Transcutaneous Bilirubinometers for Newborn Hyperbilirubinemia

A Health Technology Assessment

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Abbreviations

AOR Adjusted Odds Ratio

BC British Columbia

CHR Calgary Health Region

CI Confidence interval

ER Emergency Room

HTA Health Technology Assessment

IHE Institute for Health Economics

LY Life Year

PRISMA Preferred Reporting Items for Systematic Reviews and Meta-analyses

QALY Quality-adjusted Life Year

RCT Randomized Controlled Trial

ROC Receiver Operator Characteristic

SROC Summary Receiver Operator Characteristic

TCB Transcutaneous Bilirubinometer

TSB Total Serum Bilirubin

USA United States of America

VIHA Vancouver Island Health Authority

Executive Summary

This report presents the findings and conclusions of a provincial Health Technology Assessment on the use of transcutaneous bilirubinometers (TcB) for screening of hyperbilirubinemia in newborns. The primary research question was: how effective is TcB (in comparison to the alternatives) in screening for hyperbilirubinemia in newborns in an acute care setting?

Background: Bilirubin is produced from the normal breakdown of hemoglobin. Elevated bilirubin levels, also called *hyperbilirubinemia*, occurs in the majority of late preterm and term newborns, peaking between three and five days of life and usually resolving by two weeks of age. Elevated bilirubin levels can progress to severe hyperbilirubinemia (TSB concentration greater than 340 μmol/L) and left untreated can lead to the development of kernicterus (permanent neurological damage). The estimated incidence of severe hyperbilirubinemia is one in 2,480 live births, however some evidence suggests this has decreased over time. In British Columbia (BC), based on 2015 data, the number of new cases of severe hyperbilirubinemia per year is estimated to be 18. There are a number of risk factors associated with hyperbilirubinemia including: premature birth, darker skin tone, East Asian or Mediterranean descent, significant bruising during birth, blood type different from the mother, breast-feeding patterns, and infections or digestive system problems. Phototherapy remains the standard treatment for hyperbilirubinemia. If phototherapy fails to control the rising bilirubin level, exchange transfusion is indicated to lower bilirubin concentrations.

The current gold standard to measure bilirubin levels is total serum bilirubin (TSB) concentration from a blood sample. Visual assessment by health care professionals, although not recommended given current bilirubin measurement techniques, has been previously utilized to measure jaundice in newborns. TcBs have been used as a screening tool that provides instantaneous read-out of the cutaneous bilirubin concentration. The device measures the yellowness of the newborn's skin using the principles of reflectance densitometry. TcB can be performed in hospitals, clinics or doctor's offices, by users who must be trained on the device prior to using it on patients.

Methods: The following methodological approaches were used to gather and synthesize the available evidence:

I. Update of a systematic review conducted by the Institute for Health Economics (IHE) to determine whether TcB is a safe and accurate method of screening hyperbilirubinemia.

II. Jurisdictional scan to understand how hyperbilirubinemia is screened across Canada and where/how TcB is currently being used. Clinician and key informant interviews to understand TcB use in Canada, obtain clinician and patient perspectives on this technology, and understand implementation feasibility considerations for BC.

III. De novo cost-effectiveness analysis model comparing TcB with the gold standard diagnostic tool, TSB and visual assessment. A budget impact analysis was completed to determine the costs associated with TcB

Key Findings:

There are currently 982 TcB devices across Canada, 70 of which are located in BC. The TcBs being used in BC are distributed across the province with some in Vancouver Island Health Authority, Vancouver Coastal Health Authority, Northern Health, Fraser Health, and Interior Health.

Eight studies, including seven pre-post designs and one randomized controlled trial (RCT), assessed clinical outcomes of TcB. Most studies reported that the use of TcB decreased the number of TSB tests completed, with estimates ranging from a 23% to 34% reduction. Studies had mixed results on whether TcB resulted in a reduced need for phototherapy treatment. Overall, there was a trend towards reduced health care resources including TSB testing, phototherapy, and hospital readmissions after TcB implementation.

Nine studies on diagnostic accuracy were identified. Broadly, sensitivity ranged from 72%-100% and specificity ranged from 58%-88%. As TcB was compared to the gold standard (TSB), these studies assume that TSB has perfect diagnostic accuracy (100% sensitivity and 100% specificity). Based on this assumption, TcB has poorer diagnostic accuracy than TSB. There is no evidence on the safety of TcB, but it is assumed to have negligible risk. Significant

heterogeneity was observed; subgroup analysis by device and target TSB level did not account for the heterogeneity.

The cost-effectiveness analysis model found that overall, the differences in health outcomes (cases of kernicterus, life-years, and quality-adjusted life-years) were small. JM-105 is less costly and more effective compared with visual assessment. Compared with BiliChek, JM-105 is less costly and has equivalent benefits with respect to clinical outcomes. Both TcB devices (JM-105 and BiliChek) are less costly and marginally less effective than TSB when it is assumed that patients must wait for TSB results i.e. increasing the time in hospital for newborns. When patients do not have to wait for TSB results in the hospital, then TcB devices are costlier options, in this scenario TSB is the preferred screening option. Results suggest that health benefits (LYs and QALYs) are equivalent across screening techniques, therefore, costs per patient were the main outcome of the economic model.

Results of published economic evaluations were mixed on the appropriateness of implementation of a TcB screening program and its economic impact. Jurisdictional recommendations in the United Kingdom and Quebec concluded that there was insufficient evidence to use TcB.

Fourteen experts were interviewed about BC's experience with screening for hyperbilirubinemia, and the use of TcBs. Key informants identified several possible challenges to implementing TcBs including, cost of acquisition, calibration, ongoing maintenance, development of "trust," and development and use of appropriate nomograms. Several benefits were also identified, including, timely discharge from hospital, reduced heel pricks, and reduced demand on laboratory services.

2 Purpose of this Health Technology Assessment

The purpose of this health technology assessment (HTA) is to summarize the current evidence on the use of transcutaneous bilirubinometers (TcB) for the screening of hyperbilirubinemia in newborns. The report summarizes evidence on the effectiveness, safety, patient experience and system feasibility of screening for hyperbilirubinemia using TcB in comparison to available alternatives, including Total Serum Bilirubin (TSB) and visual inspection and provides a comprehensive Budget Impact Analysis.

3 Research Question and Research Objectives

One context-specific question was asked regarding screening newborns for hyperbilirubinemia.

- Should TcB be used to screen for hyperbilirubinemia in newborns in the hospital setting?

The research objectives of this work are:

- To determine the safety and effectiveness/efficacy of TcB for the screening of hyperbilirubinemia
- To determine the burden of illness, patterns of care and capacity in British Columbia (BC) as it relates to TcB and hyperbilirubinemia
- To understand BC's experience with bilirubin screening, and the use of TcB as a screening tool for hyperbilirubinemia, in the hospital setting
- To determine the budget impact of TcB provision

4 Background

4.1 Hyperbilirubinemia

Bilirubin is produced from the normal breakdown of hemoglobin. Bilirubin circulates in the body in two forms, indirect (unconjugated) bilirubin and direct (conjugated) bilirubin (1). Insoluble unconjugated bilirubin travels in the bloodstream to the liver to be changed into the soluble conjugated form. Conjugated bilirubin is removed from the body through stool and gives stool its colour. In newborns, bilirubin formation is two to three times greater than that in adults owing to the shorter lifespan of fetal hemoglobin compared to adult hemoglobin (2). Infants have less bacteria in their digestive tract so less bilirubin is excreted and more is reabsorbed into circulation. The developing gastrointestinal system of newborns is also immature and unable to excrete bilirubin as quickly as it is produced. Elevated bilirubin levels (hyperbilirubinemia) occur in the majority of late preterm and term newborns, peaking between three and five days of life and usually resolving by two weeks of age (2); this common finding occurs due to the imbalance between production and elimination of bilirubin. When bilirubin accumulates in the body and blood tissues, skin and eyes exhibit a yellow color, which is characteristic of jaundice (2). Hyperbilirubinemia may be harmless or harmful depending on the cause and the degree of elevation of bilirubin levels (1).

Normally bilirubin is bound and stays in the intravascular space; however, bilirubin can cross the blood-brain barrier when serum bilirubin concentration is markedly elevated or when bilirubin is displaced by competitive binders (1). Elevated bilirubin levels can progress to hyperbilirubinemia, which is often benign but, when severe, can lead to the rare development of acute bilirubin encephalopathy and ultimately kernicterus (2).

4.1.1 Disease Progression

Bilirubin is toxic to brain cells and acute bilirubin encephalopathy occurs when bilirubin passes into the brain (3). Newborns may have difficulty waking, high-pitched crying, poor sucking/feeding, backward arching of the neck and body, fever, or vomiting (3). Kernicterus is a severe symptom that occurs if acute bilirubin encephalopathy causes permanent damage to the brain and may result in involuntary and uncontrolled movements, permanent upward gaze, hearing loss, or improper development of tooth enamel (3). Data on progression of acute

bilirubin encephalopathy to kernicterus are limited. One study suggested 95% of infants with acute bilirubin encephalopathy had full resolution of symptoms and 5% had evidence of kernicterus at discharge (4). Summarizing case reports over more than 30 years, the Subcommittee on Hyperbilirubinemia of the American Academy of Pediatrics concluded that the mortality rate of kernicterus is at least 10% with a long-term morbidity rate of at least 70% (5). Hyperbilirubinemia is the most common cause of morbidity in the first week of life (6). The inability to identify and manage at-risk infants prior to discharge from hospital in a timely manner is cited as the major cause of adverse outcomes for these infants (6).

4.1.2   Prevalence and Incidence

It is estimated that 60% of term newborns develop jaundice and 2% will reach a TSB concentration above the cut-off for severe hyperbilirubinemia (2). Given the assumption of 320,000 live births per year in Canada, Sgro et al 2006 estimated the incidence of severe hyperbilirubinemia to be one in 2,480 live births (258 in 640,000 over a two-year study period) (7). In British Columbia there were approximately 44,349 live births in 2015, equating to an estimated 18 cases of severe hyperbilirubinemia. The reported rate of kernicterus is one in 50,000 births (7) equaling an estimated six kernicterus cases in Canada and one in British Columbia annually. Although kernicterus is extremely rare, the occurrence has increased in the last two decades which may be associated with early discharge practices and maternal breastfeeding habits (8).

4.1.2.1   Risk Factors

There are a number of risk factors for hyperbilirubinemia in newborns including (9, 10):

- *Premature birth before 37 weeks:* newborns born before 37 weeks may be unable to process bilirubin as quickly as full-term newborns. They may feed less and/or have fewer bowel movements which would result in less bilirubin eliminated through stool. A case-control study based in California, USA found that newborns with lower gestational age (34 to 37 weeks) had significantly higher odds of severe hyperbilirubinemia than $\geq$ 40-week infants (adjusted odds ratio [AOR] = 3.70; 95% confidence interval [CI] 0.61 to 22.4) (11).

- *East Asian or Mediterranean descent:* ethic variations in the rates of neonatal jaundice have been recognized, specifically gene mutations associated with increased production of bilirubin. One study found infants of full Asian parentage were 37% more likely to be diagnosed with jaundice than white infants (12).

- *Significant bruising during birth*: newborns may have a higher level of bilirubin from the breakdown of more red blood cells. Bruising was associated with an AOR of 2.52; 95% CI 1.16 to 5.50 in a case-control study based in California (11).

- *Blood type different from the mother (blood incompatibility)*: the mother's body makes antibodies against the newborn's blood cells and these antibodies can cross through the placenta into the newborns. These antibodies treat fetal blood cells as foreign and destroy circulating red blood cells. When the blood cells are broken down they make bilirubin which can cause the level of bilirubin in the newborn's blood stream to be dangerously high.

- *Breast-feeding*: This is a concern particularly for newborns who have difficulty nursing or getting enough nutrition from breast-feeding. Dehydration or low calorie intake may contribute to the onset of jaundice. Newborn infants who are exclusively breast-fed have low levels of intestinal bacteria that are able to convert bilirubin (13).

- *Infections and, digestive system problems:* These problems may impact the efficiency of the liver.

4.1.3   Measurement and Diagnosis

4.1.3.1   Reference Standard of Total Serum Bilirubin

The current gold standard to measure bilirubin levels is laboratory TSB determination from blood sampling (15). TSB level tests are conducted on blood samples that are often drawn from a capillary site such as the heel-prick of newborns. Although this method has been proven successful in preventing the kernicterus, bilirubin-induced brain dysfunction, it has several drawbacks. The invasive method is painful and stressful for the neonate, resulting in blood loss and increased risk for osteomyelitis (inflammation of bone or bone marrow) and infections at the site of sampling (15). Furthermore, the method is more laborious and time consuming than point of care testing. However, in the hospital setting, TSB can be done at the same time as other necessary blood tests.

It is important to note although TSB is considered the gold standard, inaccuracies in the measurement of bilirubin in clinical laboratories have been reported (14). Some instruments (Advanced Bilirubinometer, Roche COBAS, Roche Modular, Dimension, Synchron, Unistat) produce results closer to the reference method when bilirubin concentration was low but deviated from the reference method at higher concentrations (15). Given variable performance of analyzers, the goal set by the CAP Chemistry Resource Committee is to limit the total error to ±10% of the reference method value (15). Proper calibration of clinical analyzers are expected to provide accurate total bilirubin values close to those obtained by the reference method.

4.1.3.2 Visual Assessment

Infants are routinely monitored for the development of jaundice and vital signs are measured at least every eight to twelve hours (16). Assessment is best conducted in a well-lit room or in daylight by a window. Jaundice can be detected by blanching the skin with digital pressure on the forehead, mid-sternum or the knee/ankle to reveal the underlying colour of the skin and subcutaneous tissue (16). Jaundice is commonly seen in the face; however, it can sometimes appear and fade. The absence of jaundice does not necessarily indicate the absence of hyperbilirubinemia and the presence of jaundice must be corroborated by a bilirubin measurement (TSB or TcB) (16). Although assessment of the extent of jaundice is weakly correlated with bilirubin concentration, the complete absence of jaundice (when reliably recognized) may predict that infants will not develop significant hyperbilirubinemia (16). This method of diagnosis is not considered to be reliable and is not an acceptable standard when alternatives exist.

4.2 Transcutaneous Bilirubinometry

4.2.1 TcB

The measurement and monitoring of newborns' bilirubin levels are vital to prevent jaundice (hyperbilirubinemia) and to ensure adequate treatment is provided in cases where bilirubin levels exceed the acceptable limits (17). Transcutaneous bilirubinometers have been used as a screening method for hyperbilirubinemia rather than as a replacement for invasive blood sampling (18). Transcutaneous bilirubinometry is a non-invasive and painless method that provides instantaneous read-out of the transcutaneous bilirubin concentration (TcB). The device is a hand-held, battery-operated instrument that uses the principles of reflectance densitometry

(19). A fiberoptic photoprobe is placed against the newborn's skin (usually forehead or sternum) and when sufficient pressure is applied, a xenon tube emits a light pulse to the touched skin (19). The transcutaneous bilirubinometer analyzes the spectrum of light reflected by the newborn's skin to measure the yellowness of the skin and subcutaneous tissue in the jaundiced newborn. Note that transcutaneous bilirubinometry has improved over time with newer models that provide better precision and reduced weight (19).

Transcutaneous bilirubinometry can be performed in hospitals, clinics or doctor's offices by users who must be trained with the device prior to using it on patients. Trained users may include physicians, nurses, and technicians. Bilirubinometer training is provided initially by the manufacturer as well as manuals (20). One suggested usage protocol for BiliChek indicated clinical personnel should be properly trained, including a demonstration of the equipment by an experienced BiliChek operator, performing a return demonstration on three infants in the presence of an experienced BiliChek operator, and successful completion of training documented in the employee's education record (21). According to Philips, easy-to-read and step-by-step instructions on the BiliChek measurement system increases proficiency and productivity (22). The on-board Help system walks users through the process and provides access to the online Help menu.

4.2.2   Devices

Two devices for transcutaneous bilirubinometry are currently used, BiliCheck (BiliChek) or Jaundice Meter JM-105 (previous models of JM-102 and JM-103). Both BiliChek and JM-105 jaundice meters have received U.S. Food and Drug Administration and Health Canada approval (23) (Table 1).

Table 1. Devices Used for TcB

Device	Manufacturer	Approved by FDA (US) (8)	Approved by Health Canada (23)
Jaundice Meter JM-102	Air-Shields, Inc.	September 22, 1998	December 4, 2002 (no longer available)(8)
Jaundice Meter JM-103	Draeger Medical Systems, Inc	April 1, 2003	May 1, 2008
Jaundice Meter JM-105	Draeger Medical Systems, Inc	November 13, 2014 (24)	October 25, 2013
BiliChek System	Philips Medical Systems	March 19, 2001	December 4, 1998

The BiliChek transmits light containing the visual spectrum though the infant's skin and captures the reflected light by a microspectometer (25). Five measurements are required for each infant testing. The JM-103 uses two light beams that penetrate both the shallow subcutaneous tissues and to the deeper layer of skin; the difference between the two skin layers is analyzed to determine the TcB measurement (11).

The JM-105 uses two wavelengths with a dual optical path system that sends one beam of light to the shallow subcutaneous tissues and another to the deeper layers of skin (25). Blue and green photocells analyse the difference between the two skin layers to determine a TcB measurement. The number of measurements is determined by the individual institution.

The JM-105 is indicated for use to measure "… yellowness of subcutaneous tissue in newborn infants. The unit provides a visual digital measurement that has been shown to correlate with serum bilirubin in newborn infants," (24). The device is intended for use in hospitals, clinics or doctor's offices. The device is not intended to be a standalone for diagnosis of hyperbilirubinemia and should be used in conjunction with other clinical signs and laboratory measurements i.e. TSB. Special conditions for use include: use only on infants up to 14 days of age; neonatal patients born >35 weeks gestation who have not undergone exchange transfusion or phototherapy treatment; users must be trained prior to use of device; the device is used for forehead and sternum measurements in hospitals, and only sternum measurements in physician's offices; and for prescription use only. No contraindications are listed.

4.2.3   Nomograms

Nomograms are used to interpret TcB results, and plot infant age (in hours) against bilirubin levels in the blood. When the levels of detectable bilirubin in the first measurement period are lower than in the second period, i.e. the rate of excretion of bilirubin is lower than the rate of production, the newborn is then considered at risk for developing hyperbilirubinemia. Many hour- and percentile- based risk assessment nomograms have been developed to interpret serial measurements of bilirubin concentrations to assess the need for phototherapy and to determine when to terminate treatment (2). Since skin colour affects TcB measurements, a selection of nomograms may be required as part of a bilirubin management protocol in an ethnically heterogeneous population to better predict which infants develop hyperbilirubinemia later on.

One well-established nomogram by Bhutani et al. (26) is indicated for well newborns ≥ 35 weeks' gestational age based on the hour-specific serum bilirubin values before discharge and for designation of the risk of hyperbilirubinemia. These values are divided into four risk zones with the high-risk being the adjusted 95th percentile track. At this concentration in this study, infants who had serum bilirubin levels in this high-risk category 18 to 72 hours after birth had a 40% probability of subsequent, moderate severe hyperbilirubinemia (13). The zone-based predictive nomogram allows for visual identification of true positive and false negative predictions by plotting the risk zone positions of serial TSB values of each infant. Specific diagnostic sensitivity, specificity, and positive and negative predictive values have been published (2).

