National Institute for Health and Care Excellence

Draft for consultation

Addendum to Jaundice in newborn babies under 28 days: Accuracy of various tests in detecting jaundice and updated TSB thresholds

Clinical Guideline Addendum 98.1(b)

Methods, evidence and recommendations

January 2016

Draft for Consultation

Developed by the National Institute for Health and Care Excellence

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

Contents

Clinical guidelines update

The NICE Clinical Guidelines Update Team update discrete parts of published clinical guidelines as requested by NICE's Guidance Executive.

Suitable topics for update are identified through the new surveillance programme (see surveillance programme interim guide).

These guidelines are updated using a standing Committee of healthcare professionals, research methodologists and lay members from a range of disciplines and localities. For the duration of the update the core members of the Committee are joined by up to 9 additional members who are have specific expertise in the topic being updated, hereafter referred to as 'topic expert members'.

In this document where 'the Committee' is referred to, this means the entire Committee, both the core standing members and topic expert members.

Where 'standing committee members' is referred to, this means the core standing members of the Committee only.

Where 'topic expert members' is referred to this means the recruited group of members with topic expertise.

All of the core members and the topic expert members are fully voting members of the Committee.

Details of the Committee membership and the NICE team can be found in appendix A. The Committee members' declarations of interest can be found in appendix B.

1 Summary section

1.1 Update information

The NICE guideline on neonatal jaundice (NICE clinical guideline CG98) was reviewed in May 2014 as part of NICE's routine surveillance programme to decide whether it required updating. The surveillance report identified new evidence relating to three areas of the guidance:

1) The best modality of giving phototherapy
2) The correct procedure of administering phototherapy
3) The accuracy of tests in recognising neonatal jaundice

The review questions that the Committee considered were:

1) What is the best modality of giving phototherapy (clinical and cost-effectiveness)?
2) What is the correct procedure when administering phototherapy?
3) What is the accuracy of various tests (clinical history and examination, urine/stool examination, icterometer and transcutaneous bilirubin levels) in recognising neonatal jaundice or hyperbilirubinaemia?

The topic experts recruited to join the Clinical Guidelines Update Committee (CGUC) for this topic further expressed concern that the consensus-based bilirubin thresholds specified in the original NICE guideline on neonatal jaundice are not implemented by clinicians and midwives for the following reasons:

i) some of the bilirubin thresholds relating to retesting and consideration for phototherapy are too conservative
ii) repeat measurements of bilirubin before phototherapy (in 6-12 hours) as recommended by the consensus-based thresholds table are too resource intensive to be implemented, particularly for community midwives and are not used in practice
iii) the public consultation in 2010 did not manage to engage wider stakeholders, clinicians and midwives who would use the thresholds table on a day-to-day basis.

It was therefore decided to additionally update the following review question:

4) What are the optimal total serum bilirubin (TSB) thresholds for starting phototherapy and exchange transfusion in term babies with neonatal hyperbilirubinaemia?

The original guideline can be found here: http://www.nice.org.uk/guidance/cg98

The full surveillance report can be found here:

http://www.nice.org.uk/guidance/cg98/documents/cg98-neonatal-jaundice-surveillance-review-decision2

Strength of recommendations

Some recommendations can be made with more certainty than others. The Committee makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the Committee is confident that, given the information it has looked at, most people would choose the intervention. The wording used in the recommendations in this

guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the person about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also 'Patient-centred care').

Recommendations that must (or must not) be followed

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Recommendations that should (or should not) be followed– a 'strong' recommendation

We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of people, following a recommendation will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that actions will not be of benefit for most people.

Recommendations that could be followed

We use 'consider' when we are confident that following a recommendation will do more good than harm for most people, and be cost effective, but other options may be similarly cost effective. The course of action is more likely to depend on the person's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the person.

Information for consultation

You are invited to comment on the new recommendations in this update. These are not shaded in grey and marked as:

- **[new 2016]** if the evidence has been reviewed and the recommendation has been added or updated, or
- **[2016]** if the evidence has been reviewed but no change has been made to the recommended action

Where recommendations are shaded in grey and end **[2010]**, the evidence has not been reviewed since the original guideline. We will not be able to accept comments on these recommendations.

1.21 Recommendations

1. **In all babies :**
    - check whether there are factors associated with an increased likelihood of developing significant hyperbilirubinaemia soon after birth
    - examine the baby for jaundice at every opportunity especially in the first 72 hours. **[2010]**

2. **Parents, carers and healthcare professionals should all look for jaundice (visual inspection) in babies. [2016]**

3. **When looking for jaundice (visual inspection) :**
    - check the naked baby in bright and preferably natural light
    - examine the sclerae and gums, and press lightly on the skin to check for signs of jaundice in 'blanched' skin. **[2016]**

4. **Do not rely on visual inspection alone to estimate the bilirubin level in a baby with suspected jaundice. [2016]**

5. **Ensure babies with factors associated with an increased likelihood of developing significant hyperbilirubinaemia receive an additional visual inspection by a healthcare professional during the first 48 hours of life [2010].**

6. **Measure and record the bilirubin level urgently (within 6 hours) in all babies more than 24 hours old with suspected or obvious jaundice [2010].**

7. **Use serum bilirubin measurement for babies:**
    - in the first 24 hours of life **or**
    - who have a gestational age of less than 35 weeks. **[2016]**

8. **In babies who have a gestational age of 35 weeks or more and who are over 24 hours old:**
    - use a transcutatneous bilirubinometer to measure the bilirubin level
    - if a transcutaneous bilirubinometer is not available, measure the serum bilirubin
    - if a transcutaneous bilirubinometer measurement indicates a bilirubin level greater than 250 micromol/litre, measure the serum bilirubin to check the result
    - use serum bilirubin measurement if bilirubin levels are at or above the relevant treatment thresholds for their age, and for all subsequent measurements. **[2016]**

9. **Do not use an icterometer to measure bilirubin levels in babies. [2016]**

10. **In babies who are clinically well, have a gestational age of 38 weeks or more and are more than 24 hours old, and who have a serum bilirubin level that is below the phototherapy threshold but within 50 micromol/litre of the threshold (see the threshold table 13 and the treatment threshold graphs), repeat serum bilirubin measurement as follows:**
    - within 18 hours for babies with risk factors for neonatal jaundice (those with a sibling who had neonatal jaundice that needed phototherapy or a mother who intends to exclusively breastfeed)
    - within 24 hours for babies without risk factors. **[new 2016]**

11. **In babieswho are clinically well, have a gestational age of 38 weeks or more and are more than 24 hours old, and who have a serum bilirubin level that is below the phototherapy threshold by more than 50 micromol/litre (see the threshold table and the treatment threshold graphs), do not repeat serum bilirubin measurement. [new 2016]**

1.3 Patient-centred care

This guideline covers the care of newborn babies (from birth to 28 days) with jaundice.

Treatment and care should take into account parents' and carers preferences. Parents/carers of babies with neonatal jaundice should have the opportunity to make informed decisions about their babies' care and treatment, in partnership with their healthcare professionals. If parents/carers do not have the capacity to make decisions, healthcare professionals should follow the Department of Health's advice on consent and the code of practice that accompanies the Mental Capacity Act. In Wales, healthcare professionals should follow advice on consent from the Welsh Government.

Healthcare professionals should follow the guidelines in the Department of Health's Seeking consent: working with children.

Good communication between healthcare professionals and parents/carers is essential. It should be supported by evidence-based written information tailored to the parent's needs. Treatment and care, and the information parents are given about it, should be culturally appropriate. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read English.

1.41 Methods

This update was developed based on the process and methods described in the NICE guidelines manual 2014.

2 Evidence review and recommendations

2.1 Introduction

Jaundice is one of the most common conditions requiring medical attention in newborn babies. Jaundice refers to the yellow colouration of the skin and sclera (whites of the eyes) resulting from the accumulation of bilirubin in the skin and mucous membranes. This is associated with a raised level of bilirubin in the circulation, a condition known as hyperbilirubinaemia.

Levels of bilirubin can be controlled by placing the baby under a lamp emitting light in a particular spectrum, which is known as phototherapy. Light energy of the appropriate wavelength converts the bilirubin in the skin to a harmless form that can be excreted in the urine. Phototherapy has proved to be a safe and effective treatment for jaundice in newborn babies, reducing the need to perform an exchange transfusion of blood, the only other means of removing bilirubin from the body.

Traditional teaching on examination for jaundice has recommended ‘blanching’ a small area of skin (often on the nose) by pressing it, and inspecting at the whites of the eyes and palate. Jaundice is also thought to spread from the head to the toes in a ‘cephalo-caudal’ progression. Given the difficulty involved in making a diagnosis, one of the aims of this update is to address the accuracy of various tests used to recognise neonatal jaundice or hyperbilirubinaemia.

2.2 Review question 3

What is the accuracy of various tests (clinical history and examination, urine/stool examination, icterometer and transcutaneous bilirubin levels) in recognising neonatal jaundice or hyperbilirubinaemia?

2.3 Clinical evidence review

Although jaundice is typically characterised by yellow discolouration of the skin and sclera, detection of this discolouration can be difficult. Even babies with very pale skin can appear 'suntanned' rather than yellow and detection of jaundice in babies with dark skin tones can be almost impossible. Total bilirubin levels can be variable and sometimes a baby may not be obviously jaundiced yet have a serious, potentially lethal disease. This review therefore aims to evaluate the accuracy of various tests in recognising neonatal jaundice or hyperbilirubinaemia. This is a crucial part of the guideline because if babies are not recognised to be jaundiced in the first place, they cannot enter the care pathway.

An update search using the original search strategy was conducted (see Appendix D) which identified 7934 articles. The titles and abstracts were screened and 184 articles were identified as potentially relevant. Full-text versions of these articles were obtained and reviewed against the criteria specified in the review protocol (Appendix C). Of these, 159 were excluded as they did not meet the criteria. 25 met the criteria and were included with an additional 7 studies from the original NICE guideline on neonatal jaundice. Therefore, there were a total of 32 included studies for the update.

A review flowchart is provided in Appendix E and the excluded studies (with reasons for exclusion) are shown in Appendix F.

2.3.1 Methods

Summary of review protocols

The population included newborns suspected of neonatal jaundice (e.g. a clinical diagnosis) but otherwise well. Subgroups identified included preterm babies and babies of different coloured skins.

The tests of interest specified by the original guideline were:

a) clinical history and examination

b) urine/stool examination

c) icterometer

d) transcutaneous bilirubin levels/lab testing/near patient testing

The above were compared to the current reference standard which is serum total bilirubin measured using the assay diazo method calibrated to the reference SRM 916a – bilirubin.

The committee identified the following outcomes as of interest for this review:

- Correlation coefficient (r) of the index test with the serum bilirubin levels and agreement (Bland-Altman or other statistical analysis of agreement)
- Diagnostic accuracy of the index test in detecting hyperbilirubinaemia/jaundice (serum bilirubin above threshold action for intervention as stated in reference standard)
- Concordance correlation coefficient
- Summary of ROC curves if data allows for this

Quality assessment - risk of bias

As this review question assesses the accuracy and correlation between two diagnostic tests, modified GRADE methodology as described below was used for quality assessment for this particular question.

- **Risk of bias:**

The quality of individual studies was assessed using the QUADAS-2 checklist for diagnostic studies as guided in the NICE guidelines manual 2014. . This checklist addresses 4 main domains including 1) patient selection 2) execution and interpretation of the index test 3) execution and interpretation of the reference standard and 4) patient flow and timing (see appendix I for quality assessment of individual studies). The overall risk of bias for all studies examining a particular test was then assessed as follows:

  - if more than 50% of the studies did not satisfy 1 of the 4 criteria (patient selection, index test, reference standard, flow and timing) – downgrade 1 level
  - if more than 50% of the studies did not satisfy 2 or more of the 4 criteria (patient selection, index test, reference standard, flow and timing) – downgrade 2 levels

- **Indirectness:**
  - details from the PICOs in the review protocol(s) (see appendix C) were used to assess the directness of the included studies. Based on the first 3 areas of the QUADAS-2 checklist (patient selection, index test and reference standard), the applicability of the study in terms of how well it matches the predefined review protocol was assessed for each study (see appendix I for quality assessment of individual studies). The overall level of indirectness for all studies examining a particular test was then assessed as follows:
    - if more than 50% of the studies did not satisfy 1 of the 3 criteria (applicability of patient selection, index test, reference standard) – downgrade 1 level

  - If more than 50% of the studies did not satisfy 2 or more of the 3 criteria (applicability of patient selection, index test, reference standard) – downgrade 2 levels

- **Inconsistency**
  - The assessment of inconsistency was not relevant to this review question given the data was not pooled (see statistical analysis section for more information)
- **Imprecision**
  - For studies reporting Bland Altman plot analyses, the committee defined imprecision on the assumption that one might accept the index test is question only if it's as good as TSB (zero bias) and if the index test had equal or better precision than TSB across a range of bilirubin concentrations. Therefore, all studies were downgraded once for imprecision.
  - For studies reporting accuracy data, a minimally important difference could not be defined by the committee and was not readily available in the literature – a number of studies also did not report confidence intervals or the data to allow confidence intervals to be calculated and so imprecision could not be assessed.
  - A number of studies not did report confidence intervals (or the data to allow calculation of these) and so such studies have been downgraded once.
- **Overall quality**
  - As only prospective observational studies were included for this review, the quality rating began at 'high' and was further downgraded one level for each 'serious' source of bias and two levels for each 'very serious' source of bias.

