessary TSB blood sampling, whereas underestimation of TSB could miss a case of severe hyperbilirubinemia. Underestimation of TSB by more than 3 mg/dL (50 μmol/L) at 24 hours to 5 mg/dL (86 μmol/L) at 48 to 72 hours is not clinically acceptable. Based on the Bhutani TSB nomogram, this could incorrectly classify neonates who are in the high-risk zone (>95th percentile) as being in the low-risk zone (<40th percentile). Underestimation of TSB could lead to inappropriate post-discharge follow-up in neonates with false negative results.

Only one study provided results on the direct comparison between BiliCheck and JM-103. Since the study was conducted in a Thai population,[74] the usefulness and implication of their findings to the Alberta context is questionable.

Based on the evidence presented above, TcB cannot be used to replace confirmatory TSB tests because of its imprecision. TcB can be used as a screening test to determine when a confirmatory TSB test is needed. TcB measures can be used at time of discharge to safely plan care for jaundiced infants if the limits of agreement are considered and clinical judgment is maintained. Clinicians need to remain vigilant when neonates have pre-discharge screening TcB values at the lower end of the spectrum.

Sensitivity and Specificity

Hyperbilirubinemia can be expressed as: 1) value-based hyperbilirubinemia, 2) percentile-based hyperbilirubinemia, and 3) rate of TSB rise-based hyperbilirubinemia.[24]

Rate of rise cannot be used alone to manage neonatal jaundice; however, it may be useful when considered in combination with the TcB nomogram (with or without clinical risk factors evaluation) (Dr. De Luca, personal communication, December 2012).

Based on the available data, pre-defined TSB values or TSB percentiles are chosen in this report as the target condition for the sensitivity and specificity analysis.

Prevalence of significant neonatal hyperbilirubinemia

As shown in Table T.F.1 (Appendix T.F), definitions for the target condition varied across studies. Reported target TSB values ranged from 6–8 mg/dL to 17 mg/dL, usually between 12 and 15 mg/dL. Reported target TSB percentiles on the hour-specific nomogram ranged from 40th to 95th; the 95th percentile (that is, at high risk of requiring phototherapy) was used most common.

While the reported prevalence for single TSB values varied significantly across the studies, available data showed that TSB levels above the 95th percentile on TSB hour-specific nomograms occurred in about 6% of neonates before discharge.

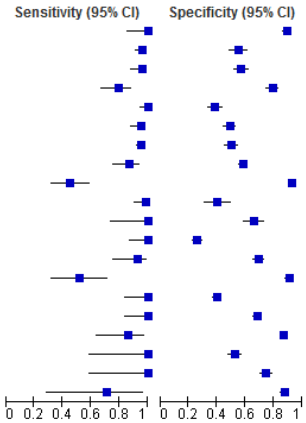
Pre-discharge

Eleven studies[16,26,30,34,36-38,61,66,71,77] reported sensitivity and specificity of TcB in predicting TSB levels in pre-discharge settings (see Table T.F.1). The number of neonates included in these studies ranged from 177 to 2,167. Seven studies[26,30,34,36,61,66,71] used BiliCheck and four studies[16,37,38,77] used JM-103 devices. Only one study[34] measured TSB by HPLC (gold standard). Two studies[16,71] compared the screening accuracy of TcB with the screening accuracy of visual assessment.

In Figure T.3, paired forest plots display sensitivity and specificity together with their 95% confidence intervals for studies with available data. A shown in Fig T.3, TcB cut-off values as well as target TSB levels varied across these studies. The summary ROC (SROC) plots were calculated and plotted using Review Manager (Computer program. Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). As the SROC plots presented were exploratory only, they have been removed from the presentation.

Figure T.3: Accuracy of TcB for detecting hyperbilirubinemia (pre-discharge)

Study	TP	FP	FN	TN	Device	TCB Cut-off (mg/dL)	Taget TSB level (mg/dL)	Sensitivity (95% CI)	Specificity (95% CI)
Bhutani 2000	23	47	0	396	BC	≥75th	>95th	1.00 [0.85, 1.00]	0.89 [0.86, 0.92]
Campbell 2011 a	157	119	7	147	BC	>10.5	>12	0.96 [0.91, 0.98]	0.55 [0.49, 0.61]
Campbell 2011 b	66	155	3	206	BC	>11.7	>15	0.96 [0.88, 0.99]	0.57 [0.52, 0.62]
Chang 2006 a	53	79	14	301	JM	>11.7	>15	0.79 [0.67, 0.88]	0.79 [0.75, 0.83]
Chang 2006 b	67	233	0	147	JM	>9.4	>15	1.00 [0.95, 1.00]	0.39 [0.34, 0.44]
De Luca 2008 a	91	301	5	289	BC	>10	>14	0.95 [0.88, 0.98]	0.49 [0.45, 0.53]
De Luca 2008 b	254	209	13	209	BC	>9.9	>12.1	0.95 [0.92, 0.97]	0.50 [0.45, 0.55]
Ho 2006 a	52	390	8	547	JM	>75th	>95th	0.87 [0.75, 0.94]	0.58 [0.55, 0.62]
Ho 2006 b	27	70	33	867	JM	>95th	>95th	0.45 [0.32, 0.58]	0.93 [0.91, 0.94]
Karon 2008	56	72	1	48	BC	>75th	>75th	0.98 [0.91, 1.00]	0.40 [0.31, 0.49]
Kolman 2007	12	61	0	119	BC	≥75th	>95th	1.00 [0.74, 1.00]	0.66 [0.59, 0.73]
Romagnoli 2012 a	27	460	0	161	BC	<50th (6.3-7.5) *	>17 or NFPT	1.00 [0.87, 1.00]	0.26 [0.23, 0.30]
Romagnoli 2012 b	25	192	2	429	BC	<75th (7.8-10.3) *	>17 or NFPT	0.93 [0.76, 0.99]	0.69 [0.65, 0.73]
Romagnoli 2012 c	14	57	13	564	BC	<90th (11.1-11.9) *	>17 or NFPT	0.52 [0.32, 0.71]	0.91 [0.88, 0.93]
Romagnoli 2012 d	21	615	0	410	BC	<50th (7.7-9.9) †	>17 or NFPT	1.00 [0.84, 1.00]	0.40 [0.37, 0.43]
Romagnoli 2012 e	21	323	0	702	BC	<75th (10.4-11.6) †	>17 or NFPT	1.00 [0.84, 1.00]	0.68 [0.66, 0.71]
Romagnoli 2012 f	18	137	3	888	BC	<90th (11.9-13.6) †	>17 or NFPT	0.86 [0.64, 0.97]	0.87 [0.84, 0.89]
Romagnoli 2012 g	7	220	0	246	BC	<50th (10-10.9) ‡	>17 or NFPT	1.00 [0.59, 1.00]	0.53 [0.48, 0.57]
Romagnoli 2012 h	7	118	0	348	BC	<75th (11.7-12.7) ‡	>17 or NFPT	1.00 [0.59, 1.00]	0.75 [0.70, 0.79]
Romagnoli 2012 i	5	57	2	409	BC	<90th (13.9-13.9) ‡	>17 or NFPT	0.71 [0.29, 0.96]	0.88 [0.84, 0.91]



Note: In the first column, author names with alphabetic order represent same studies using different TcB cutoff values/target TSB levels; * at 24 to 28 hours (n1=648); † at 49 to 72 hours (n2=1046); ‡ at 73 to 96 hours (n3=473); TP: true positive; FP: false positive; FN: false negative; TN: true negative; NFPT: need for phototherapy.

Predicting TSB value-based hyperbilirubinemia

Three studies reported sensitivity and specificity of the TcB test for predicting TSB valuesof >15 mg/dL (see Table T.4).

Table T.4: Accuracy of TcB for predicting TSB > 15 mg/dL

Study	TcB cut-off (mg/dL)	Target TSB levels (mg/dL)	Sensitivity % (95% CI)	Specificity % (95% CI)
Wainer 2009[38] Canada N = 774	>9.4	>15	100	90
Chang 2006[77] Taiwan N = 447	>9.4	>15	100 (95-100)	39 (34-44)
Campbell 2011[66] Canada N = 430	>11.7	>15	96 (88-99)	57 (52-62)

Two studies[38,77] that used the same TcB cut-off value of >9.4 mg/dL reported a 100% sensitivity but with much different specificity (90% versus 39%). A Canadian study[66] reported a sensitivity of 96% and specificity of 57% when using a TcB cut-off of 12 mg/dL (200 μmol/L) to predict TSB of > 15 mg/dL (250 μmol/L).

Predicting TSB percentile-based hyperbilirubinemia

Four studies[26,34,37,61] used a TcB cut-off of >75th percentile to predict TSB of >95th percentile of hour-specific values (see Table T.5).

Table T.5: Accuracy of TcB >75th percentile for predicting TSB >95th percentile

Study	TcB cut-off	Target TSB levels	Sensitivity % (95% CI)	Specificity % (95% CI)
Bhutani 2000[34] USA N = 490 (Caucasian 59%)	≥75th percentile	>95th percentile	100 (85-100)	88 (86-92)
Karon 2008[61] USA N = 177 (Caucasian 82%)	>75th percentile	>95th percentile	100 (75-100)	30 (23-37)
Kolman 2007[26] USA N = 192 (Hispanic 100%)	≥75th percentile	>95th percentile	100 (74-100)	66 (59-73)
Ho 2006[37] Hong Kong N = 997 (Chinese 95%)	>75th percentile	>95th percentile	87 (76-93)	58 (55-62)

The Bhutani et al.[34] study involved 490 neonates from a diverse ethnic background (Caucasian 59%, Black 30%, Hispanic 3%, and Asian 4%). TcB was measured by BiliCheck and HPLC was used as reference standard. To assess the reliability of a TcB measurement, the intra-device error was determined for one single device. For each device, two to three measurements were repeated in an infant at intervals of a few minutes. To assess the reliability among multiple devices, the inter-device error in TcB measurement was determined by repeating the test with two to four separate devices for each infant, at the same approximate site, at two- to three-minute intervals. Technicians, clinicians, and investigators at the site of data collection were blinded to the TcB data or HPLC–TSB data. This study reported a sensitivity of 100% and specificity of 88%, which indicates that, using a cut-off of >75th percentile, TcB by BiliCheck can detect all neonates with TSB levels >95th percentile. Another US study[61] that included neonates from diverse ethnic origins (mostly Caucasians) also reported a 100% sensitivity but much poorer specificity (30%).

Of the other two studies[26,37] that included neonates from a single ethnic origin, Kolman et al.[26] reported a sensitivity of 100% and specificity of 66% in a Hispanic population and Ho et al.[37] reported a sensitivity of 87% and specificity of 58% in a Chinese population.

In a large Italian multicentre study[30] that involved 2167 healthy infants, paired TcB and TSB levels were measured before hospital discharge. TcB values were plotted on a locally developed nomogram using a cut-off of hour-specific 50th, 75th, and 90th percentiles (see Table T.6). This study was not

population-based, but the enrollment was based on clinical practice at each neonatal unit. The incidence of significant hyperbilirubinemia was low (2.5%) and the majority of the included neonates were Caucasians.

Table T.6: Accuracy of TcB for predicting TSB >17 mg/dL or need for phototherapy[30]

Number of infants N=2167	Age at screening (hours)	TcB percentile (corresponding value, mg/dL)	Sensitivity % (95% CI)	Specificity % (95% CI)
648	24 to 48	<50th (6.3-7.5)	100 (87-100)	26 (23-30)
		<75th (7.8-10.3)	93 (76-99)	69 (65-73)
		<90th (11.1-11.9)	52 (32-71)	91 (88-93)
1046	49 to 72	<50th (7.7-9.9)	100 (84-100)	40 (37-43)
		<75th (10.4-11.6)	100 (84-100)	69 (66-71)
		<90th (11.9-13.6)	86 (64-97)	87 (84-89)
473	73 to 96	<50th (10-10.9)	100 (59-100)	53 (48-57)
		<75th (11.7-12.7)	100 (59-100)	75 (70-79)
		<90th (13.9-13.9)	71 (29-96)	88 (84-91)

This study found that the TcB cut-off of <50th percentile at <48 hours and TcB cut-off of <75th percentile from 48 hours onward provide 100% sensitivity for detecting TSB >17 mg/dL or TSB levels requiring phototherapy according to the AAP guidelines. Sensitivity for TcB <75th percentile before 48 hours of age was 93% because of two false negative cases. Individual, hour-specific TcB values <75th percentile between 49 and 96 hours of age are able to predict all neonates who will not develop subsequent significant hyperbilirubinemia (defined as TSB values >17 mg/dL or the need for phototherapy treatment). The data support the use of TcB for a safe discharge of term and late preterm neonates between 48 and 72 hours of life.

Post-discharge

Of the four studies[57,63,69,70] that measured TcB after 72 hours, two studies[57,70] used BiliCheck and the other two used JM-103 devices.

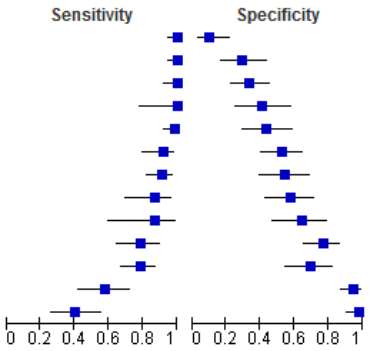
Predicting TSB value-based hyperbilirubinemia

Three studies[63,69,70] used various TcB cut-off values to detect various target TSB levels (for example, TSB>15 mg/dL or >17 mg/dL) (see Table T.F.2). Data for detecting TSB ≥15 mg/dL (257 μmol/L) were used for the forest plot because the prevalence of TSB ≥15 mg/dL was reported in the three studies (see Figure T.4).

Data from two US studies indicated that, for detecting TSB ≥15 mg/dL, TcB cut-off values of ≥11 or ≥12 mg/dL yielded 100% sensitivity but with poor specificity (29% to 34%). In the study conducted in Turkey,[70] a low TcB cut-off of ≥8 mg/dL had to be chosen to achieve 100% sensitivity with 41% specificity.

Figure T.4: TcB for detecting TSB ≥15 mg/dL in outpatients

Study	TP	FP	FN	TN	Device	TCB Cut-off (mg/dL)	Sensitivity	Specificity
Maisels 2011 a	70	44	0	5	JM	≥11	1.00 [0.95, 1.00]	0.10 [0.03, 0.22]
Maisels 2011 b	70	34	0	14	JM	≥12	1.00 [0.95, 1.00]	0.29 [0.17, 0.44]
Engle 2005 a	47	49	0	25	JM	≥11	1.00 [0.92, 1.00]	0.34 [0.23, 0.46]
Kaynak-Turkmen 2011a	15	23	0	16	BC	≥8	1.00 [0.78, 1.00]	0.41 [0.26, 0.58]
Maisels 2011 c	69	27	1	21	JM	≥13	0.99 [0.92, 1.00]	0.44 [0.29, 0.59]
Engle 2005 b	43	35	4	39	JM	≥12	0.91 [0.80, 0.98]	0.53 [0.41, 0.64]
Maisels 2011 d	64	22	6	26	JM	≥14	0.91 [0.82, 0.97]	0.54 [0.39, 0.69]
Wickremasinghe 2011	26	22	4	30	BC	≥75th	0.87 [0.69, 0.96]	0.58 [0.43, 0.71]
Kaynak-Turkmen 2011b	13	14	2	25	BC	≥10	0.87 [0.60, 0.98]	0.64 [0.47, 0.79]
Engle 2005 c	37	17	10	57	JM	≥13	0.79 [0.64, 0.89]	0.77 [0.66, 0.86]
Maisels 2011 e	55	15	15	34	JM	≥15	0.79 [0.67, 0.87]	0.69 [0.55, 0.82]
Engle 2005 d	27	4	20	70	JM	≥14	0.57 [0.42, 0.72]	0.95 [0.87, 0.99]
Engle 2005 e	19	2	28	72	JM	≥15	0.40 [0.26, 0.56]	0.97 [0.91, 1.00]



Note: In the first column, author names with alphabetic order represent same studies using different TcB cutoff values/target TSB levels. TP: true positive; FP: false positive; FN: false negative; TN: true negative.

The study by Maisels[69] also found that, as TSB levels increased, the number of false negative TcB increased. To achieve 100% sensitivity in detecting TSB of ≥17 mg/dL, reported TcB cut-off values varied from ≥9 mg/dL (with 45% specificity),[70] to ≥13 mg/dL (with 58% specificity),[63] to ≥14 mg/dL (with 41% specificity).

The authors of one US study[63] concluded that JM-103 cannot be considered a substitute for laboratory measurement of TSB, but seems to be useful as a screening tool in the outpatient population. A significant number of TSB determinations could be avoided with appropriate TcB cut-off values, and this reduction in laboratory evaluation should streamline the follow-up process for families and care providers.

Predicting TSB percentile-based hyperbilirubinemia

One US study[57] that used BiliCheck reported 87% sensitivity and 58% specificity when using TcB levels between the 75th and 95th percentiles and >95th percentile to detect TSB levels between the 75th and 95th percentiles and >95th percentile on the Bhutani TSB nomogram. This study suggested that TcB screening protocols that were developed based on the observed relationship between TcB and TSB on inpatient infants cannot be used without modification in the outpatient setting. In addition, TcB screening of outpatients with a low bilirubin threshold (for example, <13 mg/dL) may not be efficient, because only 20% of infants would have been spared a blood draw for confirmatory TSB. Therefore, TcB screening in the outpatient environment may not be safe and efficient.

Predictive accuracy of TcB test (follow-up studies)

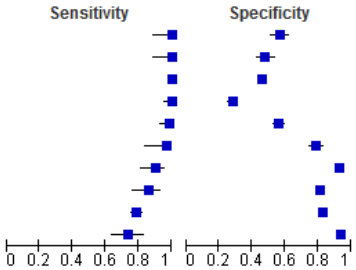
Five studies, two conducted in India,[46,58] and one each in Greece,[59] China,[45] and Thailand,[42] developed TcB nomograms using local data obtained from 322[58] to 6035[45] term or late preterm neonates (see Table T.D.4 in Appendix T.D). Application of these TcB-based predictive nomograms allows for a non-invasive, risk-based approach for neonatal hyperbilirubinemia and guides clinicians in targeting evaluation and planning for appropriate follow-up strategies in neonates with jaundice.

Four studies using BiliCheck and one study[45] using JM-103 measured TcB prior to hospital discharge and followed neonates for subsequent significant hyperbilirubinemia (see Table T.F.4, Appendix T.F). In Figure T.5, paired forest plots display sensitivity and specificity together with 95% confidence intervals for each study.

The Greece study[59] showed that the probability of significant neonatal hyperbilirubinemia would be greater than 35% for TcB values within the high-risk zone and less thatn 0.5% for TcB values within the low-risk zone of the nomogram.

Figure T.5: TcB for predicting subsequent hyperbilirubinemia

Study	TP	FP	FN	TN	Device	TCB Cut-off (mg/dL)	Sensitivity	Specificity
Sanpavat 2005b	32	155	0	205	BC	>85th	1.00 [0.89, 1.00]	0.57 [0.52, 0.62]
Sanpavat 2005a	32	187	0	173	BC	>75th	1.00 [0.89, 1.00]	0.48 [0.43, 0.53]
Yu 2011 b	565	2974	0	2496	JM	>40th	1.00 [0.99, 1.00]	0.46 [0.44, 0.47]
Mishra 2010 c	79	643	0	257	BC	≥25th	1.00 [0.95, 1.00]	0.29 [0.26, 0.32]
Mishra 2010 b	78	396	1	504	BC	≥50th	0.99 [0.93, 1.00]	0.56 [0.53, 0.59]
Sanpavat 2005c	31	76	1	284	BC	>90th	0.97 [0.84, 1.00]	0.79 [0.74, 0.83]
Varvarigou 2009 b	72	92	8	1147	BC	>11	0.90 [0.81, 0.96]	0.93 [0.91, 0.94]
Mishra 2010 a	68	167	11	733	BC	≥75th	0.86 [0.76, 0.93]	0.81 [0.79, 0.84]
Yu 2011 a	446	952	119	4518	JM	>75th	0.79 [0.75, 0.82]	0.83 [0.82, 0.84]
Varvarigou 2009 a	65	81	23	1242	BC	> 8	0.74 [0.63, 0.83]	0.94 [0.92, 0.95]



Note: In the first column, author names with alphabetic order represent same studies using different TcB cutoff values/target TSB levels. TP: true positive; FP: false positive; FN: false negative; TN: true negative.

In the Chinese study,[45] TSB was measured when TcB ≥ 204 μmol/L and these TSB measurements were used to estimate the incidence of significant neonatal hyperbilirubinemia. According to the authors, the 75th percentile curve of the age-specific TcB nomogram was the ideal cut-off point for intensive follow-up of neonates for hyperbilirubinemia, as it carried a high sensitivity (79%) and high negative predictive value (98.5%).

In the Indian study,[46] infants were followed from 72 to 168 hours of age. According to the authors, the 50th percentile curve of the age-specific TcB nomogram was an ideal cut-off point for intensive follow-up of the neonates for hyperbilirubinemia requiring phototherapy as it carried a very high sensitivity (99%), high negative predictive value (99.8%), and acceptable positive predictive value (16.4%).

Another Indian study[58] observed the changes in TcB values over time. Changes in TcB levels were almost two times greater for neonates who required phototherapy than for neonates who did not require phototherapy. The authors found that single TcB measurements at 30 to 48 hours of age predicted hyperbilirubinemia with a reasonably high degree of accuracy. Changes in TcB levels do not offer any added clinical benefits.

The Thai study[42] found that 90th percentile curve of the age-specific TcB nomogram has the highest accuracy (97% sensitivity and 79% specificity) in predicting neonates at high risk for severe hyperbilirubinemia requiring phototherapy.

One limitation of these studies was that only the neonates with TcB above certain levels received a confirmatory TSB test. Partial verification bias could lead to overestimating or underestimating the accuracy of TcB in predicting subsequent significant neonatal hyperbilirubinemia.

Overall, to predict all neonates (that is 100% sensitivity) at high risk of developing significant neonatal hyperbilirubinemia, reported TcB cut-offs varied from ≥25th percentile (with 29% specificity),[46] and ≥40th percentile (with 46% specificity),[45] to ≥85th percentile (with 58% specificity),[42] and 8.8 mg/dL (with 64% specificity).[59]

Comparison between visual assessment and TcB

Four studies[16,71,72,76] compared the accuracy of TcB with visual assessment (VA) in detecting hyperbilirubinemia in full term neonates (see Table T.7). The number of neonates involved in these studies ranged from 109 to 517. Three studies were conducted in Europe and one in India. In one

study all included neonates were Caucasian.[71] Another study included only Indian neonates.[76] In the other two studies neonates were of a mixed ethnic origin (see Table T.D.1–3).

Table T.7: Comparison of screening accuracy between TcB and visual assessment

Study	Target TSB levels (µmol/L)	VA			TcB		
		Threshold (Kramer zone)	Sn %	Sp %	Threshold (µmol/L)	Sn %	Sp %
De Luca 2008[71] Italy N=517	103 to 137	NA	93	36	NA	VA+TcB 99	VA+TcB 75
	139 to 205	NA	38	82	NA	VA+TcB 88	VA+TcB 96
	207 to 257	NA	6	99	NA	VA+TcB 31	VA+TcB 100
Kaplan 2008[16] Israel N=346	≥75th percentile	Zone 3	84	81	≥154	72	90
Szabo 2004[72] Switzerland N=140	>250	≥Zone 2	100	36	≥180	97	60
		≥Zone 3	93	46	≥190	94	72
		≥Zone 4	84	71	≥200	88	80
		Zone 5	38	95	≥210	84	86
					≥220	78	89
					≥230	63	94
					≥240	59	97
					≥250	44	97
Lodha 2000[76] India N=109	>222	NA	52	89	NA	69	89
	>257	NA	53	98	NA	47	99

Abbreviations: N – total number; NA – not available; Sn – sensitivity; Sp – specificity; TcB – transcutaneous bilirubinometer; VA – visual assessment

Three studies used BiliCheck devices and one study[16] used JM-103 devices. While no information was available about who performed the measurement in one study,[76] TcB measurement was performed by a single physician in the other three studies.[71,72 16] TcB cut-off values were not clearly reported in two studies.[71,76]

While the method used for visual assessment was not clearly described in two studies,[71,76] the other two studies used Kramer dermal zones as threshold values of visual assessment. Visual assessment was performed by an experienced pediatrician in the Indian study[76] and by nurses in the other three studies; in one of them,[72] visual assessment was also performed by a trained physician. None of the four studies measured TSB levels by the HPLC method.

One study[71] compared VA alone to the combination of VA and TcB, while the other three studies[16,72,76] compared VA with TcB alone. All four studies were conducted in a pre-discharge setting but two studies[72,76] included neonates aged 2 days (48 hours) to 7 days (168 hours).

The study by De Luca et al.[71] compared the accuracy of VA alone and of adding TcB to VA for predicting three different classes of TSB levels: Class A: 6–8 mg/dL, Class B: 8.1–12 mg/dL, and Class C: 12.1–15 mg/dL. Five hundred and seventeen neonates underwent VA, TcB, and TSB testing. However, information was incomplete on the thresholds for visual assessment (for example, Kramer's zones) and for the combination of VA and TcB when examining the test accuracy. The experience of test performers was less influential for TcB measurement than was the experience needed for visual assessment of jaundice.

The study found that VA alone led to an underestimation of TSB levels in 35% of neonates in Class A, 40% in Class B, and 17% in Class C, and to an overestimation of TSB levels in 36% of neonates in Class A, 4.9% in Class B, and 17% in Class C. TcB measurement significantly reduced screening errors when the estimated TSB level was ≤8 mg/dL and significantly reduced the risk of underestimation of TSB when the estimated TSB level was between 8.1 and 12 mg/dL. As shown in Table T.7, data from the study by De Luca et al.[71] indicated that the performance of VA became poorer when the level of TSB was >8.1 mg/dL (139 μmol/L). Adding TcB measurement to VA increased sensitivity and specificity for the TSB levels ranging from 6 to 12 mg/dL (103 to 205 μmol/L). However, adding TcB to VA only improved sensitivity from 6% to 31% for the highest target TSB range, that is, 12 to 15 mg/dL (207 to 257 μmol/L), which could be due to the small number of neonates in this category.

The authors concluded that the use of BiliCheck after visual assessment of jaundice could correct the screening error and significantly reduce the underestimation rate for TSB ranging from 6 to 12 mg/dL (103 to 205 μmol/L), but not for the higher TSB range of 12 to 15 mg/dL. This study demonstrated the usefulness of the combined use of VA and TcB in assessing the need for TSB testing. Visual assessment cannot be recommended as the only method for evaluating this need.