4.2.1   Clinical Pathway

The Canadian Paediatric Society recommends newborns are screened for elevated bilirubin within 72 hours of birth. Based on their test results, newborns will receive different care. If the TSB results indicate that the newborn is at high risk of hyperbilirubinemia, further testing or treatment is recommended. For a high-intermediate test result, newborns who have a negative direct antiglobulin test (DAT) should receive routine care, while those who are DAT positive require follow-up in 24 to 48 hours. For low-intermediate or low risk results, routine care is recommended (Figure 1).

Figure 1: Flow Chart of Clinical Care Pathway Based on Canadian Paediatric Society Recommendations
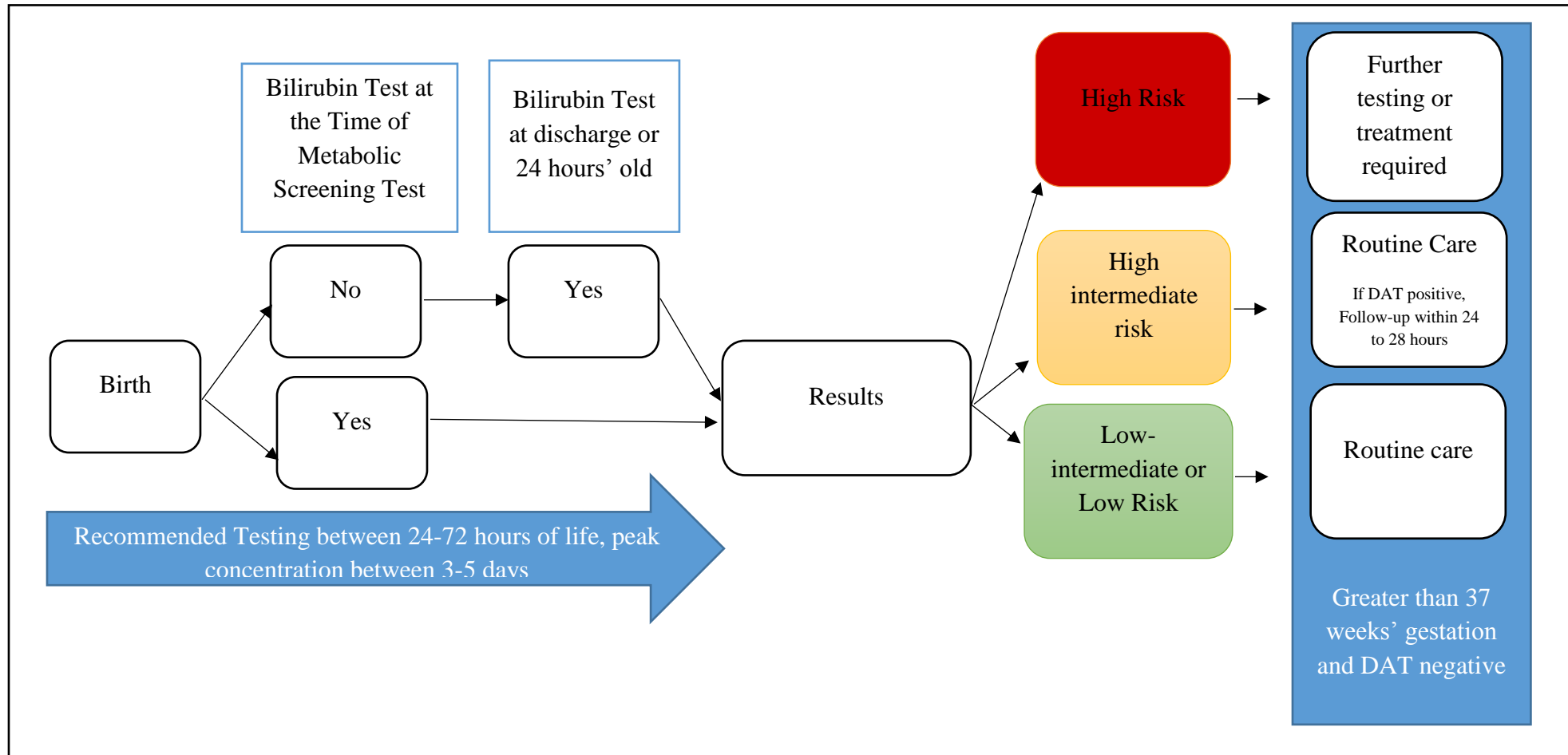
*DAT: Direct Antiglobulin Test

TcBs are described currently as a screening tool only for use in full term infants (born at 37 weeks or later). They are not being, and should not be, used as a diagnostic tool or to determine whether treatment is required; and therefore do not replace TSB.

When TcB is used in the acute setting, it replaces TSB as the screening test, but if a positive result is found with TcB, TSB is required to confirm the finding (Figure 2).

Figure 2. Clinical Pathway With and Without Use of TcB

Acute Setting
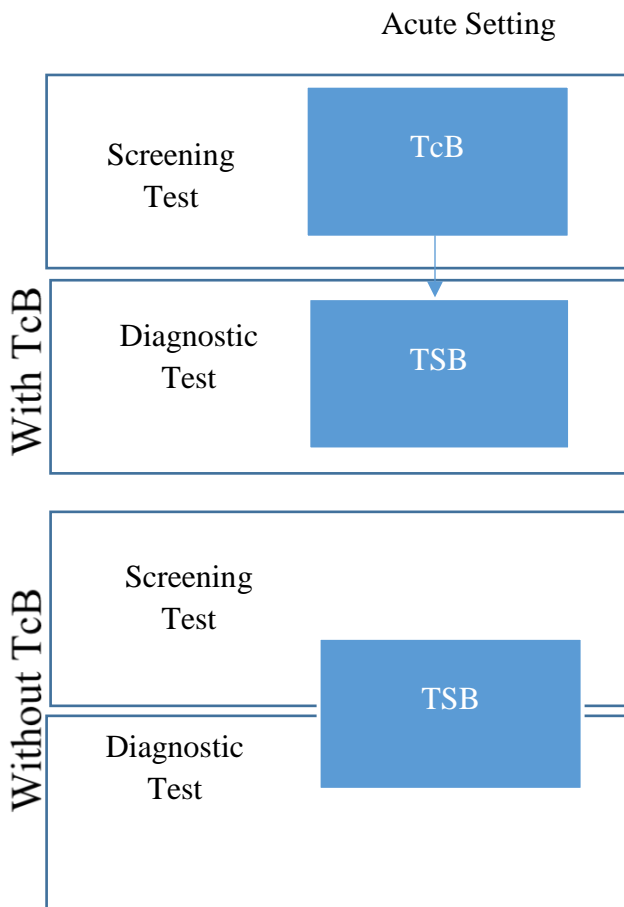
4.3 Hyperbilirubinemia Treatment Options
4.3.1 Phototherapy
Phototherapy remains the standard of care and is most commonly done with the use of fluorescent white light and more intensive phototherapy with blue light (1). The energy from the light changes bilirubin, making it water soluble and therefore easily excreted by the liver and

kidneys. Conventional phototherapy consists of a single bank of fluorescent lights placed over the incubator. Intensive phototherapy includes high intensity light applied to the greatest surface area of the infant as possible and typically requires at least two to three banks of lights (27). Phototherapy can be used to both prevent severe hyperbilirubinemia and as initial therapy for severe hyperbilirubinemia (28). Side effects of phototherapy include temperature instability, diarrhea, intestinal hypermotility, interference with maternal-infant interaction, and in rare cases, bronze discolouration of the skin (1). Bilirubin concentrations should be reassessed two to six hours after initiating treatment to confirm response.

4.3.2   *Exchange transfusion*

If phototherapy fails to control rising bilirubin level, exchange transfusion is indicated to lower TSB concentrations (28). The process of exchange transfusion includes withdrawing small amounts of blood through an umbilical vein catheter and replacing the blood with donor blood until the total desired volume is exchanged (1). Exchange transfusion is required in about 3% of patients and is associated with substantial morbidity (29). This treatment should only be performed in centres with appropriate expertise under the supervision of an experienced neonatologist (28).

4.4   Canadian Clinical Practice Guidelines

The Canadian Pediatric Society 2007 (reaffirmed 2016) (27) position statement for the detection, management, and prevention of hyperbilirubinemia in term and late preterm newborn infants recommends:

- All newborns who are visibly jaundiced in the first 24 hours of life should have their bilirubin level determined.
- Any infant discharged before 24 hours of life should be reviewed within 24 hours by an individual with experience in the care of the newborn who has access to testing and treatment facilities.
- Either TSB or TcB concentration should be measured in all infants during the first 72 hours of life. If not required earlier because of clinical jaundice, a TSB measurement should be obtained at the same time as the metabolic screening test; alternatively, a TcB

measurement should be obtained either at discharge or, if not yet discharged, at 72 hours of life.

- If the TSB concentration does not require immediate intervention, the results should be plotted on the predictive nomogram. The result of the TSB measurement, the time at which it was obtained and the zone should be recorded, and a copy should be given to the parents. Follow-up of the infant should be individualized according to the risk assessment.

- TSB concentration may be estimated on either a capillary or a venous blood sample.

- Transcutaneous bilirubinometry is 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.

- There should be a systematic approach to the risk assessment of all infants before discharge and of follow-up care if the infant develops jaundice.

- Infants with severe or prolonged hyperbilirubinemia should be further investigated, including measurement of the conjugated component of bilirubin.

5   Jurisdictional Scan

5.1   Other HTAs and Evidence Syntheses

5.1.1   Purpose

To summarize existing evidence syntheses on transcutaneous bilirubinometers for hyperbilirubinemia screening of newborns.

5.1.2   Methods

A grey literature search was performed. As an update to the 2013 review of transcutaneous bilirubinometers by IHE, centres for "economic information" and HTA agencies listed in the IHE review and Google were searched from January 1, 2013 up until August 3, 2016. Search terms included "bilirubin", "transcutaneous", and "cost-effective." HTAs were also identified from the published literature during the systematic review of clinical effectiveness, both from the HTA Database and other published sources (see section 2 for the systematic review methodology). The HTAs identified were subsequently hand-searched for mention of other HTAs.

5.1.3　Results

Eight evidence syntheses and two economic evaluations were identified. The reports were described as technology reviews (n=3), evidence reviews (n=3), rapid response (n=1), and clinical guideline (n=1). All syntheses reported some details on the literature review methodology. A narrative summary of each follows and data from each are synthesized in Table 2. Economic evaluations were summarized in a narrative summary separately below.

5.1.3.1　Economic Evaluations

Two economic evaluations were identified (28, 60). Xie et al (29) developed an economic model comparing a system-based approach of universal bilirubin screening using TSB to a traditional approach of visual assessment and selected bilirubin testing in otherwise healthy newborns born in Ontario, Canada. The model resulted in a cost per quality-adjusted life year gained of $65,698 (CAD) and cost to prevent one kernicterus case of $570,496 for the system-based approach compared to the traditional approach. The cost per child was $176 for the system-based approach and $173 for the traditional approach. The study concluded it is economically justifiable to implement the system-based approach. In the United States, Suresh et al (30) assessed the cost-effectiveness of three strategies compared with current management (current practice patterns of clinical judgment) for preventing kernicterus in 2.8 million healthy term infants ($\geq$ 37 weeks). Results suggested the prevention of one case of kernicterus would cost $10,321,463 (US) with universal follow-up (without routine pre-discharge testing), $5,743,905 with routine pre-discharge TSB (with selective follow-up and laboratory testing), and $9,191,352 with routine pre-discharge TcB (with selective follow-up and laboratory testing). The incremental annual cost for the cohort over current practice ranged from 112 to 202 million. The authors concluded it is premature to implement a large-scale routine bilirubin screening (either TSB or TcB) before hospital discharge given the high costs and uncertain effectiveness, specifically with respect to the incidence of kernicterus. Based on the two economic evaluations, there are mixed results on appropriateness of implementation of a TcB screening program, specifically whether it would result in increased costs or cost savings to the health care system.

Table 2. Findings

Organization Year Country	Type of Report	Search Dates	Device(s) Evaluated	Clinical Condition and Population	Evidence	Conclusions
Conseil d'Évaluation des Technologies de la Santé du Québec(31) 2000 Canada	Technology Review	1978 – Apr 1998 (updated to Dec 1999)	Minolta/Air Shields Jaundice Meter (101/102)	Jaundice in newborn	• Review of literature, number of studies not reported	"Since transcutaneous bilirubinometry is effective in detecting cases where a serum bilirubin measurement is required, making this technology part of a well-established perinatal program presents numerous benefits that could offset the costs associated with it." "However, even if transcutaneous bilirubinometry may play a useful role, the published data on this technology are insufficient to recommend a wide-scale program for the systematic purchase of these devices. The appropriateness of using transcutaneous bilirubinometry must therefore be assessed by the regional and local authorities."
Agency for Healthcare Research and Quality (32) 2002 USA	Evidence Review	1966 to Sept 2011	Minolta Airshields Jaundice Meter, Ingram Icterometer, and SpectRx BiliCheck	Neonatal hyperbilirubinemia in infants of at least 34 weeks gestational age	• 138 articles	Based on the evidence from the systematic review, TcB measurements of bilirubin have a linear correlation to total serum bilirubin and may be useful as screening devices to detect clinically significant jaundice and decrease the need for serum bilirubin determinations.
Health Technology Assessment Section, Ministry of Health Malaysia(33) 2009 Malaysia	Technology Review	Not Reported	BiliChekTM, Colormate IIITM and JM-102TM, SpectRx Air Shields	Neonates with hyperbilirubinaemia	• Malaysian HTA report • NICE guideline • 11 primary studies	"Transcutaneous Bilirubinometer can be recommended for use as a screening tool in term neonates to determine hyperbilirubinemia. Transcutaneous bilirubinometer application on dark skin coloured term neonates need to be cautioned. However, it should be emphasized that serum bilirubin levels estimated using transcutaneous bilirubinometer should be confirmed with chemistry analyser in the clinical laboratories."
National Collaborating Centre for Women's and Children's	Clinical Guideline	Up to Jun 2009	JM-103 and BiliChek	Neonatal jaundice	• Review of literature, number of studies not reported	"The accuracy of transcutaneous bilirubinometers (Minolta JM-103 and BiliChek) has been adequately demonstrated in term babies below treatment levels (bilirubin < 250 micromol/litre)." "There is good evidence that a risk assessment that

Health NICE(34) May 2010 United Kingdom						combines the result of a timed transcutaneous bilirubin level with risk factors for significant hyperbilirubinemia is effective at preventing later significant hyperbilirubinemia."
NSC UK National Screening Committee (35) July 2011 United Kingdom	Evidence Review	Jan 2011 to Mar 2015	BiliChek, the Minolta JM-103 and Bilimed	Neonatal screening for Kernicterus	• Review of literature, number of studies not reported	"There still remains uncertainty on an appropriate marker for risk of developing kernicterus and whether current indications for bilirubin lowering treatments would prevent new cases of kernicterus. These uncertainties prohibit the recommendation of a screening programme for kernicterus. There is no new evidence that suggests that NSC policy needs to change."
Maternal and Child Health Bureau(36) January 2012 USA	Evidence Review	1990 to Oct 2011	N/A	Newborn screening program for neonatal hyperbilirubinemia	• 112 studies	"The experts agreed that a United States population-based, large-scale (whole city or state) predischarge bilirubin newborn screening effort does not currently exist." "TcB appears to be a reliable screening tool for detecting significant hyperbilirubinemia requiring confirmatory follow-up with TSB."
Institute of Health Economics(8) 2013 Canada	Technology Review	Jan 2000 to Jan 2012	BiliChek and JM-103	Hyperbilirubinemia in Neonates ≥35 weeks' gestation	• 39 primary studies	"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."
CADTH (37) December 2013 Canada	Rapid Response	Jan 1, 2008 – Nov 26, 2013	TcB Bilirubin measurement	Transcutaneous bilirubin measurement in well newborns	• 1 HTA • 2 systematic reviews • 1 economic evaluation • 3 evidence-based guidelines	The three evidence-based guidelines recommended TcB measurements should be confirmed using serum bilirubin. Uncertain whether TcB measurement could be considered more cost-effective than visual inspection and clinical history combined with serum bilirubin testing.

5.1.4   Conseil d'Évaluation des Technologies de la Santé du Québec(31)

In February 1998, the Conseil d'Évaluation des Technologies de la Santé du Québec was asked to examine the usefulness of providing each region in Quebec with transcutaneous bilirubinometers. The assessment was based on a review of the scientific literature, the main databases searched were MedLine, Cochrane, EMBASE, PASCAL and HSTAR from 1978 to April 1998. Articles were also identified by review of the bibliographies of the articles identified in the initial search. The information was updated on a regular basis until December 1999 and complemented with searches on the Internet, consultations with health care professionals as well as the manufacturers of medical devices.

The number of studies supporting the assessment were not reported. The assessment concluded that "since transcutaneous bilirubinometry is effective in detecting cases where a serum bilirubin measurement is required, making this technology part of a well-established perinatal program presents numerous benefits that could offset the costs associated with it." However, "even if transcutaneous bilirubinometry may play a useful role, the published data on this technology are insufficient to recommend a wide-scale program for the systematic purchase of these devices." The appropriateness of implementation should be assessed by the regional and local authorities based on the instrument's benefit, ease of use, relatively high cost, limited effectiveness in certain circumstances, need for quality control, and need for assessment of budget impact of purchase.

5.1.5   Agency for Healthcare Research and Quality

The Agency for Healthcare Research and Quality (AHRQ) conducted an evidence report/technology assessment on the management of neonatal hyperbilirubinemia (32). In 1994 the American Academy of Pediatrics published guidelines on the management of neonatal hyperbilirubinemia and AHRQ reviewed evidence for five key questions with an aim to supply data for an update to these recommendations. The key questions focused on three areas, 1) association of neonatal hyperbilirubinemia with neurodevelopmental outcomes, treatment for neonatal hyperbilirubinemia, and diagnosis of neonatal hyperbilirubinemia. For the current review, results were reported for the final area of diagnosis of neonatal hyperbilirubinemia, specifically the efficacy of strategies for predicting hyperbilirubinemia and the accuracy of TcB

measurements. The target population included infants of at least 34 weeks gestational age. MedLine and PreMedLine were searched from 1966 up until September 2011 using relevant MeSH terms ("hyperbilirubinemia," "hyperbilirubinemia, hereditary," "bilirubin," "jaundice, neonatal," "kernicterus") and text words ("bilirubin," "hyperbilirubinemia," "jaundice," "kernicterus," "neonate"). Abstracts were limited to the human population and English language. For questions 4 or 5 on the diagnosis of neonatal hyperbilirubinemia, inclusion criteria included: infants ≥34 weeks of gestation or birthweight ≥2,500 grams and a sample size of more than 10 subjects. The reference standard was laboratory-based serum bilirubin.