Statistical analysis

Conventional meta-analyses were not conducted due to heterogeneity in population and outcome measures across studies including:

- Indirect population: unclear whether those tested were clinically jaundiced in 15 studies as some studies seem to have a practice of screening all infants regardless
- Reference standard not described in detail: all studies used some form of the diazo method or equivalent; none of the studies mention this had been calibrated to SRM 916a as stated in the review protocol
- Prior phototherapy: a small number of subjects either received prior phototherapy or it is unclear whether prior phototherapy was received or not in 12 studies
- Inappropriate or lack of statistical comparison in 4 studies (only reported correlation coefficients without any statistical tests of agreement)
- Postnatal age of infants not reported in 4 studies

Where appropriate, summary measures such as Bland Altman plot analyses and diagnostic accuracy measures (mainly sensitivity and specificity as reported in the studies with 95% confidence intervals, where available) were presented in the evidence summary. Very few studies reported likelihood ratios and therefore sensitivity/specificity measures were prioritised. Studies reporting correlation data only without any statistical tests of agreement werenot included as part of the evidence synthesis given such data alone did not inform the committee's discussion and formation of the recommendation. If bilirubin concentrations were presented as mg/dl, these were converted to the SI unit micromol/litre by multiplying by 17.1.

Overall summary of evidence

For a summary of included studies please see below Table 1 onwards (for the full evidence tables and GRADE profiles, please see appendices G and H). For the full details on quality assessment of the individual included studies please see appendix I.

There are 32 included studies in total for this particular review question (7 studies from CG98), however only 28 studies formed part of the evidence synthesis (Rylance 2014; Qualter 2011; Kaynak-Turkmen 2011; Willems 2004; Campbell 2011; Engle 2002; Barko 2006; Ebbesen 2012; Kosarat 2013; Wong 2002; Kolman 2007; Rodriguez-Capote 2009; Knupfer 2001; Stoniene 2009; Jangaard 2006; Maisels 2011; Wainer 2009; Mielsch 2010; Grohmann 2006; Riskin 2003; Karen 2009; Briscoe 2002; Engle 2005; Schmidt 2009; Karon 2008; Maisels 1982; Boo 2007; Samanta 2002); the remaining 4 studies reported correlation coefficients alone without any statistical tests of agreement. 7 out of the 32 studies included data on preterm infants (Wong 2002; Jangaard 2006; Rylance 2014; Schmidt 2009; Karen 2009; Willems 2004; Ebbessen 2012). Two studies including infants of varying skin tones/ethnicity contributed to the evidence synthesis (Wainer 2009; Karen 2009). The number of included studies for the different tests in question is as follows:

- Clinical history and examination: 1 study (0 old, 1 new)
- Urine/stool examination: no study identified that met the inclusion criteria
- Icterometer: no study identified that met the inclusion criteria
- Transcutaneous bilirubin levels: 31 studies (24 new, 7 old):

The various devices used to measure transcutaneous bilirubin levels and number of studies examining each type of device that contributed to the evidence synthesis was as follows:

- BiliCheck: 16 studies
- JM-102: 4 studies
- JM-103: 12 studies
- Bilimed: 1 study

Some studies examined more than one type of device.

Table 1: Summary of included studies reporting diagnostic accuracy data for visual assessment vs total serum bilirubin

Study	Population	Prior phototherapy	TSB method	Measurements/No. of subjects	Comments
Visual assessment					
Riskin (2003)	Israel; all Caucasian GA[1]: range not reported, mean (SD): 39.2 weeks (2) Not all clinically jaundiced; all infants underwent tests as part of common practice	Not reported	Conventional diazo method	371/371	• Diagnostic accuracy of visual assessment to detect TSB >68micromole/l, >127.5micromole/l and >204micromole/l

[1] *GA: gestational age*

Table 2: Summary of included studies reporting Bland-Altman difference plots for BiliCheck

Study	Population	Prior phototherapy	TSB method	Measurements/number of subjects	Comments
Site of measurement: forehead					
Qualter (2011)	Ireland; majority Caucasian GA[1]: ≥35 weeks No indication of clinical jaundice	No, excluded those with prior phototherapy	Standard diazo using Roche/Hitachi analyser	43/43	-
Kaynak-Turkmen (2011)	Turkey; all Caucasian GA[1]: 30-42 weeks No indication of clinical jaundice	No, excluded those receiving phototherapy	Diazo using Architect c8000 automatic analyser	54/54	-
Willems (2004)	Netherlands; majority Caucasian GA[1]: <30 weeks Unclear if clinically jaundiced	Possibly. TcB measurement performed minimally 12 hours after phototherapy	Vitros slides, based on classical diazo reaction	93/24 (preterm)	• Results presented separately for those with good skin conditions and those without • Only one dataset per patient analysed

Study	Population	Prior phototherapy	TSB method	Measurements/number of subjects	Comments
		had been stopped – number who received phototherapy not reported.			
Campbell (2011)	Canada; mixed ethnicity GA[1]: >35 weeks Clinically jaundiced	No, excluded those with prior phototherapy	Diazo with Synchron LX20 system	430/430	-
Wong (2002)	UK; majority Caucasian GA[1]: ≥31 weeks Clinically jaundiced	No, excluded those with prior phototherapy	Hitachi 911 multichannel analyser	64/64	• Results presented separately for term and preterm (31 to 35) infants
Rodriguez-Capote (2009)	Canada; majority Caucasian GA[1]: >35 weeks Unclear if clinically jaundiced	No, excluded those with prior phototherapy	BuBc slide Ortho Vitros 950	60/60	-
Jangaard (2006)	Canada; majority Caucasian GA[1]: range not reported, mean (SD) term infants: 39.4 (1.4) mean (SD) preterm infants: 30.8 (2.5) Unclear if clinically jaundiced	Only data for those without phototherapy has been extracted however preterm results includes those with and without phototherapy	Vitros BuBc method	99/99 (term) 65/65 (preterm)	• Results for term and preterm presented separately however preterm results includes those with and without phototherapy
Stoniene (2009)	Lithuania; ethnicity not reported GA[1]: ≥37 weeks Unclear if clinically jaundiced	Not reported	Jendrassik Grof method	130/130: 6 hours 119/119: 30 hours	• Results by newborn's age (in hours) reported

Study	Population	Prior phototherapy	TSB method	Measurements/number of subjects	Comments
				103/103: 54 hours 35/35: 78 hours 387/387: 6 to 78 hours	
Site of measurement: sternum					
Grohmann (2006)	Germany; all Caucasian GA[1]: 35-42 weeks Unclear if clinically jaundiced	No, excluded those with prior phototherapy	Hitachi 912 and Dimension RxL analysers (diazo methods), Vitros analyser (direct spectrophotometric assay)	124/122	-
Site of measurement: not specified					
Samanta (2004) *[included in CG98]*	UK; ethnicity not reported GA[1]: 33 to 42 weeks Clinically jaundiced	No, excluded those with prior phototherapy	Standard diazo (Cobas Integra 700)	300/300	-

1 [1] *GA: gestational age*

1

2 **Table 3: Summary of included studies reporting Bland-Altman difference plots for JM-102**

Study	Population	Prior phototherapy	TSB method	Measurements/ No. of subjects	Comments
Site of measurement: forehead					
Wong (2002)	UK; majority Caucasian GA[1]: 31 to 42 weeks Clinically jaundiced	No, excluded those with prior phototherapy	Hitachi 911 multichannel analyser	45/45 (term) 19/19 (preterm)	• Results for term and preterm presented separately
Site of measurement: sternum					
Grohmann (2006)	Germany; all Caucasian GA[1]: 35-42 weeks Unclear if clinically jaundiced	No, excluded those with prior phototherapy	Hitachi 912 and Dimension RxL analysers (diazo methods), Vitros analyser (direct spectrophotometric assay)	124/122	-

3 [1] *GA: gestational age*

1

2 **Table 4: Summary of included studies reporting Bland-Altman difference plots for JM-103**

Study	Population	Prior phototherapy	TSB method	Measurements/No. of subjects	Comments
Site of measurement: sternum and forehead					
Rylance (2014)	Malawi; African GA[1] (3 subgroups): • ≥37 weeks • 32-36 weeks • <32 weeks Clinically jaundiced	No, only data for those without phototherapy has been extracted	Timed endpoint diazo	167/NR[2]* *Total of 128 infants included, n for group not under phototherapy is not reported	• Results for term and preterm presented separately • Results by site of measurement not reported • Study had multiple groups; data shown here are for infants not undergoing phototherapy
Site of measurement: forehead					
Qualter (2011)	Ireland; majority Caucasian GA[1]: ≥35 weeks No indication of clinical jaundice	No, excluded those with prior phototherapy	Standard diazo using Roche/Hitachi analyser	41/41	-
Kosarat (2013)	Thailand; ethnicity not reported GA[1]: >37 weeks Clinically jaundiced	Those with prior phototherapy excluded however 61 infants received phototherapy during admission; unclear if this was before/after measurement	Roche/Hitachi Automatic analyser 902	294/257	-
Rodriguez-	Canada; majority Caucasian	No, excluded	BuBc slide Ortho	94/94	-

Study	Population	Prior phototherapy	TSB method	Measurements/No. of subjects	Comments
Capote (2009)	GA[1]: >35 weeks Unclear if clinically jaundiced	those with prior phototherapy	Vitros 950		
Site of measurement: sternum					
Kosarat (2013)	Thailand; ethnicity not reported GA[1]: >37 weeks Clinically jaundiced	Those with prior phototherapy excluded however 61 infants received phototherapy during admission; unclear if this was before/after measurement	Roche/Hitachi Automatic analyser 902	294/257	-
Grohmann (2006)	Germany; all Caucasian GA[1]: 35-42 weeks Unclear if clinically jaundiced	No, excluded those with prior phototherapy	Hitachi 912 and Dimension RxL analysers (diazo methods), Vitros analyser (direct spectrophotometric assay)	124/122	-
Schmidt (2009) *[included in CG98]*	USA; mixed ethnicity GA[1] (3 subgroups): • 24 to 28 weeks • 29 to 31 weeks • 32 to 34 weeks Unclear if clinically jaundiced	No, excluded those who had received/receiving phototherapy	Diazo Jendrassik Grof with blank method (Olympus AU640)	24 to 28 weeks: 30/30 29 to 31 weeks: 29/29 32 to 34 weeks: 31/31	• Results by gestational age reported
Site of measurement: not specified					
Mielsch (2010)	Germany; ethnicity not reported GA[1]: >32 weeks	Not reported	Vitros 350 chemistry system	230/230	-

Study	Population	Prior phototherapy	TSB method	Measurements/No. of subjects	Comments
	Unclear if clinically jaundiced		with BuBc slide		

1 [1] *GA: gestational age*
2 [2] *NR: not reported*

1

2 **Table 5: Summary of included studies reporting Bland-Altman difference plots for BiliMed**

Study	Population	Prior phototherapy	TSB method	Measurements/ No. of subjects	Comments
Site of measurement: sternum					
Karen (2009)	Switzerland; mixed ethnicity GA[1] (3 subgroups): Term 340/7 to 366/7 weeks 280/7 to 336/7 weeks Unclear if clinically jaundiced	No infants had been treated with phototherapy 'until enrolment' – unclear if any subjects received phototherapy before measurements took place	Diazo method (total bilirubin special COBAS integra)	Term: 111/99 340/7 to 366/7 weeks: 47/38 280/7 to 336/7 weeks: 21/13	• Results for term and preterm infants presented separately • Results by ethnicity reported