The study by Szabo et al.[72] compared accuracy between visual assessment, JM-102, and BiliCheck; only information regarding visual assessment and BiliCheck is reported here. The study found that, in healthy, term neonates, TcB was more accurate (ROC=0.92) than visual assessment (ROC=0.84) in detecting hyperbilirubinemia. Hyperbilirubinemia defined as TSB >15 mg/dL (250 μmol/L) can be safely ruled out by visual assessment if jaundice does not reach the abdomen or the extremities (that is, ≤ Kramer zone 2), or with a TcB cut-off of 11 mg/dL (190 μmol/L). The authors concluded that both visual assessment and TcB are well suited for the estimation of serum bilirubin.

This study also found that TcB measured by BiliCheck and visual assessment conducted by the physician were significantly less accurate in non-Caucasian neonates than in Caucasian neonates. Furthermore, inter-observer agreement between visual assessment conducted by nurses and by the physician was significantly better for Caucasian (Kappa=0.56) than for non-Caucasian (kappa=0.36) neonates ($P<0.05$).

The study by Kaplan et al.[16] compared the accuracy of VA and TcB in detecting TSB levels of ≥75th percentile based on the Bhutani nomogram. The threshold for VA was defined as ≥Kramer zone 3 and the threshold for TcB was defined as ≥9 mg/dL (≥154 μmol/L). The main limitation of this study was that TSB testing was not performed in every neonate, but only in neonates whose VA or TcB results were above the threshold values; this can bias the accuracy estimates.

This study found that, even though significantly more visually screened neonates went on to TSB testing (N=83) compared with those detected by TcB screening alone (N=49), the yield of detection of neonates with TSB ≥75th percentile was similar in both groups: VA (21/83, 25%) and TcB measurement (18/49, 37%)(P=0.4). TcB detected an additional 1.2% of neonates who would have been missed by VA alone. However, 2% of neonates with a TcB <154 μmol/L had a TSB ≥75th percentile (false negative), which would have been missed if VA had not been performed. The TSB levels of those selected by VA were lower than the levels of those chosen by TcB alone. This may reflect the greater accuracy and higher specificity of TcB as compared to VA. The authors concluded that, with TcB, fewer neonates required TSB tests than VA for similar yields of detection; however, this conclusion has yet to be confirmed by accuracy studies in which all neonates receive the reference standard test.

The Indian study[76] did not report the thresholds for VA or TcB measurements. The study found that TcB measurement and VA showed similar poor sensitivity (<70%) but relatively good specificity (>89%) in detecting TSB levels higher than 13 mg/dL.

In summary, of the four studies that compared VA and TcB in detecting hyperbilirubinemia, one study found poor performance of both tests in Indian neonates, whereas the other three European studies demonstrated favorable results of TcB compared to VA alone. One study[71] demonstrated the usefulness of the combination of VA and TcB and showed significantly improved test accuracy by adding TcB to VA for detecting neonates in the TSB range of 6 to 12 mg/dL (103 to 205 μmol/L). Test accuracy was not improved for the higher TSB range of 12 to 15 mg/dL, which may be of greater clinical interest. Another study,[16] with potential partial verification bias, demonstrated that fewer neonates required TSB testing when screened by TcB than when screened by VA, for a similar yield of detection. The other study[72] demonstrated the acceptable accuracy of both screening tests, but showed higher accuracy with TcB than with VA alone.

Comparison between BiliCheck and JM-103

One study conducted in Thailand[74] compared the test accuracy of BiliCheck and JM-103 in 134 jaundiced neonates. As shown in Table T.F.3 (Appendix T.F), using TcB cut-offs of >8, >9, >10, and >12 mg/dL, the BiliCheck device showed higher sensitivity but lower specificity than the JM-103 device at TSB levels of >10, >12, >13, and >15 mg/dL, respectively. For TSB levels of >15 mg/dL, both BiliCheck and JM-103 yielded 100% sensitivity, but specificity with JM-103 (87%) was higher than with BiliCheck (68%). Overall, BiliCheck seemed to perform better in identifying all neonates who need TSB (100% sensitivity); however, this was associated with unnecessary blood sampling in more than 50% of neonates with false positives for TSB levels of 10, 12, and 13 mg/dL, and 32% of neonates with TSB levels of 15 mg/dL. Therefore, the overall screening accuracy of the JM-103 was higher than that of BiliCheck at all TSB levels.

Clinical Outcomes

Five studies, conducted in Canada,[7] the United States,[56] Ireland,[54] Australia,[55] and India,[53] examined the impact of the implementation of a TcB protocol/program on clinical outcomes. Two concurrent comparative studies[53,54] specifically examined whether the use of TcB could reduce the subsequent use of TSB testing. The other three studies[7,55,56] compared clinical outcomes before and after the implementation of a TcB program. The details of these studies are presented in Table T.G.1 (Appendix T.G). Table T.8 summarizes the main findings of these studies.

Table T.8: Summary of clinical outcomes of using a TcB test

Study	Population/intervention	No. of TSB testing	No. of SNH	Rate of PT
Mishra et al. 2009[53] India RCT	EG (TcB by BiliCheck): N=314 CG (VA): N=303	EG: 17.5% vs. CG: 26.4% Reduced 34% (95% CI 10 to 51%) (P=0.008)	NA	EG: 5.7% vs. CG: 8.6% (P=0.17)
Allen et al. 2010[54] Ireland Non-randomized comparative study	EG (hospital A with VA+TcB by JM-103): N=15,851 CG (hospital B with VA only): N=15,701	EG: 10% vs. CG: 15% Reduced 31% (P<0.001)	TSB levels requiring ET: EG: 0.85% vs. CG: 0.13% (ss not available)	NA
Wainer et al. 2012[7] Canada Before–after study	EG (8 mos with TcB by JM-103): N=14,112 CG (8 mos VA only): N=14,769	EG: 103.6/1000 live births vs. CG: 134.4/1000 live births Reduced 22.9% (P<0.0001)	TSB ≥20 mg/dL: EG: 850.9/100 000 live births, 1:118 vs. CG: 385.2/100 000 live births, 1:260 Reduced 54.9% (P<0.0001)	EG: 4.97% vs. CG: 6.09% (P<0.0001)
Petersen et al. 2005[56] USA Before–after study	N=6,603 EG (8 mos with TcB by BiliCheck): N not available CG (8 mos VA only): N not available	EG: 36.7±8.7% vs. CG: 31.8±6.4% (P=0.21)	Readmission for SNH (No./1000): EG: 1.8±1.7 vs. CG: 4.5±2.4 (P=0.044)	EG: 7.7±1.3% vs. CG: 5.9±1.3% (P<0.05)
Hartshorn et al. 2009[55] Australia Before–after study	EG (6 mos with TcB by JM-103): N=2,197 CG (12 mos VA only): N=1169	EG: 10.2% vs. CG: 19.4% Reduced 47% (P<0.001)	TSB 350 to 400 µmol/L: EG: 0/1169 (0%) CG: 17/2197 (0.77%) (P<0.001)	EG: 35 (3.0%) vs. CG: 84 (3.8%) (P=0.2)

Abbreviations: CG – control (without TcB) group; EG – experimental (with TcB) group; ET – exchange transfusion; mos – months; N – total number; NA – not available; PT – phototherapy; SNH – severe neonatal hyperbilirubinemia; ss – statistical significance; TcB – transcutaneous bilirubinometer; TSB – total serum bilirubin; VA – visual assessment

Randomized control trial

In the randomized clinical trial,[53] 617 clinically jaundiced neonates were randomly allocated to a TcB group (N=314) or a systematic visual assessment group (N=303). TcB was measured by the BiliCheck device. An experienced physician (specifically trained for protocol-based visual assessment) performed visual assessment in an adequately illuminated room (preferably in daylight) using a semi-quantitative algorithm adapted from Kramer's original description. The need for blood sampling for TSB was determined if the bilirubin assessed by the allocated method exceeded 80% of the hour-specific bilirubin level requiring phototherapy, and corrected for risk factors for neurotoxicity. To safeguard against missing a neonate with significant jaundice, the clinical team had the authority to override the research team's decision to measure TSB.

The two groups were similar in terms of birth weight, gestational age, and postnatal age. Overriding decisions by the clinical team occurred in 1.6% of the total neonates and no statistical significance was found between the TcB group (8/314, 2.6%) and the visual assessment group (2/303, 0.7%) (P=0.063).

The number of neonates who needed TSB tests was significantly lower in the TcB group (17.5%) than in the visual assessment group (26.4%), indicating a 34% reduction in the requirement for TSB tests. No statistically significant difference was found in the number of neonates who needed phototherapy between the TcB group (5.7%) and visual assessment group (8.6%). Because only 135 neonates (21.9%), identified by either TcB or visual assessment, underwent blood sampling to confirm TSB, and because the TcB was measured at between 24 and 168 hours of age, it is not clear whether any neonates with low TcB values at an early postnatal age (≤72hours) developed significant hyperbilirubinemia at a later time.

This study concluded that, compared with systematic visual assessment, routine use of TcB significantly reduced the need for blood sampling for TSB measurement in jaundiced term and late preterm neonates.

Non-randomized controlled trial

One non-randomized controlled trial, conducted in Ireland,[54] compared clinical outcomes at two hospitals with or without a TcB protocol. A TcB cut-off value of 200 μmol/L was used to determine the need for a TSB test. TSB was measured at between 12 and 144 hours, either in hospital or at outpatient clinics, at the mean post-natal age of 65 hours in hospital A and 61 hours in hospital B (P<0.05).

The study found that, while no difference was observed between the two hospitals in the number of neonates with TSB above the levels requiring exchange transfusion, the need for TSB was reduced by 31% with the use of TcB. This finding suggested that the use of TcB significantly reduces the need for TSB testing in routine clinical practice.

Before–after studies

The Canadian study[7] assessed the impact of a TcB program on the incidence of significant neonate hyperbilirubinemia and on the measure of laboratory, hospital, and nursing resource use. In this prospective study, clinical outcomes of 14,796 healthy, term or late preterm neonates who received routine TcB measurement in both hospital and community settings were compared with clinical outcomes for a historical cohort of 14,112 neonates who received visual assessment only.

TcB was measured daily before discharge by hospital nursing staff, and 1 to 2 days after discharge by public health nurses. A locally developed and validated TcB nomogram was used to plot TcB values.

Significant neonatal hyperbilirubinemia was classified as severe (TSB ≥20 mg/dL), extreme (TSB ≥25 mg/dL), and dangerous (TSB ≥30 mg/dL). Initial TSB draws can be avoided if TSB <10 mg/dL at >48 hours of age, <12 mg/dL at >72 hours of age, <14 mg/dL at >96 hours of age, or <15 mg/dL at >120 hours of age.

This study found that the implementation of a TcB program was associated with a 23% reduction in the number of TSB testing in the community setting, a 55% reduction in severe neonatal hyperbilirubinemia, an 18% reduction in the total number of neonates requiring phototherapy (newborn nurseries and readmission), and a 15% reduction in the mean age of readmission for phototherapy, but no change in the length of readmission for phototherapy (see Table T.7, and Table T.G.1 in Appendix T.G). The study concluded that the implementation of a TcB program can

significantly enhance patient safety and result in reduced demands on both laboratory and hospital resources, but may lead to increased use of community health services.

The study conducted in the US[56] attempted to determine whether the use of TcB affects the use of laboratory bilirubin testing or decreases the number of neonates readmitted for hyperbilirubinemia within 7 days of initial discharge. The decrease in the readmission rate for clinically significant hyperbilirubinemia was most likely attributable to an increased number of neonates having undergone phototherapy in the nursery, which was not associated with an increase in the overall length of stay in the nursery.

This study included a total of 6603 neonates and compared clinical outcomes 8 months before (number of neonates for this time period not available) and after (number of neonates for this time period not available) the implementation of the TcB test. The study found that, while no significant change was found in the number of TSB tests and the length of hospital stay, access to TcB testing was associated with a reduction in the hospital readmission rate for significant hyperbilirubinemia within 7 days of the initial discharge.

The Australian study[55] compared clinical outcomes 12 months before (N=2197) and 6 months (N=1169) after the implementation of a TcB (using JM-103) protocol. No significant difference was found in the demographics of the population during the two time periods.

The study found that TcB measurement, in conjunction with their protocols, significantly reduced the number of blood samplings for TSB testing without increasing the risk of delaying treatment with phototherapy.

In summary, four of five studies[7,53-55] found that TcB was associated with a significant reduction of TSB testing, with reduction rates ranging from 23% to 47%, but without an increase in clinically significant hyperbilirubinemia.

DISCUSSION

Limitations

This systematic review is based on a comprehensive literature search and included studies published in five languages, minimizing the potential impact of publication bias.

Bias refers to a systematic error or deviation from the truth, either in the results or in their inferences. Bias can be caused by problems in the design or execution of the study (which are primarily issues of internal validity), or through recruiting the wrong participants, using the wrong test, or using the test in the wrong way (which are primarily issues of external validity).[48] Bias can act in either direction, leading to overestimations or underestimation in test accuracy.

Due to the small number of clinical outcome studies (five studies only) and variations in study design (one RCT, one non-randomized comparative study, and three before–after studies), no formal quality assessment was conducted.

Methodological quality of the included screening accuracy studies was assessed using a risk of bias tool (QUADAS-2), and quality assessment results indicated that all studies were subject to at least one source of bias. Partial verification and data-driven selection of optimal TcB cut-off values are of particular concern.

Partial verification

In some studies, TSB was only measured in those neonates who had visual assessment or TcB values

above a threshold value, therefore the true false-negative rate could not be determined.[85] Primary studies with partial verification bias were not excluded from the review because excluding these studies may result in publication bias. The clinical problem with partial verification is that neonates at low-risk, as identified by TcB before discharge, were unlikely to receive TSB after discharge, and the concern is that some false negatives might be present in this group of neonates. Unless some safeguard measures are in place for this group of neonates (such as planned clinical follow-up), a reduction in the number of TSB tests alone cannot be viewed as a measure of effective clinical resource use of a TcB program.

Data-driven selection of optimal cut-off values

The majority of studies did not pre-specify TcB cut-off values but used the ROC curve to determine the optimal TcB cut-off values. This kind of data-driven selection of optimal cut-off values for a test of a continuous variable usually lead to overestimations of sensitivity and specificity. The potential for bias should be recognized when optimal cut-off values are derived in this data-driven manner, especially when the sample size is small.[82]

Because chance variation plays a larger role in smaller studies, the observed ROC curves obtained from a single small study for such a procedure will deviate more from the true underlying ROC curve than the observed ROC curve obtained from a large study.[82] The data-driven approach specifically selects the cut-off value with the highest sum of sensitivity and specificity (that is, closest to the top left corner of the ROC plot), therefore, this value is generally a point above the true underlying ROC curve.

Summary of Main Findings

Safety

Evidence from 39 studies suggests that TcB is a safe procedure without any reports of serious adverse events associated with the use of TcB devices. The major safety concern is the clinical consequences of false negatives; however, TSB tests were usually not performed in TcB negatives during the post-discharge follow-up. For practical reasons, rather than testing all post-discharge TcB negatives, a selection of a random sample of this population for TSB testing may help address this important issue.

Correlation and agreement between TcB and TSB measurements

Evidence from the screening accuracy studies indicates a generally strong correlation between TcB and TSB measurements, with correlation coefficients ranging from 0.75 to 0.95. The correlation between TcB and TSB measurements decreased at higher TSB levels. Despite high correlation between TcB and TSB measurements, TcB can both underestimate TSB, particularly when TSB > 15 mg/dL (250 μmol/L), and overestimate TSB levels in a magnitude of more than 3 to 5 mg/dL (50 to 85 μmol/L). These differences can lead to the incorrect classification into the low-risk category of neonates who are actually at high risk for significant hyperbilirubinemia.

Accuracy of TcB

Using appropriate TcB cut-off values, mostly derived from the ROC analysis, TcB can accurately detect neonates with clinically significant hyperbilirubinemia (defined as having a bilirubin level that requires phototherapy) or predict those neonates who, after hospital discharge, will develop clinically significant hyperbilirubinemia.

The reported TcB cut-off values varied across the studies. Usually relatively low TcB cut-offs have to be chosen to reach 100% sensitivity (a mandate for screening hyperbilirubinemia), but this is associated with low specificity. The resulting high false positives limit the ability of TcB in reducing unnecessary blood sampling for TSB testing. It appears that percentile-based TcB values are more appropriate than a single TcB value because of the rapid, hourly changing bilirubin levels in neonates. Evidence from two US studies indicated a TcB of ≥75th percentile may be a good predictor of TSB of ≥95th percentile on the Bhutani nomogram.

As the five follow-up studies were conducted in exclusively White, Chinese, Indian, or Thai populations, no conclusion can be drawn about the optimal pre-discharge TcB threshold values in predicting subsequent hyperbilirubinemia that may be relevant to the Alberta neonate population.

Comparison between TcB and visual assessment

Limited evidence from four studies, three conducted in Europe and one conducted in India, suggests that, except for Indian neonates, TcB generally performed better than visual assessment (for example, by Kramer grading) in terms of test accuracy in detecting neonatal hyperbilirubinemia. One study found that adding TcB to VA significantly improved sensitivity and specificity in detecting TSB levels ranging from 6 to 12 mg/dL (103 to 205 μmol/L), but not for higher TSB levels, due to insufficient sample size in that category. Another study demonstrated that for a similar yield, VA required more TSB testing than did TcB, but both tests would have missed a small number of neonates if used alone. All these studies support the usefulness of TcB as a screening test, particularly in conjunction with VA; however, as some authors stressed, the importance of clinical assessment of neonatal jaundice cannot be ignored.

Comparison between BiliCheck and JM-103

Evidence from one study that compared BiliCheck and JM-103 in 134 jaundiced Thai neonates indicated no difference between BiliCheck and JM-103 in correlation with TSB measurement. JM-103 had a tendency to underestimate TSB levels, while BiliCheck had a tendency to overestimate TSB levels. Using TcB cut-offs of >8, 9, 10, and 12 mg/dL, BiliCheck showed higher sensitivity but lower specificity than the JM-103 device at TSB levels of 10, 12, 13, and 15 mg/dL, respectively.

Overall, BiliCheck seemed to perform better in identifying all infants who need TSB testing; however, more than 50% of TSB tests were unnecessary for detecting TSB levels of 10, 12, and 13 mg/dL. For detecting TSB levels of 15 mg/dL, 32% of TSB tests were unnecessary. Therefore, the overall screening accuracy of the JM-103 was better than that of BiliCheck at all TSB levels.

Clinical outcomes

Of the five studies that reported the clinical outcomes of implementing a TcB program, four studies found that systematic TcB screening was associated with a reduction (23 to 47%) in the number of unnecessary TSB testing. The other study[56] found that TcB testing did not decrease the number of TSB tests but did result in a reduction of the number of readmissions for hyperbilirubinemia. This was due to improved detection of hyperbilirubinemia before discharge. Three of the five studies showed reductions of the incidence of significant neonatal hyperbilirubinemia, or of readmission for hyperbilirubinemia, as a result of implementing TcB.

Factors That May Have Impacted Outcomes

Population

Factors such as gestational age at birth, ethnic background, hours of age, and inpatient versus outpatient settings at measurement may have an impact on TcB/TSB measurements; however, findings from the included studies were inconsistent.

TcB performers

In the majority of the screening accuracy studies, a single investigator, research nurse or technician performed TcB. In clinical practice, however, where TcB measurements are usually performed by a large number of nursing staff, the accuracy and precision of TcB measurements are likely to be poorer.

To more closely represent current clinical practice, one of the Canadian studies[66] involved multiple healthcare professionals in performing TcB measurements, and demonstrated poorer test performance.

Target TSB levels

All studies of the predictive value of early (pre-discharge) bilirubin levels used much lower target TSB levels (for example, >15 mg/dL), whereas the majority of neonates who develop kernicterus have TSB levels of 30 mg/dL or higher.[86,87] Neonates in hospital nurseries rarely have TSB levels higher than 15 mg/dL; therefore, the accuracy of TcB measurements for predicting TSB levels higher than 15 mg/dL remains to be established.[69] No direct evidence exists currently to conclude that the implementation of TcB programs based on these studies will reduce the risk of kernicterus.[86]

Some data indicated that the reliability of TcB devices is likely lower at the higher TSB levels. However, TcB measurements used in conjunction with nomogram-based risk categories (with or without risk factor consideration) are an approach to preventing cases of severe hyperbilirubinemia. It is very unlikely to find extremely high TSB levels in the first days of life without presence of other risk factors. When the TSB threshold for treatment is approaching, treatment decision-making, rather than screening, will be the clinical option (Dr. De Luca, personal communication, December 2012).

Training/experience

One study[71] found that, in the pre-discharge setting, the experience of test performers was less influential for TcB measurement than was the experience needed for visual assessment of jaundice.

One study[57] found that, in the outpatient setting, TcB measured on the forehead was significantly lower than that measured on the chest; however, no such difference was observed at the inpatient setting. Although inpatient and outpatient nurses underwent similar training and were only asked to perform TcB measurements once they reached a level of competency, the inpatient nurses had more experience with TcB measurements because it is performed more frequently in that setting. The impact of performers' experience on TcB measurement has not been systematically studied.

Inpatient versus outpatient settings

Several factors could potentially account for the differences in TcB performance in inpatients and outpatients.[57] After discharge, the neonate's skin may be exposed to more lights, making TcB measurements less accurate. Increased age may contribute to changes in skin thickness and hydration status, which may affect TcB measurements. As neonate bilirubin levels peak after

hospital discharge, TcB may be less accurate in the outpatient setting for neonates with higher bilirubin levels.

Potential Role of TcB Measurements

While TSB represents a measurement of circulating bilirubin, TcB is a measurement of tissue bilirubin.[63] Thus, bilirubin distribution may not always be even and may depend on variables such as rising or falling serum bilirubin levels.[63] A lag time between tissue and serum bilirubin levels may lead to less accuracy when TSB is rapidly rising.[39] Currently available evidence reveals a high correlation but substantial disagreement between TcB and TSB measurements, suggesting that TcB cannot be used to replace the TSB test. Using an appropriate TcB cut-off value, a high sensitivity can be reached in predicting significant hyperbilirubinemia, indicating that TcB can be used as a screening test to determine the need for confirmatory TSB testing. TcB values themselves are not used to determine the treatment plan, for example, the initiation of phototherapy.

The AAP clinical practice guideline[27] recommends that all infants be routinely monitored for the development of jaundice, with the recognition that visual estimation of the bilirubin levels from the degree of jaundice can lead to errors, particularly in darkly pigmented infants. In most infants with TSB less than 15 mg/dL, TcB measurement can provide a valid estimate of the TSB level and thus to reduce unnecessary TSB testing.

Requirements/barriers of Implementing a Universal TcB Screening Program

Requirements

Published information is very limited with respect to the requirements for a universal TcB screening program. Based on the information from a Canadian study[7] that provided sufficient details about a TcB program, requirements for implementing a universal TcB screening program may include the following:

- availability of TcB devices
- availability of TcB nomograms
- availability of healthcare professionals to perform TcB measurements
- provision of education/training about the use of TcB devices
- quality assurance (for example, calibration of TcB devices)
- availability of laboratory TSB testing
- formal visual assessment by experienced healthcare professionals
- availability of a screening algorithm
- appropriate resources

Barriers

Population

While some studies included neonates from diverse ethnic backgrounds, others included neonates exclusively from a single ethnic origin, such as Caucasian, Hispanic, Chinese, or Indian, which is different from the composition of the Alberta population. Evidence obtained from these single-

ethnic populations may be of limited use for an Alberta program. Studies conducted in Canada and the US may provide more useful information for developing a provincial screening program.

Selection of TcB devices

JM 103 is used most commonly in Alberta. The superiority of one TcB device over the other (that is, BiliCheck over JM-103 or vice versa) remains to be determined. Available evidence is sparse on direct comparison of the two devices. BiliCheck is more expensive than JM-103 and requires calibration before each measurement. The BiliCheck device was used in 24 studies; four of them used HPLC as the reference standard. However, no study was found that compared JM-103 to HPLC.

TSB and TcB nomograms

Due to the different ethnic origins, prevalence of glucose-6-phosphate dehydrogenase deficiency (G6PD), culture, lifestyle, and healthcare delivery systems, the TSB nomogram recommended in the AAP guidelines may not be applied to other populations.

The development of the Bhutani TSB nomogram involved 40% Black neonates. Compared to Caucasians, neonates of East Asian and Native American origin have higher TSB levels, whereas lower values have been noted in African-Americans.[39] Information on TSB levels in the Aboriginal population is very limited and it is not clear whether bilirubin levels in the Aboriginal population are higher or lower than the average in the Canadian neonate population. The generalizability of the Bhutani nomogram to the Alberta population is questionable.

Although a number of TcB nomograms have been developed in the recent years, published evidence is very limited about their use as compared to the use of the Bhutani TSB nomogram. The extent to which different population composition affects the natural history of neonatal hyperbilirubinemia is unclear. The question remains whether the TcB nomogram developed in Calgary can be used in other residential areas of the province, such as northern Alberta, where more than 40% of the population is of Aboriginal origin.

Optimal TcB cut-off values

Optimal TcB cut-offs for determining the need for TSB testing depend on the laboratory method used to measure TSB levels, which varies across laboratories. Given that neonatal bilirubin levels increase rapidly, on an hourly interval, TcB cut-off values expressed as hour-specific percentiles on bilirubin nomograms are considered more appropriate and meaningful than are single TcB values.

High sensitivity (100%) is mandatory for detecting severe hyperbilirubinemia using TcB; this translates into lower specificity, but no false negatives in neonates who may be missed if a follow-up program is not built in. If sensitivity and negative predictive value are low, it would mean that the test is providing false reassurance, delaying diagnosis and treatment of hyperbilirubinemia, and placing newborns at greater risk of significant hyperbilirubinemia or even kernicterus.[88] For a screening test, the cur-offs are set toward high sensitivity; a large number of false positives are acceptable.[89] False positives only result in additional unnecessary TSB testing, but this is without serious clinical consequences. The advantages of performing fewer blood tests must be weighed against the benefits of improved accuracy and safer practice.[16]

Quality assurance issue

In the majority of included studies, one single device was used for each neonate; this does not allow assessment for inter-device agreement.

In the study by Maisels,[65] using analysis of variance of repeated measures, the mean variability between devices was 0.02 (P=0.796) and the index of consistency, as measured by the interclass correlation, was 0.933 (95% CI: 0.989 to 0.996), indicating no difference between the devices.