After full-text screening, 138 of 253 retrieved articles were included in the AHRQ report. For the accuracy of various strategies for prediction of neonatal hyperbilirubinemia, 10 articles were included. A conclusion was difficult to make given the lack of consistency of defining clinically significant neonatal hyperbilirubinemia and study populations. With respect to accuracy of TcB measurements, the report concluded TcB measurements "have a linear correlation to total serum bilirubin and may be useful as screening devices to detect clinically significant jaundice and decrease the need for serum bilirubin determinations." They noted that BiliCheck and Colormate III devices appear to be significantly improved over older devices. They also noted that one study showed BiliCheck to be as accurate as standard laboratory methods in predicting TSB determined by the reference standard of high performance liquid chromatography.

5.1.6   *Health Technology Assessment Section, Ministry of Health Malaysia(33)*

In 2009, the HTA section for the Ministry of Health Malaysia assessed the effectiveness and cost-effectiveness of several hand held transcutaneous bilirubinometers. The detailed methodological search strategy was not reported. Literature was searched through databases including MedLine, Cochrane Library, Science Direct and Internet search of Google and Yahoo. The review was based on a Malaysian HTA report, guideline by NICE, and 11 primary studies of prospective control and cross-sectional designs.

The review found that there was sufficient evidence that a transcutaneous bilirubinometer was effective in estimating serum bilirubin in term neonates; however, there was controversial evidence for the use in dark skin coloured term neonates. With respect to costs, it was found the

direct cost for the BiliChek meter was cheaper compared to JM-103 Minolta Airshields transcutaneous bilirubinometer. Further details on this analysis were not reported. The HTA report recommendation included the following: "Transcutaneous Bilirubinometers can be recommended for use as a screening tool in term neonates to determine hyperbilirubinemia. Transcutaneous bilirubinometer application on dark skin coloured term neonates need to be cautioned... However, it should be emphasized that serum bilirubin levels estimated using transcutaneous bilirubinometer should be confirmed with chemistry analyser in the clinical laboratories."

5.1.7 National Collaborating Centre for Women's and Children's Health(34)

The National Collaborating Centre for Women's and Children's Health published a clinical guideline on neonatal jaundice in May of 2010, commissioned by the National Institute for Health and Clinical Excellence. Key priorities for implementation and for the recommendations developed included: information for parents and care givers, care for all babies, additional care, measuring bilirubin in all babies with jaundice, how to measure the bilirubin level, how to manage hyperbilirubinemia, and care of babies with prolonged jaundice. Initial scoping searches were conducted to identify relevant guidelines produced by other development groups. Systematic searches were executed up to June 2009 in the following databases via the Ovid platform: Medline (1966 onwards), Embase (1980 onwards), Cumulative Index to Nursing and Allied Health Literature (1982 onwards), and PsycINFO (1967 onwards). The most recent search was conducted using the three Cochrane databases and economic studies were identified through the above databases and the NHS Economic Evaluations Database. Searches were not date specific and no language restrictions were applied. Grey literature and hand searching of journals was not undertaken.

The final number of studies supporting the assessment were not reported. The recommendations concluded "the accuracy of transcutaneous bilirubinometers (Minolta JM-103 and BiliChek) has been adequately demonstrated in term babies below treatment levels (bilirubin <250 μmol/litre)." They also noted that "there is good evidence that a risk assessment that combines the result of a timed transcutaneous bilirubin level with risk factors for significant hyperbilirubinaemia is effective at preventing later significant hyperbilirubinaemia." A literature search was also

undertaken to assess economic evidence for strategies to prevent kernicterus in newborns. The Guideline Development Group strongly believes a more intensive testing strategy is required to improve outcomes in neonatal jaundice. They noted that the current analysis does not demonstrate that this would be cost-effective; however, it suggests the actual number of kernicterus cases needed for more intensive testing to be cost-effective is relatively small.

5.1.8   NSC UK National Screening Committee

An analysis by Bazian Ltd for the UK National Screening Committee (UK NSC) was conducted for screening to prevent kernicterus (35). This was an external review against programme appraisal criteria for the UK NSC. The most recent analysis conducted in 2011 recommended against screening due to many uncertainties. Searches of guideline sites, EMBASE.com, PubMed, Cochrane Database Syst Rev (Wiley), CENTRAL, DARE, HTA, and NHS EED were conducted from January 1, 2011 until March 17, 2015 (March 16, 2015 for PubMed).

The final number of studies supporting the assessment were not reported. The review found 1) "no evidence that national screening could identify those at risk of developing kernicterus", 2) "that there is no established bilirubin threshold associated with development of kernicterus. This means it would be difficult to know what level of bilirubin puts the baby at high risk of kernicterus" and 3) "current medical practice needs to be optimised before screening is recommended. The report concluded "there still remains uncertainty on an appropriate marker for risk of developing kernicterus and whether current indications for bilirubin lowering treatments would prevent new cases of kernicterus. These uncertainties prohibit the recommendation of a screening programme for kernicterus. There is no new evidence that suggests that NSC policy needs to change."

5.1.9   Maternal and Child Health Bureau(36)

In 2012, the United States Department of Health and Human Service's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) directed their Evidence Review Group to provide a report on the potential benefits, harms, and costs of adding neonatal hyperbilirubinemia to the list of primary conditions for newborn screening. The systematic evidence review was conducted by search of MedLine and EMBASE for all relevant studies

published over a 20-year period from 1990 up until October 2011. Additional data was collected from experts in the field. Searches were conducted combining MeSH and keywords of "hyperbilirubinemia," "bilirubin encephalopathy," and "kernicterus". The same keywords were also searched within the OVID In-Process and Other Non-Indexed Citations databases to capture articles that had not yet been assigned MeSH terms. Searches were limited to human studies, all infants, and English language studies.

A total of 112 studies were included in the final review and interviews with experts were also contacted. The experts agreed that a United States population-based large-scale pre-discharge bilirubin newborn screening effort does not currently exist. Key findings with respect to screening concluded that "TcB appears to be a reliable screening tool for detecting significant hyperbilirubinemia requiring confirmatory follow-up with TSB." They indicated no risks or harms associated with screening. With initial screening for TcB, the number of blood draws can be significantly reduced, preventing unnecessary blood draws and associated harms of pain and blood loss.

5.1.10 Institute of Health Economics (8)

In 2013, the Institute of Health Economics published a report to inform Alberta Health Services on whether there is value in increasing the availability and use of TcB to test for hyperbilirubinemia across Alberta. A systematic review and critical appraisal of the scientific evidence was performed. The key objectives were to examine evidence on safety and accuracy of TcB, the impact on changing patient management and clinical outcomes with implementing universal TcB screening programs, and identify barriers to and requirements to implementing a universal TcB screening program. A comprehensive literature search was conducted for studies published between January 2000 and 2012. Core databases included Cochrane Database of Systematic reviews, CENTRAL, MedLine, EMBASE, CRD Databases, CINAHL, and Web of Science. Grey literature searches were also conducted for further information, including HTA agencies' websites, clinical practice guidelines, and ongoing clinical trials. Reference lists of included studies were also checked for other relevant studies.

Overall, 39 primary studies were included in the review. Thirty-four studies examined the correlation/agreement between TcB and TSB values and the accuracy of TcB screening in predicting clinically significant hyperbilirubinemia. Five other studies reported the clinical outcomes of implementing a TcB screening program. Evidence from the 34 screening studies indicated a strong correlation between TcB and TSB measurements, a correlation coefficient ranging from 0.75 to 0.95. The report concluded "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."

5.1.11 CADTH

The CADTH rapid review, published in December 2013, assessed the use of transcutaneous bilirubin measurements in newborns (37). This rapid review includes a literature review on clinical effectiveness, cost-effectiveness, and guidelines. OVID's Medline, PubMED, The Cochrane Library, and the University of York Center for Reviews and Dissemination databases were searched from January 1, 2008 until November 26, 2013. Additionally, websites of major Canadian and international HTA agencies were hand searched and a focused internet search was conducted. Results were limited to: health technology assessments, systematic reviews, randomized controlled trials (RCTs), non-randomized studies, economic evaluations, and evidence-based guidelines. Filters were used to limit to human populations and English language studies.

Using this search, seven relevant citations were included (one HTA, two systematic reviews, one economic evaluation, and three evidence-based guidelines). The one HTA included was the IHE report (8) that was previously described. One systematic review concluded that TcB devices were reliable in estimating bilirubin levels and could reduce blood sampling (38). Another systematic review concluded that generally TcB were reliable at predicting which infants did not require phototherapy (32). One economic evaluation concluded that a new TcB protocol significantly reduced costs when compared with serum bilirubin measurements (39). Three evidence-based guidelines were identified, which were previously described (27, 35, 40).

5.1.12 Conclusions

Eight evidence syntheses were identified, four technology reviews (including a rapid response) of the use of transcutaneous bilirubinometers for hyperbilirubinemia newborn screening and four guidelines on hyperbilirubinemia in newborns. Two economic evaluations were identified. The results of these evaluations were mixed on the appropriateness of implementation of a TcB screening program and its economic impact. There is conflicting evidence and subsequently recommendations on implementing widespread TcB screening in various jurisdictions. Two technology/evidence reviews concluded that 1) there was no evidence to change the recommendation of no screening programme for kernicterus in the United Kingdom or, 2) there was insufficient evidence to recommend a wide-scale program with TcB screening in Quebec (35, 41). Overall, all eight evidence syntheses concluded TcB was effective and useful as a screening tool for hyperbilirubinemia; however, results still need to be followed by and confirmed with TSB.

5.2   TcB Use in Canada

Drager Medical Systems, Inc., the manufacturer of JM-103 and JM-105 devices, and McArthur Medical Sales Inc., the distributor of the BiliChek in Canada, were contacted to identify the number and distribution of TcB devices currently being used across Canada.

Nine-hundred and sixteen Drager bilirubinometers and 65 BiliChek devices have been distributed among ten provinces, most of them are in Quebec (360, Drager; 20, BiliChek), Alberta (296, Drager; 9, BiliChek), Ontario (118, Drager; 18, BiliChek) and BC (61, Drager; 9, BiliChek). Prince Edward Island (1) and Nova Scotia (2) have the fewest number of Drager bilirubinometers Table 3. The 61 Drager bilirubinometers currently being used in BC are distributed across the province with 29 in the Vancouver Island Health Authority, 16 the in Vancouver Coastal Health Authority, 7 in Northern Health, 6 in Fraser Health and 3 in Interior Health . In addition, the Vancouver Coastal Health Authority has three BiliChek devices, and the Fraser and Interior Health each have two BiliChek devices (Table 4).

Table 3. Distribution of TcB devices across Canada

Province	JM-103	JM-105	BiliChek	Total	Number of live births 2014/2015
QC	292	68	20	380	88,929
AB	249	47	9	305	52,634
ON	77	41	18	136	141,597
SK	14	16	3	33	14,850
MB	16	15	1	32	16,358
NB	9	2	5	16	7,059
NL	5	2	0	7	4,382
NS	1	1	0	2	8,774
PEI	1	0	0	1	1,312

Table 4. Distribution of TcB devices across British Columbia Health Authorities

Health Authority	JM-103	JM-105	BiliChek	Total	Number of live births 2014/2015
Island Health	13	16	3	32	5927
Vancouver Coastal	14	2	1	17	12860
Northern	4	3	1	8	3345
Fraser	6	0	2	8	15033
Interior	3	0	2	5	5936
Total	**40**	**21**	**9**	**70**	**43101**

6 Systematic Review of Diagnostic Accuracy, Safety, and Clinical Outcomes

Summary

- Eight studies, including seven pre- post- designs and one RCT, assessed clinical outcomes of TcB. Most studies reported that the use of TcB decreased the number of TSB tests done, with estimates ranging from 23% to 34% reduction. Studies were mixed on whether TcB resulted in a reduced need for phototherapy treatment. Overall, there was a trend towards reduced health care resources including TSB testing, phototherapy, and hospital readmissions after TcB implementation.
- Nine studies were included on diagnostic accuracy. Sensitivity ranged from 72%-100% and the specificity ranged from 58%-88%. Significant heterogeneity was observed; subgroup analysis by device and target TSB level did not account for heterogeneity.
- No studies assessing the safety of TcB were identified

1.1 Purpose

To determine the effect of TcB on clinical outcomes, safety and diagnostic accuracy in screening for hyperbilirubinemia.

1.2 Methods

A systematic review was conducted by the Institute for Health Economics (IHE) on the effectiveness of transcutaneous bilirubinometers from 2000-2012 (8). To leverage this work, an updated systematic review of the literature published since the IHE report (2012-current) was completed. PRISMA guidelines and reporting standards were used. Abstract and full-text review, data extraction, and quality assessment phases were performed in duplicate. Any discrepancy between reviewers was resolved through discussion and consensus.

An electronic database search, replicating the IHE search, was conducted. Nine databases were searched from January 2012 until June 30th, 2016: MEDLINE, EMBASE, CINAHL, Web of Science, HTA database, NHSEED, DARE, Cochrane Database of Systematic Reviews, and Cochrane Registry of Controlled Trials. Terms aimed at capturing the target diagnoses such as bilirubin, and hyperbilirubinemia were combined using the Boolean Operator "or." These terms were then combined, using the Boolean Operator "and" with terms describing the technology, such as TcB, JM-103, JM-102, BiliCheck, and point of care systems. Results were limited to

English and French language studies and studies involving humans. No other limitations or filters were applied. Details of this search can be found in the Appendix.

Abstracts proceeded to full-text review if they: reported original data; reported on the safety, diagnostic accuracy and/or clinical outcomes of any transcutaneous bilirubinometer; were designed as either observational studies (for safety and diagnostic accuracy), randomized or non-randomized controlled trials and quasi-experimental studies (for clinical outcomes); and were in English or French. Abstracts were excluded if they failed to meet any of the above inclusion criteria, or if they: were an animal-model; reported non-original data; case reports, editorials, opinions or qualitative studies. Abstracts selected for inclusion by either reviewer proceeded to full-text review. This initial screen was intentionally broad to ensure that all relevant literature was captured.

Studies included after abstract review proceeded to full-text review. Studies were included if they met all inclusion criteria and failed to meet any of the criteria for exclusion presented in Table 5. Studies specifically evaluating the diagnostic accuracy of a transcutaneous bilirubinometer were excluded if they did not report the accuracy of detecting hyperbilirubinemia by TSB greater than or equal to the 75th or 95th percentile as the diagnostic cut-off (i.e. percentile-based hyperbilirubinemia). This exclusion criterion was selected as it is the recommended threshold for subsequent treatment by the Canadian Pediatric Association Guideline for the Management and Prevention of Hyperbilirubinemia. Published systematic reviews and other grey literature sources were hand-searched to ensure all relevant papers were captured in the literature search.

Table 5. Inclusion and Exclusion Criteria for Clinical Systematic Review

Inclusion Criteria	Exclusion Criteria

• Healthy newborns with gestational age ≥35 weeks, from any ethnic origin and who have not previously received phototherapy
• Assess safety outcomes, diagnostic accuracy or clinical outcomes for use of any transcutaneous bilirubinometer in diagnosing hyperbilirubinemia
    o For safety outcomes*: observational studies;
    o For diagnostic accuracy** and nomogram: cross-sectional or cohort studies;
    o For clinical outcomes***: randomized or non-randomized controlled trials, quasi-experimental studies, and observational studies
• Comparator either total serum bilirubin (TSB) measurement or visual inspection (and reference standard was TSB)
• English or French
• Published between January 2012 to present
	• Non-original data
	• Conference proceedings, opinions, editorials, letters, news, case reports, animal studies
	• For diagnostic accuracy:
	    o Target TSB levels were not based on either the 75th or 95th percentile

*Examples of Safety outcomes: 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).
**Examples of screening accuracy outcomes: correlation/agreement between TcB and TSB, sensitivity and specificity, and other test performance measures.
***Examples of clinical outcomes: reduction of the need for TSB testing, early diagnosis and treatment, or reduction in hospital readmission.

Included studies were subdivided into: safety outcomes; nomogram development and/or validation; and clinical outcomes. For all studies, year of publication, country, patient selection, patient characteristics, description of technologies, research methods, outcomes measured, and instruments used were extracted using standardized data extraction forms.

For studies evaluating the diagnostic accuracy of a transcutaneous bilirubinometer, available performance data (e.g. sensitivity, specificity, positive predictive value, negative predictive value) were extracted. If a study did not report the aforementioned performance data, the reported true positive, true negative, false positive, and false negative counts were extracted, if available, in order to calculate sensitivity and specificity for a given device and study. The reported and calculated sensitivities and specificities of the transcutaneous bilirubinometers across included studies were graphically depicted in forest plots and pooled in a summary

receiver operator characteristic (SROC) curve. For studies reporting multiple sensitivity and specificity data (e.g. at different times, with different TcB cut-offs), only the first set of estimates obtained and using a $\geq 75^{th}$ percentile TcB cut-off were included in the forest plots and SROC curve. All statistical analyses were performed using STATA 13.1.

The methodological quality of the clinical accuracy, and clinical outcomes studies was evaluated using quality appraisal tools appropriate for the study design. The quality of diagnostic accuracy studies was assessed using an adapted version of the QUADAS-2 tool(42). The previously published QUADAS-2 tool consisted of 11 signaling questions or assessment items across four key domains: (1) patient selection; (2) index test; (3) reference standard; and (4) patient flow and timing (42). One particular signaling question in the reference standard domain — "Were the reference standard results interpreted without knowledge of the results of the index test?" — was not deemed relevant given that the reference standard, TSB testing, is an objective test, conducted in clinical laboratories and interpretations of TSB results are not likely affected by the results of the index test (8). Therefore, this item was removed and an adapted 10-item version of the QUADAS-2 tool was used for this present work. Studies identified for either safety or clinical outcomes were evaluated using the Downs and Black checklist (43). No formal quality assessment was conducted on studies describing the development of a nomogram.

The quality of clinical outcome studies was assessed by either the Downs and Blacks Checklist or the Cochrane Risk of Bias, depending on study design. Using the Downs and Blacks checklist, each non-randomized controlled trial (RCT) was assessed based on 27 criteria, widely covering areas reporting quality, external and internal validity, and power (43). Studies are assigned a value of "1" if they meet the question criteria, "0" if they do not or if it is not possible to determine whether they meet the criteria, with one exception where one question may be given "2" points.

Using the Cochrane Risk of Bias checklist (44), all RCTs were assessed for seven areas of bias (random assignment generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and any

additional potential sources of bias). Each study is assigned "low, "high," or "unclear" risk of bias for each of these seven potential sources of bias.

1.3 Results

In the updated search, four hundred and forty-five citations were retrieved from MEDLINE (n=139), EMBASE (n=218), CINAHL (n=47), Web of Science n=102, Cochrane Registry of Controlled Trials (n=21), HTA database (n=6), and DARE (n=4). After duplicates were removed, 306 citations were reviewed. 194 were excluded and 112 citations proceeded to full-text review. Seven full-text articles met the final inclusion criteria (Figure 3) from the updated search: two studies evaluating diagnostic accuracy of a transcutaneous bilirubinometer (45, 46); two studies reported a new TcB nomogram (47, 48); and three studies assessed the clinical outcomes of a transcutaneous bilirubinometer (49-51). Including the studies previously identified by IHE, 56 studies (36 on diagnostic accuracy, 12 on nomograms and 8 on clinical outcomes) were included. No studies evaluating safety outcomes were identified.