3 [1] *GA: gestational age*

Table 6: Summary of included studies reporting diagnostic accuracy data for BiliCheck

Study	Population	Prior phototherapy	TSB method	Measurements/No. of subjects	Comments
Site of measurement: forehead					
Campbell (2011)	Canada; mixed ethnicity GA[1]: >35 weeks Clinically jaundiced	No, excluded those with prior phototherapy	Diazo with Synchron LX20 system	430/430	• Diagnostic accuracy of TcB at thresholds 180micromole/l to 250micromole/l to detect TSB value of 200micromole/l, 250micromole/l and 300micromole/l respectively
Engle (2002)	USA; majority Hispanic GA[1]: ≥35 weeks Clinically jaundiced	6 infants were studied 8 to 22 hours after phototherapy; no infants were receiving phototherapy when TcB/TSB measurements were taken	Diazo Jendrassik-Grof with blank method (Olympus AU600)	335/268	• Diagnostic accuracy of TcB at various thresholds from >85.5micromole/l to >188.1micromole/l to detect TSB >171micromole/l • Diagnostic accuracy of TcB at various thresholds from >85.5micromole/l to >256.5micromole/l to detect TSB >256.5micromole/l
Wong (2002)	UK; majority Caucasian GA[1]: ≥31 weeks Clinically jaundiced	No, excluded those with prior phototherapy	Hitachi 911 multichannel analyser	64/64	• Diagnostic accuracy of TcB ≥150micromole/l in detecting SBR≥250micromole when sensitivity is set to 100%
Kolman (2007)	USA; Hispanic GA[1]: >35 weeks Unclear if clinically jaundiced	Not reported	Ortho Vitros 950 or the Ortho Vitros 5.1; modified diazo reaction	192/192	• Diagnostic accuracy of TcB ≥75th percentile to detect clinically significant hyperbilirubinaemia defined as TSB level above 95th percentile* *percentiles as defined by Bhutani nomagram
Engle (2005)	USA; majority Hispanic GA[1]: 35 to 41 weeks	No, excluded those with	Diazo Jendrassik-Grof with blank	121/121	• Diagnostic accuracy of various TcB cutoffs (>188.1micromole/l to

Study	Population	Prior phototherapy	TSB method	Measurements/No. of subjects	Comments
[included in CG98]	Clinically jaundiced prior to hospital discharge/during outpatient evaluation	prior phototherapy	method (Olympus AU600)		>307.8micromole/l) to detect TSB levels >256.5micromole/l to >307.8micromole/l
Karon 2008 *[included in CG98]*	USA; majority Caucasian GA[1]: median 39 weeks Unclear if clinically jaundiced	Not reported	Modification of the Diazo method and the Vitros method – vitros 250 analyser	177/177	• Diagnostic accuracy of high or high intermediate TcB for predicting a high or high intermediate TSB exceeding the 95th percentile for age on Bhutani nomogram
Boo 2007 *[included in CG98]*	Malaysia; majority Malays GA[1]: ≥37 weeks Clinically jaundiced	No, excluded those with prior phototherapy	Diazo method using the Cobas Integra system	345/345	• Diagnostic accuracy of TcB of various thresholds for detecting TSB≥300micromole/l • Data for measurements at sternum and forehead reported separately
Knupfer 2001	Germany; majority Caucasians GA[1]: range not reported, mean (SD): 31.9 (3.3) Clinically jaundiced	Not reported	Standard DPD method using automatic analyser HITACHI	135/135	• Diagnostic accuracy of TcB values in predicting the need for phototherapy for all Caucasians
Site of measurement: sternum					
Ebbessen (2012)	Denmark; ethnicity for all subjects not reported GA[1]: 28 to 34 weeks Unclear if clinically jaundiced	Not reported	Reflection densitometry Vitros 5.1	239/133	• Diagnostic accuracy of TcB ≥210micromole/l in predicting TSB above the phototherapy limit (≥300micromole/l)
Grohmann (2006)	Germany; all Caucasian GA[1]: 35-42 weeks Unclear if clinically jaundiced	No, excluded those with prior phototherapy	Hitachi 912 and Dimension RxL analysers (diazo methods), Vitros analyser (direct spectrophotometric assay)	124/122	• Diagnostic accuracy of TcB in detecting TSB of 222micromole/l and 257 micromole/l respectively when sensitivity set at 100%
Boo 2007 *[included in*	Malaysia; majority Malays GA[1]: ≥37 weeks Clinically jaundiced	No, excluded those with prior	Diazo method using the Cobas Integra system	345/345	• Diagnostic accuracy of TcB of various thresholds for detecting TSB≥300micromole/l

Study	Population	Prior phototherapy	TSB method	Measurements/No. of subjects	Comments
CG98]		phototherapy			• Data for measurements at sternum and forehead reported separately
Site of measurement: not specified					
Samanta (2004) *[included in CG98]*	UK; ethnicity not reported GA[1]: 33 to 42 weeks Clinically jaundiced	No, excluded those with prior phototherapy	Standard diazo (Cobas Integra 700)	300/300	• Diagnostic accuracy of TcB >195micromole/l for detecting significant jaundice defined as TSB >250micromole/l

[1] *GA: gestational age*

Table 7: Summary of included studies reporting diagnostic accuracy data for JM-102

Study	Population	Prior phototherapy	TSB method	Measurements/No. of subjects	Comments
Site of measurement: forehead					
Wong (2002)	UK; majority Caucasian GA[1]: 31 to 42 weeks Clinically jaundiced	No, excluded those with prior phototherapy	Hitachi 911 multichannel analyser	45/45 (term) 19/19 (preterm)	• Diagnostic accuracy of TcB ≥170micromole/l in detecting SBR≥250micromole when sensitivity is set to 100%
Briscoe (2002) *[included in CG98]*	UK; majority Caucasian GA[1]: 34 to 42 weeks 94% clinically jaundiced	No, excluded those with prior phototherapy	Standard diazo method (Cobas Integra 700)	285/285	• Diagnostic accuracy of TcB to detect significant jaundice (SBR>249micromole/l) with the greatest predictive value (TcB =18 and 19.9) • Data is for clinically jaundiced infants
Maisels (1982) *[included in CG98]*	USA; all Caucasian GA[1]: full term (range not reported) Unclear if all infants were clinically jaundiced as standard practice to obtain a serum bilirubin on 3rd day of life or at other times if clinically indicated	No	Modified diazo method using the DuPont automatic clinical analyser	157/157	• Diagnostic accuracy of TcB (threshold not reported) in detecting serum bilirubin >171micromole/l and >220.59micromole/l • Data for measurements at sternum and forehead reported separately
Site of measurement: sternum					
Grohmann (2006)	Germany; all Caucasian GA[1]: 35-42 weeks Unclear if clinically jaundiced	No, excluded those with prior phototherapy	Hitachi 912 and Dimension RxL analysers (diazo methods), Vitros analyser (direct spectrophotometric assay)	124/122	• Diagnostic accuracy of TcB in detecting TSB of 222micromole/l and 257 micromole/l respectively when sensitivity set at 100%
Maisels (1982) *[included in CG98]*	USA; all Caucasian GA[1]: full term (range not reported) Unclear if all infants were clinically jaundiced as standard	No	Modified diazo method using the DuPont automatic clinical analyser	135/135	• Diagnostic accuracy of TcB (threshold not reported) in detecting serum bilirubin >171micromole/l and

Study	Population	Prior phototherapy	TSB method	Measurements/No. of subjects	Comments
	practice to obtain a serum bilirubin on 3rd day of life or at other times if clinically indicated				>220.59micromole/l • Data for measurements at sternum and forehead reported separately

[1] *GA: gestational age*

1

2 **Table 8: Summary of included studies reporting diagnostic accuracy data for JM-103**

Study	Population	Prior phototherapy	TSB method	Measurements/No. of subjects	Comments
Site of measurement: forehead					
Wainer (2009)	Canada; mixed ethnicity GA[1]: ≥37 weeks Unclear if clinically jaundiced	No, excluded those with prior phototherapy	Diazonium method (Roche Modular, Hitachi 912 and 917)	774/774	• Diagnostic accuracy of TcB at various thresholds from 70 to 250micromole/l to detect TSB of various thresholds ranging from >150micromole/l to >250micromole/l
Site of measurement: sternum					
Barko (2006)	USA; mixed ethnicity, majority Hispanic GA[1]: 35 to 42 Mixed population; clinically jaundiced as well as infants not recognised as having clinically significant jaundice	2.5% prior phototherapy	Diazo Jendrassik-Grof with blank method (Olympus AU640E analyser)	120/120* *60 clinically jaundiced	• Diagnostic accuracy of TcB at various thresholds from >188.1micromole/l to >273.6micromole/l to detect TSB >256.5micromole/l, 273.6micromole/l, 290.7micromole/l and 307.8micromole/l respectively
Ebbessen (2012)	Denmark; ethnicity for all subjects not reported GA[1]: 28 to 34 weeks Unclear if clinically jaundiced	Not reported	Reflection densitometry Vitros 5.1	239/133	• Diagnostic accuracy of TcB≥105micromole/l in predicting TSB above the phototherapy limit (≥300micromole/l)
Maisels (2011)	USA; mixed ethnicity GA[1]: ≥35 weeks Clinically jaundiced	Not reported	TSB measurements performed in each location using the following methods: Royal Oak and Sterling Heights – Synchron Diazo Dallas – Olympus	118/118	• Diagnostic accuracy of TcB at various thresholds ≥153.9micromole/l to ≥307.8micromole/l to detect TSB ≥222.3 to ≥307.8micromole/l

Study	Population	Prior phototherapy	TSB method	Measurements/No. of subjects	Comments
			Diazo Calgary – Roche Modular, Hitachi 912 and 917 Iowa – Siemens Dimension		
Grohmann (2006)	Germany; all Caucasian GA[1]: 35-42 weeks Unclear if clinically jaundiced	No, excluded those with prior phototherapy	Hitachi 912 and Dimension RxL analysers (diazo methods), Vitros analyser (direct spectrophotometric assay)	124/122	• Diagnostic accuracy of TcB in detecting TSB of 222micromole/l and 257 micromole/l respectively when sensitivity set at 100%
Schmidt (2009) *[included in CG98]*	USA; mixed ethnicity GA[1] (3 subgroups): 24 to 28 weeks 29 to 31 weeks 32 to 34 weeks Unclear if clinically jaundiced	No, excluded those who had received/receiving phototherapy	Diazo Jendrassik Grof with blank method (Olympus AU640)	24 to 28 weeks: 30/30 29 to 31 weeks: 29/29 32 to 34 weeks: 31/31	• Diagnostic accuracy of TcB of various thresholds >68.4micromole/l to >136.8 to detect TSB >102.6micromole/l to TSB>171.1micromole/l
Site of measurement: forehead and sternum					
Rylance (2014)	Malawi; African GA[1] (3 subgroups): ≥37 weeks 32-36 weeks <32 weeks Clinically jaundiced	No, only data for those without phototherapy has been extracted	Timed endpoint diazo	167/NR[2]* *Total of 128 infants included, n for group not under phototherapy is not reported	• Diagnostic accuracy of using the lowest TcB reading to decide whether to start phototherapy or continue observation • Diagnostic accuracy of using the highest TcB reading to decide whether to start phototherapy or continue observation • Results by site of measurement not reported • Study had multiple groups; data shown here are for infants not undergoing phototherapy

Study	Population	Prior phototherapy	TSB method	Measurements/No. of subjects	Comments

[1] *GA: gestational age*

Table 9: Summary of included studies reporting diagnostic accuracy data for visual assessment vs total serum bilirubin

Study	Population	Prior phototherapy	TSB method	Measurements/No. of subjects	Comments
Visual assessment					
Riskin (2003)	Israel; all Caucasian GA[1]: range not reported, mean (SD): 39.2 weeks (2) Not all clinically jaundiced; all infants underwent tests as part of common practice	Not reported	Conventional diazo method	371/371	• Diagnostic accuracy of visual assessment to detect TSB >68micromole/l, >127.5micromole/l and >204micromole/l

[1] *GA: gestational age*

2.41 Health economic evidence review, review question 3

2.4.12 Methods

3 Evidence of cost effectiveness

4 The Committee is required to make decisions based on the best available evidence of both
5 clinical and cost effectiveness. Guideline recommendations should be based on the expected
6 costs of the different options in relation to their expected health benefits rather than the total
7 implementation cost.