Another study[69] noted that three independent measurements with the JM-103 provided three different values; the reasons for these differences are not clear. Some factors that might account for the variability include the pressure exerted on the skin and subcutaneous tissues, and variations in the seal between the electrode tip and the skin. If light enters the field, the TcB value will be falsely low.[69]

Calibration is another consideration. For the JM-103 device, calibration was required only once daily, and operating the device was easy and convenient. For the BiliCheck device, calibration for an individual tip (Bilical) was required before each measurement. Experience was needed to operate the device.[74]

As with any point-of-care test, continuing assessment of the competency of personnel using the device is extremely important.[8]

Visual assessment

Poor performance of visual assessment in predicting significant neonatal hyperbilirubinemia is well recognized; however, from a clinical perspective, implementation of a TcB program does not mean that visual assessment should be removed from the care pathway. From a cost saving perspective, the potential cost saving lies with the avoidance of unnecessary TSB tests.

Resources

Different resource demands between urban and rural areas must be taken into consideration. Demand for community resources (for example, the services of public health nurses) will increase when implementing a TcB program.

CONCLUSION

Early hospital discharge policies have resulted in increased hospital readmission rates of healthy term or late preterm neonates for phototherapy and a resurgence of kernicterus—a serious neurological condition. Timely identification of neonates at high risk for severe neonatal hyperbilirubinemia is encouraged as a preventive strategy.

TcB, a rapid, non-invasive, point-of-care test for predicting neonatal hyperbilirubinemia, has undergone clinical investigation in different countries and clinical settings to determine its reliability and accuracy. Performance of TcB in predicting hyperbilirubinemia, as measured by BiliCheck or JM-103 devices, has been examined in term or late preterm neonates from various ethnic origins. Both BiliCheck and JM-103 devices appear to be safe, with very few procedure-related adverse events having been reported. Research findings indicate that, at the present time, TcB cannot replace TSB but can be considered a valid screening tool to determine the need for a confirmatory TSB test.

Limited evidence suggested that a TcB cut-off of ≥75th percentile at 48 to 72 hours (pre-discharge) is a good predictor of TSB of ≥95th percentile. Limited evidence also suggests significantly improved screening accuracy with TcB (by BiliCheck or JM-103), or with the combination of TcB and visual assessment, than with visual assessment alone in detecting neonates with clinically significant hyperbilirubinemia. TcB appears to be a promising technology and may be a useful addition to clinical assessment in the screening of neonatal jaundice.

Evidence from five studies, one conducted in Canada, suggested that the implementation of a TcB screening program was associated with a reduction in the number of TSB tests without an increase in the incidence of significant neonatal hyperbilirubinemia.

Several aspects must be taken into consideration when planning to implement a universal TcB screening program, including: the availability and cost of TcB devices, the need to develop a local TcB nomogram, selection of appropriate TcB cutoff values (a balance between 100% sensitivity with low specificity and maximal screening accuracy), appropriate quality assurance and personnel training and education, and the impact on the demand for community resources.

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APPENDICES

Appendix T.A: Methodology

Search strategy

The IHE Research Librarian conducted a broad literature search to identify all relevant articles published between January 2000 and January 2012 (see Table T.A.1). The search was developed and carried out prior to the study selection process.

Grey literature searches were conducted for information about local context and regulatory status (Health Canada). A thorough review of HTA agency websites was conducted, as were searches for clinical practice guidelines and ongoing clinical trials. Reference lists from the included studies were also checked for other relevant studies.

Table T.A.1: Search strategy

Database	Edition or date searched	Search Terms ††
Core Databases		
The Cochrane Database of Systematic Reviews (Wiley Interface)	January 5, 2012	"bilirubin* ***in*** *Title, Abstract or Keywords* **23 results – 0 relevant** (all therapy or prevention)
CENTRAL (Ovid interface)	January 5, 2012	See MEDLINE search immediately below **25 results** for T section
MEDLINE (includes in-process articles) (OVID interface)	January 5, 2012	1. exp infant/ 2. (neonat* or infant* or newborn* or maternity ward or babies or baby).mp. 3. 1 or 2 4. Bilirubin/ 5. bilirubin*.mp. 6. hyperbilirubinemia.tw. 7. jaundice*.tw. 8. exp Hyperbilirubinemia, Neonatal/ 9. or/4-8 10. (TcB or transcutaneous).tw. 11. (JM-103 or JM-102 or bilicheck or bilichek).tw. 12. point of care.tw. 13. Point-of-Care Systems/ 14. poct*.tw. 15. poc.tw. 16. portable.tw. 17. (near adj2 patient*).tw. 18. bedside.tw. 19. non-invasive.tw. 20. ((immediate* or rapid* or same time or same visit or instant* or portable) adj5 (test* or turnaround or analys* or analyz* or measure* or assay* or results)).tw. 21. or/10-20 22. 3 and 9 and 21 23. limit 22 to yr="2000 - 2012" (223 results) 24. exp "Costs and Cost Analysis"/ 25. (cost* or economic* or expensive*).tw. 26. (expenditures or price or fiscal or financial or

		burden or efficiency or pay or valuation or spending or resource*).ti. 27. 24 or 25 or 26 28. 23 and 27 **11 results**
EMBASE (OVID interface)	January 5, 2012 2011 Week 52	1. exp infant/ 2. (neonat* or infant* or newborn* or maternity ward or babies or baby).mp. 3. 1 or 2 4. Bilirubin/ 5. bilirubin*.mp. 6. hyperbilirubinemia.tw. 7. jaundice*.tw. 8. newborn jaundice/ 9. or/4-8 10. (TcB or transcutaneous).tw. 11. (JM-103 or JM-102 or bilicheck or bilichek).tw. 12. point of care.tw. 13. "point of care testing"/ 14. poct*.tw. 15. poc.tw. 16. portable.tw. 17. (near adj2 patient*).tw. 18. bedside.tw. 19. non-invasive.tw. 20. ((immediate* or rapid* or same time or same visit or instant* or portable) adj5 (test* or turnaround or analys* or analyz* or measure* or assay* or results)).tw. 21. or/10-20 22. 3 and 9 and 21 23. limit 22 to yr="2000 - 2012" (288 results) 24. "cost"/ 25. exp economic evaluation/ 26. "health care cost"/ 27. (cost* or economic* or expensive*).tw. 28. (expenditures or price or fiscal or financial or burden or efficiency or pay or valuation or spending or resource*).ti. 29. or/24-28 30. 23 and 29 **25 results**
CRD Databases (DARE, HTA & NHS EED)	January 5, 2012	(bilirubin*) FROM 2000 TO 2012 **13 results – 6 potentially relevant**
CINAHL (Ebsco Database) Included because *Point of Care* journal is indexed in CINAHL but not in MEDLINE or EMBASE	January 5, 2012	S1 infant* OR neonat* OR newborn* OR maternity ward S2 bilirubin* OR hyperbilirubinemia OR jaundice* S3 (MH "Point-of-Care Testing") S4 TcB OR transcutaneous OR JM-103 OR JM-102 OR Bilicheck OR Bilichek OR non-invasive S5 (S1 AND S2 AND (S3 OR S4)) Limiters – Published Date from: 20000101-20111231 (91 results) S6 economic* or cost* S7 S5 AND S6 **7 results**

Web of Science	January 5, 2012	#1 TS=(neonat* or infant* or newborn* or maternity ward or babies or baby) #2 TS=(bilirubin* or hyperbilirubin* or jaundice*) #3 TS=(TcB OR transcutaneous OR JM-103 OR JM 102 OR Bilicheck OR Bilichek OR "point of care") #4 #1 AND #2 AND #3 Timespan=2000-2012 176 results #5 TS=(cost* or economic*) #6 #4 AND #5 **6 results**
Library Catalogues		
NEOS (Central Alberta Library Consortium) www.library.ualberta.ca/catalogue	January 10, 2012	(Screen$ or test$) and (jaundice$ OR bilirubin$); hyperbilirubinemia Scanned results – only **1 potentially relevant result**
Theses		
Proquest Dissertations and Theses Fulltext**	January 10, 2012	Transcutaneous bilirubin **2 non-relevant results** (bilirubin OR jaundice) AND screening **9 non-relevant results** TcB and bilirubin **0 results**
Theses Canada Portal www.nlc-bnc.ca/thesescanada	January 10, 2012	Jaundice in title **0 results** Bilirubin in title **4 non-relevant results** Hyperbilirubinemia in title **0 results** Transcutaneous bilirubin in full text **0 results**
EThOS – Beta http://ethos.bl.uk	January 10, 2012	Bilirubin OR jaundice **23 results – 0 relevant**
Clinical Trials		
ClinicalTrials.gov (US) http://clinicaltrials.gov/	January 10, 2012	Transcutaneous bilirubin; bilicheck; bilichek **5 relevant results**
CenterWatch Clinical Trials Listing Service www.centerwatch.com	January 11, 2012	Scanned results under pediatrics/neonatology **0 results**
IFPMA Clinical Trials Portal www.ifpma.org/clinicaltrials.html	January 11, 2012	Transcutaneous bilirubin; bilichek; bilicheck **20 results – 5 duplicate relevant results**
metaRegister of Controlled Trials www.controlled-trials.com/mrct	January 11, 2012	Transcutaneous bilirubin; bilichek; bilicheck **0 results**

Evidence Based Medicine		
Dynamed (Ebsco database)	January 11, 2012	Transcutaneous bilirubin – browsed the article on Neonatal hyperbilirubinemia Copied relevant sections into Grey Lit document
Trip www.tripdatabase.com	January 11, 2012	Transcutaneous bilirubin Copied relevant results into Grey Lit document
Economic Information		
Centre for Health Economics and Policy Analysis www.chepa.org/	January 11, 2012	Bilirubin, jaundice, hyperbilirubinaemia; hyperbilirubinemia; **0 results**
Centre for Health Economics Research and Evaluation http://datasearch.uts.edu.au/site_manager_sites/chere-redesign-ds/publications/index.cfm	January 11, 2012	Browsed reports and working papers sections **0 results**
Institute of Health Economics www.ihe.ca	January 11, 2012	Have not done any projects in the past on this topic.
HTA Agencies		
AETMIS www.aetmis.gouv.qc.ca/site/en_publications.phtml	January 6, 2012	Bilirubin; point of care **1 result** – "Point of care testing in private sector"; but result not relevant
CADTH www.cadth.ca/index.php/en/hta/reports-publications/search	January 6, 2012	Bilirubin **2 results**
Medical Advisory Secretariat www.health.gov.on.ca/english/providers/program/mas/mas_mn.html	January 6, 2012	Bilirubin; jaundice; point-of-care **0 relevant results**
Institute for Clinical and Evaluative Sciences (ICES), Ontario www.ices.on.ca/	January 11, 2012	Bilirubin, jaundice, transcutaneous; hyperbilirubinaemia; hyperbilirubinemia **1 relevant result**
Health Technology Assessment Unit at McGill www.mcgill.ca/tau/	January 11, 2012	Browsed list of reports **0 results**
EuroScan www.euroscan.bham.ac.uk	January 11, 2012	Bilirubin; jaundice; transcutaneous; hyperbilirubinaemia; hyperbilirubinemia **0 relevant, non-duplicate results**
MSAC www.msac.gov.au/	January 23, 2012	Bilirubin; jaundice; transcutaneous; hyperbilirubinaemia; hyperbilirubinemia **0 relevant results**
NZHTA http://nzhta.chmeds.ac.nz/publications.htm	January 23, 2012	Bilirubin; jaundice; transcutaneous; hyperbilirubinaemia; hyperbilirubinemia **0 results**

NIHR Health Technology Assessment www.hta.ac.uk/	January 23, 2012	Bilirubin; jaundice; transcutaneous; hyperbilirubinaemia; hyperbilirubinemia **0 results**
Centre for Clinical Effectiveness (CCE) www.southernhealth.org.au/page/Health_Professionals/CCE/Evidence_reviews/	January 23, 2012	Bilirubin; jaundice; transcutaneous; hyperbilirubinaemia; hyperbilirubinemia **0 relevant results**
MHRA (Medicines and Healthcare Products Regulatory Agency) (UK) www.mhra.gov.uk	January 23, 2012	Bilicheck; bilichek; transcutaneous, tcb, jaundice meter **0 relevant results**
California Health Benefits Review Program (CHBRP) www.chbrp.org/	January 23, 2012	Bilirubin; jaundice; transcutaneous; hyperbilirubinaemia; hyperbilirubinemia; TcB **0 results**
California Technology Assessment Forum (CTAF) www.ctaf.org	January 23, 2012	Bilirubin; jaundice; transcutaneous; hyperbilirubinaemia; hyperbilirubinemia; TcB **0 results**
AHRQ www.ahrq.gov	January 23, 2012	Transcutaneous bilirubin; bilicheck; bilichek; jm-103; JM-102; jaundice meter; hyperbilirubinemia **3 results**
VA Technology Assessment Program www.va.gov/VATAP/index.asp	January 23, 2012	Bilirubin; jaundice; transcutaneous; hyperbilirubinaemia; hyperbilirubinemia; TcB **0 results**
Regulatory Information		
Alberta Health www.health.gov.ab.c	January 23, 2012	Jaundice; bilirubin; hyperbilirubinemia; hyperbilirubinaemia; TcB; transcutaneous **0 relevant results**
Health Canada www.hc-sc.gc.ca	January 23, 2012	Tcb; transcutaneous bilirubin; hyperbilirubinemia; hyperbilirubinaemia **0 relevant results**
Medical Devices Active Licence Listing www.mdall.ca/	January 23, 2012	One result under Device name: Bilichek Two results under Device name: Jaundice Bilimed **0 results** Colorimeter; CR-300 **0 results** Minolta **0 relevant results**
US Food and Drug Administration www.fda.gov	January 11, 2012	510 K database JM-103; JM-102; Bilicheck; bilichek; Bilimed Saved summaries for JM-102, JM-103, Bilichek
Guidelines		
National Guideline Clearinghouse www.ngc.gov	January 24, 2012	'bilirubin' and '(jaundice or hyperbilirubinemia)' (18 results) Transcutaneous bilirubin **4 results**

AMA Clinical Practice Guidelines www.topalbertadoctors.org	January 24, 2012	Browsed list **0 results**
CMA Infobase http://mdm.ca/cpgsnew/cpgs/index.asp	January 24, 2012	Jaundice; bilirubin; hyperbilirubinemia; hyperbilirubinaemia **2 relevant results**
NICE guidance www.nice.org.uk/	January 24, 2012	Searched: jaundice; bilirubin **1 relevant result** – downloaded guideline, costing report and costing template
Canadian Paediatric Society www.cps.ca/english/publications/StatementsIndex.htm	January 24, 2012	Browsed list **2 relevant result**
Guidelines International Network www.g-i-n.net/	January 24, 2012	Jaundice; bilirubin; hyperbilirubinemia; hyperbilirubinaemia **3 non-duplicate results**
Canadian Task Force on Preventative Healthcare www.ctfphc.org/	January 24, 2012	Browsed list of current and past recommendations **0 results**
US Preventive Services Task Force (USPSTF) www.uspreventiveservicestaskforce.org	January 24, 2012	Jaundice; bilirubin; hyperbilirubinemia; hyperbilirubinaemia **2 results**
Scottish Intercollegiate Guidelines Network (SIGN) www.sign.ac.uk	January 24, 2012	Jaundice; bilirubin; hyperbilirubinemia; hyperbilirubinaemia; transcutaneous **0 results**
New Zealand Guidelines Group www.nzgg.org.nz	January 24, 2012	Jaundice; bilirubin; hyperbilirubinemia; hyperbilirubinaemia; transcutaneous **0 results**
Search Engines		
Google www.google.ca	January 24, 2012	Transcutaneous bilirubin –pubmed (reviewed first 50 results)

Note: ††, *, #, and ? are truncation characters that retrieve all possible suffix variations of the root word, e.g., surg* retrieves surgery, surgical, surgeon, etc.

Searches separated by semicolons have been entered separately into the search interface.

Study selection

Two researchers (BG and KB) screened the titles and abstracts of the citations identified by the electronic search. Full-text articles of potentially relevant studies were retrieved. Two researchers (BG and KB) piloted predefined inclusion/exclusion criteria in five studies, modified the criteria, and assessed all full-text articles for their eligibility using the modified inclusion/exclusion criteria outlined below. Agreement was achieved in 86% of the studies. Disagreements among reviewers were resolved by consensus.

Inclusion criteria

Study design:

- For safety outcomes: observational studies, grey literature
- For screening accuracy outcomes: cross-sectional, cohort
- For clinical outcomes: randomized or non-randomized controlled trials, single group before–after studies

Population: healthy neonates with gestational age ≥35 weeks, from any ethnic origin

Index test: TcB tests using the devices currently available in Canada, that is, BiliCheck and JM-103. Studies were included that used BiliCheck or JM-103 as well as other TcB devices (for example, JM-101, JM-102, BiliMed), and results reported separately, but only information about BiliCheck or JM-103 was presented in this report.

Comparator: visual assessment.

Reference standard: TSB measured by HPLC, Diazo or other standard laboratory methods.

Setting: hospital or community.

Outcomes of interest:

- For safety outcomes: any adverse events associated with the use of TcB test, which may include direct harm (for example, infection of the measurement site caused by skin contact with uncleaned TcB devices) or indirect harm (for example, TcB reading errors caused by TcB performers having insufficient training or experience, or by technical failure of the devices).
- For test performance outcomes: correlation/agreement between TcB and TSB, sensitivity and specificity, and other test performance measures.
- For clinical outcomes: reduction of the need for TSB testing, early diagnosis and treatment, or reduction in hospital readmission.

Language of publications: restricted to English, French, German, Spanish, or Chinese (languages that our research team was able to cover)

Publication period: January 2000 to January 2012

Exclusion criteria

Studies were excluded if they met any of the following criteria:

Study design: conference abstracts, letters, news, editorial comments, case reports; animal studies.

Population: preterm neonates (<35 weeks of gestation); neonates during or after phototherapy (because phototherapy "bleaches" the skin, both visual assessment of jaundice and TcB measurements in infants undergoing phototherapy are not reliable[27]); neonates with other critical conditions; studies included both preterm and term neonates but results were not reported separately.

Index test: older versions of TcB devices that are not currently in use (for example, JM 101 and JM 102); TcB devices that are used in other countries but not in Canada (for example, BiliMed); other

types of point-of-care tests for neonatal jaundice; Both TcB and TSB were used but results were are reported separately.

Comparator: older versions of TcB devices that are not currently in use (for example, JM 101 and JM 102); TcB devices that are used in other countries but not in Canada (for example, BiliMed); other types of point-of-care tests.

Reference standard: tests other than standard laboratory TSB tests (for example, other point-of-care TSB tests)

Outcomes: For test performance outcomes: studies that reported only correlation/agreement between TcB and TSB without information on sensitivity and specificity; accuracy studies that reported either sensitivity or specificity, but not both of them.

Language of publications: languages other than English, French, German, Spanish, or Chinese

Quality assessment

Two reviewers (BG and KB) independently assessed methodological quality of included screening accuracy studies using QUADUS-2 (see Appendix T.C). Quality assessment results from the two reviewers were compared and disagreements were resolved by consensus. Quality assessment results were not used to include or exclude studies.

Data extraction

One reviewer (BG) created and piloted the initial data extraction form, and used a modified data extraction form to extract information from each of the included studies.

Details of study, study design, patient characteristics, index test and reference standard, and outcomes were extracted from each study. When data were unavailable or not provided explicitly, the information was coded as "not available."

- **Study:** first author, year of publication, country
- **Study design**
- **Patients**
    - total number
    - age
    - gender
    - gestational age
    - ethnic origin (or skin tone)
    - prevalence of target condition
- **Index test** (TcB)
    - device used
    - timing of measurement
    - test positivity threshold
    - test performer

- quality control procedure

- **Reference standard** (TSB)
  - method used
  - time intervals between TcB and TSB measurements
  - setting where the test was performed
  - test performers

- **Outcomes**
  - safety (type, number, severity)
  - test performance
    - correlation/agreement between TcB and TSB measurements
    - sensitivity and specificity
  - clinical outcomes
    - avoidance of unnecessary TSB testing
    - reduction in the number of significant hyperbilirubinemia cases
    - reduction in the number of neonates readmitted for phototherapy
    - early readmission for phototherapy
    - reduction in length of hospitalization for phototherapy

Data analysis and synthesis

A narrative approach was used to summarize the research findings from the included studies. For screening accuracy studies, a forest plot of sensitivity and specificity with 95% confidence intervals was presented.

External review

External reviewers with clinical expertise in the use of TcB devices or HTA methodologies evaluated the draft report and provided feedback. In selecting reviewers, the practice of the Institute of Health Economics is to choose experts who are well recognized and have published widely in peer reviewed literature, and who can offer a provincial/national/international perspective with respect to the use of TcB tests.

Appendix T.B: Excluded Studies and Reasons for Exclusion

Abstracts (or letters) of primary studies

1. AlMadani M, Lemyre B. Correlation of transcutaneous bilirubin measurement to serum bilirubin using BiliCheck (TM) in premature infants. *Pediatric Research* 2004;55(4):534A.
2. Baptist SJ, Arif F, Sataur A, Sun SC. Transcutaneous versus total serum bilirubin levels for quality control and monitoring neonates. *Clinical Chemistry* 2005;51:A251.
3. Barroeta JE, et al. Comparative study of two transcutaneous bilirubin analyzers in hospitalized newborns. *Clinical Chemistry* 2003;49(6):A26.
4. Barroeta J, et al. Study comparing the BiliCheck (TM) and the new Minolta JM-103 transcutaneous bilirubin analyzers in hospitalized infants. *Pediatric Research* 2003;53(4):364A-5A.
5. Beck M, Kau N, Schlebusch H. Transcutaneous bilirubin measurement in newborn infants: evaluation of a new spectrophotometric method. *Archives of Disease in Childhood Fetal & Neonatal* 2003;88(4):F350-1.
6. Bhutani VK, et al. Correlation of clinical assessment of jaundice, transcutaneous and total serum bilirubin levels in healthy term and late pre-term infants. *Pediatric Research* 2004;55(4):591A.
7. Chawla D. Predictive ability of transcutaneous bilirubin: The verification bias. *Indian Journal of Pediatrics* 2009;76(10):1075.
8. Chawla D, Ramesh BY, Rao A. Transcutaneous bilirubin in predicting hyperbilirubinemia in term neonates. Correspondence. *Indian Journal of Pediatrics* 2009;76(10):1075-76.
9. Deorari AK, Lodha R, Jatana V, Paul VK. Non-invasive estimation of total serum bilirubin (TSB) in North Indian neonates using BiliCheck (TM) device. *Pediatric Research* 2000;47(4):55A.
10. De Luca D, Zecca E, Barbato G, Romagnoli C. Reference values of skin bilirubin measured by multiwavelength transcutaneous bilirubinometry during the first 96 h of life in European normal healthy neonates. *Acta Paediatrics* 2007;96:101.
11. Dorizzi RM, et al. Cutoff optimization of a transcutaneous device for the measurement of neonatal bilirubinemia. *Clinical Chemistry* 2003;49(6):A26.
12. Draque CM, et al. Transcutaneous total bilirubin levels by multiwavelength spectral reflectance: Accuracy in term newborn infants. *Pediatric Research* 2002;51(4):343A.
13. Engle WD, et al. Evaluation of transcutaneous bilirubin (TcB) in term and late pre-term neonates following hospital discharge. *Pediatric Research* 2004;55(4):460A.
14. Fouzas S, Bougioukou D, Varvarigou A, Mantagos S. Transcutaneous bilirubin measurements for assessing the risk of developing severe hyperbilirubinemia and bilirubin-induced brain injury in term and near term neonates. *Acta Paediatrics* 2008;97:19.
15. Gonthier M. Clinical and analytical evaluation of transcutaneous bilirubin measurement in term neonates. *Point of Care* 2007;6(1):53.
16. Holland L, Blick K. Evaluation of transcutaneous bilirubin measurement for assessment of neonatal jaundice. *Clinical Chemistry* 2007;53(6):A222.

17. Holland L, Blick K. Evaluation of transcutaneous bilirubin measurement for assessment of neonatal jaundice. *Point of Care* 2007;6(1):50.

18. Humoee N, Petrova A, Mehta R, Hegyi T. Prediction of neonatal hyperbilirubinemia with a transcutaneous bilirubin nomogram. *Pediatric Research* 2004;55(4):460A.

19. Leite MG, Facchini FP. Transcutaneous bilirubinometry: important method in the evaluation of newborns with hyperbilirubinemia - Reply. *Jornal de Pediatria* 2007;83(5):485-6.

20. Lyon ME, et al. Impact of a community neonatal transcutaneous hyperbilirubinometry screening program on total serum bilirubin assays as an outcome measure. *Clinical Chemistry* 2009;55(6):A235.

21. Maconi M, et al. The effectiveness of the BiliCheck method in roomed-in newborns. *Italian Journal of Pediatrics* 2002;28(3):191-2.

22. Mila M, Camprubi M, Clotet J, Balaguer A. Transcutaneous bilirubin measurement: could it be a good screening method for North African newborns? *Acta Paediatrics* 2007;96:97-8.

23. Nakamura M, et al. Evaluation of the new Minolta transcutaneous bilirubinometer JM-103 in Japanese neonates including low birth weight neonates. *Pediatric Research* 2002;51(4):342A.

24. Nanjundaswamy S, Petrova A, Mehta R, Hegyi T. The accuracy of transcutaneous bilirubin measurements in neonates. *Pediatric Research* 2003;53(4):497A-498A.

25. Nanjundaswamy S, Petrova A, Mehta R, Hegyi T. The accuracy of transcutaneous bilirubin measurements in neonates. *Journal of Investigative Medicine* 2003;51:S420.

26. Oliver P, J et al. Point-of-care bilirubin testing in the neonatal service at La Paz University Hospital. *Point of Care* 2008;7(3):186.

27. Ramachandran A, Evans J, Trays G, Kandhari A. Impact of implementing nice guidance for neonatal jaundice in a busy postnatal ward. *Archives of Disease in Childhood: Fetal and Neonatal Edition.* 2011; Conference: Perinatal Medicine 2011 Harrogate, United Kingdom. Conference Publication:Fa49.

28. Rodriguez P, Rivas L, Remon HC. POCT bilirubin evaluation after six years experience. *Point of Care* 2008;7(3):198.

29. Roy B, Coakley J, Badawi N. Is there a place for transcutaneous bilirubinometry in the NICU? *Journal of Paediatrics and Child Health.* Conference: 14th Annual Congress of the Perinatal Society of Australia and New Zealand, PSANZ 2010 Wellington New Zealand. Conference Publication:36.