Figure 3. Flow Chart of Included and Excluded Studies

Identification

Number of records identified through Database Searching
n=445

MEDLINE n=139
EMBASE n=218
CINAHL n=47
Web of Science n=102
HTA database n=6
DARE n=4
Cochrane Registry of Controlled Trials n=21
NHSEED n=0
Cochrane Database of Systematic Reviews n=0

Number of additional records identified through other sources
n=2

Screening

Number of records after duplicates removed
n=306

Number of records screened
n=306

Number of records excluded
n=194

Eligibility

Number of full-text articles assessed for eligibility
n=112

IHE Report
n=49

Reasons for Exclusion (n=105):

Abstract, poster, or conference proceeding only (no full-text) (n=23)
Not in English or French (n=10)
Not primary objective (n=6)
Published prior to 2012 (n=1)
Duplicate (n=6)
Incorrect study design (n=18)
Target TSB level was not reported as 75th or 95th percentile (n=40)
Duplicate in previous review (n=1)

Included

Number of studies included in synthesis
n=56

Diagnostic accuracy n=36
Nomogram n=12
Clinical outcomes n=8

1.3.1 Diagnostic Accuracy Studies

1.3.1.1 Characteristics of Included Diagnostic Accuracy Studies

A total of nine studies evaluating the diagnostic accuracy of a transcutaneous bilirubinometer were included (45, 46, 52-58). Table 6 summarizes the characteristics of the included studies. As many other studies report the diagnostic accuracy of the TcB without reporting the 75th or 95th percentile (thus excluded from this review), a bibliographic summary of all identified diagnostic accuracy studies is provided in Table 7.

Table 6. Characteristics of Included Diagnostic Studies (8)

Study	N	Newborn characteristics	Index test	Reference standard
Bental et al. 2009(56) 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:** NR **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:** NR **Nomogram:** locally developed TcB nomogram **TcB source funding:** NR	**Method:** TSB by colorimetric method (ApelBR –501 instrument, Saitama, Japan) **Test performer:** experienced lab technician **Time interval between TcB and TSB:** simultaneous
Bhutani et al. 2000(52) 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:** NR **Feeding type:** NR **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:** NR **Training:** NR **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
Kolman et al. 2007(53) 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:** NR **Time interval between TcB and TSB:** ≤30 min
Kaplan et al. 2008(54) Israel	346	**M/F:** 175 (51%)/171 (49%) **GA (wks):** 39.4±1.4 **BW (g):** 3278±449 **Ethnicity:** Ashkenazi Jewish (light skinned) 49%,	**Device:** JM-103 **No. of devices:** NR **Location:** forehead **Test performer:** physician	**Method:** TSB by direct spectrophotometric method at clinical biochemistry lab/visual assessment **Test performer:** NR

		Sephardic Jewish 29%, Mixed Ashkenazi-Sephardic: 13%, Arab (light pigmented) 9% **Delivery mode:** vaginal (92%) **Feeding type:** NR **All jaundiced?:** no **Age at TcB/TSB measurement** (h): 59±23	**Training:** NR **Nomogram:** Bhutani nomogram **Comparator:** VA (using Kramer grading by nurses) **TcB source funding:** NR	**Time interval between TcB and TSB:** ≤30 min
Ho et al. 2006(55) Hong Kong Retrospective	997	**M/F:** NR **GA (wks):** median 39 (range 35–42) **BW (g):** NR **Ethnicity:** Chinese 95% **Delivery mode:** NR **Feeding type:** NR **All jaundiced?:** no **Age at TcB/TSB measurement** (h): median 32.9 (range 12.1–139.6), <72 h in 97% newborns	**Device:** JM-103 **No. of devices:** single **Location:** mid-sternum **Test performer:** NR **Training:** NR **Nomogram:** Bhutani nomogram **TcB source funding:** NR	**Method:** TSB by Unistat Reflectance bilirubinometer (Reichert-Jung, Buffalo, NY, USA) **Test performer:** NR **Time interval between TcB and TSB:** ≤30 min
Mohamed *et al.*(45) 2014 Canada Prospective	141	**M/F:** 75 (53.2%)/ 66 (46.8%) **GA (wks):** 38.8+/-1.3 **BW (g):** 3394+/-485 **Ethnicity:** Asian (6.4%) African American (24% Caucasian/other (76.6%) **Delivery mode:** Caesarean (19.1%) Vaginal (80.9%) **Feeding type:** Breast (34.9%) Formula (14.9%) Mix (26.2%) **All jaundiced?:** NR **Age at TcB/TSB measurement** (h): 51+/-10	**Device:** BiliChek **No. of devices**: 1 **Location:** Forehead or sternum **Test performer:** NR **Training:** NR **Nomogram:** Bhutani; Maisals and Kring; Fouzas **TcB source funding:** NR	**Method:** Blood sample **Test performer:** NR **Time interval between TcB and TSB:** Within 34-94 mins
Taylor *et al.*(46) 2016 United States Prospective	Sample 1: 759 Sample 2: 857	**M/F:** NR **GA (wks):** <38 (17.7% in Sample 1; 15.2% in Sample 2) **BW (g):** NR **Ethnicity: Sample 1:** American Indian 1% African American 25% Asian 7.8% Pacific Islander 0.5%	**Device:** JM-103 and BiliChek **No. of devices**: 2 **Location:** NR **Test performer:** NR **Training:** NR **Nomogram:** Bhutani **TcB source funding:** NR	**Method:** Blood sample **Test performer:** NR **Time interval between TcB and TSB:** Within 2 hrs

		White 64.2% Multiple 1.5% Other 0.2% **Sample 2:** American Indian 0.5% African American 18.2% Asian 7.8% Pacific Islander 2.7% White 64.7% Multiple 3.5% Other 2.4% **Delivery mode:** NR **Feeding type:** NR **All jaundiced?:** No **Age at TcB/TSB measurement** (h): <120		
Yu et al. 2011 (57) 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:** NR	**Method:** TSB by Unistat reflectance bilirubinometer (Reichert-Jung, Buffalo, NY, USA) **Test performer:** skilled physicians **Time interval between TcB and TSB:** ≤1–2 h

Table 7. Bibliographic Summary of Studies Excluded for not Reporting 75th or 95th Percentiles

Author and Reference		
Afanetti(59)	Grabenhenrich(60)	Radfar(61)
Afjeh(62)	Hemmati(63)	Raimondi(64)
Akahira(65)	Kitsommart(66)	Romagnoli(41)
Alsaedi(67)	Kisommart(68)	Sajjadian(69)
Badiee(70)	Kosarat(71)	Samiee(72)
Bhat(73)	Kurokawa(74)	Sarici(75)
Bosschaart(18)	Mahram(76)	Simsek(77)
Casnocha(78)	Maisels(79)	Srinivas(80)
Chawla(81)	Mansouri(82)	Yaser(83)
Chawla(84)	Mazur(85)	Hoppenot(86)
Conceicao(87)	Mohieldeen(88)	Juster-Reicher(89)
Ebbesen(90)	Neocleous(91)	Jackson(92)
Engle(93)	Pratesi(23)	
Fonseca(94)	Quist(95)	

1.3.1.2   Quality Assessment

The methodological quality of the included diagnostic accuracy studies was assessed using a modified 10-item QUADAS-2 tool (42). Ratings for the ten signaling questions or assessment items for each study are summarized in Figure 4. A "Yes" response indicates when the assessment item was met and suggests that a study may have minimized bias associated within the given domain.

None of the included studies received 'Yes' responses to all 10 signaling questions contained in the QUADAS-2 assessment tool, suggesting that each was subject to at least one source of potential bias. As illustrated in Figure 4, "Yes" responses to signaling questions 2 ("Case-control design avoided), 6 ("acceptable reference standard"), and 9 ("same references standard to all patients") were observed in all studies. Of the remaining assessment items, questions 3, 4, 5, 7, 8, and 10 received "Yes" responses in over half of the studies. For the majority of studies, a consecutive or random sample of participants was not enrolled ("No" responses) or it was unclear, which may introduce selection bias within those studies and potentially overestimate the diagnostic accuracy of the TcB device.

Given that weights are not assigned to each of the assessment items, no overall or tallied quality score was used. All studies were deemed to have low risk of bias in the reference standard domain. Low risk of bias in the patient selection and index test domains were also observed in the majority of studies. In the patient flow domain, over half of the studies were found to have low risk of bias (n=5) and the remainder were deemed to have high risk of bias (n=4). The detailed results of the quality assessment using the 10-item QUADAS-2 tool for each individual study are outlined in the Appendix.

Figure 4. Summary of Methodological Quality of Diagnostic Accuracy Studies
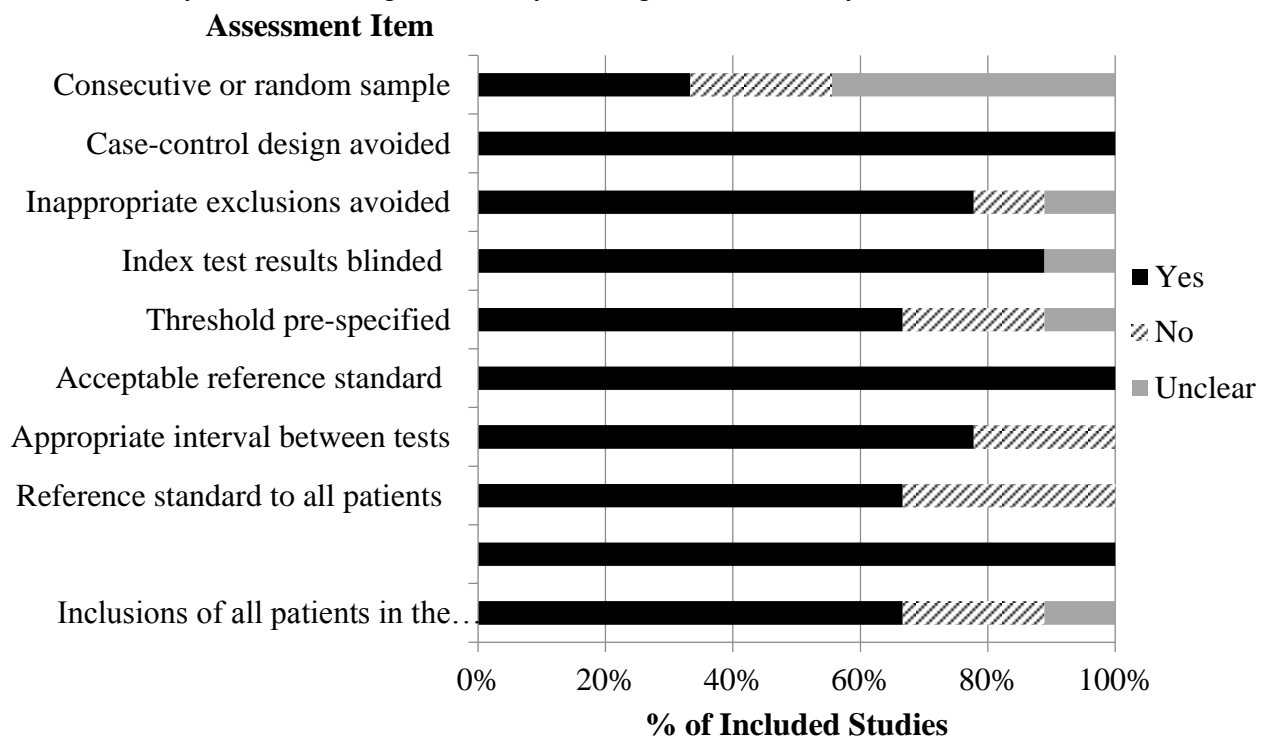
1.3.1.3   Sensitivity and Specificity of Transcutaneous Bilirubinometer Devices

The range of sensitivity and specificity estimates for transcutaneous bilirubinometers across diagnostic accuracy studies is depicted in the forest plot in Table 8 and Figure 5. As illustrated in Figure 5, point estimates for sensitivity ranged from 72% to 100%; these estimates were not significantly different as the 95% CIs overlapped for all but one study (Yu et al). In contrast, the point estimates for specificity were lower, ranging from 58% to

88% across studies and the 95% CIs were less likely to overlap compared to those for the sensitivity estimates.

Significant heterogeneity in the sensitivity and specificity estimates was observed visually and quantified in the respective I^2 values for the pooled sensitivity and specificity estimates (Figure 5). Given this heterogeneity, select subgroup analyses by device type (BiliChek or JM-103) and TSB percentile (>75th or >95th) were performed. A subgroup analysis by location of measurement was not possible, as most studies used mixed measurement locations or, in some instances, the location of measurement was not reported. The forest plots for all subgroup analyses are provided in the Appendix.

The first subgroup analysis examined diagnostic accuracy by device type: BiliChek (n=5) (45, 46, 52, 53, 58) or JM-103 (n=5) (46, 54-57). One study reported the use of both BiliChek or JM-103 bilirubinometers and because TcB measurements could not be distinguished by device in this study, the sensitivity and specificity estimates were pooled within both subgroups (46). As observed in the Appendix figures, higher point estimates of sensitivity were reported among studies that used a BiliChek device, whereas higher estimates of specificity were reported among studies using a JM-103 device. However, these differences were not statistically significant. In the second subgroup analysis, diagnostic accuracy was examined by the target TSB level: >75th percentile (n=4) (45, 46, 54, 58) or >95th percentile (n=5) (52, 53, 55-57). Studies where the target TSB level was >95% percentile had higher point estimates of both sensitivity and specificity, compared to the studies where the target TSB level was >75th percentile. These differences were not statistically significant.

Although, within both subgroup analyses there was still significant heterogeneity in the pooled sensitivity and specificity estimates (as indicated by I^2 values), suggesting that these characteristics did not account for heterogeneity observed in the overall pooled estimates.

Table 8. Accuracy of TcB for predicting TSB >75th or >95th percentile

Study	Device	Target TSB	TcB cut-off	Sensitivity (95% CI)	Specificity (95% CI)	ROC Curve number
Bhutani *et al.* (2000)(52)	BiliChek	>95th	>75th	100 (85 – 100)	88 (85 – 91)	1
Kolman *et al.* (2007)(53)	BiliChek	>95th	≥75th	100 (74 – 100)	66 (59 – 73)	2
Wickremasinghe *et al.* (2011)(58)	BiliChek	>75th	≥75th	87 (69 – 96)	58 (43 – 71)	3
Mohamed *et al.* (2014)*(45)*	BiliChek	>75th	>75th	80 (44 – 97)	83 (76 – 89)	4
Ho *et al.* (2006)*(55)*	JM-103	>95th	>40th*	100 (94 – 100)	0 (0 – 0.4)	NI
			>75th	87 (75 – 94)	58 (55 – 62)	5
			>95th*	45 (33 – 58)	93 93 (91–94)	NI
Kaplan *et al.* (2008)(54)	JM-103	>75th	≥9 μmol/L	72 (51 – 88)	88 (68 – 97)	6
Bental *et al.* (2009)(56)	JM-103	>95th	>75th within 24-48hrs	83 (52 – 98)	77 (73 – 82)	7
			>75th within 48-72hrs*	100	76	NI
Yu *et al.* (2011)(57)	JM-103	>95th	>40th*	100 (99 – 100)	46 (44 – 47)	NI
			>75th	79 (75 – 82)	83 (82 – 84)	8
			>95th*	27	97	NI
Taylor *et al.* (2016)(46)	BiliChek or JM-103	>75th	NR	100 (63 – 100)	68 (65 – 71)	9

*Sensitivity and specificity data for this TcB cut-off was not depicted in the forest plot and SROC; NI: not included in the ROC curve

Figure 5. Forest Plot of Sensitivity and Specificity of All Diagnostic Accuracy Studies

StudyId | SENSITIVITY (95% CI) | SPECIFICITY (95% CI)

Bhutani 2000 Bilicheck — 1.00 [0.85 - 1.00] | 0.88 [0.85 - 0.91]
Kolman 2007 Bilicheck — 1.00 [0.74 - 1.00] | 0.66 [0.59 - 0.73]
Wickremasinghe 2011 Bilicheck — 0.87 [0.69 - 0.96] | 0.58 [0.43 - 0.71]
Mohamed 2014 Bilicheck — 0.80 [0.44 - 0.97] | 0.83 [0.76 - 0.89]
Ho 2006 JM-103 — 0.87 [0.75 - 0.94] | 0.58 [0.55 - 0.62]
Kaplan 2008 JM-103 — 0.72 [0.51 - 0.88] | 0.88 [0.68 - 0.97]
Bental 2009 JM-103 — 0.83 [0.52 - 0.98] | 0.77 [0.73 - 0.82]
Yu 2011 JM-103 — 0.79 [0.75 - 0.82] | 0.83 [0.82 - 0.84]
Taylor 2016 Bilicheck or JM-103 — 1.00 [0.63 - 1.00] | 0.68 [0.65 - 0.71]

COMBINED — 0.86 [0.74 - 0.92] | 0.76 [0.68 - 0.82]

Q = 17.74, df = 8.00, p = 0.02 | Q = 380.71, df = 8.00, p = 0.00
I2 = 54.91 [21.13 - 88.69] | I2 = 97.90 [97.23 - 98.57]

SENSITIVITY | SPECIFICITY

Figure 6. Summary ROC for Sensitivity and Specificity of All Diagnostic Accuracy Studies
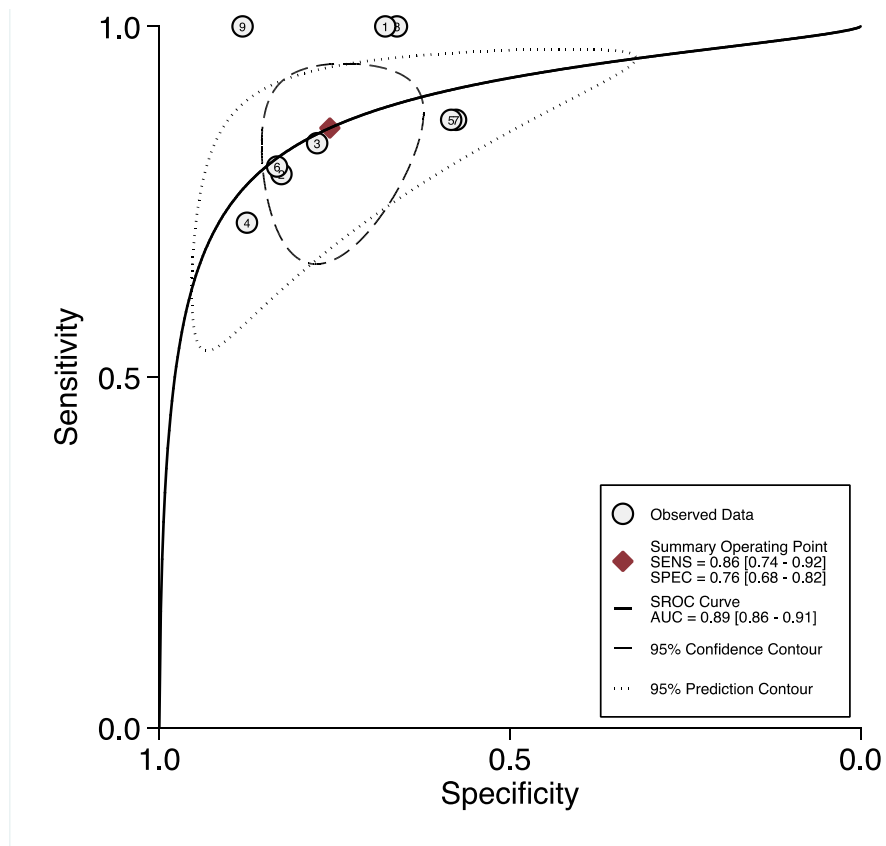
6.1   Clinical Outcomes

Eight studies, conducted in Canada (96), the United States (49, 50, 97), Ireland (98), Australia (39), and India (51, 99) examined the impact of the implementation of a TcB protocol/program on clinical outcomes. Two concurrent comparative studies (98, 99) examined whether the use of TcB could reduce the following use of TSB testing. Five studies (39, 49, 51, 96, 97) examined clinical outcomes before and after the implementation of a TcB program, and one prospective observational study (50) identified the most effective pre-discharge assessment program including clinical risk factors. The details of these studies are presented in

Table 9.