8 Evidence on cost effectiveness related to the key clinical issues being addressed in the
9 guideline update was sought. The health economist undertook a systematic review of the
10 published economic literature.

11 Economic literature search

12 A systematic search was undertaken to identify health economic evidence within published
13 literature relevant to review question 3. The evidence was identified by conducting a broad
14 search relating to neonatal jaundice in the NHS Economic Evaluation Database (NHS EED)
15 and the Health Technology Assessment database (HTA). The search also included Medline
16 and Embase databases using an economic filter combined with the clinical search terms.
17 Studies published in languages other than English were not reviewed. The search was
18 conducted on 18 March 2015. The health economic search strategies are detailed in
19 appendix J.

20 The health economist also sought out relevant studies identified by the surveillance review or
21 Committee members.

22 Economic literature review

23 The health economist:

24 • Identified potentially relevant studies for each review question from the economic search
25 results by reviewing titles and abstracts. Full papers were then obtained.
26 • Reviewed full papers against prespecified inclusion and exclusion criteria to identify
27 relevant studies.
28 • Critically appraised relevant studies using the economic evaluations checklist as specified
29 in NICE guidelines manual 2014.
30 • Extracted key information about the studies' methods and results into full economic
31 evidence tables (appendix M).
32 • Economic evidence profiles were not produced because the included studies did not
33 report their results in the format required (incremental QALYs and incremental cost-
34 effectiveness ratios). Narrative summaries are provided instead.

35 Inclusion and Exclusion criteria

36 Full economic evaluations (studies comparing costs and health consequences of alternative
37 courses of action: cost-utility, cost-effectiveness, cost-benefit and cost-consequence
38 analyses) and comparative costing studies that address the review question in the relevant
39 population were considered potentially includable as economic evidence. Studies that only
40 reported burden of disease or cost of illness were excluded. Literature reviews, abstracts,
41 posters, letters, editorials, comment articles, unpublished studies and studies not in English
42 were excluded.

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where selective exclusions occurred on this basis, this is noted in the excluded economic studies table (appendix L).

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist contained in *Appendix H* of the NICE guidelines manual 2014.
Cost-effectiveness criteria

NICE's report *Social value judgements: principles for the development of NICE guidance* sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- the intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- the intervention cost less than £20,000 per QALY gained compared with the next best strategy.

If the Committee recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'evidence to recommendations' section of the relevant chapter, with reference to issues regarding the plausibility of the estimate or to the factors set out in *Social value judgements: principles for the development of NICE guidance*.

In the absence of economic evidence

When no relevant economic studies were found from the economic literature review, and de novo modelling was not feasible or prioritised, the Committee made a qualitative judgement about cost-effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs, alongside the results of the clinical review of effectiveness evidence. The UK NHS costs reported in the guideline were those presented to the Committee and they were correct at the time recommendations were drafted; they may have been revised subsequently by the time of publication. However, we have no reason to believe they have been changed substantially.

2.4.23 Results of the economic literature review, review question 3

In total, 419 articles were identified by the search. Of these, 413 were excluded based on title and abstract. Six full papers were obtained. One of these was selected for inclusion. The modelling conducted for the original NICE guideline on neonatal jaundice was also included. The flowchart of this review process can be found in appendix K. The list of excluded studies and the reason for their exclusion can be found in appendix L. The full economic evidence tables summarising the included studies are available in appendix M. A narrative summary of the two included analyses is provided here.

Suresh et al. (2004) investigated the cost effectiveness of routine predischarge total serum bilirubin (TSB) testing, routine predischarge transcutaneous bilirubin (TcB) testing using the BiliChek device, and universal follow-up in the office or at home within 1 to 2 days of early newborn discharge in the US healthcare system. There was an assumption that all strategies were equally effective in preventing kernicterus. The authors used a decision tree to calculate the annual cost of each strategy in 2002 US dollars. The base case analysis assumed an incidence of kernicterus of 1 in 100,000 and a relative risk reduction of 70% of cases of kernicterus. The results of the base case analysis were that the cost to prevent one case of kernicterus was US$10.3 million for universal follow-up, US$5.7 million for

predischarge TSB, and US$9.2 million for predischarge TcB. These results were very sensitive to changes in the incidence of kernicterus and relative risk reduction. For example, the cost per case of kernicterus prevented for the predischarge TcBstrategy was US$109,135 for an incidence of 1 in 10,000 and $6.1 million when this strategy was 100% effective at reducing kernicterus. This study was 'partially applicable' and had 'potentially serious limitations'.

The National Collaborating Centre for Women's and Children's Health (NCCWCH) conducted original modelling in 2010 for the development of CG98. The NCCWCH compared 3 strategies:

1. TSB for 10% babies with a positive visual examination (current practice at the time);
2. TSB for all babies with a positive visual examination; and
3. TCB for all babies with a positive visual examination followed by a TSB for those babies with a positive TcB (it was assumed that 25% of TcBtests would be positive in the visually jaundiced population).

This analysis assumed that all strategies were equally effective at detecting hyperbilirubinaemia and preventing kernicterus and that phototherapy rates were the same for all strategies. The total cost per year of each strategy according to the base case analysis was £1.02 million for strategy 1, £10.22 million for strategy 2, £6.26 million plus the annual equivalent cost for TcB using the BiliChek device, and £3.23 million plus the annual equivalent cost for TcB using the JM-103 device. Results were not reported in terms of cost per case of kernicterus prevented per se. Rather, threshold analysis was conducted in order to identify the volume of TcB meters that would result in an equivalent cost to strategy 2. TcB using the JM-103 was expected to cost less than the TSB strategy if it could be delivered using less than 9200 meters. The £9.14 million total cost of this strategy could be equalised by the cost savings of preventing 1.52 cases of kernicterus per year.

Three sensitivity analyses were conducted. The cost of meters was varied between £600 and £3600 (base case £3400). As the cost of meters fell, the number of meters had far less impact in determining the incremental cost of the TcB strategy. For example, at a cost of £2400, the TcB strategy remained cost saving compared with TSB up to 13,000 meters. The mean number of tests per baby was varied between 1 and 2 (base case 1.33). The incremental cost of the TcB test strategy relative to the TSB test strategy fell as the average number of tests per baby increased. This reflected that TSB had the higher marginal cost. For example, if just one test per baby were required then the threshold number of meters for cost neutrality was 7000. However, if babies were tested twice on average, the cost neutrality of TcBrose to approximately 14,000 meters compared with TSB. The QALY gain and cost per kernicterus case prevented were simultaneously varied in the third and final sensitivity analysis. An example of this analysis is that for a given number of averted cases, a much higher saving and QALY gain is necessary for cost-effectiveness when the TcB strategy requires 9200 meters compared with when 2000 meters are required. This study was 'directly applicable' with 'potentially serious limitations'.

2.4.3 Unit costs

Table 10: Cost of transcutaneous bilirubinometers

Item	Cost
Draeger/Minolta JM105 Standard	£3,992
Draeger/Minolta JM-105 Barcode	£4,437.45
Bilichek Advanced System	£3,000
Bilical, 50 pack	£100

2.5 Evidence statements

2.5.1 Clinical evidence statement

2.5.1.1 Clinical history and examination

Very low quality evidence from one study (371 participants) on term caucasian infants clinically assessed for jaundice before discharge indicated that neonatologists had a reasonable clinical impression of jaundice at bilirubin levels >204micromole/l (sensitivity of 81% and specificity of 71%) but much lower sensitivities at lower thresholds of 68micromole/l and 127.5micromole/l.

2.5.1.2 Urine/stool examination

No studies were identified that met the inclusion criteria for this test.

2.5.1.3 Icterometer

No studies were identified that met the inclusion criteria for this test.

2.5.1.4 Transcutaneous bilirubin

2.5.1.4.1 BiliCheck

Bland Altman plot analyses

Very low quality evidence from 7 studies (1137 participants) including term/near term infants indicated that transcutaneous bilirubin measurement from the forehead ranges from an underestimation of -13micromole/l to an overestimation of +13micromole/l (range for CI of mean difference: -76micromole/l to +77micromole/l). The very low quality evidence from 1 study (122 participants) in term/near term infants indicated that transcutaneous bilirubin measurement from the sternum overestimates serum bilirubin by 11micromole/l (range for CI of mean difference:
-28micromole/l to +50micromole/l) .

Very low quality evidence from 3 studies (108 participants) including preterm infants of <30 weeks, 31 to 35 weeks and a mean age of 30.8 weeks respectively indicated that transcutaneous bilirubin measurement from the forehead using BiliCheck ranges from an underestimation of
-5micromole/l to an overestimation of +1micromole/l (range for CI of mean difference: -72micromole/l to +73micromole/l). No evidence of measurement at sternum using BiliCheck was identified for this subgroup.

A subgroup analysis for babies of different skin tones was not available given that the majority of studies were performed in Caucasian infants.

Accuracy data

Despite differences in the populations studied, in the threshold cut-off values of transcutaneous bilirubin and in the levels of laboratory serum bilirubin used as the reference test, very low quality evidence from 11 studies (2287 participants) mainly including term/near term infants indicated that the sensitivity of BiliChek to detect bilirubin levels was generally reported to be high (>75%), but specificity was variable (40 to 66%) for measurements taken at both the forehead (n=8) and sternum (n=3). For the 2 studies looking at preterm infants separately (n=1 at forehead and 1 at sternum), both sensitivity and specificity were variable across the studies.

2.5.1.4.21 Minolta JM-102

Bland Altman plot analyses

Very low quality evidence from one study (45 participants) indicated transcutaneous bilirubin measurement from the forehead using JM-102 overestimates serum bilirubin in preterm infants by +23micromole/l (range for CI of mean difference: -23 to +69micromole/l) but underestimates in term infants by -10micromole/l (range for CI of mean difference: -75 to +56micromole/l). Very low quality evidence from anther study (122 participants) indicated transcutaneous bilirubin measurement from the sternum had an almost negligible difference compared to serum bilirubin in term/near term infants (mean difference: +0.3micromole/l, range for CI of mean difference: -44 to +44micromole/l).

A subgroup analysis for babies of different skin tones was not available given that both studies were performed in mainly Caucasian infants.

Accuracy data

Three studies (506 participants) provided very low quality evidence on accuracy for the Minolta JM-102. As with the BiliCheck, although there were differences in the populations studied, in threshold cut-off values of transcutaneous bilirubin and in the levels of laboratory serum bilirubin used as the reference test, the sensitivity of JM-102 at the forehead to detect bilirubin levels was generally reported to be high (>86%), but with variable results for the specificity (31.9% to 96.7%). For the 2 studies measuring transcutaneous bilirubin at the sternum in term/near infants, both sensitivities and specificities were high (sensitivity: 100% in both studies and specificity 81% to 96.2%).

2.5.1.4.22 Minolta JM-103

Bland Altman plot analyses

Very low quality evidence from 3 studies (392 participants) in term/near term infants indicated transcutaneous bilirubin measurement from the forehead using JM-103 ranges from an underestimation of
-38micromole/l to an overestimation of +16micromole/l (range for CI of mean difference: -86micromole/l to +73micromole/l).

Very low quality evidence from 3 studies (474 participants) indicated transcutaneous bilirubin measurement from the sternum overestimates serum bilirubin in one study including term infants by +17micromole/l (range for CI of mean difference: -35micromole/l to +69micromole/l) and underestimates in the other including term infants by -10.78micromole/l (range for CI of mean difference: -54micromole/l to +32micromole/l). In the final study including preterm infants of 24 to 28 weeks, 29 to 31 weeks and 32 to 34 weeks respectively, transcutaneous bilirubin at the sternum underestimates serum bilirubin in all 3 groups by -18.81micromole/l (range for CI of mean difference: -82 to +45), -14micromole/l (range for CI of mean difference: -57 to +30) and -17micromole/l (range for CI of mean difference: -71 to +37) respectively.

Accuracy data

The sensitivity of JM-103 at the forehead (1study, 774 participants, very low quality) to detect bilirubin levels was variable (31% to 100%) as was the specificity (25% to 100%). The same study did a subgroup analysis by skin tone and found sensitivities were higher at lower TcB thresholds (range: 45.6% to 100%) but specificity generally high (>72%) for light tone infants; a similar trend was seen in medium tone infants with sensitivity ranging from 55% to 100% but more variable specificities depending on the TcB threshold (range 17% to 100%).