30. Samanta S, et al. Abstract title: Screening for neonatal jaundice with 'Bilicheck,' a new transcutaneous bilirubinometer. *Pediatric Research* 2002;52(5):786.

31. Sankaran K. Transcutaneous bilirubinometry in neonates. *Paediatrics & Child Health* 2006;11(2):75-6.

32. Schafer K, Fuchs H, Hummler H. Evaluation of a transcutaneous bilirubinometer in newborns at 35 weeks of gestation. *Klinische Padiatrie* 2010;222:S23.

33. Sellitto M, et al. Measuring transcutaneous bilirubin: A comparative analysis of three devices. *Journal of Maternal-Fetal and Neonatal Medicine* 2010; Conference: 22nd European Congress of Perinatal Medicine, 2010 Granada Spain. Conference Publication:(var.pagings):560-1.

34. Shin SM, Lee YK, Ko SY, Kim KA. Transcutaneous bilirubinometry in Korean infants. *Pediatric Research* 2003;54(4):611.

35. Slusher TM, et al. Transcutaneous bilirubin measurements correlate well with serum total bilirubin levels in indigenous African infants. *Pediatric Research* 2002;51(4):329A.

36. Stevenson DK, Wong RJ, Vreman HJ. Reduction in hospital readmission rates for hyperbilirubinemia is associated with use of transcutaneous bilirubin measurements. *Clinical Chemistry* 2005;51(3):481-82.

37. Teran CG, Mohamed T, Casey J. Transcutaneous bilirubinometry: comparison of two multiwavelength devices in healthy term newborns. *European Journal of Pediatrics* 2011;170(11):1485.

38. Thomson J, Culley V, Monfrinoli A, Sinha A. Transcutaneous bilirubinometers and ethnicity. *Archives of Disease in Childhood Fetal & Neonatal Edition* 2008;93(6):F474.

39. Touch, et al. A transcutaneous bilirubinometer as a screening tool for neonatal hyperbilirubinemia. *Pediatric Research* 2003;54(4):615.

40. Yu Z-B. Reply to the correspondence letter: "Transcutaneous bilirubinometry: Comparison of two devices in healthy term newborns." *European Journal of Pediatrics* 2011;170(11):1487.

Duplications

1. Holland L, Blick K. Evaluation of transcutaneous bilirubin measurement for assessment of neonatal jaundice. *Clinical Chemistry* 2007;53(6):A222.

2. Holland L, Hu J, Blick K. Evaluation of transcutaneous bilirubin measurement in the neonate. *American Journal of Clinical Pathology* 2006;126(4):636.

3. Lyngsnes RL, et al. In vivo spectroscopy of jaundiced newborn skin reveals more than a bilirubin index. *Acta Paediatrica, International Journal of Paediatrics* 2005;94(1):65-71.

4. Marco LN, et al. Neonatal jaundice: Clinical evaluation of a transcutaneous bilirubinometer. *Anales de Pediatria* 2009;71(2):157-60.

Not primary study or summary of retrieved primary studies

1. Crawford-Faucher A. Universal screening effective in identifying severe hyperbilirubinemia. *American Family Physician* 2010;82(4):433.

2. Crawford-Faucher A. Single transcutaneous bilirubin value adequate to predict hyperbilirubinemia. *American Family Physician* 2010;82(4):428-33.

3. Crawford-Faucher A. Transcutaneous bilirubin nomogram can predict significant hyperbilirubinemia. *American Family Physician* 2010;82(4):427-28.

4. Thayyil S, Marriott L. Can transcutaneous bilirubinometry reduce the need for serum bilirubin estimations in term and near term infants? *Archives of Disease in Childhood* 2005;90(12):1311-12.

Other languages

1. Ahn YM, Kim MR, Lee SM, Jun YH. Assessment of neonatal hyperbilirubinemia using a transcutaneous bilirubinometry. *Daehan Ganho Haghoeji* 2003;33(1):51-59.

2. Korver CRW, Tel RM. Transcutaneous bilirubin measurements in newborns can avoid the need for invasive blood tests. *Nederlands Tijdschrift voor Klinische Chemie en Laboratoriumgeneeskunde* 2008;33(3):158-62.
3. Mat'asova K, et al. Reliability of noninvasive measurement of bilirubin concentration in healthy newborns. *Cesko-Slovenska Pediatrie* 2005;60(11):599-605.
4. Romagnoli C, et al. Validation of an hourly transcutaneous bilirubin nomogram in a population of term or late preterm newborn infants: preliminary results. *Minerva Pediatrica* 2010;62(3 Suppl 1):113-15.

Patients not eligible

1. Kazmierczak SC, et al. Transcutaneous measurement of bilirubin in newborns: comparison with an automated Jendrassik-Grof procedure and HPLC. *Clinical Chemistry* 2004;50(2):433-35.
2. Leite MG, Granato VA, Facchini FP, Marba ST. Comparison of transcutaneous and plasma bilirubin measurement. *Jornal de Pediatria* 2007;83(3):283-86.
3. Mahajan G, et al. Transcutaneous bilirubinometer in assessment of neonatal jaundice in northern India. *Indian Pediatrics* 2005;42(1):41-5.
4. Nanjundaswamy S, et al. The accuracy of transcutaneous bilirubin measurements in neonates: a correlation study. *Biology of the Neonate* 2004;85(1):21-5.
5. Poland RL, Hartenberger C, McHenry H, Hsi A. Comparison of skin sites for estimating serum total bilirubin in in-patients and out-patients: chest is superior to brow. *Journal of Perinatology* 2004;24(9):541-53.
6. Povaluk P, Shwetz EA, Kliemann R. Comparative study between plasma and transcutaneous bilirubin measurements in newborns. *Revista Paulista de Pediatria* 2011;29(1):6-12.
7. Randeberg LL, et al. In vivo spectroscopy of jaundiced newborn skin reveals more than a bilirubin index. *Acta Paediatrics* 2005;94(1):65-71.
8. Slusher TM, et al. Transcutaneous bilirubin measurements and serum total bilirubin levels in indigenous African infants. *Pediatrics* 2004;113(6):1636-41.
9. Stillova L, et al. Transcutaneous bilirubinometry in preterm neonates. *Indian Pediatrics* 2009;46(5):405-8.
10. Wong CM, van Dijk PJ, Laing IA. A comparison of transcutaneous bilirubinometers: SpectRx BiliCheck versus Minolta AirShields. *Archives of Disease in Childhood Fetal & Neonatal* 2002;87(2):F137-F140.
11. Yasuda S, et al. New transcutaneous jaundice device with two optical paths. *Journal of Perinatal Medicine* 2003;31(1):81-8.

Index test is not JM-103 or BiliCheck

1. Bertini G, Pratesi S, Cosenza E, Dani C. Transcutaneous bilirubin measurement: evaluation of Bilitest. *Neonatology* 2008;93(2):101-5.
2. Bhat YR, Rao A. Transcutaneous bilirubin in predicting hyperbilirubinemia in term neonates. *Indian Journal of Pediatrics* 2008;75(2):119-23.

3. Bhutani VK, Johnson LH, Schwoebel A, Gennaro S. A systems approach for neonatal hyperbilirubinemia in term and late pre-term newborns. *Journal of Obstetric, Gynecologic, & Neonatal Nursing* 2006;35(4):444-55.
4. Briscoe L, Clark S, Yoxall CW. Can transcutaneous bilirubinometry reduce the need for blood tests in jaundiced full term neonates? *Archives of Disease in Childhood Fetal & Neonatal* 2002;86(3):F190-F192.
5. Carbonell X, Botet F, Figueras J, Riu-Godo A. Prediction of hyperbilirubinaemia in the healthy term newborn. Acta Paeditrics 2001;90(2):166-70.
6. Eggert LD, Wiedmeier SE, Wilson J, Christensen RD. The effect of instituting a prehospital-discharge newborn bilirubin screening program in an 18-hospital health system. *Pediatrics* 2006;117(5):e855-e862.
7. Felc Z. Improvement of conventional transcutaneous bilirubinometry results in term newborn infants. *American Journal of Perinatology* 2005;22(4):173-79.
8. Goncalves A, et al. Prospective validation of a novel strategy for assessing risk of significant hyperbilirubinemia. *Pediatrics* 2011;127(1):e126-e131.
9. Karen T, Bucher HU, Fauchere JC. Comparison of a new transcutaneous bilirubinometer (Bilimed) with serum bilirubin measurements in preterm and full-term infants. *BMC Pediatrics* 2009;9:70, 2009.
10. Kazmierczak SC, et al. Direct spectrophotometric method for measurement of bilirubin in newborns: Comparison with HPLC and an automated diazo method. *Clinical Chemistry.* 2002;48(7):1096-1097.
11. Keren R, et al. A comparison of alternative risk-assessment strategies for predicting significant neonatal hyperbilirubinemia in term and late pre-term infants. *Pediatrics* 2008;121(1):e170-e179.
12. Kuzniewicz MW, Escobar GJ, Newman TB. Impact of universal bilirubin screening on severe hyperbilirubinemia and phototherapy use. *Pediatrics* 2009;124(4):1031-39.
13. Mahieu L, et al. Implementation of a multi-parameter point-of-care-blood test analyzer reduces central laboratory testing and need for blood transfusions in very low birth weight infants. *Clinica Chimica Acta* 2012;413(1-2):325-30.
14. Mielsch C, Zimmermann A, Wagner D et al. Point-of-care determination of neonatal bilirubin with the blood gas analyzer RapidLab 1265. *Clinical Chemistry & Laboratory Medicine* 2010;48(10):1455-61.
15. Ochoa SC, et al. Evaluation of a transcutaneous bilirubinometer. *Anales Espanoles de Pediatria* 2000;52(6):561-8.
16. Sun G, Wang YL, Liang JF, Du LZ. Predictive value of umbilical cord blood bilirubin level for subsequent neonatal jaundice. *Zhonghua Erke Zazhi* 2007;45(11):848-52.

No outcome of interest

1. Bredemeyer SL, Polverino JM, Beeby PJ. Assessment of jaundice in the term infant—accuracy of transcutaneous bilirubinometers compared with serum bilirubin levels: part two. *Neonatal, Paediatric & Child Health Nursing* 2007;10(1):5.

2. Carceller AM, et al. Evaluation of transcutaneous bilirubin measurement and agreement with bilirubinemia. *Annales de Biologie Clinique* 2006;64(6):575-79.
3. Corzo Pineda JA, Jurado HV, Tejera Orozco JL, Martinez Gonzalez MO. Transcutaneous bilirubinometry and early hospital discharge in low risk newborns with jaundice. *Ginecologia y Obstetricia de Mexico* 2001;69:194-9.
4. Holland L, Blick K. Implementing and validating transcutaneous bilirubinometry for neonates. *American Journal of Clinical Pathology* 2009;132(4):555-61.
5. Jangaard K, Curtis H, Goldbloom R. Estimation of bilirubin using BiliChektrade mark, a transcutaneous bilirubin measurement device: Effects of gestational age and use of phototherapy. *Paediatrics & Child Health* 2006;11(2):79-83.
6. Janjindamai W, Tansantiwong T. Accuracy of transcutaneous bilirubinometer estimates using BiliCheck in Thai neonates. *Journal of the Medical Association of Thailand* 2005;88(2):187-90.
7. Lam TS, Tsui KL, Kam CW. Evaluation of a point-of-care transcutaneous bilirubinometer in Chinese neonates at an accident and emergency department. *Hong Kong Medical Journal* 2008;14(5):356-60.
8. Maisels MJ, Deridder JM, Kring EA, Balasubramaniam M. Routine transcutaneous bilirubin measurements combined with clinical risk factors improve the prediction of subsequent hyperbilirubinemia. *Journal of Perinatology* 2009;29(9):612-17.
9. McKenzie J, Palmer B. Cost comparison of heel stick procedures and transcutaneous sample methods for bilirubin evaluation. *Neonatal Intensive Care* 2010;23(5):39-42.
10. Qualter YM, Allen NM, Corcoran JD, O'Donovan DJ. Transcutaneous bilirubin--comparing the accuracy of BiliChek[REGISTERED] and JM-103[REGISTERED] in a regional postnatal unit. *Journal of Maternal Fetal & Neonatal Medicine* 2011;24(2):267-70.
11. Punaro E, Mezzacappa MA, Facchini FP. Systematic follow-up of hyperbilirubinemia in neonates with a gestational age of 35 to 37 weeks. *Jornal de Pediatria* 2011;87(4):301-306.
12. Robertson A, Kazmierczak S, Vos P. Improved transcutaneous bilirubinometry: comparison of SpectR(X) BiliCheck and Minolta Jaundice Meter JM-102 for estimating total serum bilirubin in a normal newborn population. *Journal of Perinatology* 2002;22(1):12-14.
13. Siu L, Kwong N. Minolta JM-103 jaundice meter: A screening tool for neonatal jaundice in Chinese Neonates in Maternal and Child Health Centres. *Hong Kong Journal of Paediatrics* 2010;15(3):204-13.
14. Yap SH, Mohammad I, Ryan CA. Avoiding painful blood sampling in neonates by transcutaneous bilirubinometry. *Irish Journal of Medical Science* 2002;171(4):188-90.

Other

1. Bertini G. Transcutaneous bilirubin measurement: Evaluation of Bilitest. *Neonatology* 2008;93(3):152.
2. el-Beshbishi SN, Shattuck KE, Mohammad AA, Petersen JR. Hyperbilirubinemia and transcutaneous bilirubinometry [German]. *Journal of Laboratory Medicine / Laboratoriums Medizin* 2010;34(1):29-37.

3. Panburana J, Boonkasidach S, Rearkyai S. Accuracy of transcutaneous bilirubinometry compare to total serum bilirubin measurement. *Journal of the Medical Association of Thailand* 2010;93 Suppl 2:S81-6.
4. Szabo P, Bucher HU, Fauchere JC. A comparison between two transcutaneous bilirubinometers and assessment with the method of Kramer in term newborns. *Pediatric Research* 2002;52(5):823.

Appendix T.C: Methodology Quality Appraisal

Overview of the quality assessment tools

The recently published QUADUS-2,[90] a revised version of QUADAS published in 2003,[91] was used to assess methodological quality of included screening accuracy studies. QUADAS-2 consists of four key domains:

1) patient selection
2) index test
3) reference standard
4) flow and timing

Each is assessed in terms of risk of bias, and the first three domains are also assessed in terms of applicability concerns.

In the development of QUADAS-2, the main decision was to separate "quality" into "risk of bias" and "concerns regarding applicability." "Quality" was defined as both the "risk of bias" (the degree to which estimates of diagnostic accuracy avoided risk of bias) and the "applicability" (the extent to which primary studies are applicable to the review's research question) of a study. There are 11 signaling questions for assessing risk of bias (see Table T.C.1).

QUADAS-2 is applied in four phases:

1) Summarizing the review questions:
   - Population: healthy neonates with gestational age of ≥35 weeks, regardless of ethnicity
   - Index test: TcB (models currently on the Canadian market)
   - Reference standard: TSB test
   - Target condition: significant neonatal hyperbilirubinemia
   - Setting: hospital or community
   - Intended use of the index test: as a screening test for clinically significant hyperbilirubinemia in otherwise healthy, full term or late preterm neonates
2) Tailoring the tool to the review (by adding or omitting signaling questions) and producing review-specific guidance (and piloting of it by two independent raters).
3) Constructing a flow diagram for the primary study.
4) Assessing risk of bias and concerns regarding applicability.

Judgment on risk of bias:

Risk of bias is judged as "high," "low," or "unclear."

High risk of bias: all signaling questions for a domain are answered "No"

Low risk of bias: all signaling questions for a domain are answered "Yes"

Unclear: used only when insufficient data are reported to permit a judgment

Table T.C.1: Risk of bias and applicability judgments in QUADAS-2[90]

Domain	Patient selection	Index test	Reference standard	Flow and timing
Description	Describe methods of patient selection: Describe included patients (prior testing, presentation, intended use of index test, and setting)	Describe the index test and how it was conducted and interpreted.	Describe the reference standard and how it was conducted and interpreted.	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.
Signaling questions (Yes/No/Unclear)	Was a consecutive or random sample of patients enrolled?	Were the index test results interpreted without knowledge of the results of the reference standard?	Is the reference standard likely to correctly classify the target condition?	Was there an appropriate interval between index test(s) and reference standard?
	Was a case-control design avoided?	If a threshold was used, was it pre-specified?	Were the reference standard results interpreted without knowledge of the results of the index test?	Did all patients receive a reference standard?
	Did the study avoid inappropriate exclusions?			Did all patients receive the same reference standard?
				Were all patients included in the analysis?
Risk of bias (high/low/unclear)	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?
Concerns regarding applicability (high/low/unclear)	Are there concerns that the included patients do not match the review question?	Are there concerns that the index test, its conduct, or its interpretation differ from the review question?	Are there concerns that the target condition, as defined by the reference standard, does not match the review question?	

Adaptation of QUADAS-2

One reviewer (BG) developed a draft review-specific guidance for the 11 signaling questions for risk of bias. Two reviewers (BG and KB) piloted the QUADAS-2, with the draft guidance, in four primary studies. Discrepancies between the reviewers and the issues associated with the use of the tool were discussed.

After the discussion, one signaling question in the domain of reference standard "Were the reference standard results interpreted without knowledge of the results of the index test?" was removed from the tool. This is because the reference standard –TSB testing is an objective test that is, in most cases, conducted in clinical laboratories. Interpretations of TSB results are unlikely to be affected by the results of the index test –TcB, a point-of-care test that is always conducted at patients' bedsides, and the results are available immediately. No new item was added to the tool as it was thought that the QUADAS-2 tool covered all the important aspects adequately. Thus, the QUADAS-2 tool tailored for this report consists of 10 signaling questions.

The rating guidance was refined and finalized based on discussion between the two reviewers.

Quality assessment results

The quality assessment results of each of the included screening accuracy studies are summarized in Tables C.2–4. As recommended by the developers of the QUADAS-2,[90] rating results of QUADAS-2 were not used to generate a summary "quality score" because of the problems associated with such scores.[80] Instead, the results of the quality assessment were incorporated into the systematic review through the investigation of the association of individual quality items with estimates of diagnostic accuracy.[80,84]

Table T.C.2: Quality assessment of studies using BiliCheck

Domain	Questions for risk of bias	Romagnoli[30]	Wickremasinghe[57]	Kaynak-Turkman[70]	Mishra[46]	Dalal[46]	Varvarigou[59]	De Luca[71]
Patient selection	Was a consecutive or random sample of patients enrolled?	?	?	?	×	×	?	√
	Was a case-control design avoided?	√	√	√	√	√	√	√
	Did the study avoid inappropriate exclusions?	√	?	√	√	×	√	√
	Risk of bias	unclear	unclear	unclear	high	high	unclear	low
Index test	Were the index test results interpreted without knowledge of the results of the reference standard?	√	?	√	?	√	√	√
	If a threshold was used, was it pre-specified?	√	?	×	√	√	√	×
	Risk of bias	low	unclear	high	unclear	low	low	High
Reference standard	Is the reference standard likely to correctly classify the target condition?	√	√	√	?	√	×	×
	Risk of bias	low	low	low	unclear	low	high	High
Patient flow and timing	Was there an appropriate interval between index test(s) and reference standard?	?	×	√	√	?	√	√
	Did all patients receive a reference standard?	√	√	√	×	×	√	√
	Did all patients receive the same reference standard?	√	√	√	?	√	√	√
	Were all patients included in the analysis?	√	?	?	√	×	×	√
	Risk of bias	unclear	high	unclear	high	high	high	low

Domain	Questions for risk of bias	Karon[61]	De Luca[36]	Kolman[26]	Boo[31]	Ho[62]	Samanta[64]
Patient selection	Was a consecutive or random sample of patients enrolled?	×	×	×	?	?	√
	Was a case-control design avoided?	√	√	√	√	√	√
	Did the study avoid inappropriate exclusions?	?	√	×	√	?	?
	Risk of bias	high	high	high	unclear	unclear	unclear
Index test	Were the index test results interpreted without knowledge of the results of the reference standard?	√	√	√	√	√	√
	If a threshold was used, was it pre-specified?	√	×	√	×	×	×
	Risk of bias	low	high	low	high	high	high
Reference standard	Is the reference standard likely to correctly classify the target condition?	√	×	√	√	?	√
	Risk of bias	low	high	low	low	unclear	low
Patient flow and timing	Was there an appropriate interval between index test(s) and reference standard?	√	√	√	√	√	√
	Did all patients receive a reference standard?	√	√	√	√	√	√
	Did all patients receive the same reference standard?	√	√	√	√	?	√
	Were all patients included in the analysis?	√	?	√	√	?	×
	Risk of bias	low	unclear	low	low	unclear	high

Domain	Questions for risk of bias	Engle[63]	Ebbesen[73]	Rubaltelli[28]	Bhutani[34]	Lodha[76]	Campbell[66]	Martinez[67]
Patient selection	Was a consecutive or random sample of patients enrolled?	?	×	?	?	?	?	?
	Was a case-control design avoided?	√	√	√	√	√	√	√
	Did the study avoid inappropriate exclusions?	?	√	√	√	√	√	√
	Risk of bias	unclear	high	unclear	unclear	unclear	unclear	unclear
Index test	Were the index test results interpreted without knowledge of the results of the reference standard?	√	√	√	√	√	√	√
	If a threshold was used, was it pre-specified?	×	×	×	√	×	×	×
	Risk of bias	high	high	high	low	high	high	high
Reference standard	Is the reference standard likely to correctly classify the target condition?	√	√	√	√	×	√	√
	Risk of bias	low	low	low	low	high	low	low
Patient flow and timing	Was there an appropriate interval between index test(s) and reference standard?	√	?	√	√	√	√	√
	Did all patients receive a reference standard?	√	√	√	√	√	√	√
	Did all patients receive the same reference standard?	√	√	√	√	√	√	√
	Were all patients included in the analysis?	√	?	√	×	?	√	√
	Risk of bias	low	unclear	low	high	unclear	low	low

Table T.C.3: Quality assessment of studies using JM-103

Domain	Questions for risk of bias	Maisels[69]	Yu[45]	Sanpavat[42]	Wainer[38]	Bental[44]
Patient selection	Was a consecutive or random sample of patients enrolled?	?	√	×	×	×
	Was a case-control design avoided?	√	√	√	√	√
	Did the study avoid inappropriate exclusions?	?	√	×	√	√
	Risk of bias	unclear	low	high	high	high
Index test	Were the index test results interpreted without knowledge of the results of the reference standard?	√	√	√	√	√
	If a threshold was used, was it pre-specified?	×	√	×	×	×
	Risk of bias	high	low	high	high	high
Reference standard	Is the reference standard likely to correctly classify the target condition?	√	√	?	√	√
	Risk of bias	low	low	unclear	low	low
Patient flow and timing	Was there an appropriate interval between index test(s) and reference standard?	√	×	?	√	√
	Did all patients receive a reference standard?	×	×	√	√	√
	Did all patients receive the same reference standard?	√	√	?	√	√
	Were all patients included in the analysis?	×	√	√	×	√
	Risk of bias	high	high	unclear	high	low

Domain	Questions for risk of bias	Kaplan[16]	Ho[37]	Engle[63]	Sanpavat[75]	Maisels[65]	Chang[77]
Patient selection	Was a consecutive or random sample of patients enrolled?	√	√	?	?	×	?
	Was a case-control design avoided?	√	√	√	√	√	√
	Did the study avoid inappropriate exclusions?	√	√	?	√	?	?
	Risk of bias	low	low	unclear	unclear	high	unclear
Index test	Were the index test results interpreted without knowledge of the results of the reference standard?	√	√	√	√	√	?
	If a threshold was used, was it pre-specified?	×	√	?	?	×	×
	Risk of bias	high	low	unclear	unclear	high	high
Reference standard	Is the reference standard likely to correctly classify the target condition?	√	√	√	√	√	×
	Risk of bias	low	low	low	low	low	high
Patient flow and timing	Was there an appropriate interval between index test(s) and reference standard?	√	√	√	√	√	√
	Did all patients receive a reference standard?	×	×	√	√	√	√
	Did all patients receive the same reference standard?	√	√	√	√	√	√
	Were all patients included in the analysis?	√	?	?	√	√	?
	Risk of bias	high	high	unclear	low	low	unclear

Table T.C.4: Quality assessment of studies using BiliCheck and JM-103

Domain	Questions for risk of bias	Sanpavat[74]	Rodriguez-Capote[60]
Patient selection	Was a consecutive or random sample of patients enrolled?	?	×
	Was a case-control design avoided?	√	√
	Did the study avoid inappropriate exclusions?	√	√
	Risk of bias	unclear	high
Index test	Were the index test results interpreted without knowledge of the results of the reference standard?	√	√
	If a threshold was used, was it pre-specified?	√	×
	Risk of bias	low	high
Reference standard	Is the reference standard likely to correctly classify the target condition?	×	√
	Risk of bias	high	low
Patient flow and timing	Was there an appropriate interval between index test(s) and reference standard?	√	√
	Did all patients receive a reference standard?	√	√
	Did all patients receive the same reference standard?	√	√
	Were all patients included in the analysis?	√	×
	Risk of bias	low	high

Appendix T.D: Summary of Included Studies

Abbreviations for Appendix T.D

BC	BiliCheck
BF	breast-feeding
BW	birth weight
CI	confidence interval
CS	Cesarean section
FF	formula feeding
GA	gestational age
HPLC	high performance liquid chromatography
LOS	length of stay
NLR	negative likelihood ratio
PLR	positive likelihood ratio
NA	not available
NH	neonatal hyperbilirubinemia
NICU	neonatal intensive care unit
PHN	public health nurse
PI	primary investigator
RD	risk difference
SNH	significant neonatal hyperbilirubinemia
TcB	transcutaneous bilirubinometry
TSB	total serum bilirubin
VA	visual assessment

Data are expressed as mean ±SD unless indicated otherwise. The conversion of the unit of bilirubin concentration: 1 mg/dL = 17.1 μmol/L

Table T.D.1: Summary of included screening accuracy studies (pre-discharge)