Table 9. Summary of clinical outcomes of using a TcB test

Study	Population/Intervention	Number of TSB testing	Number of severe neonatal hyperbilirubinemia	Rate of Photo Therapy
Petersen et al. 2005(97) USA Before–after study	N=6,603 Experimental group (8 months with TcB by BiliChek): N not available Control group (8 months VA only): N not available	Experimental group: 36.7±8.7% vs. Control group: 31.8±6.4% (P=0.21)	Readmission for severe neonatal hyperbilirubinemia (No./1000): Experimental group: 1.8±1.7 vs. Control group: 4.5±2.4 (P=0.044)	Experimental group: 7.7±1.3% vs. Control group: 5.9±1.3% (P<0.05)
Hartshorn et al. 2009(39) Australia Before–after study	Experimental group (6 months with TcB by JM-103): N=2,197 Control group (12 months VA only): N=1169	Experimental group: 10.2% vs. Control group: 19.4% Reduced 47% (P<0.001)	TSB 350 to 400 µmol/L: Experimental Group: 0/1169 (0%) Control group: 17/2197 (0.77%) (P<0.001)	Experimental group: 35 (3.0%) vs. Control group: 84 (3.8%) (P=0.2)
Mishra et al. 2009(99) India RCT	Experimental group (TcB by BiliChek): N=314 Control group (VA): N=303	Experimental group: 17.5% vs. CG: 26.4% Reduced 34% (95% CI 10 to 51%) (P=0.008)	NA	Experimental group: 5.7% vs. Control group: 8.6% (P=0.17)
Allen et al. 2010(98) Ireland Non-randomized comparative study	Experimental group (hospital A with VA+TcB by JM-103): N=15,851 Control group (hospital B with VA only): N=15,701	Experimental group: 10% vs. Control group: 15% Reduced 31% (P<0.001)	TSB levels requiring exchange transfusion: Experimental group: 0.85% vs. Control group: 0.13% (ss not available)	NA
Wainer et al. 2012(96) Canada Before–after study	Experimental group (8 months with TcB by JM-103): N=14,112 Control group (8 months VA only): N=14,769	Experimental group: 103.6/1000 live births vs. Control group: 134.4/1000 live births Reduced 22.9% (P<0.0001)	TSB ≥20 mg/dL: Experimental group: 850.9/100 000 live births, 1:118 vs. Control group: 385.2/100 000 live births, 1:260 Reduced 54.9% (P<0.0001)	Experimental group: 4.97% vs. Control group: 6.09% (P<0.0001)
Wickremasinghe et al. 2012(49) USA Before-after study	Experimental group (11 months with TcB by BiliChek): N=1801 Control group (10 months VA only): N=1580	Experimental group: 713/1000 infants Control group: 717/1000 infants (P=0.008)	TcB>75th percentile Experimental group: 713/1000 infants Control group: 717/1000 infants Reduced <1% P=0.008	Experimental group: 4.4% vs. Control group: 5.6% (P<0.0001) for rate per

				1000 infants
Bhutani et al. 2013(50) USA Prospective observational study	TSB/TcB with or without identified clinical risk factors: N=1157	NA	Defined as subsequent use of phototherapy (age ≥ 60 hours)	7.6%
Morgan et al. 2016(51) India Before-after study	Experimental group (12 months with TcB by MBJ20): N=568 control group (12 months VA only): N=624	Experimental group: 7.0% vs. Control group: 5.9% (P=0.44)	TSB >95th percentile Experimental group: 5/568 (0.88%) Control group: NA	Experimental group: 3.3% vs. Control group: 2.3% (P=0.26)

CI: confidence interval, N: total number, NA: Not applicable, TSB: total serum bilirubin, TcB: Transcutaneous bilirubinometer,

A randomized clinical trial conducted in India evaluated the usefulness of TcB in decreasing the need for TSB testing in the management of jaundiced, healthy Indian newborns (99). Newborns were randomly assigned to a TcB group (N=314) or a systematic visual assessment group (N=303). TcB was measured by a BiliChek device and an experienced physician performed visual assessment in an adequately illuminated room. Both groups were similar with respect to birth weight, gestational age, and postnatal age. The number of newborns that required TSB tests was significantly lower in the TcB group compared with the visual assessment group, with a 34% reduction (17.5% versus 26.4%). There were no significant differences in the number of newborns requiring phototherapy. The study concluded that compared with visual assessment, routine use of TcB significantly reduced the need for TSB blood sampling in jaundiced term and late preterm newborns. Another study conducted in Ireland compared clinical outcomes at two hospitals with (N=15,851) or without a TcB program (N=15,701) (98). A TcB cut-off value of 200 µmol/L was used to determine the need for a TSB test. The study concluded that, although there was no difference in the number of newborns with TSB above the levels requiring exchange transfusion, the need for TSB was reduced by 31% with the use of TcB.

Three before-after studies assessed the impact of TcB screening on clinical outcomes (39, 96, 97). A Canadian prospective study compared clinical outcomes of 14,796 healthy, term or late preterm newborns who received routine TcB measurement in both hospital and community

settings, with a historical cohort of 14,112 newborns who received visual assessment only (96). TcB was measured daily before discharge and one to two days after discharge. A locally developed and validated TcB nomogram was used to plot the TcB values. The study found implementation of a TcB program was associated with a 23% reduction in community TSB testing, a 55% reduction in severe neonatal hyperbilirubinemia, and an 18% reduction in the total number of newborns requiring phototherapy. No change in the length of readmission for phototherapy was found. The study concluded that implementation of a TcB program significantly improved patient safety and resulted in reduced use of both laboratory and hospital sources. An American study was conducted to determine whether the use of TcB affects the use of laboratory bilirubin testing or decreases the number of newborns that are readmitted for hyperbilirubinemia within seven days of initial discharge (97). A total of 6,603 newborns were examined for clinical outcomes eight months before and after the implementation of the TcB program. The study found no significant change in the number of TSB tests and length of hospital stay; however, TcB testing was associated with a reduction in the hospital readmission rate for significant hyperbilirubinemia. Lastly, an Australian study compared clinical outcomes 12 months before (n=2,197) and 6 months (n=1,169) after the implementation of a TcB protocol (39). No significant differences were found in the demographics of the population over the two time periods. The study found that TcB programs significantly reduced the number of blood samples for TSB testing without increasing the risk of delayed phototherapy treatment.

A retrospective review in the United States was conducted over two periods to examine the effect of a universal TcB screening protocol on laboratory utilization and phototherapy usage. During period 1, TSB measurements were ordered based on clinical judgment of the attending physicians and during period 2, all infants underwent pre-discharge screening with TcB. A total of 3,381 infants were included in period 1 (N=1,580) and period 2 (N=1,801). The study found TSB measurement per 1000 infants decreased between the two periods, with more outpatient and less inpatient blood draws in period 2. Phototherapy also decreased from 59 to 39 per 1000 infants, with less inpatient and more readmission phototherapy. The study concluded universal TcB screening was implemented without increasing blood draws or phototherapy; however, use was shifted from inpatient to outpatient services.

A prospective observational multicenter cohort study conducted in the United States was designed to determine the relative diagnostic performance of a TcB used pre- TSB compared with using clinical risk factors to predict severe neonatal hyperbilirubinemia. Severe neonatal hyperbilirubinemia was defined by the use of phototherapy. Overall, 1,157 infants were enrolled between October 2005 and April 2007 and 1,144 remaining infants had a bilirubin measurement before discharge. Of these infants, 75 of 982 (7.3%) had phototherapy and none received an exchange transfusion. Only one-half (3.5%) of these infants were readmitted for treatment. The study concluded the combined use of TcB and TSB at 24-48 hours postnatal age and gestational age is the best predictor for subsequent use of phototherapy.

A resource-limited hospital in rural India evaluated the acceptability and feasibility of implementing universal TcB screening; specifically, whether it was associated with improved recognition of high-risk hyperbilirubinemia compared to visual inspection. Overall, 624 infants were in the pre-TcB implementation phase and 568 infants were in the post-TcB implementation phase. The proportion of infants who had TSB testing was similar between implementation periods (pre- 6% versus post-implementation 7%). Likewise, the rate of phototherapy was not significantly different after implementation. In addition, five cases of high-risk hyperbilirubinemia were identified in the post-implementation phase. The results show no difference in TcB versus visual inspection. Overall, the study concluded that universal TcB screening in the hospital was acceptable and feasible.

Broadly, eight studies, half of which were based in Canada or the United States, were identified that examined the impact of the implementation of a TcB protocol/program on clinical outcomes. Studies were of overall moderate quality, seven were pre-post designs (concurrent comparative or before-after) and one was a randomized controlled trial. With respect to clinical outcomes, six studies reported a significant reduction in the number of TSB testing following the use of TcB (ranging from 23% to 34% reduction). Of the remaining studies that reported on this outcome, similar proportions of TSB testing pre and post-implementation (6% versus 7%, respectively) with universal TcB screening were reported (51). Studies noted the number of hyperbilirubinemia and readmissions for hyperbilirubinemia was reduced with TcB testing, and this finding was statistically significant in four studies (39, 49, 96, 97). Seven of eight studies

reported reductions in the rate of phototherapy with TSB screening. However, results were mixed with three studies reporting a significant reduction and another three reporting a non-significant reduction in rates of phototherapy. One study found a reduction in the number of patients requiring exchange transfusion (98). Overall, the literature on clinical outcomes is of moderate quality.

6.2 Quality

Using the Downs and Blacks checklist, the seven non-randomized controlled trial studies had total scores of 13, 15, 16 and 17 (Table 10). All seven studies were clear in their objectives, provided estimates of random variability, and used appropriate statistical tests. None of the included studies blinded outcome assessors, or randomized participants. The full results of the quality assessment can be found in the Appendix.

Table 10. Quality Assessment for non-randomized controlled trials

Study	Quality Assessment Score (Downs and Blacks Checklist)
Bhutani (2013) (50)	16/32
Hartshorn (2010) (39)	17/32
Allen (2016) (98)	13/32
Morgan (2016) (51)	16/32
Petersen (2005) (97)	13/32
Wainer (2011) (96)	17/32
Wichremasinghe (2012) (49)	15/32

The one included RCT was of moderate quality (

Table 11. Quality Assessment for randomized controlled trial

Author	Random Sequence Generation	Allocation Concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective Reporting	Any Other Bias?
Mishra, 2009 (99)	Low	Low	Unclear	Low	Low	Unclear	Low

). It was unclear whether participants and personnel were blinded, and whether there was selective reporting, however, all other areas of bias were found to be low risk.

Table 11. Quality Assessment for randomized controlled trial

Author	Random Sequence Generation	Allocation Concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective Reporting	Any Other Bias?
Mishra, 2009 (99)	Low	Low	Unclear	Low	Low	Unclear	Low

6.3   Nomograms

Twelve studies identified the development of nomograms to help physicians determine which newborns are at risk of developing severe hyperbilirubinemia. Five of these nomograms were developed in heterogeneous populations with respect to ethnicity although Caucasians ranged from 46% to 98% of these patients (47, 56, 96, 100, 101). The seven remaining nomograms were developed in populations with 100% Caucasian, Mongolian, Hispanic, Chinese, Indian, and Thai populations. Six studies used JM-103 TcB devices, five used BiliChek, and one used OHC Photo-Ictometer, model IV. Overall, nomograms have been developed in over ten countries, reflecting the demand for context-specific nomograms that can be appropriately applied to each ethnically diverse population. Studies that have developed instruments (nomograms) have been summarized in Table 12.

Table 12. Studies reporting the validity of nomograms not included in the IHE report

Study	N	Ethnicity	TcB Measurement	Time Frame (Hours)
Akahira-Azuma (48) 2015 Japan	1137	Mongolian (100%)	Device: JM-103 TcB Performer: trained pediatrician or research technician	6 to 144
Romagnoli (47) 2012 Italy	1708	White (90.1%), Asian (4.9%), Black (2.5%), Hispanic (2.5%)	Device: OHC Photo-Ictometer, model IV) TcB Performer: Not reported	12 to 72
Wainer (96) 2012 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(100) 2006 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(56) 2009 Israel	628	Ashkenazi 33%, mix of Ashkenazi and Sephardic 24%, Sephardic 41%, Ethiopian 2%	Device: JM-103 TcB performer: NA	12 to 168
Draque (101) 2011 Brazil	223	Caucasian 46%, mixed race 34%, Black 20%,none of Asian ethnicity	Device: BiliCheck TcB performer: NA	24 to 288
De Luca(102) 2008 Italy	2198	Caucasian 100%	Device: BiliCheck TcB performer: a single fellow-neonatologist	First 96
Fouzas(103) 2010 Greece	2646	Caucasian 100%	Device: BiliCheck TcB performer: trained physicians	12 to 120
Engle(104) 2009 USA	2005	Hispanic 100%	Device: JM-103 TcB performer: nursing personnel	First 72

Yu(57) 2011 China	6035	Chinese 100%	Device: JM-103 TcB performer: trained physician	0 to 168
Mishra(105) 2010 India	625	Indian 100%	Device: BiliCheck TcB performer: a single fellow-neonatologist	First 72
Sanpavat(106) 2005 Thailand	248	Thai 100%	Device: BiliCheck TcB performer: NA	First 96

6.4 Conclusions

Overall point estimates for sensitivity ranged from 72% to 100%, and from 58% to 88% for sensitivity across all studies. As TcB was compared to the gold standard (TSB), these studies assume that TSB has perfect diagnostic accuracy (100% sensitivity and 100% specificity). Based on this assumption, TcB has poorer diagnostic accuracy than TSB. Subgroup analyses by device suggested that BiliChek is more sensitive whereas JM-103 is more specific; however, these differences were not statistically significant. Within the overall and subgroup analyses there was significant heterogeneity. There is no evidence on the safety of TcB, but it is assumed to have negligible risk due to the non-invasive nature of the testing.

Five of seven studies (39, 49, 96, 98, 99) on clinical outcomes found that TcB was associated with a significant reduction of TSB testing. Studies found a trend in reduced health care resources including TSB testing, phototherapy, and hospital readmissions. Currently, there are 12 published nomograms providing interpretation guidelines for TcB results on a variety of ethnic populations.

7 Clinician and Key Informant Interviews

Summary

- Interviews were conducted with 14 key informants to gain insight into the current BC experience with screening for hyperbilirubinemia, the use of transcutaneous bilirubinometers for screening, key factors with respect to implementation, and plans for the future

7.1 Purpose

The primary purpose is to understand the BC experience with bilirubin screening, and the use transcutaneous bilirubinometers as a screening tool for hyperbilirubinemia, in both hospital and community settings. A secondary purpose was to obtain insights from others outside of BC who have considerable experience with TcBs.

7.2 Methods

Key informant interviews were conducted to collect information about: the current bilirubin screening program; the use of TcBs as a screening tool; and to understand the current context in BC with respect to bilirubin screening. A snowball sampling method was used to identify key informants who would have valuable information with respect to the research question of interest. Eleven interviews were conducted with fourteen individuals in August and September 2016. The interviews were conducted with health professionals based in BC: one individual from BC Women's and Children's Hospital, three individuals from Perinatal Services BC, two individuals from Fraser Health, three individuals from Interior health, two individuals from

Vancouver Island Health (VIHA), and one individual with experience in Vancouver Coastal Health. We were unable to complete an interview with an individual from Northern Health. We also conducted an interview with the program regarded as the leading program in Canada for hyperbilirubinemia (the Calgary-based program). The interview participants had a range of experiences with perinatal care including: perinatal services managers and planners, physicians, clinical nurse specialists, nurse educators, a public health nurse, and a midwife.

7.3   **Findings**

7.3.1   Current standard processes of screening for hyperbilirubinemia in BC

Three health authorities have universal screening programs. Two health and the BC Women's and Children's hospital have targeted screening programs (Table 13). In health authorities with universal screening programs and no community-based TcB devices, when a newborn is discharged before 24 hours, parents make an appointment to come back to the hospital lab for a screening TSB test.

Table 13. Current status of screening strategies for hyperbilirubinemia and use of TcB

Health Authority	Screening strategy for hyperbilirubinemia	Use of TcBs and location
BC Women's & Children's Hospital (PHSA)	Targeted screening, moving towards universal screening	No current use
Interior	Universal screening	1-2 of 16 hospitals (Penticton)
Northern	Universal screening	Unknown
Fraser	Targeted screening, moving towards universal screening	All 8 hospitals
Vancouver Coastal	Targeted screening, moving towards universal screening	Some hospitals, unknown total number (e.g., Richmond General)
Vancouver Island	Universal screening	All 13 Island hospitals and all 10 public health units

7.3.2   Integration of TcB into screening for hyperbilirubinemia in BC

TcBs are being used as a screening tool in most health authorities, with the exception of the tertiary BC Women's and Children's Hospital operated by the Provincial Health Services Authority (PHSA) (Table 13). Health Authorities are in various stages of integrating TcBs into their screening program. TcBs are being used in hospitals that provide perinatal care in some Interior Health hospitals, all eight Fraser Health hospitals, and all Vancouver Island hospitals.

The only known widespread use of TcBs in the community is Vancouver Island Health Authority. The devices most commonly used are the Drager JM 103 and JM 105.

7.3.2.1 Training and education

Although use of a TcB is a simple procedure, education on the use and interpretation of the nomograms and related decisions is required. It is necessary to ensure that nurses have guidance on interpreting the results and on how to operate the device. Key informants commented that having a clinical nurse educator who could provide the needed support at the smaller sites was very helpful.

7.3.2.2 Benefits and challenges of TcB in a hospital

Key informants identified several possible benefits to implementing TcB in hospitals. There may be a reduction in the number of heel pricks required, which informants commented would be preferred by families. There may be more timely discharge from the hospital as families do not have to wait to receive the results of the TSB. In addition, the demand on laboratory services may decrease as fewer TSB tests would be required. The challenges to implementing TcB in the hospital include: cost of acquisition, calibration and ongoing maintenance of TcB, development and application of appropriate nomograms and development of "trust" in the machine results.

7.3.2.3 TcB in the Community

When newborns are discharged within 24 hours, screening for hyperbilirubinemia in the community is required to ensure that all newborns are screened within the timeframe identified as best practice within the Canadian guidelines. Adoption of TcB by public health clinics allows for this screening location to be the clinic rather than requesting that families of newborns return to the hospital or ER for TSB testing. Given that visual inspection was felt to be an inappropriate screening tool by the key informants, TcB is the only feasible way to achieve community-based screening.