Very low quality evidence from 3 studies (360 participants) at the sternum to detect bilirubin levels had moderate to high sensitivities (range: 67% to 100%) but variable specificities

(range: 4% to 92%) for term or near term infants. Two studies (223 participants) on preterm infants reported variable sensitivity and specificity.

2.5.1.4.4 BiliMed

Very low quality evidence from one study (150 participants) indicated that transcutaneous bilirubin measurement from the sternum using BiliMed overestimates serum bilirubin in near term infants (34 to 36 weeks gestational age) by +16micromole/l (range for CI of mean difference: -75micromole/l to +107micromole/l) but somewhat underestimates in term and preterm infants 28 to 33 weeks by -14micromole/l (range for CI of mean difference: -158micromole/l to +130micromole/l) and -8micromole/l respectively (range for CI of mean difference:
-84micromole/l to +68micromole/l). The overestimate observed for Caucasian infants was greater but not significantly greater than Non-Caucasians (+16micromole and +10micromole/l respectively).

2.5.2 Health economic evidence statements

A 2004 US study found that the cost effectiveness of predischarge TSB and TcB screening was dependent on the incidence of kernicterus and the relative risk reduction of reducing kernicterus. A cost analysis developed by the NCCWCH found that TcB following positive visual examination had the potential to be cost saving depending on the number of cases of kernicterus it prevented and the number of meters required to implement the strategy. Both studies had potentially serious limitations. Economic modelling was not conducted for this update.

2.6 Evidence to recommendations

	Committee discussions
Relative value of different outcomes	The Committee discussed and agreed that the critical outcome for this review question was to establish the diagnostic accuracy of various tests (clinical history and examination, urine/stool examination, icterometer and transcutaneous bilirubin levels) in recognising neonatal jaundice or hyperbilirubinemia. An emphasis was placed on sensitivity and specificity given this was the commonly reported outcome measure across all studies; very few studies reported the 2x2 contigency table and so it was not possible to calculate further measures such as likelihood ratios (or confidence intervals) for studies not reporting them. The committee also specified statistical tests of agreement as one of the outcomes (specifically the Bland Altman test of agreement) which gave a feel of the overall level of underestimation/overestimation in bilirubin between the different tests.
Quality of evidence	The Committee noted the evidence base for each of the tests in question was as follows: Clinical history and examination: 1 study Urine and stool examination: no evidence Icterometer: no evidence Transcutaneous bilirubin: 31 studies (25 studies from the update search + 7 studies from the original guideline) The Committee noted that all evidence was of low to very low quality for the following reasons: • Indirect population: unclear whether those tested were clinically jaundiced at baseline in 15/32 studies as some studies seem to have a practice of screening all infants regardless of clinical signs of jaundice – current practice is to test only clinically jaundiced babies rather than screening all babies . • Reference standard not described in detail: all studies used some form

	Committee discussions
	of the diazo method or equivalent; none of the studies mention this had been calibrated to SRM 916a as stated in the review protocol • Prior phototherapy: a small number of subjects had either received prior phototherapy or it was unclear whether prior phototherapy was received or not in 12 studies; the aim of this question was not to determine the accuracy of tests in response to treatment as through its bleaching effect on the skin, phototherapy would affect the correlation between TcB and the bilirubin values • Postnatal age of infants not reported in 4 studies • High uncertainty on precision of the effect estimates as indicated by wide confidence intervals for mean differences between TcB and TSB obtained from the Bland Altman plots • No confidence intervals (or data to calculate confidence intervals) in a number studies reporting diagnostic accuracy data The above limitations, in addition to the fact that the range of accuracies/mean differences in bilirubin observed for devices measuring TcB were not clinically acceptable for diagnosing jaundice in preterm infants, overall meant that the committee did not feel the evidence was sufficient to inform their recommendations.
Trade-off between benefits and harms	<u>Clinical history and examination</u> The committee noted very limited evidence from one study in 371 caucasian term infants assessing the accuracy of visual assessment to detect various total serum bilirubin thresholds. The committee noted that neonatologists had a reasonable clinical impression of jaundice at bilirubin levels >204micromole/l (sensitivity of 80.9% and specificity of 70.9%) but much lower sensitivities at thresholds as low as 68 micromole/l and 127.5 micromole/l and therefore relying on visual assessment alone would not be sufficient. <u>Urine/stool examination</u> The committee noted the lack of evidence assessing the accuracy of urine/stool examination for recognising jaundice or hyperbilirubinaemia and did not form a recommendation on this test. <u>Icterometer</u> The committee noted the lack of evidence assessing the accuracy of icterometer for recongising jaundice or hyperbilirubinaemia and did not change the recommendation on this test. <u>Transcutaneous bilirubin (TcB)</u> The committee noted the trigger for the update of this review question was new evidence on the use of TcB in preterm infants, as identified by the surveillance review. The original recommendation on TcB was in those >35 weeks gestational age (and greater than 24 hours of age) and therefore the primary aim of upating this question was to assess whether the existing recommendation should be extended to preterm babies or not. Overall, 31 studies (25 studies from the update search and 7 studies from original guideline) examining the accuracy of TcB measured using various devices was identified for this review. However only 7 studies included preterm infants. The committee noted that a very wide range of mean differences in bilirubin when comparing TcB against TSB was seen across the 7 studies. The

	Committee discussions
	confidence intervals ranged from an underestimation of around 70micromole/l to an overestimation +70micromole/l for BiliCheck and -80micromole/l to +110micromole/l for JM-103. The committee further felt that the evidence for accuracy of transcutaneous bilirubinometers in this group was unclear and evidence on babies of different skin tones was limited. The committee noted that the Minolta JM-102 which has a different algorithm to other devices measuring TcB is no longer available for purchase from the manufacturers and therefore the evidence from studies examining JM-102 were included but not useful for decision making. The committee were not convinced that the range of accuracy/mean difference in bilirubin observed for the different devices measuring TcB were clinically acceptable for diagnosing jaundice in preterm infants despite the non-invasive, instant and hence more acceptable nature of TcB devices. The committee discussed that preterm infants were more vulnerable than term babies to kernicterus at relatively low levels of bilirubin and therefore need more accurate testing. The committee further noted that babies <35 weeks were already likely to be hospitalised and therefore a blood test (if needed) was readily available. Given the above reasons, the committee decided against extending the recommendation to those <35 weeks gestation. With regards to term infants, the committee discussed the evidence and agreed to keep the existing recommendation on the use of TcB in babies with a gestational age of 35 weeks or more and postnatal age of more than 24 hours. In line with the original guideline development group's conclusions, the committee agreed that TcB can be used in this group of infants who are less at risk of kernicterus to avoid the practical problems and time issues of taking and acting upon blood samples both on the postnatal wards and in the community. If transcutaneous bilirubinometers aren't readily available, it was deemed appropriate to measure serum bilirubin levels as the original guideline already recommends. The committee further noted that the evidence base for those >35 weeks had not changed substantially since the time of the original guideline in the following ways: - The evidence for babies of different skin tones was still limited. - There are differences in the design of different devices used to measure TcB however the committee were unable to recommend a particular device over another given there were no obvious differences in accuracy. - The majority of studies included in this update measured TcB at the forehead. The committee noted and agreed with the original guideline development group that measurement over the sternum is more acceptable to parents and babies and there was no robust evidence to overturn this conclusion. The committee noted that sternal measurement avoids the problem of failing to obtain a reading because the baby wrinkles his or her forehead when crying. Measurement using the forehead carries a potential risk of injuring the eye if the baby struggles. - The difference in correlation between transcutaneous bilirubin and serum bilirubin widens at levels above 250 micromol/litre and, as few babies with high levels were studied, transcutaneous bilirubinometry cannot be recommended at levels above 250 micromol/litre. If a transcutaneous bilirubinometer records a bilirubin

	Committee discussions
	level above 250 micromol/litre, a serum bilirubin level should be taken to check the bilirubin level accurately.
Trade-off between net health benefits and resource use	Two analyses were included in the economic systematic review. Both analyses were considered during the development of the current guideline. The 2004 US study was 'partially applicable', downgraded from 'directly applicable' because (a) the costs were based on the US healthcare system which may not be representative of the costs incurred in the UK and (b) the predischarge screening strategies may not be appropriate for the update of this guideline where a more targeted approach to identifying jaundice through visual examination prior to testing (not screening) was recommended by the original Guideline Development Group. The study was found to have potentially serious methodological limitations. The main limitation was that most parameters were based on expert opinion and estimated. Another limitation was that equivalent effectiveness was assumed across all strategies, contrary to the findings of the present systematic review that the diagnostic accuracy of TcBis not the same as TSB. The cost analysis prepared for the original guideline for neonatal jaundice was 'directly applicable' and not downgraded for applicability because it was conducted for the recommendations the present update relates to. It had potentially serious methodological limitations. The main limitation was that most parameters were based on expert opinion and estimated. Another limitation was that equivalent effectiveness was assumed across all strategies, contrary to the findings of the present systematic review that the diagnostic accuracy of TcB is not the same as TSB. Also, it was a basic cost analysis and did not attempt to answer important questions, such as whether the diagnostic strategies reduced kernicterus or increased phototherapy rates. Overall, the committee determined that both studies were of limited usefulness for the present update. Economic modelling was not undertaken for this review question because it was not feasible. The main reason for this was topic expert advice that the natural history of kernicterus is unknown. Kernicterus is related to high bilirubin but as babies get kernicterus at different levels of serum bilirubin, there are other contributing factors such as gestational age and concomitant sepsis. The diagnostic accuracy of transcutaneous bilirubinometers could not be established from the clinical evidence. Various bilirubin thresholds were used across studies to estimate diagnostic accuracy. The incidence of kernicterus is extremely rare and fluctuates year on year. Essentially, there was very little evidence with which to populate a model. The recommendations were retained in their current form due to clinical evidence with no implications for resource use.
Other considerations	None.

1

2.7 Recommendations

1. **In all babies :**
   - check whether there are factors associated with an increased likelihood of developing significant hyperbilirubinaemia soon after birth
   - examine the baby for jaundice at every opportunity especially in the first 72 hours. **[2010]**

2. **Parents, carers and healthcare professionals should all look for jaundice (visual inspection) in babies. [2016]**

3. **When looking for jaundice (visual inspection) :**
   - check the naked baby in bright and preferably natural light
   - examine the sclerae and gums, and press lightly on the skin to check for signs of jaundice in 'blanched' skin. **[2016]**

4. **Do not rely on visual inspection alone to estimate the bilirubin level in a baby with suspected jaundice. [2016]**

5. **Ensure babies with factors associated with an increased likelihood of developing significant hyperbilirubinaemia receive an additional visual inspection by a healthcare professional during the first 48 hours of life [2010].**

6. **Measure and record the bilirubin level urgently (within 6 hours) in all babies more than 24 hours old with suspected or obvious jaundice [2010].**

7. **Use serum bilirubin measurement for babies:**
   - in the first 24 hours of life **or**
   - who have a gestational age of less than 35 weeks. **[2016]**

8. **In babies who have a gestational age of 35 weeks or more and who are over 24 hours old:**
   - use a transcutatneous bilirubinometer to measure the bilirubin level
   - if a transcutaneous bilirubinometer is not available, measure the serum bilirubin
   - if a transcutaneous bilirubinometer measurement indicates a bilirubin level greater than 250 micromol/litre, measure the serum bilirubin to check the result
   - use serum bilirubin measurement if bilirubin levels are at or above the relevant treatment thresholds for their age, and for all subsequent measurements. **[2016]**

9. **Do not use an icterometer to measure bilirubin levels in babies. [2016]**

2.8 Introduction

Bilirubin thresholds for the initiation, monitoring and management of hyperbilirubinaemia are crucial to ensure optimal treatment and management for neonates with hyperbilirubinaemia.

2.9 Review question 4

What are the optimal total serum bilirubin (TSB) thresholds for starting phototherapy and exchange transfusion in term babies with neonatal hyperbilirubinaemia?

2.10 Clinical evidence review

A systematic search was conducted (see appendix D) which identified 1949 articles. The titles and abstracts were screened and 100 articles were identified as potentially relevant. Full-text versions of these 100 articles were obtained and reviewed against the criteria specified in the review protocol (appendix C). Of these, 99 were excluded as they did not meet the criteria, 1 met the criteria and was included. From the 99 excluded studies, 4 studies were summarised as additional supportive information. These 4 studies do not constitute direct evidence, but as supportive information to assist the Committee's discussion due to the scarcity of direct evidence.