Study	N	Neonate characteristics	Index test	Reference standard
Bhutani et al. 2000[34] USA Prospective	490	**M/F:** NA **GA** (wks): 38.9±1.5 **BW** (g): 3404±518 **Ethnicity:** Caucasian 59%, Black 30%, Hispanic 3%, Asian 4% **Delivery mode:** NA **Feeding type:** NA **All jaundiced?:** no **Age at TcB/TSB measurement** (h): median 39 (range 18 to 96)	**Device:** BiliCheck **No. of devices**: 11 **Location:** forehead **Test performer:** NA **Training:** NA **Nomogram:** Bhutani nomogram **TcB source funding:** SpectRx personnel for technical, bioengineering, and funding support	**Method:** HPLC **Test performer:** technicians **Time interval between TcB and TSB:** ≤30 min
Campbell et al. 2011[66] Canada Prospective	430	**M/F:** 236 (55%)/194 (45%) **GA** (wks): 38.8±1.4 **BW** (g): 3289±458 **Ethnicity (maternal):** Asian 34%, Caucasian 33%, Latino 10%, Indian 8%, Black 8%, Middle Eastern 4%, other/unknown 3% **Delivery mode:** C-S 34% **Feeding type:** breast 65% **All jaundiced?:** yes (10% in NICU) **Age at TcB/TSB measurement** (h): 55±27	**Device:** BiliCheck **No. of devices:** NA **Location:** forehead **Test performer:** nurses **Training:** 1 h training session **Nomogram:** NA **TcB source funding:** NA	**Method:** Diazo method with the Synchron LX 20 Clinical Chemistry System (Beckman Coulter Inc, USA) **Test performer:** NA **Time interval between TcB and TSB**: ≤30 min
Romagnoli et al. 2012[30] Italy (5 neonatal units) Prospective	2167	**M/F:** 1137 (52.5%)/1030 (47.5%) **GA** (wks): 38.9±1.5 (range 35–42) **BW** (g): 3237±471 (range 2000–5090) **Ethnicity:** Caucasian 90% **Delivery mode:** spontaneous (53.5%), CS 44% **Feeding type:** breast 58.5%, both 39.1%, formula 2.4% **All jaundiced?**: no **Age at TcB/TSB measurement:** 63±21 h	**Device:** BiliCheck **No. of devices:** single device at each unit **Location:** forehead **Test performer:** experienced neonatologists **Training:** NA **Nomogram:** TcB nomogram developed using BC in 100% white neonates[40] **TcB source funding:** NA	**Method:** TSB by direct spectrophotometer (Microbilimeter Dual Beam Plus model 11144A73G, Ginevri, Rome, Italy) **Test performer:** trained technician, blind to TcB value **Time interval between TcB and TSB:** simultaneous

Table T.D.1: Summary of included screening accuracy studies (pre-discharge) (cont'd)

Study	N	Neonate characteristics	Index test	Reference standard
De Luca et al. 2008[36] Italy Prospective	686	**M/F:** 345 (50%)/341 (50%) **GA** (wks): 38.2±1.7 **BW** (g): 3089±531 **Ethnicity:** Caucasian: 100% **Delivery mode:** C-section or vaginal **Feeding type:** NA **All jaundiced?:** no **Age at TcB/TSB measurement** (h): 24 to 96	**Device:** BiliCheck **No. of devices:** NA **Location:** forehead **Test performer:** single investigator **Training:** NA **Nomogram:** NA **TcB source funding:** NA	TSB (Microbilimeter Twin Beam Plus (conducted in the nursery lab) **Test performer:** single qualified lab technician **Time interval between TcB and TSB:** ≤15 min
De Luca et al. 2008[71] Italy	517	**M/F:** 299 (58%)/218 (42%) **GA** (wks): 39.1±1.5 **BW** (g): 3295±426 **Ethnicity:** Caucasian 100% **Delivery mode:** NA **Feeding type:** NA **All jaundiced?**: no **Age at TcB/TSB measurement:** <72 h (all)	**Device:** BiliCheck **No. of devices:** NA **Location:** forehead **Test performer:** fellow-neonatologist **Training:** NA **Nomogram:** NA **Comparator:** VA by full-time, experienced pediatric nurses. **TcB source funding:** NA	**Method:** TSB by direct spectrophotometer (Microbilimeter Twin Beam Plus mod.11144A73, Ginevri, Rome, Italy) **Test performer:** single lab technician, blind to both TcB and VA **Time interval between TcB and TSB:** ≤10 min
Karon et al. 2008[61] USA Prospective	177	**M/F:** NA **GA** (wks): median 39 (range $32^{6}/_{7}$ to $41^{3}/_{7}$, IQR 38-$39^{6}/_{7}$) **BW** (g): NA **Ethnicity:** Caucasian 82%, Asian 11%, Hispanic 5%, Africa American 2% **Delivery mode:** NA **Feeding type:** NA **All jaundiced?:** no **Age at TcB/TSB measurement (h)**: median 48 (range 8–81, IQR 42–45)	**Device:** BiliCheck **No. of devices:** 2 **Location:** forehead **Test performer:** nurses **Training:** a training session that described use of the device according to the manufacturer's instruction **Nomogram:** Bhutani nomogram (bilitool.org) **TcB source funding:** NA	**Method:** TSB by modified Diazo or Vitros method **Test performer:** NA **Time interval between TcB and TSB:** ≤30 min

Table T.D.1: Summary of included screening accuracy studies (pre-discharge) (cont'd)

Study	N	Neonate characteristics	Index test	Reference standard
Kolman et al. 2007[26] USA	192	**M/F:** NA **GA** (wks): 39±1.5 **BW** (g): 3368±489 **Ethnicity:** Hispanic 100% **Delivery mode:** NA **Feeding type:** NA **All jaundiced?:** no **Age at TcB/TSB measurement** (h)**:** 40±13.4	**Device:** BiliCheck **No. of devices:** single device **Location:** forehead **Test performer:** trained nursery nurse **Training:** one-on-one instruction provided **Nomogram:** Bhutani nomogram **TcB source funding:** NA	**Method:** TSB by modified Diazo (on Ortho Vitros Chemistry system) **Test performer:** NA **Time interval between TcB and TSB:** ≤30 min
Wainer 2009[38] Canada Prospective	774	**M/F:** 377 (49)/397 (51%) **GA** (wks): 39.1±1.2 (range 37–42) **BW** (g): 3166±447 (range 2096–4765) **Ethnicity:** Caucasian 42%, Asian 41%, Middle Eastern 10%; Aboriginal 3%; Skin tone: light 44%, medium 52%, dark 2% **Delivery mode:** NA **Feeding type:** NA **All jaundiced?:** no **Age at TcB/TSB measurement** (h): <72: 95% (<24: 0.8%, 24–47: 87%, 48–71: 7.5%, 72–95: 4.3%, ≥96: 0.9%)	**Device:** JM-103 **No. of devices:** 4 in the community and 1 in the hospital **Location:** forehead **Test performer:** study nurses or device-trained public health nurses **Training:** NA **Nomogram:** NA **TcB source funding:** NA	**Method:** TSB by Diazo (Roche Modular, Hitachi 912 and 917 instruments, Roche Diagnostics, Indianapolis, IN, USA) **Test performer:** NA **Time interval between TcB and TSB:** <60 minutes
Kaplan et al. 2008[16] Israel	346	**M/F:** 175 (51%)/171 (49%) **GA** (wks): 39.4±1.4 **BW** (g): 3278±449 **Ethnicity:** Ashkenazi Jewish (light skinned) 49%, Sephardic Jewish 29%, Mixed Ashkenazi-Sephardic: 13%, Arab (light pigmented) 9% **Delivery mode:** vaginal (92%) **Feeding type:** NA **All jaundiced?:** no **Age at TcB/TSB measurement** (h): 59±23	**Device:** JM-103 **No. of devices:** NA **Location:** forehead **Test performer:** physician **Training:** NA **Nomogram:** Bhutani nomogram **Comparator:** VA (using Kramer grading by nurses) **TcB source funding:** NA	**Method:** TSB by direct spectrophotometric method at clinical biochemistry lab/visual assessment **Test performer:** NA **Time interval between TcB and TSB:** ≤30 min

Table T.D.1: Summary of included screening accuracy studies (pre-discharge) (cont'd)

Study	N	Neonate characteristics	Index test	Reference standard
Ho et al. 2006[37] Hong Kong Retrospective	997	**M/F:** NA **GA** (wks): median 39 (range 35–42) **BW** (g): NA **Ethnicity:** Chinese 95% **Delivery mode:** NA **Feeding type:** NA **All jaundiced?:** no **Age at TcB/TSB measurement** (h): median 32.9 (range 12.1–139.6), <72 h in 97% neonates	**Device:** JM-103 **No. of devices:** single **Location:** mid-sternum **Test performer:** NA **Training:** NA **Nomogram:** Bhutani nomogram **TcB source funding:** NA	**Method:** TSB by Unistat Reflectance bilirubinometer (Reichert-Jung, Buffalo, NY, USA) **Test performer:** NA **Time interval between TcB and TSB:** ≤30 min
Chang et al. 2006[77] Taiwan	447	**M/F:** 229 (51%)/218 (49%) **GA** (wks): 36.8±1.3 (range 35–41) **BW** (g): 3185±400 (range 2280–4368) **Ethnicity:** Taiwanese 100% **Delivery mode:** normal spontaneous (47%), C-section 50%, assisted vaginal delivery (3.6%) **Feeding type:** breast 44%, formula 4%, both 52% **All jaundiced?:** no **Age at TcB/TSB measurement** (h): <72 (all)	**Device:** JM-103 **No. of devices:** NA **Location:** forehead & chest **Test performer:** NA **Training:** NA **Nomogram:** NA **TcB source funding:** NA	**Method:** TSB by Reichert Unistat bilirubinometer (Reichert, Inc., Depew, NY, USA) **Test performer:** NA **Time interval between TcB and TSB:** ≤60 min

Table T.D.2: Summary of included screening accuracy studies (post-discharge)

Study	N	Neonate characteristics	Index test	Reference standard
Wickremasinghe et al. 2011[57] USA Prospective	79	**M/F:** NA **GA** (wks): mean 39 2/7 (range 36 2/7–41 5/7) **BW** (g): mean 3495 (range 2305–4985) **Ethnicity:** Caucasian 62%, Asian 11%, Hispanic 6%, Other: 5%; Unknown: 15% **Delivery mode:** NA **Feeding type:** NA **All jaundiced?:** yes **Age at TcB/TSB measurement** (h): mean 101 (range 53–204) h	**Device:** BiliCheck **No. of devices:** 2 **Location:** chest **Test performer:** nurse **Training:** attending a training session on the proper use of BC device and demonstrating competency before performing TcB measurements **Nomogram:** Bhutani nomogram **TcB source funding:** NA	**Method:** TSB by modified Diazo method **Test performer:** NA **Time interval between TcB and TSB:** ≤90 minutes
Kaynak-Turkmen 2011[70] Turkey	54	**M/F:** 31 (57%)/23 (43%) **GA** (wks): 30–37: 32%, 38–42: 68% **BW** (g): 2979±656 (range 1550–4200) **Ethnicity:** Caucasian 100% **Delivery mode:** NA **Feeding type:** NA **All jaundiced?:** no **Age at TcB/TSB measurement** (h): 160±99 (range 72–456)	**Device:** BiliCheck **No. of devices:** NA **Location:** forehead **Test performer:** NA **Training:** NA **Nomogram:** NA **TcB source funding:** NA	**Method:** TSB by HPLC and by Diazo method **Test performer:** NA **Time interval between TcB and TSB:** ≤30 min
Maisels et al. 2011[69] North American multicentres (five clinics, one in Calgary)	120	**M/F:** 64 (53%)/56 (47%) **GA** (wks): 35–38: 30%, >38: 76%, unknown: 4% **BW** (g): NA **Ethnicity:** Caucasian 35%, Africa-American 9%; Asian 16%; Hispanic 31%; Middle Eastern 3%; Native Canadian 4%; Unknown 3% **Delivery mode:** NA **Feeding type:** breast 48%, formula 13%, both 38% **All jaundiced?:** yes **Age at TcB/TSB measurement** (h): 90±33 (range 27–313)	**Device:** JM-103 **No. of devices:** NA **Location:** mid-sternum **Test performer:** nurses **Training:** NA **Nomogram:** Calgary local nomogram used by Calgary centre **TcB source funding:** lead author received funding from Dräeger Medical Inc for previous studies of the JM-103	**Method:** TSB by Diazo **Test performer:** NA **Time interval between TcB and TSB:** ≤30 min

Table T.D.2: Summary of included screening accuracy studies (post-discharge) (cont'd)

Study	N	Neonate characteristics	Index test	Reference standard
Engle et al. 2005[63] USA Prospective	121	**M/F:** 68 (56%)/53 (44%) **GA** (wks): median 40 (range 35–41) **BW** (g): median 3280 (range 2265–4590) **Ethnicity:** Hispanic 92%, Africa-American 3%, Asian 3%, Caucasian 2% **Delivery mode:** NA **Feeding type:** breast 33%, formula: 22%, both 45% **All jaundiced?:** yes **Age at TcB/TSB measurement** (h): median 91 (range 53–166)	**Device:** JM-103 **No. of devices:** single device **Location:** sternum **Test performer:** one investigator **Training:** NA **Nomogram:** Bhutani nomogram **TcB source funding:** JM-103™ was provided without charge by Hill Rom Air-Shields	**Method:** TSB by Diazo **Test performer:** NA **Time interval between TcB and TSB:** ≤30 min

Table T.D.3: Summary of screening accuracy studies (during the first week of life)

Study	N	Neonate characteristics	Index test	Reference standard
Rubaltelli 2001[28] European multicentres (6 countries)	210	**M/F:** NA **GA** (wks): ≤36: 20%, >36: 80% **BW** (g): <2500 16%, 2500–3499 534%, ≥3500 30% **Ethnicity:** Caucasian 67%, Asian 15%, Hispanic 7%, African 4%, other 7% **Delivery mode:** NA **Feeding type:** NA **All jaundiced?:** no **Age at TcB/TSB measurement** (h): range from <48 to ≥96 (<48: 16%, 48–71: 24%, 72–95: 35%, ≥96: 24%)	**Device:** BiliCheck **No. of devices:** NA **Location:** forehead & sternum **Test performer:** NA **Training:** NA **Nomogram:** NA **TcB source funding:** This study was supported in part by SpectRx Inc, Norcross, Georgia.	**Method:** TSB by standard lab methods at each centre & HPLC **Test performer:** NA **Time interval between TcB and TSB:** ≤30 minutes
Martinez et al. 2005[67] Argentina Prospective	246	**M/F:** NA **GA** (wks): ≤38: 32%, >38: 68% **BW** (g): <2500: 2%, 2500-3499: 60%, ≥3500: 38% **Ethnicity:** NA (skin tone: light 69%, medium 30%, dark: 0.4%) **Delivery mode:** NA **Feeding type:** NA **All jaundiced?:** no **Age at TcB/TSB measurement** (h): <48: 46%, 48–71: 14%, 72–95: 7%, ≥96: 33%	**Device:** BiliCheck **No. of devices:** NA **Location:** forehead **Test performer:** NA **Training:** NA **Nomogram:** NA **TcB source funding:** NA	**Method:** TSB by spectrophotometry (Bilitron) & HPLC **Test performer:** NA **Time interval between TcB and TSB:** ≤30 minutes
Engle et al. 2002[68] USA Retrospective	304	**M/F:** 168 (55%)/136 (45%) **GA** (wks): Hispanic: 38.9±1.7, Non-Hispanic: 38.7±1.4 **BW** (g): Hispanic: 3304±5.74, Non-Hispanic: 3239±455 **Ethnicity:** Hispanic 82%, non-Hispanic: 18% **Delivery mode:** C-S 18% **Feeding type:** breast 34% **All jaundiced?:** yes **Age at TcB/TSB measurement** (h): range from ≤24 to >96	**Device:** BiliCheck **No. of devices:** 4 **Location:** forehead **Test performer:** one investigator **Training:** NA **Nomogram:** NA **TcB source funding:** study was funded in part by Respironics, Inc.	**Method:** TSB by Diazo method **Test performer:** NA **Time interval between TcB and TSB:** ≤30 min

Table T.D.3: Summary of screening accuracy studies (during the first week of life) (cont'd)

Study	N	Neonate characteristics	Index test	Reference standard
Samanta et al. 2004[64] UK Prospective	300	**M/F:** 150 (50%)/150 (50%) **GA** (wks): median 39 (range 33–42) **BW** (g): median 3295 (range 1972–4720) **Ethnicity:** NA **Delivery mode:** NA **Feeding type:** NA **All jaundiced?:** yes **Age at TcB/TSB measurement** (h): median 72 (range 24–264)	**Device:** BiliCheck **No. of devices:** NA **Location:** forehead **Test performer:** phlebotomist **Training:** NA **Nomogram:** NA **TcB source funding:** NA	**Method:** TSB by Diazo method **Test performer:** NA **Time interval between TcB and TSB:** concurrently
Ebbesen et al. 2002[73] Denmark	227	**M/F:** 126 (55%)/101 (45%) **GA** (wks): mean 38.6 (range 35–43) **BW** (g): mean 3362 (range 2170–5000) **Ethnicity:** Northern European 93%; non-Northern European 7% **Delivery mode:** NA **Feeding type:** NA **All jaundiced?:** yes **Age at TcB/TSB measurement** (h): mean 74 (range 48–360)	**Device:** BiliCheck **No. of devices:** NA **Location:** forehead, sternum, knee, foot **Test performer:** routine lab technicians **Training:** NA **Nomogram:** NA **TcB source funding:** NA	**Method:** TSB by Vitros 950 analyzer (BuBc slide) **Test performer:** NA **Time interval between TcB and TSB:** NA
Szabo et al. 2004[72] Switzerland	140	**M/F:** NA **GA** (wks): median 39 (range 37–42) **BW** (g): median 3320 (range 2050–4400) **Ethnicity:** Caucasian 66%, Asian 13%, Indian or African 21% **Delivery mode:** NA **Feeding type:** NA **All jaundiced?:** yes **Age at TcB/TSB measurement** (h): <144	**Device:** BiliCheck **No. of devices:** NA **Location:** forehead & sternum **Test performer:** primary investigator **Training:** NA **Nomogram:** NA **Comparator:** VA (using Kramer's dermal zones; by nurses and the same primary investigator, independently) **TcB source funding:** NA	**Method:** TSB by Bilimeter II (Pfaff, Neuburg, Germany) **Test performer:** NA **Time interval between TcB and TSB:** ≤10 min

Table T.D.3: Summary of screening accuracy studies (during the first week of life) (cont'd)

Study	N	Neonate characteristics	Index test	Reference standard
Ho et al. 2006[62] Hong Kong Prospective	83	**M/F:** 46 (55%)/37 (45%) **GA** (wks): 38.8±1.5 (range 34.3–41.9) **BW** (g): 3120±490 (range 1950–4580) **Ethnicity:** Chinese 100% **Delivery mode:** NA **Feeding type:** NA **All jaundiced?:** yes **Age at TcB/TSB measurement** (h): 95±41 (range 48–216)	**Device:** BiliCheck **No. of devices:** NA **Location:** forehead & sternum **Test performer:** NA **Training:** NA **Nomogram:** NA **TcB source funding:** NA	**Method:** TSB by bedside Unistat Bilirubinometer or by Diazo method in the lab **Test performer:** NA **Time interval between TcB and TSB:** NA
Lodha et al. 2000[76] India	109	**M/F:** NA **GA** (wks): 38.4±1.5 **BW** (g): 2870±330 **Ethnicity:** Indian 100% **Delivery mode:** NA **Feeding type:** NA **All jaundiced:** yes **Age at TcB/TSB measurement** (h): 71.8±27	**Device:** BiliCheck **No. of devices:** NA **Location:** forehead **Test performer:** NA **Training:** NA **Nomogram:** NA **Comparator:** VA by experienced pediatrician **TcB source funding:** Medisphere Marketing Ltd, New Delhi provided the instrument and accessories	**Method:** TSB by twin beam Microbilimeter **Test performer:** NA **Time interval between TcB and TSB:** ≤30 min
Boo & Ishak 2007[31] Malaysia Prospective	345	**M/F:** 207 (60%)/138 (40%) **GA** (wks): median 38 (50% CI 37, 39) **BW** (g): 3056±487 **Ethnicity:** Malays 63.8%, Chinese 30.7%, Indian 5.5% **Delivery mode:** NA **Feeding type:** NA **All jaundiced?:** yes **Age at TcB/TSB measurement** (h): median 70 (range 9.0–388)	**Device:** BiliCheck **No. of devices:** NA **Location:** forehead & mid sternum **Test performer:** NA **Training:** NA **Nomogram:** NA **TcB source funding:** NA	**Method:** TSB by Diazo method **Test performer:** technicians blind to TcB values **Time interval between TcB and TSB:** ≤30 minutes

Table T.D.3: Summary of screening accuracy studies (during the first week of life) (cont'd)

Study	N	Neonate characteristics	Index test	Reference standard
Maisels et al. 2004[65] USA Prospective	849	**M/F:** NA **GA** (wks): NA **BW** (g): NA **Ethnicity:** Caucasian 59%, Black 30%, Eastern Asian 5%, Middle Eastern 4%, Indian/Pakistani 2%, Hispanic 1% **Delivery mode:** NA **Feeding type:** NA **All jaundiced?:** yes **Age at TcB/TSB measurement** (h): NA	**Device:** JM-103 (Both BC and JM-103 for a subset of 146 infants) **No. of devices:** NA **Location:** mid-sternum **Test performer:** research nurse or technicians **Training:** NA **Nomogram:** NA **TcB source funding:** supported by a grant from Minolta (Osaka, Japan) and from Hill-Rom Air-Shields (Hatboro, PA). Respironics (Marietta, GA) provided the BiliCheck.	**Method:** TSB measured in hospital clinical chemistry labs using Advanced Instruments Bilirubinometer; Dupont Dimension XL, or Beckman LX20 **Test performer:** NA **Time interval between TcB and TSB:** ≤60 min
Bental et al. 2009[44] Israel Prospective	628	**M/F:** NA **GA** (wks): 39.4±1.35 (range 35–42) **BW** (g): 3280±448 (range 2020–4985) **Ethnicity:** Ashkenazi 33%, mix of Ashkenazi and Sephardic 24%, Sephardic 41%, Ethiopian 2% **Delivery mode:** NA **Feeding type:** breast >90% **All jaundiced?:** yes **Age at TcB/TSB measurement** (h): 56±25 (range 8–161)	**Device:** JM-103 **No. of devices:** single device **Location:** forehead & mid-sternum (average of the two measurements) **Test performer:** experienced lab technician **Training:** NA **Nomogram:** locally developed TcB nomogram **TcB source funding:** NA	**Method:** TSB by colorimetric method (ApelBR –501 instrument, Saitama, Japan) **Test performer:** experienced lab technician **Time interval between TcB and TSB:** simultaneous
Sanpavat et al. 2004[75] Thailand	388	**M/F:** 223 (58%)/165 (42%) **GA** (wks): ≥36 (100%) **BW** (g): 3118±425 **Ethnicity:** Thai 100% **Delivery mode:** NA **Feeding type:** breast >90% **All jaundiced?:** yes **Age at TcB/TSB measurement** (h): 64±2.5 (range 11–216)	**Device:** JM-103 **No. of devices:** NA **Location:** forehead **Test performer:** one investigator **Training:** NA **Nomogram:** NA **TcB source funding:** NA	**Method:** TSB by Leica Unistate Bilirubinometer (Leica Inc. Buffalo, NY, USA **Test performer:** NA **Time interval between TcB and TSB:** ≤15 min

Table T.D.3: Summary of screening accuracy studies (during the first week of life) (cont'd)

Study	N	Neonate characteristics	Index test	Reference standard
Rodriguez-Capote et al. 2009[60] Canada Prospective	154 (JM-103: 94, BC: 60)	**M/F:** 74 (48%)/80 (52%) **GA** (wks): 39.2±1.3 for both groups **BW** (g): 3392±487 for BC group, 3344±399 for JM-103 group **Ethnicity:** Caucasian 68%, non-Caucasian 32% **Delivery mode:** vaginal 77% in BC group, 69% in JM-103 group **Feeding type:** NA **All jaundiced?:** no **Age at TcB/TSB measurement** (h): 43±31.9 for the BC group, 40.6±15.6 for the JM-103 group	**Device:** BiliCheck or JM-103 **No. of devices:** single device **Location:** forehead **Test performer:** 6 nurses **Training:** trained by the company for both devices **Nomogram:** Bhutani TSB nomogram **TcB source funding:** Trudell Canada loaned the BiliCheck™ and disposables, and Hill-Rom Canada loaned the Minolta Air-Shields JM-103®	**Method:** TSB by B_uB_c Slide Ortho VITROS 950 (Ortho-Clinical Diagnostics, Rochester, NY) **Test performer:** NA **Time interval between TcB and TSB:** ≤30 min
Sanpavat & Nuchprayoon 2005[74] Thailand	134	**M/F:** 77 (57%)/57 (43%) **GA** (wks): ≥36 (100%) **BW** (g): 3077±414 (range 2080–3950) **Ethnicity:** Asian 100% **Delivery mode:** NA **Feeding type:** NA **All jaundiced?:** yes **Age at TcB/TSB measurement** (h): ≤96: 90%, >96: 10%	**Device:** BiliCheck and JM-103 **No. of devices:** NA **Location:** forehead **Test performer:** one investigator **Training:** NA **Nomogram:** NA **TcB source funding:** NA	**Method:** TSB by Unistat (Leica Unistat Bilirubinometer, Buffalo, NY) **Test performer:** NA **Time interval between TcB and TSB:** ≤30 min

Table T.D.4: Summary of follow-up studies

Study	N	Neonate characteristics	Index test	Reference standard
Varvarigou et al. 2009[59] Greece Prospective	2039	**M/F:** 999 (49%)/1040 (51%) **GA** (wks): 38 5/7±1 3/7 **BW** (g): 3202±439 **Ethnicity:** Caucasian 100% **Delivery mode:** C-section 38%, vaginal 62% **Feeding type:** breast 43%, formula 45%, both 12% **All jaundiced:** no **Age at TcB/TSB measurement** (h): 12–96	**Device:** BiliCheck **No. of devices:** single device **Location:** forehead **Test performer:** single trained physician **Training:** properly trained **Nomogram:** locally developed nomogram (data presented in the same apublication[59]) **TcB source funding:** NA	**Method:** TSB by Unistat bilirubinometer (Richert, Depew, NY) Diazo method used for babies requiring PT **Test performer:** skilled physician **Time interval between TcB and TSB:** NA
Yu et al. 2011[45] China Prospective	6035	**M/F:** 3164 (52%)/2871 (46%) **GA** (wks): 38.2±1.6 **BW** (g): 2914±325 **Ethnicity:** Chinese 100% **Delivery mode:** C-section 55.5%, vaginal 44.5% **Feeding type:** 25%, formula 46%, both 29% **All jaundiced?:** No **Age at TcB/TSB measurement** (h): 0–168	**Device:** JM-103 **No. of devices:** single device **Location:** forehead & mid sternum (mean of both measurements) **Test performer:** properly trained physicians **Training:** no details **Nomogram:** locally developed nomogram (presented in the same publication) **TcB source funding:** NA	**Method:** TSB by Unistat reflectance bilirubinometer (Reichert-Jung, Buffalo, NY, USA) **Test performer:** skilled physicians **Time interval between TcB and TSB:** ≤1–2 h
Sanpavat et al. 2005[42] Thailand Prospective	248	**M/F:** 1.1/1 **GA** (wks): 38.6±1.2 **BW** (g): NA **Ethnicity:** Thai 100% **Delivery mode:** C-section 100% **Feeding type:** breast+formula 100% **All jaundiced?:** no **Age at TcB/TSB measurement** (h): <96	**Device:** BiliCheck **No. of devices:** NA **Location:** forehead **Test performer:** NA **Training:** NA **Nomogram:** local TcB nomogram **TcB source funding:** NA	**Method:** TSB (method not described) **Test performer:** NA **Time interval between TcB and TSB:** NA

Table T.D.4: Summary of follow-up studies (cont'd)

Study	N	Neonate characteristics	Index test	Reference standard
Dalal et al. 2009[58] India Prospective	322	**M/F:** 150 (47%)/172 (53%) **GA** (wks): 35-36: 13.7%, ≥37: 86.3% **BW** (g): 2781±374 **Ethnicity:** Indian 100% **Delivery mode:** C-section 33.6%, ventous/forceps 8.4% **Feeding type:** breast 100% **All jaundiced?:** no **Age at TcB/TSB measurement** (h): TcB1: 23.8±3.7; TcB 2: 42.4±3.9	**Device:** BiliCheck **No. of devices:** single device **Location:** forehead **Test performer:** one physician **Training:** NA **Nomogram:** Bhutani nomogram **TcB source funding:** NA	**Method:** TSB using twin-beam spectrophotometry (EN 606011, Ginevri, Rome, Italy) **Test performer:** NA **Time interval between TcB and TSB:** NA
Mishra et al. 2010[46] India Prospective	625	**M/F:** 324 (52%)/301 (48%) **GA** (wks): 35–36 (N=65): 35.7±0.5; >37 (N=560): 38.3±1.0 **BW** (g): 2808±437 **Ethnicity:** Indian 100% **Delivery mode:** NA **Feeding type:** BF (all) **All jaundiced?:** no **Age at TcB/TSB measurement** (h): ≤72	**Device:** BiliCheck **No. of devices:** NA **Location:** forehead **Test performer:** fellow-level physician **Training:** NA **Nomogram:** locally developed TcB nomogram in Indian population (data presented in the same publication[46]) **TcB source funding:** NA	**Method:** TSB (method not described) **Test performer:** NA **Time interval between TcB and TSB:** NA

Appendix T.E: Evidence on Correlation and Agreement Between TcB and TSB

Abbreviations for Appendix T.E

BCF	BiliCheck (forehead)
BCS	BiliCheck (sternum)
HPLC	high performance liquid chromatography
L	litre
Mg	milligram
N	total number
NA	not available
TcB	transcutaneous bilirubinometry
TSB	total serum bilirubin
VA	visual assessment

Data presentation

For the Bland-Altman plot, all data were presented as TcB–TSB; for those studies that reported TSB–TcB, the mean difference and 95% limits of agreement are converted to TcB–TSB.