Communication between the hospital and community providers was identified as a requirement for successful use of TcB in the community. Information from acute care to public health needs to be accurate, timely and precise regarding where and when follow-up is to occur. Family

physicians need to be informed that they should expect to get faxes from a particular public health clinic. This may require ongoing auditing and feedback to ensure that the healthcare system does not lose sight of a particular client. As with TcB in the hospital, cost of acquisition, calibration and ongoing maintenance of TcB, development and application of appropriate nomograms would be required.

7.3.3   *Description of exemplar comprehensive TcB screening program*

In 2007, the then Calgary Health Region (CHR) initiated the first comprehensive TcB screening program in Canada. The program utilizes the efforts of pediatricians, hospital nurses, public health nurses, and clinical laboratory services within CHR. The program committee includes a medical doctor, representation from nursing, laboratory services and an overall coordinator.

Within this screening program, all newborn infants are screened with TcB prior to discharge. Following discharge, infants should be seen by a public health nurse within 48 hours, and, if eligible, the infant should be reassessed with a transcutaneous bilirubinometer. The eligibility criteria for TcB testing includes gestation greater than or equal to 35 weeks, age less than ten days for a newborn that has not received phototherapy or exchange transfusion. Timing and frequency of these post-discharge home visits are based on identified risk factors such as feeding method, multiple pregnancy, gestational age and birth weight. The public health nurse should evaluate the eligibility criteria for TcB testing and the newborn's clinical situation at the moment of assessment and follow the appropriate guidelines. Guidelines are setup for several different clinical situations such as: the newborn has received a TcB test prior to discharge; the newborn has not received any previous TcB tests; the newborn shows high TcB measurement; the newborn shows clinical symptoms of Hyperbilirubinemia; and the newborn shows an accelerating trend of TcB measurements. Once the TcB testing has been done according to the appropriate guideline, TcB measurements are compared with the appropriate Bilirubin Risk Nomogram. The appropriate nomogram is chosen based on the gestational age and the newborn's skin tone and these nomograms are repeatedly updated to maintain high sensitivity. Further testing with TSB or TcB may be required depending on the results of the nomogram. The program guidelines are reported in detail elsewhere (107).

This program was evaluated to assess its effectiveness and has been shown that the implementation of the TcB screening program in CHR was associated with reductions in, the overall incidence of TSB draws (134.4 vs 103.6 draws per 1000 live births, $p<0.0001$), overall phototherapy rate (5.27% vs 4.30%, $p<0.0001$), average age at readmission (104.3 hours vs 88.9 hours, $p<0.005$) and average duration of phototherapy readmissions (24.8 hours vs 23.2 hours, $p<0.05$), compared to pre-implementation of the program (96). Costs were not reported.

One challenge identified was the inconsistent performance of the TcB devices. The Calgary TcB screening program has identified that 25% of the TcB devices that have been purchased by them have failed the in-house quality control process and more than 60% of devices have been returned for repair or recalibration (96). Therefore, a routine device validation process is a necessary part of a TcB program. In the Calgary program, a technologist is assigned to manage in-house quality assessments, the return of TcB devices to and from vendor for repair or recalibration and the validation process again upon receipt back from vendor.

In addition, there remain challenges with ensuring that all newborns have a public health nurse visit. With the increased demand on public health, the Calgary program is a mixture of home visits and clinic visits. There is a constant strive to ensure that no newborns are "lost" after discharge.

7.3.4   Family experience with jaundice, screening, and TcBs

Parents were not directly spoken to about the use of TcB on their newborn infants as the Patient Voices Network does not have any such members. Key informants were asked their perception of the parent's experience with the device. Key informants noted that jaundice generally causes anxiety for parents. Often newborns with jaundice are sleepy and not feeding well which causes stress in parents. Broadly, informants commented that parents would prefer to avoid multiple heel pricks. Parents also often comment on the challenge for taking their newborn infant to the hospital for blood work, so if un-necessary blood tests can be avoided it is likely that parents would view that as beneficial.

7.3.5 The role of TcBs in the future

Some experts described new research coming out that may increase the role of TcBs in the future. For example, it may be possible to use TcBs as a screening tool for hyperbilirubinemia in some pre-term infants (i.e., born at less than 37 weeks), and for use in accessing bilirubin levels post-phototherapy treatment. With the increase of home births and early discharges (i.e., <24 hrs.) from hospital, the need for effective community-based bilirubin screening is likely to increase.

8 Cost-effectiveness and Economic Impact

Summary

- A de novo cost-effectiveness analysis and budget impact analysis were completed
- In the base case, no screening program and TSB are given in hospital, TcB was the least expensive option in the hospital setting.
- When there are no additional costs to waiting in the hospital for TSB results and obtaining blood samples, TSB was the least expensive option in the hospital setting.
- Differences in outcomes (cases of kernicterus, life-years and quality-adjusted life-years) were very small.
- Cost differences depended on whether TcB was used within a newly developed screening program and whether TSB required extra time in hospital to receive results

8.1 Methods

8.1.1 Economic Model

Simple decision models were created to compare screening with TcB to TSB and visual assessment (Figure 7). Two transcutaneous bilirubinometers (BiliChek and JM-105) were compared. The primary outcome for the model is the cost per quality-adjusted life year (QALY) gained. Other outcomes considered in the model included costs per patient (total and diagnostic only), life years (LYs) gained, and numbers of correctly diagnosed, false negative, and kernicterus cases. The economic evaluation by Xie et al (29) was adapted, as it incorporates clinical outcomes beyond kernicterus such as QALYs, is transparent with respect to the structure of the model as well as input values, and is a Canadian model.

Figure 7. The overview of the model
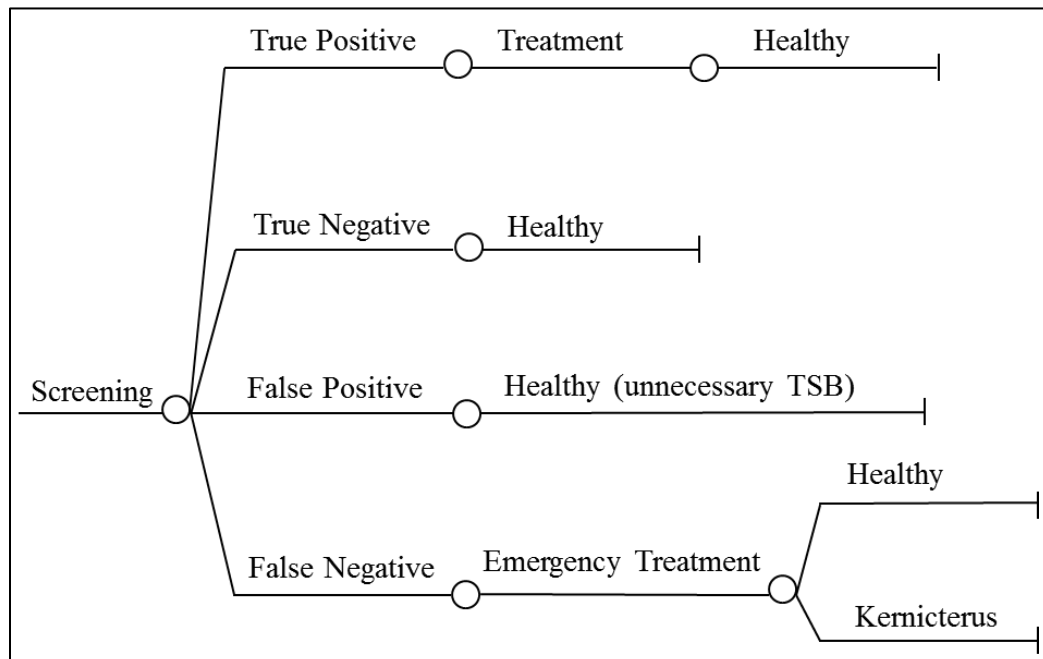
8.1.2   Model Inputs

8.1.2.1   Perspective, Target Population, and Time Horizon

The perspective of the publically funded health care system is adopted. The target population is term and late-term (≥35 weeks) infants who are eligible for screening with TcB. The time horizon adopted is a lifetime horizon.

8.1.2.2   Clinical Accuracy

Screening accuracy for the various comparators were obtained from the clinical review (Section 6) and the reviewed economic literature (Table 14). The studies included in the review of diagnostic accuracy were meta-analyzed using a random effects model to obtain pooled estimates of sensitivity and specificity for TcB (BiliChek and JM-103). The meta-analysis showed that the sensitivity and specificity of the devices is not statistically different. In the base case analysis, the pooled estimate was used for BiliChek and JM-103. Estimates for visual assessment came from a previous analysis by the UK's National Institute for Health and Care Excellence (NICE). TSB is assumed to be the Gold Standard and to have perfect accuracy. Diagnostic accuracy data was based on JM-103 not JM-105; however, it was assumed the sensitivity and specificity has not

changed. This was confirmed by the manufacturer that indicated that they expected the accuracy to be similar.

Table 14. Screening accuracy

Comparators	Sensitivity (95%CI)	Specificity (95%CI)	Reference
Visual Assessment	0.76	0.60	NICE, 2010(34)
TcB BiliChek	0.86 (0.74-0.92)	0.76 (0.68-0.82)	Pooled data (page 39)
TcB JM-105	0.86 (0.74-0.92)	0.76 (0.68-0.82)	Pooled data (page 39)
TSB	1.00	1.00	Gold standard

The rate of hyperbilirubinemia and the rate of kernicterus was the same for all comparators (Table 15). The rate of kernicterus used in the model was 0.00002 per birth: i.e. one in 50,000(7). The model assumes identification of hyperbilirubinemia at screening prevents the development of kernicterus. However, this does not account for those patients who test negative for hyperbilirubinemia and later develop kernicterus beyond the first screening assessment. It is clear that some newborns will still develop hyperbilirubinemia and will need follow-up; however, those with low bilirubin at the time of measurement, who might go on to have hyperbilirubinemia, will be the same for all of the tests. Therefore, we focused on the possible benefits of accurate diagnosis and assumed there would be no difference in the later development. The mortality rates for kernicterus and treatment with exchange transfusion did not differ across tests and were also obtained from the literature Table 15.

Table 15. Clinical inputs used in the economic evaluation (%)

Input	Value	Reference
Rate of hyperbilirubinemia	4.8 (126 per 2,620 infants)	Xie et al, 2010(29)
Rate of exchange transfusion	3 (3 in 8,640 infants)	Xie et al, 2010(29)
Mortality rate of exchange transfusion	0.003 (3 per 1000 infants)	Ip et al, 2004(5)
Mortality rate of kernicterus	10 (8 per 82 infants)	Ip et al, 2004(5)
Rate of kernicterus	0.00002 (1 in 50,000 births)	Sgro et al, 2006(7)

8.1.2.3   Costs

There were 43,101 births in the 52 BC hospitals with planned obstetrical services in 2014/2015 (excluding 1,417 with midwives at home). This suggests an average of 829 babies per hospital

that are eligible for screening for hyperbilirubinemia per year. Based on personal communication with the manufacturers/suppliers of JM-105 and BiliChek, TcB devices were able to be linked to 18 hospitals in BC (108, 109). The average number of babies per device in these hospitals was 546. Draeger also noted that a high capacity department may deliver 7000 babies a year and the only limiting factors are that the JM-105 can take approximately ▮▮▮▮ readings on a full charge and how the use of the device is organized within a department (108). NICE conducted a review of TcB devices and noted it was difficult to obtain data on TcB in primary setting; in their review, based on expert opinion, they assumed one meter per every 500 births (34). Quebec's review of TcB devices assumed that institutions of birth in Quebec (health centres) follow 500 infants per year and that two devices per institution would be needed with a range of one to four (31). The Calgary Health Region initiated the first comprehensive TcB screening program in Canada and results of this program have been published (96). The study noted there was a pool of 42 devices in regular circulation and a total of 16,879 births post-TcB implementation. This is an average of 402 babies per TcB device over the TcB implementation period. Overall, there is a wide range and uncertainty around the number of babies that can screened per TcB device.

In the current decision models, it was assumed one TcB meter per 402 babies was needed and at least one TcB meter will be purchased at a hospital with planned obstetrical services. The average number of babies per device was selected as the base case as it is based on results from implementing a TcB program in Canada and aligns with the average based on hospitals in BC with TcB devices. Overall, it is a conservative assumption to assume a lower capacity of volume for TcB devices.

In order to account for the cost of the device and maintenance over the device's lifespan, TcB screening test costs were averaged over the number of babies in each hospital. McArthur Medical which distributes the Phillips BiliChek and Draeger the manufacturer of JM-103 and JM-105 were contacted for further information with respect to costs, device maintenance, and consumables (108, 109). Both McArthur Medical and Draeger noted quantity discounts are available based on the volume purchased. For BiliChek consumable tips, a volume discount would apply once the number of units are established.

To calculate the annual unit cost of the TcB meters, the costs of the bilirubinometer, accessories such as batteries, service contracts, and yearly calibrations were averaged over the device's lifetime of five years. The cost per screening test was averaged over 402 newborns and the cost per use of flush wipes (and calibration tips for the BiliChek device) was incorporated.

It was assumed the nursing time required for screening and interpretation of screening results was equivalent across the various comparators and that all patients who tested positive for hyperbilirubinemia received an outpatient post-discharge TSB.

For the cost per screening test for TSB, we included the costs of obtaining a blood specimen, gloves, and additional time in hospital for patients to wait for TSB screening results. It is important to note that the cost of obtaining blood specimens may change depending on the volume of work, level of automation, and staff's experience (31). Hospital cost was obtained from the Patient Cost Estimator by the Canadian Institute for Health Information (110) based on the Case Mix Group (CMG) in British Columbia for "594 Newborn/Newborn 2500+ grams, Jaundice". This CMG had an estimated average cost of $1,587 and acute length of stay of 1.5 days. In the base case model, it was assumed patients screened with TSB had an additional in-hospital stay of five hours compared to other screening techniques, although not all hospitals require patients to wait for their TSB results so this assumption was tested in the scenario analysis. All costs are in 2016 Canadian dollars. It was assumed there would be no additional costs for visual assessment as it is part of routine care while the costs per screening test for BiliChek, JM-105, and TSB are $8.14, $7.92, and $246.91.

Table 16. Cost calculations for screening techniques

	TcB BiliChek	TcB JM-105	Reference(s)
Device lifetime (years)	5	5	Expert opinion
Cost of bilirubinometer	■	■	Drager(108), McArthur Medical(109)
Batteries	-	■ &	Quebec, 2000(31)
Service contract[*]	-	■	Quebec, 2000(31)
Yearly calibration	-	■	Drager(108)
Flush wipes	0.15	0.15	NICE, 2010(34)
Calibration tip	■	-	McArthur Medical(109)
Cost per use	■	0.15	
Annual cost[**]		■	
Cost per screening test (TcB)	*8.14*	*7.92*	

	TSB	
Cost of total serum bilirubin test	1.61	BC Schedule of Fees(111)
Cost of obtaining blood specimen	24.76	Quebec, 2000(31)
Cost of glove	0.12	NICE, 2010(34)
Cost of extra hospital stay	220.42	CIHI Patient Cost Estimator(110)
Cost per screening test (TSB)	*246.91*	

&Replacement every two years required(108)

*Assuming instrument under warranty during the first year and there are no maintenance fees

**[Cost of JM 105 (▮▮▮▮) + Battery cost (▮▮▮▮) X the number of batteries needed over 5 years (2.5) since need to be replaced every 2 years + cost of the service contract i.e. maintenance fees (▮▮▮▮) X the number of years out of 5 needed (4) since the first year it is under warranty]/ the number of years of use (5)

Resource use and clinical outcomes as well as their associated costs were included in the model (Table 17). Costs included visits for follow-up, emergency room visits, and readmission. Treatment for hyperbilirubinemia and kernicterus included phototherapy and exchange transfusion. The lifetime medical cost for kernicterus was obtained from the literature and has been previously utilized in economic evaluations for approaches to prevent kernicterus (29).

Table 17: Cost inputs used in the economic evaluation

Costs	Value ($)	Reference
Screening technique		
Visual Assessment	0.00	Assumption
TcB BiliChek	8.14	See Table 16
TcB JM-105	7.92	See Table 16
TSB	246.91	See Table 16
Outcomes		
Hospital Stay	1,587.00	CIHI Patient Cost Estimator(110)
Kernicterus	1,329,388.71	Xie et al, 2010(29)
Follow-up Visit by Pediatrics	219.2	BC Schedule of Fees(111)
Phototherapy	2220.61	Xie et al, 2010(29)
Exchange Transfusion	9,825.87	Xie et al, 2010(29)
Bilirubin measurement at follow-up	5.52	Xie et al, 2010(29)
Emergency room visit	127.77	BC Schedule of Fees(111)
Readmission	3,240.34	Xie et al, 2010(29)

8.1.2.4   Utilities

There were three separate health states within the model: healthy, kernicterus, and dead (Table 18). The utilities for the healthy and kernicterus states were extracted from literature from de Lissovoy et al (112) and Werner et al (113); the utility for kernicterus was 0.401, healthy was 1,

and dead (from either kernicterus or treatment with exchange transfusion) was 0. The average life expectancy in British Columbia was 82.63 years (114). The life expectancy for a severely disabled child was assumed to be 40 years.(115) Quality-adjusted life-years (QALYs) are calculated by multiplying the life expectancy and the expected health related quality of life (utility) over their life. The estimated QALY for a child with kernicterus was 16.04, meaning that the 40-year life expectancy with kernicterus is equivalent to 16.04 years of perfect health. The estimated difference in QALYs between a child with kernicterus and a healthy child was 66.59 QALYs.

Table 18. The life-expectancy, utilities and QALYs associated with each health state

	Life Expectancy	Utility	Quality-adjusted Life-Years
Kernicterus	40	0.401 (SD = 0.106)	16.04
Healthy	82.63	1	82.63
Dead	0	0	0

8.1.3 Uncertainty Analysis

Sensitivity analyses were run on the sensitivity and specificity of transcutaneous bilirubinometers, visual assessment and TSB:

1. Utilizing the 95% CIs associated with pooled results of transcutaneous bilirubinometers
2. 0.01 change in sensitivity/specificity

Other sensitivity analyses included varying:

1. The price of the transcutaneous bilirubinometer device
2. The lifespan of bilirubinometer
3. The number of extra hospital stay hours associated with TSB
4. The number of extra hospital stay hours and cost of obtaining blood specimen associated with TSB
5. The mortality rate of kernicterus
6. The number of eligible newborns for screening to reflect varying sizes of hospitals
7. The utility values of health states

Scenario analyses were conducted incorporating the cost of implementation and management of a full TcB screening program, similar to that currently in place in Calgary, Alberta (

Table 19). It was assumed that each health region would have their own program that undertook quality assurance and updated the nomogram. These costs were incorporated into costs for BiliChek and JM-105.