A review flowchart is provided in appendix E, and the excluded studies (with reasons for exclusion) are shown in appendix F.

2.10.1 Methods

Summary of review protocol

The aim of review question 4 is to identify optimal TSB thresholds for starting phototherapy and exchange transfusion for term babies based on their age. Where appropriate and if sufficient data available, information on these TSB thresholds for starting phototherapy may be used to draw suggestions for monitoring thresholds (e.g. different timings for the initiation of phototherapy and their associated outcomes; outcomes or consequences of not starting phototherapy at specific TSB threshold, etc. could inform decision on the frequency and thresholds for monitoring the term babies).

For this particular review question, the population included term babies (≥37 gestational weeks) with hyperbilirubinaemia or suspected hyperbilirubinaemia.

The intervention of interest was the use of different TSB thresholds for starting phototherapy or exchange transfusion based on the age of the babies, and the associated outcomes or consequences. The outcomes of interest are listed as below:

- Number of term babies needing phototherapy
- Number of term babies needing exchange transfusion
- Number of babies with acute bilirubin encephalopathy
- Number of babies with kernicterus
- Number of babies with other complications as a results of their hyperbilirubinaemia

For the full review protocol, please see appendix C.

GRADE methodology (see section 2.3) was used to assess the quality of the 1 included study. For the other 4 studies that constitute additional supportive information, no formal quality assessment was conducted as these 4 studies did not qualify as direct evidence.

A targeted engagement exercise prior to the public consultation was also conducted with midwives and clinicians working in neonatology. The aim of this targeted consultation was to seek the views and opinion from clinicians and healthcare professionals who are working in the field, about the updated draft recommendations (please refer to appendix O for further details on the targeted consultation).

Overall summary of evidence and the additional supportive information

Only 1 cohort study met the inclusion criteria. This cohort study (very low quality) compared 3 groups (with 3 different TSB thresholds for the initiation of phototherapy) of term babies who had clinical jaundice. The outcome of interest was the number of term babies from each group who subsequently had complications (e.g. readmission, exchange transfusion, etc.).

Of the 4 studies that formed the additional supportive information, 3 were derivation studies of TSB nomogram, and 1 was a survey questionnaire to collect TSB thresholds used in neonatal units across the UK.

For a summary of the included study and the additional supportive information, please see Table 11 and [1] *PT: phototherapy*

Table 12 (for the full evidence tables and full GRADE profiles please see appendices G and H).

Table 11: Summary of included studies

Study reference (including study design)	Study population	Intervention & comparator	Outcomes reported
Argent (1985) Cohort	Total = 92 Babies delivered at term (> 37 weeks, > 2500 g) through normal pregnancy, labour and delivery, with evidence of clinical jaundice. Group A = 32; group B = 32; group C = 28	Group A: PT[1] started when >170 micromole/l and continued until bilirubin levels had decreased to < 170 micromole/l. Group B: PT[1] started when > 257 micromole/l and continued until bilirubin levels had decreased to < 257 micromole/l. Group C: PT[1] started when >300 micromole/l and continued until bilirubin levels had decreased to < 257 micromole/l.	*Number of infants in phototherapy:* Group A = 31/32 (97%); Group B = 15/32 (47%); Group C = 5/28 (18%) *Complications:* Group A = 0/32; Group B = 0/32; Group C = 2/28 (1 x readmission; 1 x exchange transfusion)

[1] *PT: phototherapy*

Table 12: Summary of indirect supportive information

Study reference (including study design)	Study population	Methods and analysis	Outcomes reported
Bhutani (1999) Cross-sectional	Total = 2840 Term or near-term babies with appropriate for gestational age (GA[1]) as defined by a birth weight (BW[2]) ≥2000 g for ≥36 weeks; GA[1] or BW[2] ≥2500 g for ≥35 weeks GA[1].	• Data were recorded in epochs of 4 hours (or, age 6± 2 hours) for the first 48 hours and in epochs of 12 hours (or age 6± 6 hours) until 96 hours age and at epochs of 24 hours (or age 6± 12 hours) for age 5 to 7 days. • For each epoch at least 300 data points and demonstration of a Gaussian distribution were required for inclusion in the nomogram. From these data, hour-specific TSB percentiles for each of the epochal periods were calculated. • The 5th, 25th, 40th, 50th, 75th, 90th, and 95th percentiles of TSB values were determined from the Gaussian distribution for each epoch and connected as percentile tracks.	TSB nomogram based on different risk zones.

Study reference (including study design)	Study population	Methods and analysis	Outcomes reported
Sarici (2004) Cross-sectional	Total = 365 Newborn babies with a gestational age between 35 and 42 completed weeks (245–294 days)	• A Gaussian distribution curve, the 5th, 30th, 60th, and 95th percentiles, and 4 percentile tracks were obtained from mean serum total bilirubin values.	TSB nomogram based on different risk zones.
Romagnoli (2012) Cross-sectional	Total = 1708 Healthy full term infants (gestational age ≥ 37 weeks), appropriate for gestational age (birth weight > 10th centile), delivered by vaginal birth or caesarean section after uneventful pregnancy, without asphyxia (Apgar score ≥ 7 at 1 and 5 minutes).	• TSB percentiles for each designated time were calculated, and these data were used for the design of an hour specific nomogram with Microsoft Excel.	TSB percentiles nomogram.
Rennie (2009) Survey questionnaire	Of the 263 hospitals contacted, 163 responded, of which 140 sent information which could be interpreted.	• Bilirubin levels were extracted from each of the graphical charts received, and entered into an Excel spreadsheet. • Each curve was summarised as a series of straight line segments that captured the shape of the curve, by recording the time (in decimal days) and corresponding bilirubin level at the start and end of each segment.	The range of bilirubin levels chosen for action lines in term babies (initiation of phototherapy).

1 [1] *GA: gestational age*

2 [2] *BW: birthweight*

Table 13: Updated consensus-based bilirubin thresholds for management of babies 38 weeks or more gestational age with hyperbilirubinaemia

Age (hour)	Bilirubin measurement (micromole/litre)	
Action	Start phototherapy	Perform an exchange transfusion unless the bilirubin level falls below the threshold while treatment is being prepared
0	>100	>100
6	>125	>150
12	>150	>200
18	>175	>250
24	>200	>300
30	>212	>350
36	>225	>400
42	>237	>450
48	>250	>450
54	>262	>450
60	>275	>450
66	>287	>450
72	>300	>450
78	>312	>450
84	>325	>450
90	>337	>450
96+	>350	>450

2.11 Health economic evidence review

2.11.1 Methods

Please refer to the methods specified in section 2.4.1.

2.11.2 Results of the economic literature review

No study was identified at the title abstract stage that met the inclusion criteria.

2.12 Evidence statements

2.12.1 Clinical evidence statement

Very low quality evidence from one study (92 participants) compared 3 groups (with 3 different TSB thresholds for initiation of phototherapy) of term babies who had clinical jaundice. This study found that the number of babies who subsequently had complications (e.g. readmission, exchange transfusion) was higher in the group in which phototherapy was initiated at a higher TSB threshold). Four studies (4913 participants) formed additional supportive information (3 were derivation studies of TSB nomograms and one was a survey questionnaire of TSB thresholds used in neonatal units across the UK).

2.12.2 Health economic evidence statements

No economic evidence was identified.

2.13.1 Evidence to recommendations

	Committee discussions
Relative value of different outcomes	The ultimate aim of this question was to identify optimal TSB thresholds for starting phototherapy and exchange transfusion in term babies with neonatal hyperbilirubinaemia. The committee therefore prioritised the following outcomes for comparing the different TSB thresholds used for starting phototherapy/exchange transfusion: • Number of term babies needing phototherapy • Number of term babies needing exchange transfusion • Number of babies with acute bilirubin encephalopathy • Number of babies with kernicterus • Number of babies with other complications as a results of their hyperbilirubinaemia
Quality of evidence	No studies relevant to this review question were identified in the original guideline. As anticipated, the clinical evidence base in this area has not improved since 2010 and one very low quality cohort study was identified for this update. This cohort study compared 3 groups (with 3 different TSB thresholds used for the initiation of phototherapy) of term babies who were clinically jaundiced. The committee noted that when phototherapy was initiated at lower thresholds, no further complications were observed compared to the group in which phototherapy was initiated at a higher threshold (one infant needed to be readmitted and another required exchange transfusion). The committee further noted 4 studies formed additional supportive information: 3 were derivation studies of TSB nomograms and one was a survey questionnaire of TSB thresholds used in neonatal units across the UK however only one of these additonal studies (Bhutani 1999) contributed towards the committee's discussion for this review question. The Committee noted that in this study none of the babies with TSB below Bhutani's 40th centile required phototherapy and the first column of the 2010 bilirubin threshold chart maps this line almost exactly. Consequently the current NICE guideline (CG98) recommends repeat bilirubin measurements 6-12 hourly in a group of babies who, the evidence suggests, will never need any intervention. Given the lack of direct evidence to inform this review question, expertise and opinions from the committee was required to reach informal consensus. To ensure the updated bilirubin thresholds were appropriately consulted on with clinicians and midwives who would use it on the ground, a targeted consultation (which took place before the public consultation) was also undertaken. The committee's considerations of the findings from the survey are described in the below section named - 'trade-off between benefits and harms' (please refer to appendix O for further information on the targeted consultation.
Trade-off between benefits and harms	The topic experts recruited to join the Clinical Guidelines Update Committee (CGUC) for this topic expressed concern that the consensus-based bilirubin thresholds specified in the original NICE guideline on neonatal jaundice are not implemented by clinicians and midwives for the following reasons: • some of the bilirubin thresholds relating to retesting and consideration for phototherapy are too conservative • repeat measurements of bilirubin before phototherapy (in 6-12 hours) as recommended by the consensus-based thresholds table are too resource intensive to be implemented, particularly for community midwives and are not commonly used in practice • the public consultation in 2010 did not manage to engage a

	Committee discussions
	wider audience of stakeholders, clinicians and midwives who would use the thresholds table on a day-to-day basis. In order to address the above issues, the committee noted that there were 3 main areas where the existing guidance for babies with a gestational age of 38 weeks or more and more than 24 hours old needed to be revised: i) <u>The use of the bilirubin treatment thresholds in the threshold table when considering the use of phototherapy/exchange transfusion</u> • The committee proposed to adapt the original consensus based threshold table by removing the first 2 columns as in practice, the testing requirements advised by these columns are not being implemented (Table 13). • The committee noted that clinicians followed the final 2 columns of the threshold table which are reproduced by the threshold charts used in practice. • The committee further highlighted that actions for when bilirubin levels fall below the phototherapy thresholds should be addressed in separate recommendations (recommendations 8 and 9 below). • The committee proposed to make no changes to the actual treatment thresholds within the gestational age-based charts themselves given there seemed to be no issues implementing these. ii) <u>Repeat bilirubin measurements if bilirubin is within 50micromole below the phototherapy threshold (recommendation 8)</u> • The committee proposed to change the timing of repeat bilirubin measurements for babies with risk factors (i.e. a previous sibling with neonatal jaundice requiring phototherapy and/or an intention to exclusively breastfeed) to within 18 hours (instead of the current 6-12 hours) given that there was no evidence to support more frequent repeated measurements. • The committee acknowledged that midwives measuring bilirubin levels at 5pm in the evening for example are realistically only able to carry out a repeat measurement the following morning. Based on clinical experience and opinion, it was therefore decided to propose retesting within 18 hours for those with risk factors. • The committee further noted that midwives should be able to prioritise repeat measurements according to the baby's risk so that repeat measurement for those with risk factors is prioritised over babies without risk factors. • For babies without risk factors, based on clinical expertise of the committee members, the committee proposed to repeat measurements within a longer time frame of 24 hours. • The committee further noted that the main purpose of treatment for hyperbilirubinemia is to prevent kernicterus (a serious bilirubin-induced brain dysfunction). However, kernicterus is very rare and extremely unlikely at levels below the treatment thresholds for phototherapy. The committee therefore believed that the new proposed timings for retesting which prioritise infants at high risk of hyperbilirubinemia balance the risk of kernicterus with practical and economic considerations, and the harms of over-testing (such as finding clinically irrelevant results causing unnecessary anxiety to the family as well as the