The conversion of the unit of bilirubin concentration: 1 mg/dL = 17.1 μmol/L

Table T.E.1: Correlation and agreement between TcB and TSB Values (pre-discharge)

Study	N	Population	Reference standard	Correlation coefficient	Bland-Altman plot	
					Mean difference (µmol/L)	95% limits of agreement (µmol/L)
BiliCheck and TSB						
Bhutani 2000[34] USA	490	Caucasian 59%, Black 30%, Hispanic 3%, Asian 4%	TSB by HPLC	0.91	-8	-55 to 39
Campbell 2011[66] Canada	430	Asian 34%, Caucasian 33%, Latino 10%, Indian 8%, Black 8%, Middle Eastern 4%, other/unknown 3%	TSB by Diazo method	0.83	13	-52 to 77
Karon 2008[61] USA	177	Caucasian 82%, Asian 11%, Hispanic 5%, African-American 2%	TSB by modified Diazo or by Vitros methods	0.81 (TcB/Diazo) 0.81 (TcB/Vitros)	34 (TcB-Diazo) 22 (TcB-Vitros)	33 to 39 (TcB-Vitros) 17 to 27 (TcB-Vitros)
Kolman 2007[26] USA	192	Hispanic 100%	TSB by modified Diazo	0.87	-1	-43 to 43
Romagnoli 2012[30] Italy	2167	Caucasian 90%	TSB by Microbilimeter Dual Beam Plus	0.86	17	-41 to 77
De Luca 2008[36] Italy	686	Caucasian 100%	TSB by Microbilimeter Twin Beam Plus	0.75	14	-63 to 87
JM-103 and TSB						
Wainer 2009[38] Canada	938	Caucasian 42%, Asian 41%, Middle Eastern 10%, Aboriginal 3%	TSB by Diazo	0.91	-12 (all) -13 (light skin tone) -10 (medium skin tone)	-88 to 28 (all) -60 to 14 (light skin tone) -51 to 32 (medium skin tone)
Ho 2006[37] Hong Kong	997	Chinese 95%	TSB by Unistat bilirubinometer	0.83	22	-20 to 63
Chang 2006[77] Taiwan	447	Taiwanese 100%	TSB by Unistat bilirubinometer	0.84	-17	-71 to 36

Table T.E.2: Correlation and agreement between TcB and TSB measurements (post-discharge)

Study	N	Population	Reference standard	Correlation coefficient	Bland-Altman plot	
					Mean difference (µmol/L)	95% limits of agreement (µmol/L)
BiliCheck and TSB						
Kaynak-Turkmen 2011[70] Turkey	54	Caucasian 100%	TSB by HPLC and by Diazo method	0.85 (TcB/HPLC) 0.83 (TcB/Diazo)	-32 (TcB-HPLC) -70 (TcB-Diazo)	-142, 79 (TcB-HPLC) -189, 49 (TcB-Diazo)
Wickremasinghe 2011[57] USA	79	Caucasian 62%, Asian 11%, Hispanic 6%, Other 5%, Unknown 15%	TSB by modified Diazo method	NA	26	-46 to 98
JM-103 and TSB						
Engle 2005[63] USA	121	Hispanic 92%, African American 3%, Asian 3%, Caucasian 2%	TSB by Diazo	0.77	-27	-82 to 29
Maisels 2011[69] USA	120	Caucasian 35%, African-American 9%, Asian 16%, Hispanic 31%, Middle Eastern 3%, Native Canadian 4%, Unknown 3%	TSB by Diazo	0.78	NA	NA

Table T.E.3: Correlation and agreement between TcB and TSB values (during the first week of life)

Study	N	Population	Reference standard	Correlation coefficient	Bland-Altman plot	
					Mean difference (µmol/L)	95% limits of agreement (µmol/L)
BiliCheck and TSB						
Rubaltelli 2001[28] Italy	210	Caucasian 66.7%, Asian 14.8%, Hispanic 6.7%, African 4.3%, other 7.6%	TSB by HPLC & standard lab methods	TcB/HPLC 0.89 (forehead) 0.88 (sternum) TcB/Lab methods 0.87 (forehead) 0.85 (sternum) (Lab/HPLC 0.93)	 -16 (BCF-HPLC) 0.7 (BCS-HPLC) -2.4 (BCF-Lab) 15 (BCS-Lab) 14 (HPLC-Lab)	 -92, 60 (BCF-HPLC) -78, 79 (BCS-HPLC) -74, 68 (BCF-Lab) -62, 92 (BCS-Lab) -49, 77 (HPLC-Lab)
Martinez et al. 2005[67] Argentina	246	Skin tone: degree 1 (69%); degree 2 (30%); degree 3 (0.4%) No Black	TSB by HPLC & Bilitron	0.94 (TcB/HPLC) 0.95 (TcB/Bilitron) (Bilitron/HPLC 0.99)	-18 (TcB-HPLC) -14 (TcB-Bilitron) 32 (HPLC-Bilitron)	-99 to 63 (TcB-HPLC) -41, 69 (TcB-Bilitron) 26, 90 (HPLC-Bilitron)
Samanta et al. 2004[64] UK	300	NA	TSB by Diazo method	0.77	-11	-80 to 60
Ebbesen et al. 2002[73] Denmark	227	Northern European 93%, non-Northern European 7%	TSB by Vitros 950 analyzer (BuBc slide)	0.87	NA	-120 to 65
Szabo et al. 2004[72] Switzerland	140	Caucasian 66%, Asian 13%, Indian or African 21%	TSB by Bilimeter II	0.95 (Caucasian) 0.93 (non-Caucasian)	-15 (Caucasian) -25 (non-Caucasian)	-67 to 37 (Caucasian) -93 to 43 (non-Caucasian)
Lodha et al. 2000[76] India	109	Indian 100%	TSB by twin beam Microbilimeter	0.82 (for all) 0.64 (for 46 neonates with TSB>13 mg/dL)	-0.2 (for all) -17 (for 46 neonates with TSB>13 mg/dL)	-64 to 64 (for all) -75 to 41 (for 46 neonates with TSB>13 mg/dL)
Boo & Ishak 2007[31] Malaysia	345	Malay 63.8%, Chinese 30.7%, Indian 5.5%	TSB by Diazo method	0.80 (forehead) 0.86 (sternum)	Difference between TcB and TSB widened more markedly from line of agreement at average level of TcB and TSB>250	
Ho et al. 2006[62] Hong Kong	83	Chinese 100%	TSB by Unistate	0.76 (forehead), 0.79 (sternum)	NA	NA
Engle et al. 2002[68] USA	304	Hispanic 82%	TSB by Diazo method	0.84	NA	NA

Table T.E.3: Correlation and agreement between TcB and TSB (during the first week of life) (cont'd)

Study	N	Ethnic background	Reference standard	Correlation coefficient	Bland-Altman plot	
					Mean difference (µmol/L)	95% limit (µmol/L)
JM-103 and TSB						
Maisels et al. 2004[65] USA	849	Caucasian 59%, Black 30%, Eastern Asian 5%, Middle Eastern 4%, Indian/Pakistani 2%, Hispanic 1%	TSB by Advanced Instruments bilirubinometer	0.92 (all) 0.95 (White) 0.94 (Asian American) 0.87 (Middle Eastern) 0.82 (Black)	9 (all neonates) 9 (White) 26 (Black) -3.4 (Asian, Middle Eastern, Hispanic)	-38 to 51 (all neonates) -22 to 34 (White) -29 to 82 (Black) -39 to 34 (Asian, Middle Eastern, Hispanic)
Bental et al. 2009[44] Israel	628	Ashkenazi (light skin tone) 33%, mix of Ashkenazi and Sephardic 24%, Sephardic 41%, Ethiopian (Black) 2%	TSB by colorimetric method	0.92 (mean of values from forehead and sternum) 0.90 (forehead) 0.90 (sternum)	-21	-58 to 17
Sanpavat et al. 2004[75] Thailand	388	Thai 100%	TSB by Unistate	0.80	-12	-65 to 41
BC/JM-103 and TSB						
Rodriguez-Capote et al. 2009[60] Canada	154	Caucasian 68%, non-Caucasian 32%	TSB by Vitros 95	0.93 (BC/TSB) 0.92 (JM-103/TSB)	-5.2 (BC-TSB) -38.3 (JM-103-TSB)	-51 to 40 (BC-TSB) -78.4 to 1.8 (JM-103-TSB)
Sanpavat & Nuchprayoon 2005[74] Thailand	134	Thai 100%	TSB by Unistat bilirubinometer	0.82 (BC/TSB) 0.80 (JM-103/ TSB)	10 (BC-TSB) -12 (JM-103-TSB)	-41 to 62 (BC-TSB) -65 to 41 (JM-103-TSB)

Appendix T.F: Evidence on Screening Accuracy

Abbreviations for Appendix T.F

BC	BiliCheck
CI	**c**onfidence interval
HPLC	high performance liquid chromatography
LOS	length of stay
NLR	negative likelihood ratio
PLR	positive likelihood ratio
NA	not available
NH	neonatal hyperbilirubinemia
NICU	neonatal intensive care unit
PHN	public health nurse
PI	primary investigator
PT	phototherapy
RD	risk difference
ROC curve	receiver operating characteristic curve
SNH	significant neonatal hyperbilirubinemia
TcB	transcutaneous bilirubinometry
TSB	total serum bilirubin
VA	visual assessment

Data are expressed as mean±SD unless indicated otherwise

Table T.F.1: Screening accuracy of TcB in detecting neonatal hyperbilirubinemia (pre-discharge)

Study	TcB	TSB	Prevalence of target condition	Results			
				Target TSB mg/dL (µmol/L)	TcB cut-off mg/dL (µmol/L)	Sensitivity % (95% CI)	Specificity % (95% CI)
Wainer 2009[38] Canada N=774	**Device:** JM-103 **TcB values** (mg/dL): range from 0–17.7 **Nomogram:** NA	**Method:** Diazo **TSB values:** (mg/dL): range from 0.6–29.3	NA	All (N=774)			
				>11.7 (200)	>7.6 (130)	100	81
					>8.2 (140)	99	86
					>12.9 (220)	55	100
					>13.5 (230)	46	100
				>14.6 (250)	>9.4 (160)	100	90
					>10 (170)	97	92
					>14 (240)	61	100
				Light tone (N=347)	>14.6 (250)	58	100
				>11.7 (200)	>7.6 (130)	100	85
					>8.2 (140)	96	90
					>11.7 (200)	63	100
					>12.3 (210)	54	100
				>14.6 (250)	>9.4 (160)	100	93
					>10 (170)	92	94
					>13.5 (230)	50	100
					>14 (240)	42	100
				Medium tone (N=412)			
				>11.7 (200)	> 8.2 (140)	100	82
					>8.8 (150)	95	88
					>12.9 (220)	62	100
					>13.5 (230)	55	100
				>14.6 (250)	>11.1 (190)	100	94
					>11.7 (200)	95	95
					>14 (240)	71	100
					>14.6 (250)	67	100

Table T.F.1: Screening accuracy of TcB in detecting neonatal hyperbilirubinemia (pre-discharge) (cont'd)

Study	TcB	TSB	Prevalence of target condition	Results			
				Target TSB mg/dL (µmol/L)	**TcB cut-off** mg/dL (µmol/L)	**Sensitivity %** (95% CI)	**Specificity %** (95% CI)
Campbell et al. 2011[66] Canada N=430	**Device:** BC **TcB values** (mg/dL): 12.3 ±3.2 **Nomogram:** Bhutani TSB nomogram	**Method:** Diazo method **TSB values** (mg/dL): 11.4±3.5	TSB >200 µmol/L (12 mg/dL): 164 (38%); TSB >250 µmol/L (15 mg/dL): 68 (16%)	At 24 h > 11.7 (200) At 48 h >14.6 (250)	>10.5 (180) >11.7 (200)	96 (91-98) 96 (88-99)	55 (49-61) 57 (52-62)
Chang et al. 2006[77] Taiwan N=447	**Device:** JM-103 **TcB values** (mg/dL): 10.3±2.6 (range 1.0–17.0); <9.4: 140 (31%) **Nomogram:** NA	**Method:** Unistat bilirubinometer **TSB values** (mg/dL): 11.4±2.9 (1.0–19.1; 67 (15%) ≥15	TSB >15 mg/dL: 67 (15%)	>15 (255)	>9.4 (160) >11.7 (200)	100 (95–100) 79 (67–88)	39 (34–44) 79 (75–83)
De Luca et al. 2008[36] Italy N=686	**Device:** BC **TcB values** (mg/dL): NA **Nomogram:** NA	**Method:** Microbilimeter Twin Beam Plus **TSB values** (mg/dL): 9.7 ±3	TSB <205.2 µmol/L: 418 (61%); 205.2-239.4 µmol/L: 171 (25%); >239.4 µmol/L (14 mg/dL): 97 (14%)	>12.1 (205.2) >14.1 (239.4)	>6.8 (116.3) >9.9 (167.6) >6.6 (112.9) >10 (171)	99 95 98 95 (88-98)	20 50 11 49 (45-53)

Table T.F.1: Screening accuracy of TcB in detecting neonatal hyperbilirubinemia (pre-discharge) (cont'd)

Study	TcB	TSB	Prevalence of target condition	Results			
				Target TSB mg/dL (µmol/L)	TcB cut-off mg/dL (µmol/L)	Sensitivity % (95% CI)	Specificity % (95% CI)
Bhutani 2000[34] USA N=490	**Device:** BC **TcB values** (mg/dL): NA **Nomogram:** Bhutani TSB nomogram	**Method:** HPLC **TSB values** (mg/dL): <5: 19.3%, 5.1–10: 58%, 10.1–15: 21.9%, >15: 1.1%	TSB >95th: 6.1% 40th to 95th: 50.1% <40th: 43.8%	>95th	≥75th	100 (85–100)	88 (86–92)
Karon et al. 2008[61] USA N=177	**Device:** BC **TcB values** (mg/dL): median 12.2 (range 6.4–18.9, IQR 10.7-13.9) **Nomogram:** Bhutani TSB nomogram	**Method:** modified Diazo or Vitros **TSB values** (mg/dL): Diazo median 10.1 (range 5.3–16.6, IQR 8.7–11.5); Vitros median 10.9 (range 5.8–17.9, IQR 9.4–12.3)	High-intermediate risk (>75th) and high risk (>95th): 128/177 (72%) by Diazo; 68/131 (52%) by Vitros method	**Diazo** >75th >95th **Vitros** >75th >95th	 >75th >75th >95th or >75th >95th or >75th	 98 (90–100) 100 (75–100) 94 (85–98) 100 (79–100)	 40 (31–49) 30 (23–37) 55 (42–67) 34 (25–3)
Kolman et al. 2007[26] USA N=192	**Device:** BC **TcB values:** NA (73 >TcB 75th percentile, 12>TSB 95th percentile) **Nomogram:** Bhutani TSB nomogram	**Method:** modified Diazo **TSB Values** (mg/dL)**:** range 1.7–13.9	TSB level >95th: 6% 75th to 95th: 31% <75th: 63%	>95th	≥75th	100 (74–100)	66 (59–73)
Ho et al. 2006[37] Hong Kong N=997	**Device:** JM-103 **TcB values** (mg/dL): NA **Nomogram:** Bhutani TSB nomogram	**Method:** TSB by Unistat **TSB values** (mg/dL): range from 3–16 (>15: 3 neonates)	Severe NH requiring phototherapy (AAP, >95th): 60 (6.0%)	>95th	>40th >75th >95th	100 (94–100) 87 (76–93) 45 (33–58)	0 (0–0.4) 58 (55–62) 93 (91–94)

Table T.F.1: Screening accuracy of TcB in detecting neonatal hyperbilirubinemia (pre-discharge) (cont'd)

Study	TcB	TSB	Prevalence of target condition	Results			
				Target TSB mg/dL (µmol/L)	TcB cut-off mg/dL (µmol/L)	Sensitivity % (95% CI)	Specificity % (95% CI)
Romagnoli et al. 2012[30] Italy N=2167	**Device:** BC **TcB values** (mg/dL): 8.5±0.8 **Nomogram:** local TcB nomogram[40]	**Method:** direct spectrophotometer (Microbilimeter Dual Beam Plus) **TSB values** (mg/dL): 9.4±0.6	Total SNH 55 (2.5%): TSB>17 mg/dL: 9 (0.4%) Requiring PT (AAP guidelines): 47 (2.1%)	>17 (289) or need for PT	<u>at 24–48 h</u> <50th (6.3–7.5) <75th (7.8–10.8) <90th (11.1–11.9) <u>at 49–72 h</u> <50th (7.7–9.9) <75th (10.4–11.6) <90th (11.9–13.6) <u>at 73–96 h</u> <50th (10.0–10.9) <75th (11.7–12.7) <90th (13.7–13.9)	 100 (87-100) 93 (76-99) 52 (32-71) 100 (84-100) 100 (84-100) 86 (64-97) 100 (59-100) 100 (59-100) 71 (29-96)	 26 (23-30) 69 (65-73) 91 (88-93) 40 (37-43) 69 (66-71) 87 (84-89) 53 (48-57) 75 (70-79) 88 (84-91)
De Luca et al. 2008[71] Italy N=517	**Device:** BC **TcB values** (mg/dL): 8.3±3.8 **Nomogram:** NA	**Method:** direct spectrophotometer (Microbilimeter Twin Beam Plus) **TSB values** (mg/dL): 8.4±3.6	TSB (mg/dL) 6-8: 69.2%, 8-12: 27.3% 12.1-15: 3.5%	6–8 8.1–12 12–15 6–8 8.1–12 12.1–15	VA VA VA VA+TcB VA+TcB VA+TcB	93 (90-96) 38 (30-46) 6 (0-27) 99 (97-100) 88 (81-93) 31 (13-59)	36 (28-43) 82 (78-86) 99 (98-100) 75 (68-82) 96 (93-98) 100 (99-100)
Kaplan et al. 2008[16] Israel N=346	**Device:** JM-103 **TcB values** (mg/dL): NA **Nomogram:** Bhutani TSB nomogram	**Method:** direct spectrophotometric method **TSB values** (mg/dL): 12.4±1 for TSB ≥75th percentile (N=25)	TSB ≥75th percentile: 25 (7.2%)	≥75th percentile	≥9 (154) VA≥Kramer zone 3	72 (51-88) 84 (64-95)	90 (87-93) 81 (76-85)

Table T.F.2: Screening accuracy of TcB in detecting neonatal hyperbilirubinemia (post-discharge)

Study	TcB	TSB	Prevalence of target condition	Results			
				Target TSB mg/dL (µmol/L)	TcB cut-off mg/dL (µmol/L)	Sensitivity % (95% CI)	Specificity % (95% CI)
Wickremasinghe 2011[57] USA N= 79	**Device**: BC **TcB values** (mg/dL): mean 15.1 (range 7.8–19.9) **Nomogram**: Bhutani TSB nomogram	**Method:** modified Diazo **TSB values** (mg/dL): mean 13.6 (range 7.6–19.5)	TSB in 75th–95th and ≥95th: 36.6%	75th to 95th and ≥95th	75th to 95th and ≥95th	87 (69-96)	58 (43-71)
Kaynak-Turkmen 2011[70] Turkey N=54	**Device**: BC **TcB values** (mg/dL): 9.8±4.44 (range 1.20–18.40) **Nomogram**: NA	**Method:** HPLC and Diazo method **TSB values** (mg/dL): HPLC: 11.8±6.1 (range 0.9–29.4) Diazo: 13.9±6.2 (range 0.5–33.2)	TSB ≥15 mg/dL: 27.8%	HPLC			
				>17	≥17 (289)	50	98
					≥15 (255)	70	98
					≥13 (221)	70	91
					≥9 (153)	100	45
				>15	≥15 (255)	53	100
					≥13 (221)	60	95
					≥11 (187)	73	72
					≥10 (171)	87	64
					≥8 (136)	100	41
				>13	≥13 (221)	45	97
					≥11 (187)	64	75
					≥9 (153)	91	56
					≥8 (136)	100	50
				Diazo			
				>17	≥17 (289)	100	84
					≥16 (274)	100	75
					≥15 (255)	100	64
				>15	≥15 (255)	100	72
					≥14 (238)	100	62
				>13	≥13 (221)	100	66
					≥12 (204)	100	53

Table T.F.2: Screening accuracy of TcB in detecting neonatal hyperbilirubinemia (post-discharge) (cont'd)

Study	TcB	TSB	Prevalence of target condition	Results			
				Target TSB mg/dL (µmol/L)	**TcB cut-off** mg/dL (µmol/L)	**Sensitivity %** (95% CI)	**Specificity %** (95% CI)
Maisels et al. 2011[69] USA N=120	**Device:** JM-103 **TcB values** (mg/dL): 14.4 2.9, ≥15: 58% **Nomogram:** one centre in Calgary used local TcB nomogram	**Method:** Diazo **TSB values** (mg/dL): 15.1 3.1 (range 5.7–23.2), ≥15: 59%	TSB ≥15 mg/dL: 59%	≥15 (257)	≥11 (187)	100 (95-100)	10 (3-22)
					≥12 (205)	100 (95-100)	29 (17-44)
					≥13 (221)	99 (92-100)	44 (29-59)
					≥14 (238)	92 (82-97)	54 (39-69)
					≥15 (255)	79 (67-87)	70 (55-82)
				≥17 (290)	≥13 (221)	100	30
					≥14 (239)	100	41
					≥15 (255)	92	58
					≥16 (274)	81	69
					≥17 (289)	60	84
				≥18 (308)	≥14 (238)	100	34
					≥15 (255)	95	50
					≥16 (274)	85	61
					≥17 (289)	75	80
					≥18 (308)	60	90

Table T.F.2: Screening accuracy of TcB in detecting neonatal hyperbilirubinemia (post-discharge) (cont'd)

Study	TcB	TSB	Prevalence of target condition	Results			
				Target TSB mg/dL(µmol/L)	TcB cut-off mg/dL (µmol/L)	Sensitivity % (95% CI)	Specificity % (95% CI)
Engle et al. 2005[63] USA N=121	**Device:** JM-103 **TcB values** (mg/dL): NA **Nomogram:** Bhutani TSB nomogram	**Method:** Diazo **TSB values** (mg/dL): median 14.8 (range 9.2–22.1), ≥15: 47%, ≥16: 29%, ≥17: 13%, ≥18: 9%. **AAP risk zone:** <40th: 13%, 40th–75th: 32%, 75th–95th: 32%, >95th: 23%	TSB ≥15 mg/dL: 47%	>15	>11 (187)	100 (92-100)	34 (23-46)
					>12 (204)	91 (80-98)	53 (41-64)
					>13 (221)	79 (64-89)	77 (66-86)
					>14 (238)	58 (42-72)	95 (87-99)
					>15 (255)	40 (26-56)	97 (91-100)
				>17	>13 (221)	100	58
					>14 (238)	94	80
					>15 (255)	75	88
					>16 (274)	56	95
					>17 (289)	31	95
				>18	>14 (238)	100	77
					>15 (255)	73	85
					>16 (274)	55	93
					>17 (289)	36	98
					>18 (308)	36	100
				>95th	>95th	25	96
				>95th	≥75th	79	84
				≥75th	≥75th	54	98
				≥75th	≥40th	54	59