Table 19. Implementation Cost inputs of full TcB program

Full TcB program			
	FTE	Salary per year ($)	Annual cost ($)
Medical Director	0.5	150,000	75,000
Technologist	0.5	60,000	30,000
Public Health Nurse	0.5	64,000-74,000	34,500
Acute Care Nurse	0.5	58,831.50-78,000	34,208
Manager	1	60,000	60,000
Total costs per program	233,707.88		
Cost per screening test	27.11		
Full TcB program with public health nurse follow-up visit			
Public Health Nurse	1	64,000-74,000	69,000
Total costs per program	302,707.88		
Cost per screening test*	35.12		
Number of regions	5		
Number of births	43,101		

*total costs multiplied by the number of regions (1 program per region) divided by the number of babies born in the province

8.2 Results

Total costs results from the base case suggest the cost per patient is lowest when screening with JM-105 ($233.25) and highest with TSB ($379.45) (

Table 20). The total costs include the per patient screening cost, the cost of diagnosis and the cost of treatment. Tests that have more false negatives have higher treatment costs due to the higher rate of kernicterus associated with a false negative. False negatives also result in higher diagnostic costs as missed diagnoses result in additional emergency room visits and admissions. Screening and diagnostic costs including TSB bilirubin measurement at follow-up accounted for

33-65% of total costs per patient with screening techniques; visual assessment had the lowest and TSB had the highest associated screening costs.

Results of the base case analysis suggested JM-105 was the least costly and most effective screening technique compared with BiliChek and visual assessment when comparing total costs, diagnostic costs, incremental cost per kernicterus case, incremental cost per correctly diagnosed case, incremental cost per false negative avoided, incremental cost-effectiveness ratio (cost/LY gained), and incremental cost-utility ratio (cost/QALY gained). The total costs were lowest with JM-105, followed by BiliChek, visual assessment, and TSB.

The benefits were almost equivalent with all screening techniques (

Table 20). The overall benefits with respect to LYs and QALYs across screening techniques were the same at 82.63 LY/QALY per patient. There were no false negative cases with TSB and there were 2.7 with JM-105 and BiliChek and 4.6 with visual assessment. The probability of kernicterus was 0.000012 (1.2 in 100,000) with JM-105 and BiliChek and 0.00002 (2 in 100,000) with visual assessment.

Although there were very small differences in the probability of kernicterus, results suggest that health benefits (LYs and QALYs) are equivalent across screening techniques, therefore, minimizing costs was the key outcome of the economic evaluation. The least costly and therefore the cost-effective option was the JM-105 (Table 20).

Table 20. Cost and benefit results for visual assessment, BiliChek, JM-105, and TSB

	Visual Assessment	BiliChek	JM-105	TSB
Costs and benefits per patient				
Screening cost	$0.00	$8.14	$7.92	$246.91
Diagnostic cost	$105.94	$68.30	$68.31	$0
Treatment cost	$182.98	$157.03	$157.02	$133.45
Total cost	$288.92	$233.47	$233.25	$379.45
Probability of being FN	0.011520	0.006720	0.006720	0.00
Probability of Kernicterus	0.00002	0.000012	0.000012	0.00
LYs	82.63	82.63	82.63	82.63
QALYs	82.63	82.63	82.63	82.63

Results of sensitivity analyses are presented in Table 21. As sensitivity and specificity, i.e. accuracy, is dependent on the nomogram used, sensitivity analyses were conducted on the accuracy for the various screening techniques. Diagnostic accuracy values, based on the pooled results stratified by device, suggested lower total cost per patient for BiliChek and higher for JM-105. However, the overall results were not sensitive (<10% change in total cost per patient) to changes in sensitivity and specificity values for the various screening techniques.

With respect to the price of TcB devices, as there are quantity discounts associated with volume purchases of devices, the price of TcB devices was lowered to $██████ and $██████. Total cost per patient for BiliChek and JM-105 were insensitive to changes in this input. Similar results were seen in varying the lifespan of TcB devices. A lower mortality rate associated with kernicterus had little impact on total cost per patient for the various screening techniques.

As there is uncertainty in TSB related costs with respect to the number of additional hospital stay hours needed to obtain TSB bilirubin screening results or the costs of obtaining blood specimen, a sensitivity analysis was conducted removing these costs. When no costs for hospital stays associated with TSB pre-discharge was considered, the total cost per patient was reduced for all comparators since all comparators diagnose with TSB. This scenario resulted in TSB having the lowest total costs per patient of $148.45. Removing the cost of taking a blood specimen in addition to hospital stay hours decreased the cost of all comparators further, but had the largest effect on the TSB arm resulting in a per patient cost of $122.51. These scenarios represent a situation in which hospitals do not require the newborn to stay in the hospital until the TSB result is returned and where other blood tests are being done at the same time as the TSB, so there is no additional cost of obtaining the blood specimen.

Results were sensitive to the number of newborns screened which reflected the varying sizes of hospitals in British Columbia. When considering the lowest number of newborns delivered in a hospital in British Columbia (n=5), visual assessment had the lowest total costs with $288.92 and JM-105 had the highest with $850.02. JM-105 was the preferred option when considering screening 201 newborns (half the base estimate), 804 newborns (double the base estimate), and the highest number of newborns delivered in a hospital in British Columbia (n=7,125). This reflects the difference in the fixed costs (higher for JM-105) and the variable costs (higher for

BiliChek). If more babies are tested then the fixed prices are less important and the variable

costs are more important.

Table 21. Results of sensitivity analyses for visual inspection, BiliChek, JM-105, and TSB

| | VI | TcB | | TSB |
		BiliChek	JM-105	
Base case total costs per patient	$288.92	$233.47	$233.25	$379.45
Sensitivity				
Upper 95%CI (0.92) to TcB	--	$217.88	$217.67	--
Lower 95%CI (0.74) to TcB	--	$264.64	$264.43	--
-0.01 change	$290.52	$235.47	$235.26	$382.01
Specificity				
Upper 95%CI (0.82) to TcB	--	$219.36	$219.15	--
Lower 95%CI (0.68) to TcB	--	$252.27	$252.06	--
-0.01 change	$291.27	$235.82	$235.60	$381.80
Pooled results for BiliChek (sensitivity=0.94, specificity=0.74)	--	$217.38	$217.17	--
Pooled results for JM-105 (sensitivity=0.83, specificity=0.75)	--	$243.61	$243.40	--
Price of TcB Device				
███	--	$232.97	$231.91	--
███	--	$233.47	$232.41	--
Lifespan of TcB Device				
6 years	--	$232.89	$232.59	--
8 years	--	$232.16	$231.76	--
TSB related costs				
No costs for hospital stay	$196.94	$174.01	$173.79	$148.45
No costs for hospital stay and obtaining blood specimen	$186.61	$167.33	$167.12	$122.51
Mortality rate of kernicterus				
4%	$290.51	$234.40	$234.18	$379.45
Eligible newborns				
Half (201)	--	$241.02	$236.95	--
Double (804)	--	$231.72	$229.37	--
Lowest number of newborns per hospital (5)	--	$509.98	$850.02	--
Highest number of newborns per hospital (7,125)	--	$230.18	$225.92	--

Results of the scenario analyses for incorporating the cost of implementation and management of a full TcB screening program in hospital increased total cost per patient to $260.36 for JM-105 and $260.58 for BiliChek. These costs represent an increase of $27.11 per patient for both TcB devices. Similar results were seen with implementation and management of a full TcB screening program in the community. The total cost per patient was $268.37 for JM-105 and $268.58 for BiliChek, representing an increase in $35.12. The program in the community is more expensive because it requires additional Public Health Nurse time and additional devices.

8.3   Budget Impact Analysis Results

There are 52 hospitals with planned obstetrical services in British Columbia, of which 34 were linked to a specific JM-103/105 or BiliChek device. Based on the jurisdictional scan there are a total of 70 TcB devices; however, 36 devices are not linked to any hospital, a conservative assumption was taken assuming hospitals do not have a device if there was no evidence of a device being available. The budget impact analysis was conducted with the introduction of JM-105, given that this was the less costly and equivalently effective TcB in the cost-effectiveness analysis. The time horizon in the budget impact analysis was six years to reflect the lifespan of TcB devices (5 years) in addition to a year of purchasing new TcB devices. Taking into account the currently known devices, it was assumed 108 additional devices are needed in total to cover all hospitals in British Columbia. This is based on the assumption that one device is needed per every 402 newborns, the average number of newborns per TcB device utilized previously in the cost-effectiveness analysis. Overall, 127 devices are needed across British Columbia to screen the entire population of newborns. At 6 years it was assumed that 127 new devices would need to be purchased.

At a minimum, it was assumed each hospital with planned obstetrical services would purchase one TcB device (JM-105) at $ per device, which includes the price for accessories such as batteries and the yearly calibration fee. The maximum number of TcB devices that would be purchased to ensure one TcB meter per 402 births was 18 for BC Women's Hospital & Health Centre which would cost $ for the initial devices and its first year implementation costs. At the regional health authority level, the range of TcB devices that would need to be purchased

was 14 (Northern) to 38 (Fraser), which resulted in initial annual device costs of $███████ to $██████, respectively.

Total costs in the budget impact analysis included costs for device, screening (TcB wipes, hospital stay and blood specimen for TSB), diagnostics (TSB bilirubin pre and post-discharge), treatment (phototherapy and exchange), visits for follow-up, readmission (emergency room and readmission), and kernicterus. Unit costs for these categories as well as sensitivity and specificity values were based on those previously utilized in the cost-effectiveness analysis. It was assumed the cost of kernicterus was equally distributed over the life expectancy of patients with kernicterus.

The overall results of the budget impact analysis by regional health authority are presented in

Table 22. The incremental six-year budget impact with JM-105 TcB devices for all of BC in the hospital setting was estimated to be cost-savings with $30,017,337. Compared with the reference scenario in hospitals where TSB and JM-105 is currently being utilized, JM-105 resulted in incremental cost savings over six years, ranging from $1,221,308 in Vancouver Island and $12,441,604 in Fraser. Cost savings are reflective of the size of the population served by the regional health authorities.

Table 22. Budget impact results of JM-105 compared with current care (combination of TSB and JM-105)

Regional Health Authority	Budget Impact	Current Care	JM-105	*Incremental*
Vancouver Island	1-Year	████	████	-$165,632
	6-Year			-$1,221,308
Vancouver Coastal	1-Year			-$1,528,383
	6-Year			-$10,056,936
Northern	1-Year			-$261,515
	6-Year			-$1,943,894
Fraser	1-Year			-$1,865,381
	6-Year			-$12,441,604
Interior	1-Year			-$606,353
	6-Year			-$4,353,595
British Columbia	1-Year			-$4,427,264
	6-Year	████	████	-$30,017,337

Results broken down for each regional health authority and by cost categories are presented in Table 23, Table 24, Table 25, Table 26, and Table 27. Trends based on cost categories are similar across all regional health authorities with varying magnitudes in budget impact based on unique characteristics of each regional health authorities (number of babies born per institutions, number of hospitals, current number of TcB devices). Device costs are higher with implementing JM-105, however, device costs are incurred in current care as some hospitals in each regional health authority have TcB devices in place. Device costs for implementing JM-105 incorporate costs for yearly maintenance of all devices (current and new) in addition to the purchasing of all devices in the sixth year. It is important to note, as TSB has perfect accuracy and JM-105 has lower accuracy, there are greater costs of diagnostics, follow-up, readmission, treatment, and kernicterus costs associated with implementing JM-105. Taking into consideration costs for screening versus treatment for JM-105 and TSB, there are overall cost savings with implementing JM-105 in all hospitals in all regional health authorities.

Table 23. Budget impact results of JM-105 compared with current care (combination of TSB and JM-105) by cost category for Vancouver Island

Vancouver Island

1 Year

Budget Impact	Devices	TcB per Use[*]	TSB - Hospital Stay	TSB per Use[^]	Diagnostics[&]	Follow-up	Readmission	Treatment[%]	Kernicterus	Total
Current	■	$694	$314,367	$35,314	$316,846	$6,630	$101,869	$715,617	$20	■
JM-105	■	$914	$0	$0	$394,991	$8,731	$134,150	$715,617	$26	■
1-Year Incremental	-$165,632									

6 Years

Budget Impact	Devices	TcB per Use[*]	TSB - Hospital Stay	TSB per Use[^]	Diagnostics[&]	Follow-up	Readmission	Treatment[%]	Kernicterus	Total
Current	■	$4,163	$1,886,200	$211,882	$1,901,074	$39,778	$611,213	$4,293,704	$422	■
JM-105	■	$5,482	$0	$0	$2,369,945	$52,384	$804,900	$4,293,704	$556	■
6-Year Incremental	-$1,221,308									

[*]Flush wipes per use; [^]Costs of obtaining blood specimen, TSB test, and glove; [&]Costs of pre- and post-discharge confirmatory TSB; [%]Cost of phototherapy and exchange transfusion

Table 24. Budget impact results of JM-105 compared with current care (combination of TSB and JM-105) by cost category for Vancouver Coastal

Vancouver Coastal

1 Year

Budget Impact	Devices	TcB per Use[*]	TSB - Hospital Stay	TSB per Use[^]	Diagnostics[&]	Follow-up	Readmission	Treatment[%]	Kernicterus	Total
Current	■	$310	$2,391,652	$268,661	$262,508	$2,960	$45,480	$1,552,698	$9	■
JM-105	■	$1,983	$0	$0	$857,024	$18,943	$291,069	$1,552,698	$57	■
1-Year Incremental	-$1,528,383									

6 Year

Budget Impact	Devices	TcB per Use[*]	TSB - Hospital Stay	TSB per Use[^]	Diagnostics[&]	Follow-up	Readmission	Treatment[%]	Kernicterus	Total
Current	■	$1,859	$14,349,912	$1,611,964	$1,575,048	$17,759	$272,882	$9,316,185	$188	■

Budget Impact	Devices	TcB per Use*	TSB - Hospital Stay	TSB per Use^	Diagnostics&	Follow-up	Readmission	Treatment%	Kernicterus	Total
JM-105	▉	$11,895	$0	$0	$5,142,144	$113,659	$1,746,416	$9,316,185	$1,206	▉
6-Year Incremental	-$10,056,936									

*Flush wipes per use; ^Costs of obtaining blood specimen, TSB test, and glove; &Costs of pre- and post-discharge confirmatory TSB; %Cost of phototherapy and exchange transfusion

Table 25. Budget impact results of JM-105 compared with current care (combination of TSB and JM-105) by cost category for Northern

Northern										
1 Year										
Budget Impact	Devices	TcB per Use*	TSB - Hospital Stay	TSB per Use^	Diagnostics&	Follow-up	Readmission	Treatment%	Kernicterus	Total
Current	▉	$171	$493,513	$55,438	$100,242	$1,629	$25,033	$403,870	$5	▉
JM-105	▉	$516	$0	$0	$222,920	$4,927	$75,710	$403,870	$15	▉
1-Year Incremental	-$261,515									
6 Year										
Budget Impact	Devices	TcB per Use*	TSB - Hospital Stay	TSB per Use^	Diagnostics&	Follow-up	Readmission	Treatment%	Kernicterus	Total
Current	▉	$1,023	$2,961,078	$332,626	$601,454	$9,775	$150,197	$2,423,222	$104	▉
JM-105	▉	$3,094	$0	$0	$1,337,517	$29,564	$454,258	$2,423,222	$314	▉
6-Year Incremental	-$1,943,894									

*Flush wipes per use; ^Costs of obtaining blood specimen, TSB test, and glove; &Costs of pre- and post-discharge confirmatory TSB; %Cost of phototherapy and exchange transfusion

Table 26. Budget impact results of JM-105 compared with current care (combination of TSB and JM-105) by cost category for Fraser

Fraser										
1 Year										
Budget Impact	Devices	TcB per Use*	TSB - Hospital Stay	TSB per Use^	Diagnostics&	Follow-up	Readmission	Treatment%	Kernicterus	Total
Current	▉	$241	$2,969,285	$333,548	$263,734	$2,301	$35,348	$1,815,062	$7	▉
JM-105	▉	$2,318	$0	$0	$1,001,838	$22,144	$340,252	$1,815,062	$67	▉
1-Year Incremental	-$1,865,381									

6 Year										
Budget Impact	Devices	TcB per Use[*]	TSB - Hospital Stay	TSB per Use[^]	Diagnostics[&]	Follow-up	Readmission	Treatment[%]	Kernicterus	Total
Current	▮	$1,445	$17,815,712	$2,001,287	$1,582,407	$13,803	$212,091	$10,890,374	$146	▮
JM-105	▮	$13,905	$0	$0	$6,011,030	$132,864	$2,041,514	$10,890,374	$1,410	▮
6-Year Incremental	-$12,441,604									

[*]Flush wipes per use; [^]Costs of obtaining blood specimen, TSB test, and glove; [&]Costs of pre- and post-discharge confirmatory TSB; [%]Cost of phototherapy and exchange transfusion

Table 27. Budget impact results of JM-105 compared with current care (combination of TSB and JM-105) by cost category for Interior

Interior										
1 Year										
Budget Impact	Devices	TcB per Use[*]	TSB - Hospital Stay	TSB per Use[^]	Diagnostics[&]	Follow-up	Readmission	Treatment[%]	Kernicterus	Total
Current	▮	$135	$1,140,462	$128,111	$119,884	$1,294	$19,890	$730,816	$4	▮
JM-105	▮	$933	$24,713	$2,776	$404,709	$8,916	$136,999	$744,353	$27	▮
1-Year Incremental	-$606,353									
6 Year										
Budget Impact	Devices	TcB per Use[*]	TSB - Hospital Stay	TSB per Use[^]	Diagnostics[&]	Follow-up	Readmission	Treatment[%]	Kernicterus	Total
Current	▮	$813	$6,842,772	$768,667	$719,305	$7,767	$119,338	$4,384,896	$82	▮
JM-105	▮	$5,599	$148,277	$16,656	$2,428,251	$53,496	$821,995	$4,466,118	$568	▮
6-Year Incremental	-$4,353,595									

[*]Flush wipes per use; [^]Costs of obtaining blood specimen, TSB test, and glove; [&]Costs of pre- and post-discharge confirmatory TSB; [%]Cost of phototherapy and exchange transfusion

A scenario analysis was undertaken assuming that there are no additional costs with TSB for the extra time in hospital waiting for the TSB results or for obtaining the blood specimen (Table 28). This resulted in JM-105 being more costly than TSB at every year. The incremental six-year budget impact with JM-105 TcB devices for all of BC in this scenario was $18,221,870. In the first year the budget impact for JM-105 ranged from an increased cost of $170,273 in Vancouver Island to $1,414,148 in Fraser. The six-year budgetary impact in this reference scenario for JM-105 ranged from an increased cost of $828,204 in Vancouver Island to $7,235,572 in Fraser.

Table 28. Budget impact results of JM-105 compared with current care (combination of TSB and JM-105) at lower TSB costs

Regional Health Authority	Budget Impact	Current Care	JM-105	*Incremental*
Vancouver Island	1-Year			$170,273
	6-Year			$828,204
Vancouver Coastal	1-Year			$1,113,159
	6-Year			$5,792,318
Northern	1-Year			$283,563
	6-Year			$1,326,570
Fraser	1-Year			$1,414,148
	6-Year			$7,235,572
Interior	1-Year			$625,781
	6-Year			$3,039,206
British Columbia	1-Year			$3,606,923
	6-Year			$18,221,870

Budget impact results for all of BC for the various scenarios (TSB costs, TSB costs without hospital stay and obtaining blood specimen) as well as per hospital are presented in the Appendix.