	Committee discussions
	uneccessary use of resources), while ensuring safe care. • The 50micromole threshold referred to in the recommendation was partly based on clinical experience and evidence presented to the committee from Bhutani (1999) - see part iii. below for further details. iii) <u>No retesting of bilirubin measurement when bilirubin is more than 50micromole below the phototherapy threshold (recommendation 9)</u> • The committee concluded that no retesting is needed if the bilirubin measurement is more than 50micromole below the phototherapy threshold. The rationale for this particular threshold was partly based on clinical experience and evidence presented to the committee from Bhutani (1999) which showed that none of the babies with TSB below Bhutani's 40th centile required phototherapy - the first column of the 2010 bilirubin threshold chart maps this line almost exactly. Consequently the committee concluded that the the current NICE guideline (CG98) recommends repeat bilirubin measurements 6-12 hourly in a group of babies who, the evidence suggests, will never need any intervention. Furthermore, there was no evidence or clinical consensus to support retesting at lower levels as recommended in the original guideline; these thresholds were thought to be too conservative by the update committee. The committee further noted that no changes needed to be made to the original guidance for babies within the first 24 hours of birth as this was outside the scope of this question which focuses on bilirubin thresholds for term babies greater than 24 hours old. Following the close of the targeted consultation (see appendix O), the committee discussed the survey results and concluded further that: - No minimum threshold needs to be specified for repeat testing for both babies with and without risk factors: the committee highlighted this would give clinicians and midwives greater flexibility to consider a range of clinical factors, shift patterns and difficulties of undertaking the test during the night. The committee noted the uncertainty around the rate of change of bilirubin levels and felt that within 18 hours is a safe period for the vast majority of babies. Specifying a minimum threshold of 6 hours for example may persuade clinicans to not only keep babies hospitalised for an extra 6 hours and thereby increase the length of stay, but also encourage testing earlier than needed. - No third line needs to be drawn onto the threshold charts to indicate when 'no-retesting' is needed: the committee discussed 3 main reasons for this decision. 1) As indicated by the results of the targeted survey, some practices already draw a third line themselves to indicate when transcutaneous measurements are acceptable – further lines could therefore complicate the chart and lead to misinterpretation 2) The committee wanted to shift the emphasis to not test unless clinically indicated and thereby give clinicians the flexibility to take the full clinical picture into account. A third line would emphasise retesting and encourage more testing than needed especially (for example) by less experienced members of staff 3) This review question addresses clinically well term babies only

	Committee discussions
	and so having a third line on term babies' charts but no equivalent on preterm charts could lead to confusion. - The need to take the full clinical picture into account including checking records of maternal antibodies, ensuring that the baby is feeding adequately and has no signs of sepsis. These are addressed in chapter 6 of the full guideline and have now been referred to in this update. - The need to clarify that it is 'clinically well' babies this update addresses via this particular review question.
Trade-off between net health benefits and resource use	No economic evidence was identified for inclusion in the economic systematic review. The committee discussed how resource intensive the current recommendations were, particularly the requirement to conduct retesting within 6 to 12 hours. This was rarely implemented in practice due to the unrealistic demands it placed on staff. The new recommendations are expected to reduce the demand on resource use by providing flexibility for staff to retest at a later, more convenient point in time according to the risk profile of the baby. Topic experts advised that the new timeframes are just as safe as the current recommendations, and continue to minimise the risk of the baby developing kernicterus, avoiding the high cost and adverse health consequences associated with it.
Other considerations	None

2.142 Recommendations

10. In babies who are clinically well, have a gestational age of 38 weeks or more and are more than 24 hours old, and who have a serum bilirubin level that is below the phototherapy threshold but within 50 micromol/litre of the threshold (see the threshold table 13 and the treatment threshold graphs), repeat serum bilirubin measurement as follows:

- within 18 hours for babies with risk factors for neonatal jaundice (those with a sibling who had neonatal jaundice that needed phototherapy or a mother who intends to exclusively breastfeed)
- within 24 hours for babies without risk factors. **[new 2016]**

11. In babies who are clinically well, have a gestational age of 38 weeks or more and are more than 24 hours old, and who have a serum bilirubin level that is below the phototherapy threshold by more than 50 micromol/litre (see the threshold table and the treatment threshold graphs), do not repeat serum bilirubin measurement. [new 2016]

3 References

3.1 Review question 3

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4 Glossary and abbreviations

Please refer to the NICE glossary.

1 Appendices

2 Appendix A: Committee members and 3 NICE teams

A.1 4 Core members

Name	Role
Damien Longson (Chair)	Consultant Liaison Psychiatrist, Manchester Mental Health and Social Care Trust
Catherine Briggs	GP Principal, Bracondale Medical Centre, Stockport
John Cape	Director of Psychological Therapies Programme, University College London
Alun Davies	Professor of Vascular Surgery and Honorary Consultant Surgeon, Charing Cross & St Mary's Hospital & Imperial College NHS Trust
Alison Eastwood	Professor, Centre for Reviews and Dissemination, University of York
Sarah Fishburn	Lay Member
Jim Gray	Consultant Medical Microbiologist, The Birmingham Children's Hospital NHS Foundation Trust
Kath Nuttall (until November 2015)	Director, Lancashire & South Cumbria Cancer Network (- April 2013)
Tilly Pillay	Consultant Neonatologist, Staffordshire, Shropshire and Black Country Newborn Network, Royal Wolverhampton Hospitals Trust
Nick Screaton	Radiologist, Papworth Hospital NHS Foundation Trust
Lindsay Smith	Principal in General Medical Practice, Somerset
Philippa Williams	Lay Member
Sophie Wilne	Paediatric Oncologist, Nottingham Children's Hospital

A.2 5 Topic experts

Name	Role
Yvonne Benjamin	Community Midwife
Chris Chaloner	Deputy Head of Service, Clinical Biochemistry
Jane Coyne	Community Midwife
Chris Edwards (non-voting expert)	Consultant Medical Physicist
Rajesh Gupta	General Pediatrician
Maria Jenkins	Lay member
Janet Rennie	Consultant in Neonatal Medicine
Aung Soe	Consultant Neonatal Paediatrician
Julia Thomson	Paediatric Consultant

A.3 6 NICE project team

Name	Role
Catharine Baden-Daintree	Editor
Mark Baker	Clinical Advisor

Name	Role
Steven Barnes	Technical Lead
Christine Carson	Guideline Lead
Joy Carvill/Trudie Willingham	Guideline Co-ordinator
Jessica Fielding	Public Involvement Advisor
Bhash Naidoo/Ross Maconanchie	Technical Lead (Health Economics)
Louise Shires/Rupert Franklin	Programme Manager

A.41 Clinical guidelines update team

Name	Role
Philip Alderson	Clinical Advisor
Emma Banks	Co-ordinator
Jenny Craven	Information Specialist
Paul Crosland	Health Economist
Nicole Elliott/Lorraine Taylor	Associate Director
Kathryn Hopkins	Technical Analyst
Nick Lowe	Administrator
Susannah Moon	Programme Manager
Rebecca Parsons/Jane Birch	Project Manager
Nitara Prasannan	Technical Analyst
Toni Tan	Technical Adviser

1 Appendix B: Declarations of interest

B.12 Core members

Name	Interest declared	Type of interest	Decision
Damien Longson	Family member employee of NICE.	Personal Non-financial Non-specific	Declare and participate
Damien Longson	Director of Research & Innovation, Manchester Mental Health & Social Care NHS Trust.	Personal Non-financial Non-specific	Declare and participate
Catherine Briggs	Husband is a consultant anaesthetist at the University Hospital of South Manchester.	Personal Non-financial Non-specific	Declare and participate
Catherine Briggs	Member of the Royal College of Surgeons, the Royal College of General Practitioners, the Faculty of Sexual and Reproductive Health and the BMA.	Personal Non-financial Non-specific	Declare and participate
Catherine Briggs	Chaired a discussion panel on urinary tract infections in women for Amco.	Personal Financial Non-specific	Declare and participate
John Cape	Trustee of the Anna Freud Centre, a child and family mental health charity which applies for and receives grants from the Department of Health and the National Institute for Health Research.	Personal Non-financial Non-specific	Declare and participate
John Cape	Member of British Psychological Society & British Association for Behaviour & Cognitive Psychotherapists who seek to influence policy towards psychology & psychological therapies.	Personal Non-financial Non-specific	Declare and participate
John Cape	Clinical Services Lead half-day a week to Big Health, a digital health company that has one commercial product; an online CBT self-help programme for insomnia with online support	Personal Non-financial Non-specific	Declare and participate
Alun Davies	Research grant funding – commercial: Vascular Insights; Acergy Ltd; Firstkind; URGO laboratoire. All administered by Imperial College London as Sponsor and Professor Davies as CI.	Non-personal Financial Non-specific	Declare and participate

Name	Interest declared	Type of interest	Decision
Alun Davies	Research grant funding – non-commercial: National Institute for Health Research, British Heart Foundation, Royal College of Surgeons, Circulation Foundation, European Venous Forum.	Non-Personal Financial Non-specific	Declare and participate
Alun Davies	Non-commercial: Attendance at numerous national & international meetings as an invited guest to lecture where the organising groups receive funding from numerous sources including device and pharmaceutical manufacturers. Organising groups pay expenses and occasionally honoraria - the exact source of funding is often not known.	Personal Financial Non-specific	Declare and participate
Alun Davies	National Institute for Health Research grant for DVT prophylaxis (pharmalogical and mechanical)	Non-personal Financial Non-specific	Declare and participate
Alun Davies	Bayer Lecturer on Direct oral anticoagulants for European Society for Vascular Surgery	Personal Financial Non-specific	Declare and participate
Alison Eastwood	Member of an independent academic team at Centre for Review & Dissemination, University of York commissioned by NICE through National Institute for Health Research to undertake technology assessment reviews.	Non-personal Non-financial Non-specific	Declare and participate
Sarah Fishburn	Organises workshops for physiotherapists treating pelvic girdle pain. Paid for this work.	Personal Financial Non-specific	Declare and participate
Sarah Fishburn	Payment and expenses from the Nursing and Midwifery Council as a lay panellist of the Fitness to Practise Investigating Committee.	Personal Financial Non-specific	Declare and participate
Sarah Fishburn	Lay reviewer for the National Institute for Health Research; has reviewed a number of research proposals being considered for funding. Paid for carrying out these reviews.	Personal Financial Non-specific	Declare and participate
Sarah Fishburn	Chair of the Pelvic Partnership, a support group for women with pregnancy-	Personal Non-financial	Declare and participate

Name	Interest declared	Type of interest	Decision
	related pelvic girdle pain (voluntary position).	Non-specific	
Sarah Fishburn	Trained as a chartered physiotherapist and qualified in 1988 but have not been in clinical practice since 1997. Remains a non-practicing member of the Chartered Society of Physiotherapy.	Personal Non-financial Non-specific	Declare and participate
Sarah Fishburn	Appointed by Mott MacDonald to carry out reviews as a lay reviewer on behalf to the Nursing and Midwifery Council of Local Supervising Authorities and Universities providing courses for nurses and midwives. This is paid work.	Personal Financial Non-specific	Declare and participate
Jim Gray	Editor-in-Chief Journal of Hospital Infection, funded by the Healthcare Infection Society.	Personal Financial Non-specific	Declare and participate
Jim Gray	Co-investigator in four major trials (3 HTA-funded; 1 British Council funded. Two trials are about antibiotic prophylaxis on obstetrics and gynaecology to prevent pelvic infections, one is comparing different suture materials and the fourth is a diagnostic test accuracy study for use in woman in labour).	Non-personal Financial Non-specific	Declare and participate
Jim Gray	Associate Editor, International Journal of Antimicrobial Agents.	Personal Non-financial Non-specific	Declare and participate
Jim Gray	Associate Editor Journal of Pediatric Infectious Diseases.	Personal Non-financial Non-specific	Declare and participate
Jim Gray	Expert Advisor, British National Formulary for Children.	Personal Non-financial Non-specific	Declare and participate
Jim Gray	My Department is in receipt of an Educational Grant from Pfizer Ltd to develop improved diagnosis of invasive fungal infections in immunocompromised children	Non-personal Financial Non-specific	Declare and participate
Jim Gray	Small shareholding (under £2000) in Glaxo Smith Kline	Personal Financial Non-specific	Declare and participate
Kath Nuttall (until November 2015)	None	Not applicable	Declare and participate