Table T.F.3. Screening accuracy of TcB in detecting neonatal hyperbilirubinemia (during the first week of life)

Study	TcB	TSB	Prevalence of target condition	Results			
				Target TSB mg/dL (µmol/L)	TcB cut-off mg/dL (µmol/L)	Sensitivity % (95% CI)	Specificity % (95% CI)
Rubaltelli 2001[28] Italy N=210	**Device:** BC **TcB values** (mg/dL): NA **Nomogram:** NA	**Method:** HPLC **TSB values** (mg/dL): NA	NA	>17 (290)	>17 (289)	50	99
					>16 (274)	63	96
					>15 (255)	77	91
					>14 (238)	90	87
				>15 (256)	>15 (255)	52	95
					>14 (238)	63	92
					>13 (221)	81	82
					>12 (204)	92	71
				>13 (222)	>13 (221)	66	89
					>12 (204)	86	85
					>11 (187)	93	73
					>10 (171)	97	64
Martinez et al. 2005[67] Argentina N=246	**Device:** BC **TcB values** (mg/dL): NA **Nomogram:** NA	**Method:** HPLC & Bilitron **TSB values** (mg/dL): <13: 57%, 13–15: 9%, 15–17: 5%, ≥17: 29%	TSB >15 mg/dL: 35%	>13 (221)	≥10 (171)	98	83
					≥11 (187)	97	90
					≥12 (203)	94	96
					≥13 (221)	88	99
				>15 (255)	≥12 (203)	98	85
					≥13 (221)	93	89
					≥14 (238)	78	93
					≥15 (257)	68	94
				>17 (289)	≥14 (238)	86	91
					≥15 (257)	77	93
					≥16 (274)	65	97
					≥17 (291)	38	99

Table T.F.3. Screening accuracy of TcB in detecting neonatal hyperbilirubinemia (during the first week of life) (cont'd)

Study	TcB	TSB	Prevalence of target condition	Results			
				Target TSB mg/dL (µmol/L)	**TcB cut-off** mg/dL (µmol/L)	**Sensitivity %** (95% CI)	**Specificity %** (95% CI)
Engle et al. 2002[68] USA N=268	**Device:** BC **TcB values** (mg/dL): NA **Nomogram:** NA	**Method:** Diazo method **TSB values:** NA	TSB ≥15 mg/dL: 27%	>15 (255)	>5 (86)	100	3
					>7 (119)	100	13
					>8 (136)	99	17
					>9 (153)	98	33
					>11 (188)	92	59
					>12 (205)	85	74
					>13 (222)	76	84
					>15 (257)	33	96
				>10 (171)	>5 (86)	100	10
					>7 (119)	100	40
					>8 (136)	98	51
					>9 (153)	92	77
					>10 (171)	83	88
					>11 (187)	73	97
Samanta et al. 2004[64] UK N=300	**Device:** BC **TcB values** (mg/dL): median 11 (range 1.5–18.4) **Nomogram:** NA	**Method:** Diazo method **TSB values** (mg/dL): median 11.7 (range 2.3–23.3)	TSB > 15 mg/dL (250 µmol/L): 55 (18%)	>14.6 (250)	>11.4 (195)	91 (88–94)	66 (60–71)
Ebbesen et al. 2002[73] Denmark N=227	**Device:** BC **TcB values** (mg/dL): NA **Nomogram:** NA	**Method:** Vitros 950 analyzer (BuBc slide) **TSB values** mg/dL): NA	TSB >350 µmol/L (20.5 mg/dL) (the level requiring PT, according to Danish Pediatric Society): 0.9%	≥20.5 (350)	≥14.3 (245) (70% of currently used PT limits)	100	81

Table T.F.3. Screening accuracy of TcB in detecting neonatal hyperbilirubinemia (during the first week of life) (cont'd)

Study	TcB	TSB	Prevalence of target condition	Results			
				Target TSB mg/dL (µmol/L)	TcB cut-off mg/dL (µmol/L)	Sensitivity % (95% CI)	Specificity % (95% CI)
Szabo et al. 2004[72] Switzerland N=140	**Device:** BC **TcB values** (mg/dL): NA **Nomogram:** NA	**Method:** Bilimeter II Germany) **TSB values** (mg/dL): NA	NA	>14.6 (250)	10.6 (180) 11.1 (190) 11.8 (200) 12.4 (210) 12.9 (220) 13.5 (230) 14.1 (240) 14.7 (250) VA Kramer zone 2 VA Kramer zone 3 VA Kramer zone 4 VA Kramer zone 5	97 94 88 84 78 63 59 44 100 93 84 38	60 72 80 86 89 94 94 97 36 46 71 95
Ho et al. 2006[62] Hong Kong N=83	**Device:** BC **TcB values** (mg/dL): NA **Nomogram:** NA	**Method:** bedside Unistat bilirubinometer or by Diazo method in the lab **TSB values** (mg/dL): range 4.0–22.6	TSB >250 µmol/L (level requiring PT)	>14.6 (250)	forehead 14.6 (250) sternum 15.2 (260)	 100 100	 62 70
Lodha et al. 2000[76] India N=109	**Device:** BC **TcB values** (mg/dL): NA **Nomogram:** NA	**Method:** TSB by twin beam Microbilimeter **TSB values** (mg/dL): range 4.5–21.7	TSB >13 mg/dL: 42%	>13 (221) >15 (255)	TcB VA TcB VA	69 (56–82) 52 (38–67) 47 (27–67) 53 (33–73)	89 (82–96) 89 (82–96) 99 (97–100) 98 (95–100)

Table T.F.3. Screening accuracy of TcB in detecting neonatal hyperbilirubinemia (during the first week of life) (cont'd)

Study	TcB	TSB	Prevalence of target condition	Results			
				Target TSB mg/dL (µmol/L)	**TcB cut-off** mg/dL (µmol/L)	**Sensitivity %** (95% CI)	**Specificity %** (95% CI)
Boo & Ishak 2007[31] Malaysia N=345	**Device:** BC **TcB values** (mg/dL): NA **Nomogram:** NA	**Method:** Diazo method **TSB values** (mg/dL): median 13.6 (range 6.3–34.4)	Severe NH: TSB ≥300 µmol/L: 95 (27.5%)	≥17.5 (300)	<u>Forehead</u> >250 >260 <u>Sternum</u> 200 280	 100 76 100 93	 39 85 34 84
Maisels et al. 2004[65] USA N=849	**Device:** JM-103 **TcB values** (mg/dL): NA **Nomogram:** NA	**Method:** Advanced Instruments bilirubinometer **TSB values** (mg/dL): 8.7±3.1 (range from 1.1–20.8)	TSB >10 mg/dL: 178 (21%); TSB >15 mg/dL: 28 (3.3%)	>10 (170) >13 (221) >13 (221) >15 (255)	>7 (119) >8 (136) >9 (153) >9 (153)	100 100 100 100	60 58 41
Bental et al. 2009[44] Israel N=628	**Device:** JM-103 **TcB values** (mg/dL): 8.3±2.8 (range 0.75–8) **Nomogram:** local TcB nomogram[44]	**Method:** colorimetric method **TSB value** (mg/dL): 9.4±2.8 (range 2.5–21.8)	TSB >10 mg/dL: 407 (65%) TSB >13 mg/dL: 125 (20%) TSB >15 mg/dL: 41 (6.5%)	>95th >95th >10 (170) >13 (221) >15 (255)	>75th (at 24–48 h) >75th (at 48–72 h) >8.75 (149) >10.8 (184) >11.05 (188)	83 100 90 94 87	78 76 88 91 11

Table T.F.3. Screening accuracy of TcB in detecting neonatal hyperbilirubinemia (during the first week of life) (cont'd)

Study	TcB	TSB	Prevalence of target condition	Results			
				Target TSB mg/dL (µmol/L)	**TcB cut-off** mg/dL (µmol/L)	**Sensitivity %** (95% CI)	**Specificity %** (95% CI)
Sanpavat et al. 2004[75] Thailand N=388	**Device:** JM-103 **TcB values** (mg/dL): NA **Nomogram:** NA	**Method:** Unistate **TSB value** (mg/dL): 10.5±2.5 (range 4–19.6)	TSB >10 mg/dL 58%; TSB>15 mg/dL (by tests, not by patients): 2.8% (local CPG for TSB levels requiring phototherapy)	>10 (171)	>7 (120)	99	31
					>8 (137)	97	48
					>9 (154)	85	70
					>10 (171)	65	86
				>12 (205)	>8 (137)	99	30
					>9 (154)	95	50
					>10 (171)	86	72
					>11 (188)	75	87
					>12 (205)	57	94
				>13 (222)	>8 (136)	99	27
					>9 (154)	97	46
					>10 (171)	92	67
					>11 (188)	85	82
					>12 (205)	72	92
					>13 (222)	48	96
				>15 (257)	>10 (170)	100	59
					>11 (188)	100	73
					>12 (205)	93	84
					>13 (222)	79	91

Table T.F.3. Screening accuracy of TcB in detecting neonatal hyperbilirubinemia (during the first week of life) (cont'd)

Study	TcB	TSB	Prevalence of target condition	Results			
				Target TSB mg/dL (µmol/L)	**TcB cut-off** mg/dL (µmol/L)	**Sensitivity %** (95% CI)	**Specificity %** (95% CI)
Rodriguez-Capote et al. 2009[60] Canada N=154	**Device:** JM-103 (on 94 neonates), BC (on 60 neonates) **TcB values** (mg/dL): NA **Nomogram:** Bhutani TSB nomogram	Method: B_uB_c Slide Ortho VITROS 950 **TSB values** (mg/dL): range from 4–20 (BC group), range 1.1–15 (JM-103 group)	TSB >40th percentile: 84%	>40th percentile	>40th percentile BiliCheck JM-103	94 38	NA* NA*
Sanpavat & Nuchprayoon 2005[74] Thailand N=134	**Device:** BiliCheck and JM-103 **TcB values** (mg/dL): NA **Nomogram:** NA	**Method:** Unistat **TSB values** (mg/dL): 10.4±2.5 (range 4.5–17.5)	TSB (mg/dL) >10: 55% >12: 25% >13: 15% >15: 1.9%	>10 (170) >12 (204) >13 (221) >15 (255)	>8 (136) >9 (153) >10 (170) >12 (204)	JM: 99 BC: 100 JM: 93 BC: 100 JM: 93 BC: 96 JM: 100 BC: 100	JM: 51 BC: 28 JM: 50 BC: 30 JM: 68 BC: 43 JM: 87 BC: 68

* Analysis for sensitivity and specificity was mentioned in Method section but was not reported in the Results section. The author was contacted but no response was received.

Table T.F.4: Screening accuracy of TcB in predicting subsequent SNH (follow-up studies)

Study	TcB	TSB	Prevalence of target condition	Results			
				Target TSB mg/dL (µmol/L)	**TcB cut-off** mg/dL (µmol/L)	**Sensitivity %** (95% CI)	**Specificity %** (95% CI)
Varvarigou et al. 2009[59] Greece N=2039	**Device:** BC **TcB values** (mg/dL): NA **Nomogram:** local TcB nomogram	**Method:** Unistat bilirubinometer; Diazo method used for babies requiring PT **TSB values:** NA	TSB level requiring PT (AAP guideline): 122 (6%)	Subsequent SNH (TSB levels requiring PT)	At 48 h (N=1319) >11 (N=164) >9.5 (N=411) >8.8 (N=527)	 90 99 100	 93 73 64
Yu et al. 2011[45] China N=6035	**Device:** JM-103 **TcB values** (mg/dL): NA **Nomogram:** local TcB nomogram	**Method:** Unistat **TSB values:** NA	TSB >95th percentile for age (AAP guidelines): NA	>95th	>75th ≥40th	79 (75-82) 100 (99-100)	82 (82-84) 46 (44-47)
Mishra et al. 2010[46] India N=679	**Device:** BC **TcB values** (mg/dL): NA **Nomogram:** local TcB nomogram	**Method:** not described **TSB values:** NA	Requirement of PT within first 7 days (AAP guidelines): 11.6%	Requirement of PT within first 7 days	≥97th ≥90th ≥75th ≥50th ≥25th	27 66 86 (76-93) 99 (93-100) 100 (95-100)	99 95 81 (79-84) 56 (53-59) 29 (26-32)

Table T.F.4: Screening accuracy of TcB in predicting subsequent SNH (follow-up studies) (cont'd)

Study	TcB	TSB	Prevalence of target condition	Results			
				Target TSB mg/dL (µmol/L)	TcB cut-off mg/dL (µmol/L)	Sensitivity (95% CI)	Specificity (95% CI)
Dalal et al. 2009[58] India N=322	**Device:** BC **TcB values** (mg/dL): TcB1: 6.4±1.6; TcB2: 8.7±2.3 **Nomogram:** local TcB nomogram	**Method:** twin-beam spectrophotometry **TSB values:** NA	Requirement of PT (AAP guidelines): 14.9%	Requirement of PT	TcB1		
					>95th	39	91
					>75th	80	51
					>40th	98	19
					TcB2		
					>95th	39	96
					>75th	83	79
					>40th	94	38
					Change in TcB (mg/dL/h)		
					>95th (>0.26)	27	99
					>75th(>0.18)	83	83
					>50th (>0.12)	90	57
					>25th (>0.08)	98	24
Sanpavat et al. 2005[42] Thailand N=392	**Device:** BC **TcB values** (mg/dL): NA **Nomogram:** local TcB nomogram	**Method:** NA **TSB values:** NA	Requirement of PT (local guidelines): 32 (8.2%)	Requirement of PT (TSB 10–12 at ≤48 h, ≥13 at 49–72 h, ≥ 15 at >72 h)	>95th	75	89
					>90th	97 (84-100)	79 (74-83)
					>85th	100 (89-100)	57 (52-62)
					>75th	100 (89-100)	48 (43-53)
					>50th	100	24
					>25th	100	5
					>10th	100	5

Appendix T.G: Evidence on Clinical Outcomes

Abbreviations for Appendix T.G

AA	African American
As	Asian
BC	BiliCheck
Ccs	Caucasian
CG	control group
CI	confidence interval
EG	experimental group
Hp	Hispanic
HPLC	high performance liquid chromatography
ME	Middle Eastern
NA	not available
NICU	neonatal intensive care unit
OR	odds ratio
PHN	public health nurse
PT	phototherapy
RD	risk difference
ROC curve	receiver operating characteristic curve
SNH	significant neonatal hyperbilirubinemia
TcB	transcutaneous bilirubinometry
TSB	total serum bilirubin
VA	visual assessment

Table T.G.1: Summary of clinical outcomes

Study	Participants	TcB	Reference standard	Results	Author's conclusion
Mishra et al. 2009[53] India **Study design:** RCT EG: TcB CG: Visual assessment **Study objective:** To determine usefulness of TcB to decrease the need for blood sampling to assay TSB in the management of jaundiced, healthy Indian neonates	**No. of infants:** EG: N = 314 CG: N = 303 **Gender** (M/F): EG: 165 (52.5%)/149 CG: 165 (54.5%)/138 **Ethnicity:** Indian 100% **Inclusion criteria:** developed jaundice at between 1 and 7 days of age. **Excl.**: Rh hemolytic disease; requiring NICU admission for >24 hrs	**Device:** BiliCheck **No. of devices**: NA **Personnel: e**xperienced pediatrician **Training:** NA **Quality assurance:** NA **TcB source funding:** NA	**Method:** TSB measured by twin-beam spectrophotometry **Comparator:** visual assessment conducted in an adequately illuminated room preferably in daylight using semi-quantitative algorithm adapted from Kramer's original description.	**No. of TSB testing** EG: 55/314 (17.5%) vs. CG: 80/303 (26.4%) Reduction 34% (95% CI 10 to 51%) RD (95% CI): -8.9% (-2.4%–15.4%) (P=0.008) **No. requiring PT** EG: 18/314 (5.7%) vs. CG: 26/303 (8.6%) (P=0.17)	Routine use of TcB compared with systematic visual assessment of bilirubin significantly reduced the need for blood sampling to assay TSB in jaundiced term and late-term neonates

Table T.G.1: Summary of clinical outcomes (cont'd)

Study	Participants	TcB	Reference standard	Results	Author's conclusion
Allen et al. 2010[54] Ireland **Study design:** Non-randomized comparative study Retrospective EG: hospital A (VA + TcB) CG: hospital B (VA alone) **Study objectives:** 1. to compare the number of TSB in hospital A with those in hospital B in the routine evaluation of jaundiced neonates. 2. to investigate the factors that resulted in any initial TSBs above the exchange transfusion level in both neonatal cohorts.	**No. of infants:** EG: N = 15,851 CG: N = 15,701 **Gender** (M/F): EG: 52%/48% CG: 52%/48% **Ethnicity:** EG: Ccs 86%, AA 7%, As 6%, other 0.4% CG: Ccs 88%, AA 5%, As 6%, other 0.6% **Inclusion criteria:** weight ≥2500; gestational age ≥36 wks; TSB measured between 12 and 144 h of age	**Device:** JM-103 **No. of devices**: NA **Personnel:** NA **Training:** NA **Quality assurance:** NA **TcB source funding:** NA	**Method:** TSB **Comparator:** visual assessment	**No. of TSB testing** EG: 1645 (10.4%) vs. CG: 2373 (15.1%) Reduction 31% (P<0.001) **No. requiring exchange transfusion** EG: 14 (0.85%) vs. CG: 3 (0.13%) (statistical significance not available)	The findings suggest that TcB significantly reduces TSB testing in routine clinical practice. Additionally, TSB levels above recommended exchange transfusion levels often arise from poor recognition of potentially preventable factors regarding detection, testing, and follow-up of otherwise healthy newborns.

Table T.G.1: Summary of clinical outcomes (cont'd)

Study	Participants	TcB	Reference standard	Results	Author's conclusion
Wainer et al. 2012[7] Canada **Study design:** Before-and-after comparison Prospective EG: 8 mos post-TcB implementation CG: 8 mos pre-TcB implementation **Study objective:** To assess the impact of programmatic and coordinated use of TcB on the incidence of SNH and measure of laboratory, hospital, and nursing resource use.	**No. of infants:** EG: N = 14,112 CG: N = 14,769 **Gender** (M/F): EG: 7063/7049 CG: 7496/7300 **Ethnicity:** NA **Exclusion criteria:** gestational age <35 weeks, >10 days of age; delivered at home under midwife care, home address outside of Calgary health region geographic boundaries	**Device:** JM-103 **No. of devices**: 42 TcB devices in regular circulation; seven spare devices **Personnel:** Pre-discharge: hospital nursing staff Post-discharge: PHN **Training:** NA **Quality assurance:** Validation measures at the time of device purchase using wavelength verification and precision and accuracy checks. Ongoing surveillance for significant TcB to TSB discrepancy through a scheduled maintenance program **TcB source funding:** NA	**Method:** Roche Modular; Hitachi 912 and 917; Plasma: Diazo Jendrassik-Grof method (transported to Calgary Laboratory Services by taxi, in light-protected container) **Comparator:** visual assessment	**No. of TSB testing** (community) EG: 103.6/1000 live births CG: 134.4/1000 live births Reduction: 22.9% (OR 1.33; 95% CI 1.23 to 1.45)(P<0.0001) **No. of SNH** EG: 91/10694 (850.9/ 100 000 live births, 1:118 CG: 43/11162 (385.2/ 100 000 live births), 1:260 Reduction: 54.9% (OR 2.22; 95% CI 1.54-3.19)(P<0.0001) **No. requiring PT (pre-discharge)** EG: 257/14796 (1.74%) CG: 370/14112 (2.62%) Reduction: 34% (calculated) (OR 1.52, 95% CI 1.30-1.79 (P<0.0001) **Age at readmission for PT (h):** EG: 88.9±70.5 CG: 104.3±52.1 Reduction: 15.4% (P<0.005) **Length of readmission for PT** (mean±SD, h) EG: 23.2±9.8 CG: 24.8±13.6	Programmatic TCB implementation can significantly enhance patient safety with reduced demands on both laboratory and hospital resources, but may lead to increased community health services use.

Table T.G.1: Summary of clinical outcomes (cont'd)

Study	Participants	TcB	Reference standard	Results	Author's conclusion
Petersen et al 2005[56] USA **Study design:** Before-and-after comparison Retrospective EG: 8 mos post-TcB implementation CG: 8 mos pre-TcB implementation **Study objective:** To determine whether the use of TcB affects the use of laboratory bilirubin testing or decreases the number of neonates readmitted for hyperbilirubinemia within 7 days of initial charge.	**No. of infants:** N = 6,603 **Gender** (M/F): EG: 53%/47% CG: 51%/49% **Ethnicity:** EG: Hp 72%, Ccs 18%, AA 8%, other 3% CG: Hp 72%, Ccs 15%, AA 11%, other 3% **Inclusion criteria:** NA **NH requiring PT:** 446 (6.8%)	**Device:** BiliCheck (Respironics) **No. of devices**: NA **Personnel:** NA **Training:** NA **Quality assurance:** NA **TcB source funding:** NA	**Method:** NA **Comparator:** No	**No. of TSB testing** (in hospital) EG: 36.7±8.7% vs. CG: 31.8±6.4% Reduction **Readmission rate for SNH** EG: 1.8±1.7/1000 newborns/month vs. CG: 4.5±2.4/1000 newborns/month (P=0.044) **No. requiring PT** EG: 32.1±3.9 (7.7±1.3%) vs. CG: 23.6±5.2 (5.9±1.3%) (P<0.05) **LOS** ***For normal infants*** EG: 2.1±1.1 vs. CG: 2.2±1.1 (P=0.53) ***For infants requiring PT*** EG: 2.9±1.3 vs. CG: 2.9±1.3 (P=0.67)	Access to TcB testing is associated with a reduction in the rate of readmission to hospital, within 7 days of initial discharge, for hyperbilirubinemia.

Table T.G.1: Summary of clinical outcomes (cont'd)

Study	Participants	TcB	Reference standard	Results	Author's conclusion
Hartshorn et al. 2009[55] Australia **Study design:** Before-and-after comparison EG: 12 mos post-TcB implementation CG: 6 mos pre-TcB implementation **Study objective:** To assess the impact of implementing a new jaundice protocol incorporating the use of JM-103 in the setting of an Australian post-natal ward.	**No. of infants:** EG: N=2,197 CG: N=1,169 **Gender** (M/F): EG: 52%/48% CG: 52%/48% **Ethnicity:** predominantly Caucasians **Inclusion criteria:** Gestational age ≥36 wks; age >24 h and < 8 days	**Device:** JM-103 **No. of devices**: NA **Personnel:** nursing staff **Training:** education to nursing and medical staff **Quality assurance:** NA **TcB source funding:** NA	**Method:** NA **Comparator:** visual assessment	**No. of TSB testing** EG: 119/1169 (10.2%) CG: 426/2197 (19.4%) Odd ratio 0.47 (95% CI 0.38 to 0.58) (P=0.000) Reduction 47% (calculated) **No. of SNH** (TSB 350 to 400 µmol/L) EG: 0/1169 (0%) CG: 17/2197 (0.77%) (P<0.001) **No. requiring PT** EG: 35 (3.0%) vs. CG: 84 (3.8%) (P=0.2)	TcB measurement in conjunction with our protocol significantly reduces painful procedures and costs without increasing the risk of delaying phototherapy treatment.

ECONOMIC ANALYSIS

Andy Chuck, PhD, MPH; Charles Yan, PhD

OBJECTIVE AND SCOPE

Objective

To review and synthesize the economic literature regarding the cost implications or cost effectiveness of TcB and/or TSB testing. Specific research questions to be addressed include:

1. Does TcB used as a screening test result in decreased use of TSB confirmatory testing in the context of a programmatic screening program?
2. What are the cost implications of using TcB testing as a screening test in the context of a programmatic screening program?
3. Is the use of TcB as a screening test cost effective in the context of a programmatic screening program?

METHODS

Search Strategy

Selected databases were searched for economic studies regarding TcB or TSB testing. Databases searched include Medline, EMBASE, CINAHL, CENTRAL, Cochrane Library Licensed Resource, and Web of Science. To supplement the electronic searches, reference lists of retrieved articles were also reviewed to find further studies. The literature search summary is presented in Appendix E.1.

Selection Criteria

The search was limited to human studies and English language publications from 2000 onward. Eligible studies met the following predefined inclusion/exclusion criteria:

Inclusion Criteria:

- Study design: cost effectiveness or cost analyses conducted via randomized or non-randomized controlled trials, cross-sectional, cohort, single group before-and-after studies
- Population: full term (≥35 weeks) newborn infants, any origin of ethnicity
- Intervention: TcB tests using the devices currently available in Canada
- Comparator: total serum bilirubin (TSB) measured by 2,5-dichlorophenyldiazonium (DPD) or modified DPD method (using either capillary or venous blood samples)
- Outcomes of interest—at least one of the following:
    - differences in health service use
    - differences in costs
    - differences in health outcomes
- Languages: restricted to English

- Publication period: January 2000 to January 2012

Exclusion Criteria:

- Study design: abstracts, case series studies, narrative reviews, letters, and editorials
- Population: preterm newborn infants of <35 weeks of gestation; babies under phototherapy (because phototherapy "bleaches" the skin, both visual assessment of jaundice and TcB measurements in infants undergoing phototherapy are not reliable)
- Intervention: tests other than TcB (for example, other point-of-care tests), technical aspects of the tests
- Comparator: tests other than standard lab TSB tests (for example, other point-of-care TSB tests)
- Outcomes: studies that did not report any of the pre-defined outcomes listed above

Quality Assessment

A formal quality assessment of economic studies will be applied on health economic evaluation studies using the Quality of Health Economic Studies (QHES) instrument.[1] The QHES instrument was designed to evaluate health economic analyses, including the analysis of cost minimization, cost effectiveness, and cost utility. It includes a weighting system to score and aggregate across individual criteria, providing a summative index of quality. The quality index ranges from 0 to 100, with a score of 75 or greater indicating acceptable quality. Note that the QHES is not designed to assess cost studies.

Data Extraction

Data extracted from studies include study objective, target population, comparators, cost components, health outcome measures, results and conclusions.

RESULTS

The literature search identified 36 references. After reviewing the titles and abstracts/summaries, 10 were retrieved for further review. Of those 10, four studies met the final inclusion/exclusion criteria. Three[2,3,4] studies assessed the impact of TcB screening on healthcare resource use and costs. One[5] study assessed the cost-effectiveness of strategies for the prevention of kernicterus in newborn infants. See Appendix E.2 for data extraction from the studies and Appendix E.3 for the quality assessment scores of the single cost-effectiveness study.