8.4   Conclusions

Overall, there are very little differences in benefits with the screening techniques because of the rarity of kernicterus and the low probability of death from kernicterus or treatment with exchange transfusion. Although the clinical benefits are very similar, there is still benefit in understanding these differences and in minimizing costs associated with the screening techniques. JM-105 is less costly and more effective compared with visual assessment. Compared with BiliChek, JM-105 is less costly and has equivalent benefits with respect to kernicterus cases, correctly diagnosed patients, and long-term outcomes of LYs/QALYs. Both of the TcB devices are less costly and less effective than TSB when it is assumed that patients must wait for TSB results i.e. increasing the time in hospital. When patients do not have to wait for TSB results in the hospital, TcB devices are costlier and less effective. In this scenario TSB is the preferred screening option.

Given the current guidelines to test all newborns pre-discharge, the comparison of TcB with TSB is relevant for making a decision about whether TcB should be used in the hospital. The results of this analysis demonstrate that the difference in cases of kernicterus and QALYs are very small. The analysis also demonstrates that TcB is less expensive if newborns are required to stay in the hospital to receive their TSB results.

As outcomes with respect to clinical benefits are almost identical, there is potential benefit in minimizing costs associated with the screening techniques. JM-105 is overall less costly compared with BiliChek, despite costs associated with the device (batteries, yearly calibration, and service contract); BiliChek consumable costs per use are 33% more than JM-105 due to the cost of calibration tips. Whether TcB devices are less costly than TSB depends on the assumptions regarding hospital stay.

It is important to note that the sensitivity and specificity of a screening technique is dependent on the nomogram used to interpret bilirubin levels. These values are adjusted depending on thresholds used in the associated nomogram, and nomograms may be updated to be local program specific. In the models, modifying the specificity of screening techniques impacted total costs more than sensitivity; however, the difference in cost was small. The low cost but higher

probability of false positive rates resulted in similar costs to the high cost, but a low probability of being false negative. This sensitivity analysis suggests that improving the specificity is as important as improving the sensitivity in terms of total costs.

There are some limitations with the economic model. Informal care costs are not taken into account with any of these models. Long-term outcomes only considered kernicterus mortality and quality of life and mortality from exchange transfusions. Short-term outcomes during hospitalization and morbidity associated with treatment were not included. Some of the costs were from other provinces which may limit the applicability to the BC context.

In the economic model it was assumed each patient is screened once by either visual assessment, TcB, or TSB. It is important to note that screening with TcB may involve multiple tests (multiple measurements dependent on hour-specific nomograms) and when implemented, the frequency of use increases. Both JM-105 and BiliChek have costs per use (consumables of flush wipes and calibration tips) which would result in greater total costs with greater frequency of TcB measurements per patient. Overall, JM-105 would remain the preferred option compared with BiliChek given the lower total costs and cost per use per patient.

9   Conclusions

Overall, TcB appears to be an effective screening tool for identifying hyperbilirubinemia, with sensitivity ranging from 72% to 100% and specificity ranging from 58% to 88%. It has poorer diagnostic accuracy than TSB, but is better compared to visual assessment. Results from the cost-effectiveness model suggest that the use of TcB as a screening tool is good value for money. Based on the model, the accuracy of the screening devices did not affect the LYs or QALYs. JM-105 was the least costly, followed by BiliChek, visual assessment, and TSB. However, TSB was the least costly option if it was assumed that there was no additional cost due to waiting in the hospital and no cost of taking the blood sample.

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10 Appendix

Search Strategies

MEDLINE (OVID Interface), CENTRAL (OVID Interface)
1. exp infant/
2. (neonat* or infant* or newborn* or maternity ward or newborns or newborn).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="2012-current"

EMBASE (OVID interface)
1. exp infant/
2. (neonat* or infant* or newborn* or maternity ward or newborns or newborn).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="2012-current"

CRD Databases (DARE, HTA & NHS EED)
1. (bilirubin*) FROM 2012 to current

CINAHL (Ebsco Database)
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: 20120101-20160631

Web of Science
#1 TS=(neonat* or infant* or newborn* or maternity ward
     or newborns or newborn)
#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=2012-curren

Table 1: Detailed Results of Quality Assessment of Diagnostic Accuracy Studies using the QUADAS-2 Tool

Domain	Questions for risk of bias	Bhutani	Kolman	Wickre-masinghe	Ho	Kaplan	Bental	Yu	Mohamed	Taylor
Patient selection	Was a consecutive or random sample of patients enrolled?	Unclear	×	Unclear	√	√	×	√	√	√
	Was a case-control design avoided?	√	√	√	√	√	√	√	√	√
	Did the study avoid inappropriate exclusions?	√	×	Unclear	√	√	√	√	√	√
	Risk of bias	Unclear	High	Unclear	Low	Low	High	Low	Low	Low
Index test	Were the index test results interpreted without knowledge of the results of the reference standard?	√	√	Unclear	√	√	√	√	√	√
	If a threshold was used, was it pre-specified?	√	√	Unclear	√	×	×	√	√	√
	Risk of bias	Low	Low	Unclear	Low	High	High	Low	Low	Low
Reference standard	Is the reference standard likely to correctly classify the target condition?	√	√	√	√	√	√	√	√	√
	Risk of bias	Low	Low	Low	Low	Low	Low	Low	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?	×	√	Unclear	Unclear	√	√	√	√	√
	Risk of bias	High	Low	High	High	High	Low	High	Low	Low

Figure 1: Forest Plot Subgroup Analysis by Device Type

A. Bilicheck Devices
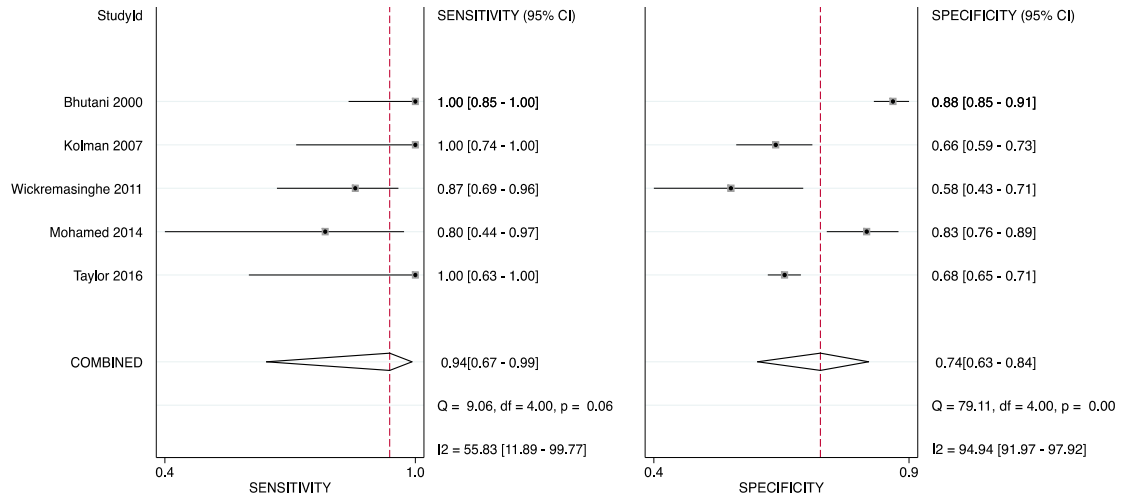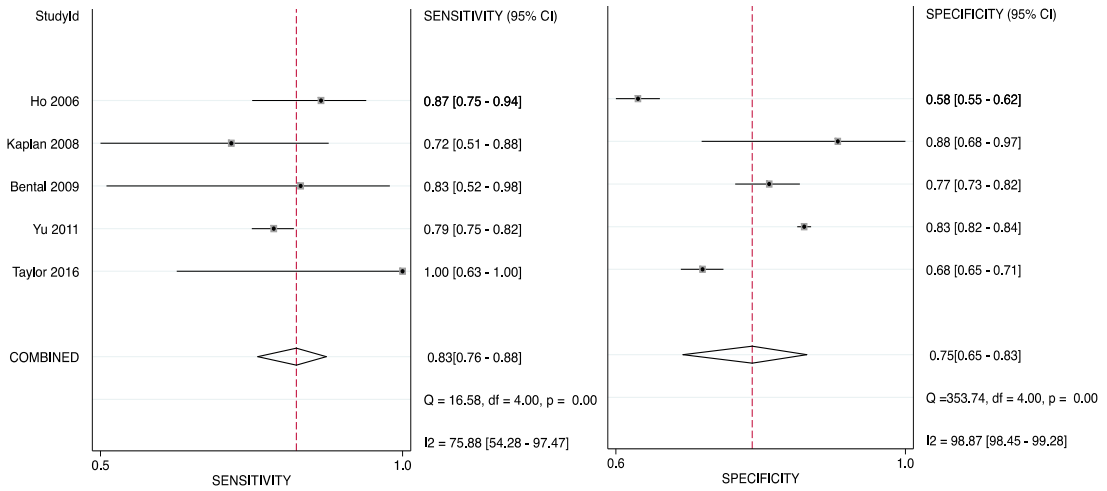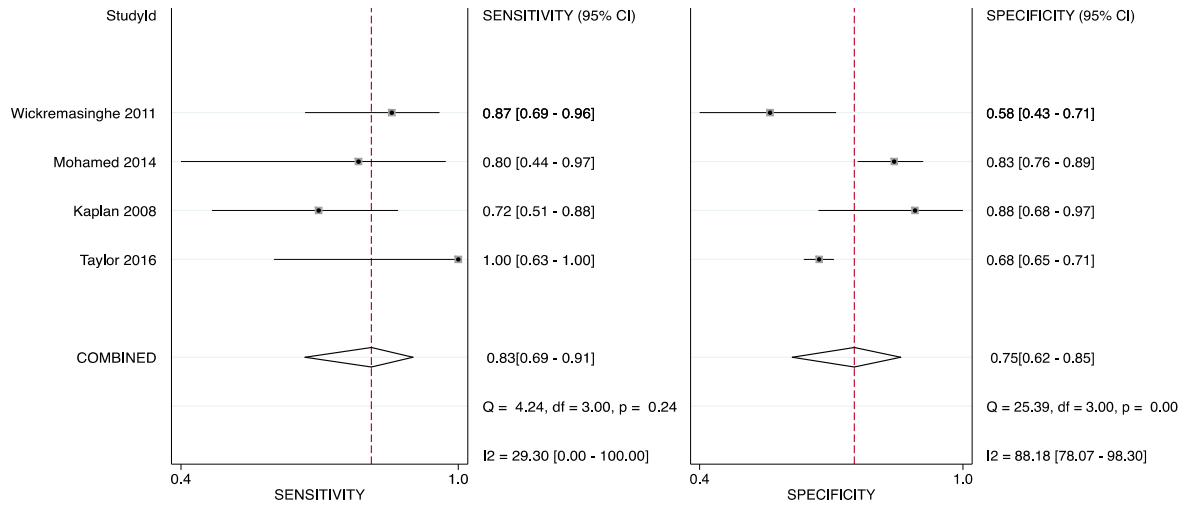

B. JM-103

Figure 2: Forest Plot Subgroup Analysis by Target TSB Level

A. Target TSB > 75th Percentile

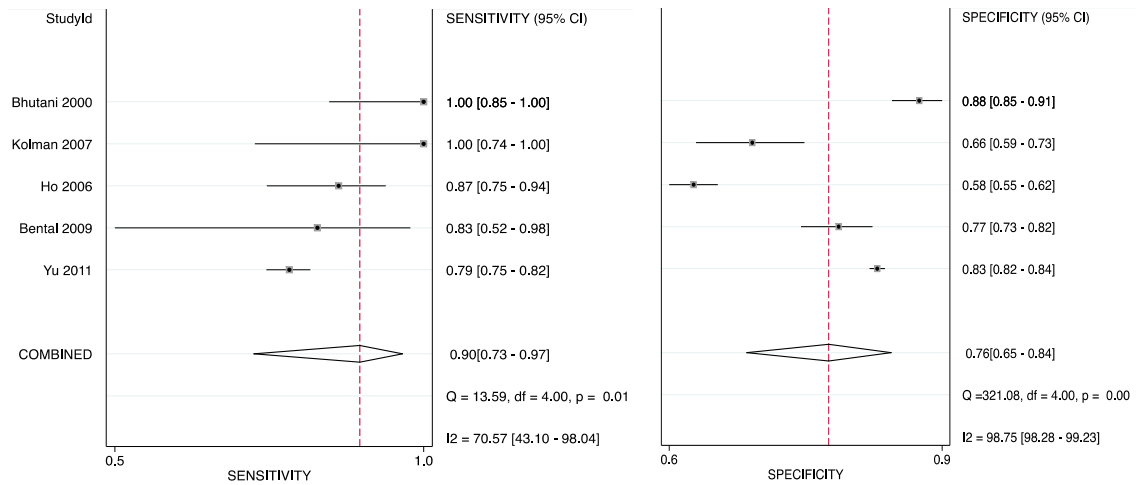
B. Target TSB > 95th Percentile

Table 2: Full Downs and Blacks Quality Assessment from Clinical Outcome Studies

Author	Bhutani, 2013	Hartshorn, 2010	Allen, 2016	Morgan, 2016	Peterson, 2005	Wainer, 2011	Wichremasinghe, 2012
Is the hypothesis of the study clearly described?	1	1	1	1	1	1	1
Are the main outcomes to be measured clearly described?	1	1	1	1	0	1	1
Are the characteristics of the patients included in the study clearly described?	1	1	0	1	0	1	1
Are the interventions of interest clearly described?	1	1	1	1	0	1	1
Are the distributions of principal confounders in each group of subjects to be compared clearly described?	1	1	0	1	1	1	0
Are the main findings of the study clearly described?	0	1	1	1	1	1	1
Does the study provide estimates of the random variability in the data for the main outcomes?	1	1	1	1	1	1	1
Have all important adverse events that may be a consequence of the intervention been reported?	1	0	0	0	0	0	0
Have the characteristics of patients lost to follow-up been described?	1	1	0	0	0	0	0
Have actual probability values been reported for the main outcomes, except where the probability value is less than 0.001?	1	1	0	1	1	1	1
Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	0	0	0	0	0	1	0
Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	0	0	0	0	0	0	0
Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	1	1	1	1	1	1	1
Was an attempt made to blind study subjects to the intervention they have received?	0	0	1	0	0	0	0
Was an attempt made to blind those measuring the main outcomes of the intervention?	0	0	0	0	0	0	0
If any of the results of the study were based on "data dredging" was this made clear?	1	1	0	1	1	1	1
In trails and cohort studies, do the analyses adjust for different lengths of follow-up of patients?	1	1	1	1	1	1	1
Were the statistical tests used to assess the main outcomes appropriate?	0	1	1	1	1	1	1
Was compliance with the intervention reliable?	1	1	1	1	1	1	1

Were the main outcome measures used accurate?	1	1	1	1	1	1	1
Were the patients in different intervention groups or were the cases and controls recruited from the same population?	1	1	1	1	1	1	1
Were study subjects in different intervention groups recruited over the same period of time?	0	0	0	0	0	0	0
Were the study subjects randomized to intervention groups?	0	0	0	0	0	0	0
Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	0	0	0	0	0	0	0
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	0	0	0	0	0	1	0
Were losses of patients to follow-up taken into account?	1	1	1	1	1	1	1
TOTALS	16	17	13	16	13	18	15

Table 3: Budget impact results for British Columbia by setting

Total Costs ($)	Reference	Reference 2[*]	JM-105	JM-105*
Year 1	███	███	███	███
Six Year Budget impact	███	███	███	███
Incremental (vs. Reference)	--	--	-30,051,103	--
Incremental (vs. Reference 2*)	--	--	--	18,221,870

*No costs associated with additional hospital stay hours and obtaining blood specimen

Table 4: Budget impact results of JM-105 compared with Current Care (a combination of TSB and JM-105) in hospital setting

Hospital	# of Annual Births	# of Current Devices	# of Additional Devices Needed	Total Costs (Current Care)		Total Costs (JM-105)	
				Year 1	6-Year Budget	Year 1	6-Year Budget
Campbell River Hospital	392	2	0	■	■	■	■
Cowichan District Hospital	462	1	1				
Lady Minto/Gulf Islands Hospital	15	0	1				
Nanaimo Regional General Hospital	1,244	0	4				
Port McNeill Hospital	6	0	1				
St. Joseph's General Hospital	503	1	1				
Victoria General Hospital	3,075	11	0				
West Coast General Hospital	230	2	0				
Vancouver Island	5,927	17	8	■	■	■	■
Incremental Year 1				*-$165,632*			
Incremental 6-Year Budget				*-$1,221,308*			
BC Women's Hospital & Health Centre	7,125	0	18	■	■	■	■
Lions Gate Hospital	1,462	0	4				
Powell River General Hospital	120	0	1				
Richmond Hospital	2,184	3	3				
Sechelt Hospital	158	0	1				
Squamish General Hospital	218	0	1				
St. Paul's Hospital	1,593	2	2				
Vancouver Coastal	12,860	5	30	■	■	■	■
Incremental Year 1				*-$1,528,383*			
Incremental 6-Year Budget				*-$10,056,936*			
Bulkley Valley District Hospital	249	1	0	■	■	■	■
Dawson Creek and District Hospital	390	1	0				
Fort St. John Hospital	649	0	2				
GR Baker Memorial Hospital	172	1	0				
Kitimat General Hospital	76	0	1				
Lakes District Hospital & Health Centre	4	0	1				
Mills Memorial Hospital	295	1	0				
Prince Rupert Regional Hospital	179	0	1				
Queen Charlotte Islands General Hospital	10	0	1	■	■	■	■

St. John Hospital	156	0	1								
Stuart Lake Hospital	9	0	1								
University Hospital of Northern British Columbia	1,156	0	3								
Northern	12,860	5	11								
Incremental Year 1	-$261,515										
Incremental 6-Year Budget	-$1,943,894										
Abbotsford Regional Hospital & Cancer Centre	2,448	0	7								
Burnaby Hospital	1,470	1	3								
Chilliwack General Hospital	766	0	2								
Fraser Canyon Hospital	4	0	1								
Langley Memorial Hospital	1,456	0	4								
Peace Arch Hospital	1,057	0	3								
Ridge Meadows Hospital	758	2	0								
Royal Columbian Hospital	2,913	1	7								
Surrey Memorial Hospital	4,161	0	11								
Fraser	15,033	4	38								
Incremental Year 1	-$1,865,381										
Incremental 6-Year Budget	-$12,441,604										
100 Mile District General Hospital	27	1	0								
Cariboo Memorial Hospital	353	0	1								
Creston Valley Hospital & Health Centre	48	1	0								
East Kootenay Regional Hospital	466	0	2								
Elk Valley Hospital	129	0	1								
Golden & District General Hospital	57	0	1								
Invermere & District Hospital	18	0	1								
Kelowna General Hospital	1,580	0	4								
Kootenay Boundary Regional Hospital	227	0	1								
Kootenay Lake Hospital	285	1	0								
Lillooet Hospital & Health Centre	18	0	1								
Penticton Regional Hospital	514	1	1								
Queen Victoria Hospital	67	0	1								
Royal Inland Hospital	1,218	0	4								
Shuswap Lake General Hospital	197	0	1								
Vernon Jubilee Hospital	732	0	2								
Interior	5,936	4	21								

Incremental Year 1	-$606,353
Incremental 6-Year Budget	-$4,353,595