Evidence from the Economic Literature

Cost studies

Wainer et al. 2012[2] conducted a pre/post assessment comparing TSB testing referred by means of visual inspection (pre-period) with that of programmatic and coordinated use of TcB screening to determine the appropriateness of TSB (post-period) in acute care and community settings in Calgary. The TcB program offered TcB measurement to infants older than 35 weeks gestation, but excluded those who had received phototherapy before discharge from nursery. With TcB screening, a TSB was performed if TcB measurements were greater than 200 μmol/L for infants aged 48 hours and were deemed unnecessary if readings were less than 150 μmol/L for infants aged 48 hours. If TcB

measurements were between 150 μmol/L and 200 μmol/L at 48 hours, additional TcB measurement was performed. Primary outcome measures included:

- the incidence of severe neonatal hyperbilirubinemia
- overall incidence of TSB draws
- overall phototherapy rate
- whether there was a reduced age at readmission for phototherapy
- duration of phototherapy readmission
- frequency of early post-discharge public health nurse encounters
- related health service costs for laboratory, hospital, and nursing resources

Results indicated that, compared with TSB based on visual inspection, screening with TcB was associated with:

- a 54.9% reduction in the incidence of severe total serum bilirubin values and reductions in overall TSB draws (134.4 vs. 103.6 draws per 1000 live births)
- an increased phototherapy rate (5.27% vs. 4.30%)
- an older age at readmission for phototherapy (104.3 vs. 88.9 hours)
- a longer duration of phototherapy readmission (24.8 6 vs. 23.2 hours)

TcB measurement, however, was associated with an increase in public health nurse encounters (1.33 vs. 1.66 visits per infant) during the first week of life. The authors concluded that TcB screening within a public health follow-up program is associated with improvements in resource use. It is unknown whether TcB screening resulted in net efficiencies because it was unclear how the study accounted for resources related to quality assurance, including the development of nomograms, which are required components for TcB screening.

Hartshorn et al. 2010[3] conducted a pre/post assessment comparing TSB testing referred by means of visual inspection (pre-period) with that of TcB screening to determine the appropriateness of TSB (post-period) in the postnatal ward in an Australian hospital for infants having a gestational age of 36 weeks and weighing greater than 2500 g. The assessment excluded infants born before 36 weeks' gestation or who had their first test (TSB or TcB) at earlier than 24 hours or later than 8 days of age. The primary outcome measure was the percentage of infants requiring one or more TSBs. The rates of phototherapy and peak serum bilirubin during phototherapy were also reported. The results showed that, compared with TSB based on visual inspection, TcB screening was associated with a significant reduction in the number of live-birth infants requiring TSB (19.4% vs. 10.2%). No significant difference was found in rates of phototherapy (3.8% vs. 3.0%) or peak SBR during phototherapy (301.9 vs.303.2 mmol/L). The estimated cost saving per year is $6,966.00. However, the study did not describe how the costing was conducted. The study concluded that TcB screening leads to reductions in:

- the number of painful procedures (that is, TSB) without increasing the risk of missing cases requiring treatment
- costs

The National Institute of Clinical and Health Excellence (NICE) in the United Kingdom[4] assessed the cost impact of TSB testing based on a visual screen compared with TSB testing based on screening with TcB. Cost components included labour (for example, nursing time, midwifery), laboratory, and supply costs. Results indicated that the cost per test was £1.3 for TcB (excluding the cost of meters) and £19.23 for TSB. At over 669,448 live births per year, the total testing cost was estimate to be £2.0 million for TSB testing based on visual inspection and £6.3 million for TSB testing based on screening with TcB (£1.2 for testing and £5.1 for purchasing TcB meters).

Economic evaluations

Suresh et al. 2004[5] developed a simulation model to assess the cost effectiveness of three alternative strategies for preventing kernicterus in newborn infants, compared to current practice, for 2.8 million healthy infants with gestation age of 37 weeks and over in the United States. Current practice consisted of TSB testing referred by means of a review of clinical history and visual inspection. The three alternative strategies included

- universal follow-up 1 to 2 days after newborn discharge (without routine pre-discharge testing)
- routine pre-discharge TSB with selective follow-up and laboratory testing
- routine pre-discharge TcB with selective follow-up and laboratory testing

The study was conducted from the societal perspective and adopted a lifetime time horizon. Resources included laboratory tests, transcutaneous bilirubinometry, nursing time, office visits, home visits, hospitalization, phototherapy, and kernicterus management. The kernicterus costs were based on lifetime direct and indirect costs of people with cerebral palsy and mental retardation. The number of kernicterus cases prevented was used as the measure of health outcomes. Important assumptions used by the authors included the incidence of kernicterus (1:100 000) and the relative risk reduction with each strategy (0.7), which translated to 20 additional cases prevented per year.

Results indicated that, for a cohort of 2.8 million infants, the annual cost was $152.4 million with the current practice. The annual incremental cost over current practice was $202.3 million with universal follow-up strategy, $112.6 million with pre-discharge serum bilirubin strategy, and$180.1 with pre-discharge transcutaneous bilirubin. The marginal analysis showed that the cost-per-case-prevented was highest with universal early follow-up ($10.3 million), followed by routine pre-discharge transcutaneous bilirubin ($9.2 million) and routine pre-discharge serum bilirubin screening ($5.7 million). The authors concluded that widespread implementation of these strategies is likely to increase healthcare costs significantly, with uncertain benefits. The study had a quality score of 66.

DISCUSSION

The objective of the literature review was to assess the resource implications and cost effectiveness of TcB or TSB testing. Strategies employing TcB screening to determine the appropriateness of TSB testing may be cost effective if they are either associated with lower costs and improved health outcomes or if they are associated with higher costs but with significant improvements in health outcomes. If TcB screening is associated with only marginal improvements in health outcomes or with equivalent health outcomes, then costs become the primary consideration.

When examining costs alone, three studies found that, compared to TSB testing referred by means of visual inspection, TSB testing referred by means of a TcB screen was associated with reduced health service use, but it did not necessarily result in a net cost savings. One study conducted in Australia found that TSB testing referred by means of a TcB screen reduced the rate of TSB testing but had no

impact on phototherapy rates. The study conducted in Calgary (which has direct relevance to the Alberta context) found that TcB screening resulted in reducing the incidence of hyperbilirubinemia, TSB testing, and phototherapy rate, while also lowering the age of the neonate at readmission for phototherapy. However, the study found identified earlier and more frequent contacts with public health nurses.

Altogether, according to the Calgary study, it is uncertain whether net savings or efficiencies would result, particularly when factoring in not only the costs related to additional quality assurance protocols, including the development and periodic refinement of nomograms which are required components for TcB testing, but also the cost of purchasing the required number of meters to provide TcB testing in a programmatic fashion. For instance, the analysis conducted by NICE in the United Kingdom found that for a population of 669,448 live births, the cost of TcB screening compared to visual inspection was lower by £0.8 million when the cost of the TcB meters was excluded, but higher by £3.1 million when the cost of the TcB meters was included.

When examining both costs and health outcomes, the single study on cost effectiveness estimated that, compared to visual inspection, the cost-per-case of kernicterus prevented was greater when testing with TcB at pre-discharge than when testing with TSB (note that both strategies include selective follow-up and laboratory testing in the community). This suggests that testing with TcB at pre-discharge is not cost effective compared to testing with TSB.

CONCLUSION

Limited published evidence is available to inform the economic implications of alternative screening strategies for severe hyperbilirubinemia. Current literature suggests that, compared to visual inspection and evaluation of the neonate's clinical history, screening with TcB to assess the need for TSB testing may be associated with reduced use of specific healthcare resources such as TSB testing and phototherapy, but may not provide a net cost savings when the costs associated with quality assurance and equipment are included. Consequently, the cost effectiveness of TcB screening remains uncertain as it cannot be determined whether TcB provides a net cost savings to the health system and produces equivalent or significantly better health outcomes.

REFERENCES

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4. NICE. *National costing report: Neonatal jaundice.* London, UK: National Institute for Health and Clinical Excellence, 2010.
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APPENDICES

Appendix E.1: Literature Search Summary: Point-of-Care Bilirubin Testing in Neonates

Publication dates: 2000–2011

Table E.1: Search strategy

Database	Edition or date searched	Search Terms††
Core Databases		
The Cochrane Database of Systematic Reviews (Wiley Interface)	January 5, 2012	"**bilirubin*** ***in Title, Abstract or Keywords*** **23 results – 0 relevant** (all therapy or prevention)
CENTRAL (Ovid interface)	January 5, 2012	See MEDLINE search, immediately below **25 results** for T section
MEDLINE (includes in-process articles) (OVID interface)	January 5, 2012	1. exp infant/ 2. (neonat* or infant* or newborn* or maternity ward or babies or baby).mp. 3. 1 or 2 4. Bilirubin/ 5. bilirubin*.mp. 6. hyperbilirubinemia.tw. 7. jaundice*.tw. 8. exp Hyperbilirubinemia, Neonatal/ 9. or/4-8 10. (TcB or transcutaneous).tw. 11. (JM-103 or JM-102 or bilicheck or bilichek).tw. 12. point of care.tw. 13. Point-of-Care Systems/ 14. poct*.tw. 15. poc.tw. 16. portable.tw. 17. (near adj2 patient*).tw. 18. bedside.tw. 19. non-invasive.tw. 20. ((immediate* or rapid* or same time or same visit or instant* or portable) adj5 (test* or turnaround or analys* or analyz* or measure* or assay* or results)).tw. 21. or/10-20 22. 3 and 9 and 21 23. limit 22 to yr="2000 - 2012" (223 results) 24. exp "Costs and Cost Analysis"/ 25. (cost* or economic* or expensive*).tw. 26. (expenditures or price or fiscal or financial or burden or efficiency or pay or valuation or spending or resource*).ti. 27. 24 or 25 or 26

		28. 23 and 27 **11 results**
EMBASE (OVID interface)	January 5, 2012 2011 Week 52	1. exp infant/ 2. (neonat* or infant* or newborn* or maternity ward or babies or baby).mp. 3. 1 or 2 4. Bilirubin/ 5. bilirubin*.mp. 6. hyperbilirubinemia.tw. 7. jaundice*.tw. 8. newborn jaundice/ 9. or/4-8 10. (TcB or transcutaneous).tw. 11. (JM-103 or JM-102 or bilicheck or bilichek).tw. 12. point of care.tw. 13. "point of care testing"/ 14. poct*.tw. 15. poc.tw. 16. portable.tw. 17. (near adj2 patient*).tw. 18. bedside.tw. 19. non-invasive.tw. 20. ((immediate* or rapid* or same time or same visit or instant* or portable) adj5 (test* or turnaround or analys* or analyz* or measure* or assay* or results)).tw. 21. or/10-20 22. 3 and 9 and 21 23. limit 22 to yr="2000 - 2012" (288 results 24. "cost"/ 25. exp economic evaluation/ 26. "health care cost"/ 27. (cost* or economic* or expensive*).tw. 28. (expenditures or price or fiscal or financial or burden or efficiency or pay or valuation or spending or resource*).ti. 29. or/24-28 30. 23 and 29 **25 results**
CRD Databases (DARE, HTA & NHS EED)	January 5, 2012	(bilirubin*) FROM 2000 TO 2012 **13 results (6 potentially relevant)**
CINAHL (Ebsco Database) Included because *Point of Care* journal is indexed in CINAHL but not in MEDLINE or EMBASE	January 5, 2012	S1 infant* OR neonat* OR newborn* OR maternity ward S2 bilirubin* OR hyperbilirubinemia OR jaundice* S3 (MH "Point-of-Care Testing") S4 TcB OR transcutaneous OR JM-103 OR JM-102 OR Bilicheck OR Bilichek OR non-invasive S5 (S1 AND S2 AND (S3 OR S4)) Limiters – Published Date from: 20000101-20111231 (91 results) S6 economic* or cost* S7 S5 AND S6 **7 results**

Web of Science	January 5, 2012	#1 TS=(neonat* or infant* or newborn* or maternity ward or babies or baby) #2 TS=(bilirubin* or hyperbilirubin* or jaundice*) #3 TS=(TcB OR transcutaneous OR JM-103 OR JM-102 OR Bilicheck OR Bilichek OR "point of care") #4 #1 AND #2 AND #3 Timespan=2000-2012 176 results #5 TS=(cost* or economic*) #6 #4 AND #5 **6 results**
Library Catalogues		
NEOS (Central Alberta Library Consortium) www.library.ualberta.ca/catalogue	January 10, 2012	(Screen$ or test$) and (jaundice$ OR bilirubin$); hyperbilirubinemia Scanned results – only **1 potentially relevant result**
Theses		
Proquest Dissertations and Theses Fulltext**	January 10, 2012	Transcutaneous bilirubin **2 non-relevant results** (bilirubin OR jaundice) AND screening **9 non-relevant results** TcB and bilirubin **0 results**
Theses Canada Portal www.nlc-bnc.ca/thesescanada	January 10, 2012	Jaundice in title **0 results** Bilirubin in title **4 non-relevant results** Hyperbilirubinemia in title **0 results** Transcutaneous bilirubin in full text **0 results**
EThOS – Beta http://ethos.bl.uk	January 10, 2012	Bilirubin OR jaundice **23 results** – 0 relevant
Clinical Trials		
ClinicalTrials.gov (US) http://clinicaltrials.gov/	January 10, 2012	Transcutaneous bilirubin; bilicheck; bilichek **5 relevant results**
CenterWatch Clinical Trials Listing Service www.centerwatch.com/	January 11, 2012	Scanned results under pediatrics/neonatology **0 results**
IFPMA Clinical Trials Portal www.ifpma.org/clinicaltrials.html	January 11, 2012	Transcutaneous bilirubin; bilichek; bilicheck **20 results – 5 duplicate relevant results**
metaRegister of Controlled Trials www.controlled-trials.com/mrct	January 11, 2012	Transcutaneous bilirubin; bilichek; bilicheck **0 results**
Evidence Based Medicine		
Dynamed (Ebsco database)	January 11, 2012	Transcutaneous bilirubin – browsed the article on Neonatal hyperbilirubinemia Copied relevant sections into Grey Literature document

Trip www.tripdatabase.com	January 11, 2012	Transcutaneous bilirubin Copied relevant results into Grey Literature document
Economic Information		
Centre for Health Economics and Policy Analysis www.chepa.org/	January 11, 2012	Bilirubin, jaundice, hyperbilirubinaemia; hyperbilirubinemia **0 results**
Centre for Health Economics Research and Evaluation http://datasearch.uts.edu.au/site_manager_sites/chere-redesign-ds/publications/index.cfm	January 11, 2012	Browsed reports and working papers sections **0 results**
Institute of Health Economics www.ihe.ca	January 11, 2012	Have not done any projects in the past on this topic
HTA Agencies		
AETMIS www.aetmis.gouv.qc.ca/site/en_publications.phtml	January 6, 2012	Bilirubin; point of care **1 result** – "Point of care testing in private sector" but not relevant
CADTH www.cadth.ca/index.php/en/hta/reports-publications/search	January 6, 2012	Bilirubin **2 results**
Medical Advisory Secretariat www.health.gov.on.ca/english/providers/program/mas/mas_mn.html	January 6, 2012	Bilirubin; jaundice; point-of-care **0 relevant results**
Institute for Clinical and Evaluative Sciences (ICES), Ontario www.ices.on.ca/	January 11, 2012	Bilirubin, jaundice, transcutaneous; hyperbilirubinaemia; hyperbilirubinemia **1 relevant result**
Health Technology Assessment Unit at McGill www.mcgill.ca/tau/	January 11, 2012	Browsed list of reports **0 results**
EuroScan www.euroscan.bham.ac.uk	January 11, 2012	Bilirubin; jaundice; transcutaneous; hyperbilirubinaemia; hyperbilirubinemia **0 relevant, non-duplicate results**
MSAC www.msac.gov.au/	January 23, 2012	Bilirubin; jaundice; transcutaneous; hyperbilirubinaemia; hyperbilirubinemia **0 relevant results**
NZHTA http://nzhta.chmeds.ac.nz/publications.htm	January 23, 2012	Bilirubin; jaundice; transcutaneous; hyperbilirubinaemia; hyperbilirubinemia **0 results**
NIHR Health Technology Assessment www.hta.ac.uk/	January 23, 2012	Bilirubin; jaundice; transcutaneous; hyperbilirubinaemia; hyperbilirubinemia **0 results**
Centre for Clinical Effectiveness (CCE) www.southernhealth.org.	January 23, 2012	Bilirubin; jaundice; transcutaneous; hyperbilirubinaemia; hyperbilirubinemia **0 relevant results**

au/page/Health_Professionals/CCE/Evidence_reviews/		
MHRA (Medicines and Healthcare Products Regulatory Agency) (UK) www.mhra.gov.uk	January 23, 2012	Bilicheck; bilichek; transcutaneous, tcb, jaundice meter **0 relevant results**
California Health Benefits Review Program (CHBRP): www.chbrp.org/	January 23, 2012	Bilirubin; jaundice; transcutaneous; hyperbilirubinaemia; hyperbilirubinemia; TcB **0 results**
California Technology Assessment Forum (CTAF) www.ctaf.org	January 23, 2012	Bilirubin; jaundice; transcutaneous; hyperbilirubinaemia; hyperbilirubinemia; TcB **0 results**
AHRQ www.ahrq.gov	January 23, 2012	Transcutaneous bilirubin; bilicheck; bilichek; jm-103; JM-102; jaundice meter; hyperbilirubinemia **3 results**
VA Technology Assessment Program www.va.gov/VATAP/index.asp	January 23, 2012	Bilirubin; jaundice; transcutaneous; hyperbilirubinaemia; hyperbilirubinemia; TcB **0 results**
Regulatory Information		
Alberta Health www.health.gov.ab.ca	January 23, 2012	Jaundice; bilirubin; hyperbilirubinemia; hyperbilirubinaemia; TcB; transcutaneous **0 relevant results**
Health Canada www.hc-sc.gc.ca	January 23, 2012	Tcb; transcutaneous bilirubin; hyperbilirubinemia; hyperbilirubinaemia **0 relevant results**
Medical Devices Active Licence Listing www.mdall.ca/	January 23, 2012	One result under Device name: Bilichek Two results under Device name: Jaundice Bilimed **0 results** Colorimeter; CR-300 **0 results** Minolta **0 relevant results**
US Food and Drug Administration www.fda.gov	January 11, 2012	510 K database JM-103; JM-102; Bilicheck; bilichek; Bilimed Saved summaries for JM-102, JM-103, Bilichek
Guidelines		
National Guideline Clearinghouse www.ngc.gov	January 24, 2012	'bilirubin' and '(jaundice or hyperbilirubinemia)' (18 results) Transcutaneous bilirubin **4 results**
AMA Clinical Practice Guidelines www.topalbertadoctors.org	January 24, 2012	Browsed list **0 results**
CMA Infobase http://mdm.ca/cpgsnew/cpgs/index.asp	January 24, 2012	Jaundice; bilirubin; hyperbilirubinemia; hyperbilirubinaemia **2 relevant results**

NICE guidance www.nice.org.uk/	January 24, 2012	Searched: jaundice; bilirubin **1 relevant result** – downloaded guideline, costing report and costing template
Canadian Paediatric Society www.cps.ca/english/publications/StatementsIndex.htm	January 24, 2012	Browsed list **2 relevant results**
Guidelines International Network www.g-i-n.net/	January 24, 2012	Jaundice; bilirubin; hyperbilirubinemia; hyperbilirubinaemia **3 non-duplicate results**
Canadian Task Force on Preventative Healthcare www.ctfphc.org/	January 24, 2012	Browsed list of current and past recommendations **0 results**
US Preventive Services Task Force (USPSTF) www.uspreventiveservicestaskforce.org	January 24, 2012	Jaundice; bilirubin; hyperbilirubinemia; hyperbilirubinaemia **2 results**
Scottish Intercollegiate Guidelines Network (SIGN) www.sign.ac.uk	January 24, 2012	Jaundice; bilirubin; hyperbilirubinemia; hyperbilirubinaemia; transcutaneous **0 results**
New Zealand Guidelines Group www.nzgg.org.nz	January 24, 2012	Jaundice; bilirubin; hyperbilirubinemia; hyperbilirubinaemia; transcutaneous **0 results**
Search Engines		
Google www.google.ca	January 24, 2012	Transcutaneous bilirubin –pubmed (reviewed first 50 results)

Note: ††, *, #, and ? are truncation characters that retrieve all possible suffix variations of the root word, e.g., surg* retrieves surgery, surgical, surgeon, etc.

Searches separated by semicolons have been entered separately into the search interface.

Appendix E.2: Summarized Evidence from Selected Studies

Author/ Country	Study Type	Objective	Target population/ Setting	Comparators	Results	Conclusion
Wainer et al. 2012[2]	Pre/Post	To assess the impact of programmatic and coordinated use of TcB on the incidence of SNHB and measures of laboratory, hospital, and nursing resource use.	Healthy newborn ≥35 wks gestation Hospital and community Calgary, Alberta	TcB (post-) vs. TSB (pre-) based on visual inspection	• 54.9% reduction in the incidence of SNHB (OR: 2.219 P .0001) • reductions in the overall incidence of TSB draws (134.4 vs. 103.6 draws per 1000 live births)* • overall phototherapy rate (5.27% vs. 4.30%)* • reduced age at readmission for phototherapy (104.3±52.1 vs. 88.9±70.5 hours)*. • duration of phototherapy readmission (24.8±13.6 vs. 23.2±9.8 hours)* • earlier and more frequent contacts with public health nurses (1.33 vs. 1.66)*	TcB screening with a public health follow-up program is associated with improvements in resource use.
Hartshorn et al. 2012[3]	Pre/Post	To assess the impact of TcB screening on the number of TSB tests performed without delaying treatment for hyperbilirubinaemia	Newborn ≥36 wks gestational age and weight of ≥2500 g Post-natal ward Australia	TcB (post-) vs. TSB based on post-natal age and visual inspection (pre-)	• reduction in the number of live births requiring TSB (19% vs. 10%)* • no significant difference in phototherapy rate (3.8% vs. 3.0%; P = 0.2) • no significant difference in peak SBR during phototherapy (301.9 vs.303.2 mmol/L; P = 0.45)	TcB screening leads to a reduction in the number of painful procedures without increasing the risk of missing cases that requiring treatment

NICE 2010[4]	Costing	To determine the cost impact of implementing clinical practice guidelines	Newborns
			Hospital and community
			England
				NA	Over 669,448 live births:
					• cost of testing visibly jaundiced babies with TcB meters is £6.3 million in the first year:
					  ○ £1.2 million for testing costs
					  ○ £5.1 million for purchasing meters
					• cost of testing visibly jaundiced babies in current practice is £2.0 million
						NA

Suresh et al. 2004[5]	CEA via Decision Model	To assess the cost-effectiveness of 3 strategies for the prevention of kernicterus in newborn infants, compared with current pattern of practice.	Newborns Hospital and community USA	Current management (a review of clinical history and visual inspection of skin colour) vs.: • universal follow-up 1 to 2 days after newborn discharge • routine pre-discharge serum bilirubin with selective follow-up and laboratory testing • routine pre-discharge transcutaneous bilirubin with selective follow-up and laboratory testing	• an additional 20 cases per year prevented for each strategy, compared to current practice. For a cohort of 2.8 million infants: • annual cost of $152.4 million with current practice • annual incremental cost of $202.3 million with universal follow-up strategy • $112.6 million with pre-discharge serum bilirubin strategy • $180.1 million with pre-discharge transcutaneous bilirubin The cost-per-case-prevented was: • $10.3 million with universal early follow-up • $9.2 million with routine pre-discharge transcutaneous bilirubin • $5.7 million with routine pre-discharge serum bilirubin	Widespread implementation of these strategies is likely to increase healthcare costs significantly, with uncertain benefits. It is premature to implement routine pre-discharge serum or transcutaneous bilirubin screening on a large scale

SNHB – severe neonatal hyperbilirubinemia; TCB – transcutaneous hyperbilirubinemia; TSB – total serum bilirubinemia; CEA – cost-effectiveness analysis; QALY – quality-adjusted life year; QA – quality assurance

* $p<.05$

Appendix E.3: Quality Assessment Scores

#	Questions	Suresh et al. 2004[5]
1	Was the study objective presented in a clear, specific, and measurable manner?	7
2	Were the perspective of the analysis (societal, third-party payer, etc.) and the reasons for its selection stated?	1
3	Were variable estimates used in the analysis from the best available source (i.e., randomized control trial = best; expert opinion = worst)?	3
4	If estimates came from a subgroup analysis, were the groups pre-specified at the beginning of the study?	1
5	Was uncertainty handled by: (1) statistical analysis to address random events? (2) sensitivity analysis to cover a range of assumptions?	9
6	Was incremental analysis performed between alternatives for resources and costs?	0
7	Was the methodology for data abstraction (including the value of health states and other benefits) stated?	2
8	Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	7
9	Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	8
10	Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term, long-term, and outcomes?	5
11	Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	2
12	Were the economic model (including structure), study methods and analysis, and components of the numerator and denominator displayed in a clear, transparent manner?	5
13	Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	5
14	Did the author(s) explicitly discuss direction and magnitude of potential biases?	3
15	Were the conclusions/recommendations of the study justified and based on the study results?	8
16	Was there a statement disclosing the source of funding for the study?	0
	TOTAL POINTS	**66**

Author Contribution Statements

Ken Bond was responsible for the conception, design, and writing of the Background section; acted as the second reviewer for the Technology section; and approved the final version of the assessment.

Bing Guo was responsible for the conception, design, data analysis and interpretation, and writing of the Technology section, revised the draft report, and approved the final version of the assessment.

Christa Harstall contributed to the conception and design of the assessment (Background, Technology, Economic), revised the draft report for critical content, and approved the final version of the assessment.

Charles Yan acted as the primary reviewer for the Economic section, revised the draft report for critical content, and approved the final version of the assessment.

Anderson Chuck acted as second reviewer for the review of the economic literature and approved the final version of the assessment.

This report was prepared for Alberta Health Services (AHS) and focuses on the published evidence about the safety, test accuracy, and clinical impact of the use of transcutaneous bilirubin (TcB) test for the screening of significant hyperbilirubinemia in term or late pre-term neonates. This report also provides information regarding the current practices with TcB/total serum bilirubin (TSB) tests in AHS zones, and a brief review of economic literature regarding the cost implications and potential cost-effectiveness of TcB and/or TSB testing.

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