Name	Interest declared	Type of interest	Decision
Tilly Pillay	None	Not applicable	Declare and participate
Nick Screaton	Clinical Commissioning Group stakeholder member	Personal Non-financial Non-specific	Declare and participate
Nick Screaton	Senior Editor British Journal of Radiology	Personal Non-financial Non-specific	Declare and participate
Nick Screaton	Advisory Editor Clinical Radiology	Personal Non-financial Non-specific	Declare and participate
Nick Screaton	Chair East of England British Institute of Radiology	Personal Non-financial Non-specific	Declare and participate
Nick Screaton	Director – Cambridge Clinical Imaging LTD	Personal Financial Non-specific	Declare and participate
Nick Screaton	British Thoracic Society Bronchiectasis Guidelines Group	Personal Non-financial Non-specific	Declare and participate
Nick Screaton	Specialised Imaging Clinical Commissioning Group stakeholder member	Personal Non-financial Non-specific	Declare and participate
Nick Screaton	Member of the Faculty Board for the Royal College of Radiologists	Personal Non-financial Non-specific	Declare and participate
Nick Screaton	Member of the Editorial Board of Pulmonary Circulation	Personal Non-financial Non-specific	Declare and participate
Lindsay Smith	None	Not applicable	Declare and participate
Philippa Williams	None	Not applicable	Declare and participate
Sophie Wilne	Recipient of NHS Innovation Challenge Award for clinical awareness campaign to reduce delays in diagnosis of brain tumours in children & young adults. Award will be used to develop the campaign.	Personal Financial Non-specific	Declare and participate
Sophie Wilne	Co-investigator for RFPB grant to undertake systematic reviews in childhood brain tumours.	Non-personal Financial Non-specific	Declare and participate
Sophie Wilne	Co-investigator for grant awards from charity to evaluate impact of brain tumour awareness campaign.	Non-personal Financial Non-specific	Declare and participate
Sophie Wilne	Talked at a Novartis sponsored meeting on	Personal Financial	Declare and participate

Name	Interest declared	Type of interest	Decision
	tuberous sclerosis	Non-specific	

B.21 Topic experts

Name	Interest declared	Type of interest	Desicion
Yvonne Benjamin	None	Not applicable	Declare and participate
Christopher Chaloner	Consultancy with Alexion Pharma on the topic of laboratory investigation of hypophosphatasia	Personal Financial Non-specific	Declare and participate
Jane Coyne	None	Not applicable	Declare and participate
Chris Edwards	Run a Dosimetry Course that includes teaching medical physicists how to calibrate neonatal phototherapy equipment. This course is run by my private phototherapy clinic, Clearskin, Cardiff. No manufacturers of neonatal phototherapy equipment are involved	Personal Financial Non-Specific	Declare and participate
Maria Jenkins	None	Not applicable	Declare and participate
Gupta Rajesh	None	Not applicable	Declare and participate
Janet Rennie	Provide expert opinion for children with kernicterus both for claimant solicitors and solicitors appointed to advise the NHS litigation authority	Non-personal Financial Specific	Declare and participate
Janet Rennie	Author of one of the papers considered by the committee for review question 4	Personal Non-financial Specific	Declare and participate
Aung Soe	Attended the Joint European Neonatal Research Societies meeting sponsored by Capnia without a financial payment. At the meeting I discussed with other investigators regarding the feasibility of joining a study on identification of neonatal haemolysis in Jaundice by measuring end tidal CO. This is an investigator-driven study with no conflicts of interest and Capnia will serve as only a technology partner to provide short term loan for	Personal Non-financial Specific	Declare and participate

Name	Interest declared	Type of interest	Desicion
	the Co-sense device.		
Julia Thomson	None	Not applicable	Declare and participate

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1 Appendix C: Review protocol

C.1 2 Review question 3

	Details
Review question 3	What is the accuracy of various tests (clinical history and examination, urine/stool examination, icterometer and transcutaneous bilirubin levels) in recognising neonatal jaundice or hyperbilirubinaemia?
Background/Objectives	Although jaundice is typically characterised by yellow discolouration of the skin and sclera, detection of this discolouration can be difficult. Even babies with very pale skin can appear 'suntanned' rather than yellow and detection of jaundice in babies with dark skin tones can be almost impossible. Total bilirubin levels can be variable and sometimes a baby may not be obviously jaundiced yet have a serious, potentially lethal disease. This review therefore aims to evaluate the accuracy of various tests in recognising neonatal jaundice or hyperbilirubinaemia. This is a crucial part of the guideline because if babies are not recognised to be jaundiced in the first place, they cannot enter the care pathway.
Original review questions (if relevant)	Same as above
Type of review question	Prediction and early identification review
Language	English language only
Study design	Prospective cohorts, diagnostic accuracy studies
Status	Published studies (full text only)
Population	Newborns suspected of neonatal jaundice (eg: a clinical diagnosis) but otherwise well *Subgroups: preterm versus term babies, and babies of different coloured skins
Intervention	a) clinical history and examination b) urine/stool examination c) icterometer d) transcutaneous bilirubin levels/lab testing/near patient testing
Comparator/reference standard	Serum total bilirubin levels - assay diazo method calibrated to SRM 916a – bilirubin
Outcomes	1) Correlation coefficient (r) of the index test with the serum bilirubin levels and agreement (Bland-Altman or other statistical analysis of agreement 2) Diagnostic accuracy of the index test (sensitivity, specificity, PPV, NPV, LR+/-) in detecting hyperbilirubinaemia/jaundice (serum bilirubin above threshold action for intervention as stated in reference standard) 3) Concordance correlation coefficient 4) Summary of ROC curves if data allows for this
Other criteria for inclusion / exclusion of studies	For inclusion: - prospective studies - diagnostic accuracy of the test or its correlation evaluated against the reference standard (serum bilirubin levels) - test and the reference standard performed within 1 hour of each other (if bilirubin sample has been protected from light)
Review strategies	*A list of excluded studies will be provided following sifting of the database

	*Data on all included studies will be extracted into evidence tables *Where statistically possible, a meta-analytical approach will be used to give an overall summary effect *For this diagnostic question, all evidence will be presented in modified GRADE profiles and further summarised in evidence statements.

C.21 Review question 4

	Details
Review question 4	What are the optimal total serum bilirubin (TSB) thresholds for starting phototherapy and exchange transfusion in term babies with neonatal hyperbilirubinaemia?
Background/ objectives	To identify optimal TSB thresholds for starting phototherapy and exchange transfusion for term babies based on their age. Where appropriate and if with sufficient data, evidence on TSB thresholds for starting phototherapy may be used to draw suggestions for monitoring thresholds.
Types of study to be included	Include: RCTs, systematic reviews of RCT Non-randomised studies, systematic reviews of non-randomised studies, including cross sectional surveys. Published national and international clinical guidelines. Exclude: Qualitative studies, case series and case reports. Note: if no evidence was identified from randomised and non-randomised studies, case series may be considered for inclusion.
Language	English only
Status	Published articles
Population	Term babies (≥37 gestational weeks) with hyperbilirubinaemia or suspected hyperbilirubinaemia
Intervention	Different TSB thresholds used for starting phototherapy based on the age of the babies Different TSB thresholds used for starting exchange transfusion based on the age of the babies
Comparator	Comparing the different TSB thresholds used for starting phototherapy or exchange transfusion.
Outcomes	Number of term babies needing phototherapy Number of term babies needing exchange transfusion Number of babies with acute bilirubin encephalopathy Number of babies with kernicterus Number of babies with other complications as a results of their hyperbilirubinaemia
Any other information or criteria for inclusion/exclusion	Selection of papers: i) Selection based on titles and abstracts A full double-sifting of titles and abstracts will not be conducted due to the nature of the review question (very narrow question), and that there will be very limited relevant evidence expected. ii) Selection based on full papers A full double-selecting of full papers for inclusion/exclusion will not be conducted due to the nature of the review question, and that only a small number of full papers expected to be ordered for selection. Other mechanisms will be in place for QA:

	Details
	The Committee will be sent the list of included and excluded studies prior to the committee meeting, and the Committee will be requested to cross check whether any studies have been excluded inappropriately, and whether there are any relevant studies they have known of which haven't been picked up by the searches. An additional engagement exercise with an existing neonatal expert forum will be conducted and this platform will also be used to double check whether any relevant studies haven't been picked up by the searches.
Analysis of subgroups or subsets	Data will be summarised based on the age of the term babies (in hours or days).
Data extraction and quality assessment	Data extraction: Information from included studies will be extracted into evidence table. Quality assessment: As this is neither an intervention question nor a diagnostic question, GRADE methodology will not be used to assess the quality of evidence as the quality criteria will not be fully applicable to this review question. Depending on the study designs of the included studies, appropriate checklists as recommended in the Developing NICE guidelines: the manual (2014), Appendix H, will be used to assess the quality of included studies accordingly. For any included national and international guidelines, AGREE II will be used to assess the quality. Reliability of quality assessment: A full double-scoring quality assessment will not be conducted due to the nature of the review question and the studies that are likely to be included. Other quality assurance mechanisms will be in place as the following: Internal QA by CGUT technical adviser on the quality assessment that is being conducted. The Committee will be sent the evidence synthesis prior to the committee meeting and the Committee will be requested to comment on the quality assessment, which will serve as another QA function.
Strategy for data synthesis	Due to the nature of the review question, where possible, data will be summarised narratively with simple descriptive summary statistics if appropriate.
Searches	To include: sources to be searched plans to use any supplementary search techniques, when known at the protocol development stage, and the rationale for their use limits to be applied to the search

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Appendix D: Search strategy

Databases that were searched, together with the number of articles retrieved from each database for each question are shown in table 11. The search strategy is shown in table 12. The same strategy was translated for the other databases listed.

D.1 Review question 3

Table 14: Clinical search summary

Databases	Date searched	No. retrieved
CDSR (Ovid, Wiley)*	11/02/2015	11
Database of Abstracts of Reviews of Effects – DARE (CRD, Ovid, Wiley)*	11/02/2015	3
HTA database (CRD, Ovid, Wiley)*	11/02/2015	4
CENTRAL (Ovid, Wiley)*	11/02/2015	255
MEDLINE (Ovid)	09/04/2015	4616
MEDLINE In-Process (Ovid)	09/04/2015	2386
EMBASE (Ovid)	09/04/2015	5503

Table 15: Clinical search terms

Line number/Search terms/Number retrieved
Ovid MEDLINE
1 exp Infant, Newborn/ (504495)
2 (newborn* or neonat* or preterm* or premature).tw. (376524)
3 1 or 2 (694809)
4 Hyperbilirubinemia/ (3919)
5 exp Jaundice/ (11929)
6 Kernicterus/ (1043)
7 (bilirubin* or hyperbilirubin* or jaundice* or kernicterus* or icterus*).tw. (54324)
8 (bilirubin adj2 encephalopath*).tw. (355)
9 or/4-8 (59989)
10 Jaundice, Neonatal/ (5346)
11 Hyperbilirubinemia, Neonatal/ (571)
12 10 or 11 (5840)
13 3 and 9 (11164)
14 12 or 13 (12565)
15 predictive value of tests/ (149455)
16 (sensitiv: or diagnos: or predictive value: or accurac:).mp. or di.fs. (4132385)
17 history*.ti. (62473)
18 Physical Examination/ (29794)
19 ((clinical* or visual* or physical*) adj4 examin*).tw. (119679)
20 Skin Pigmentation/ (5841)
21 ((skin or urine or stool*) adj4 (colo?r* or discol?r*)).tw. (5255)
22 ((urine or stool*) adj4 examin*).tw. (5851)
23 Bilirubin/bl [Blood] (13305)
24 (transcutaneous* adj4 bilirubin*).tw. (284)
25 (jaundice adj4 (meter* or metre*)).tw. (44)

Line number/Search terms/Number retrieved	
26	(jaundice-meter or jaundice-metre).tw. (42)
27	((point-of-care or "point of care" or bedside or bed-side or lab*) adj4 test*).tw. (48328)
28	(icterometer or bilicheck or bilirubinometer).tw. (135)
29	or/15-28 (4283168)
30	14 and 29 (6115)
31	animals/ not human/ (3926996)
32	30 not 31 (6019)
33	limit 32 to english language (4616)

D.21 Review question 4

2 **Table 16: Clinical search summary**

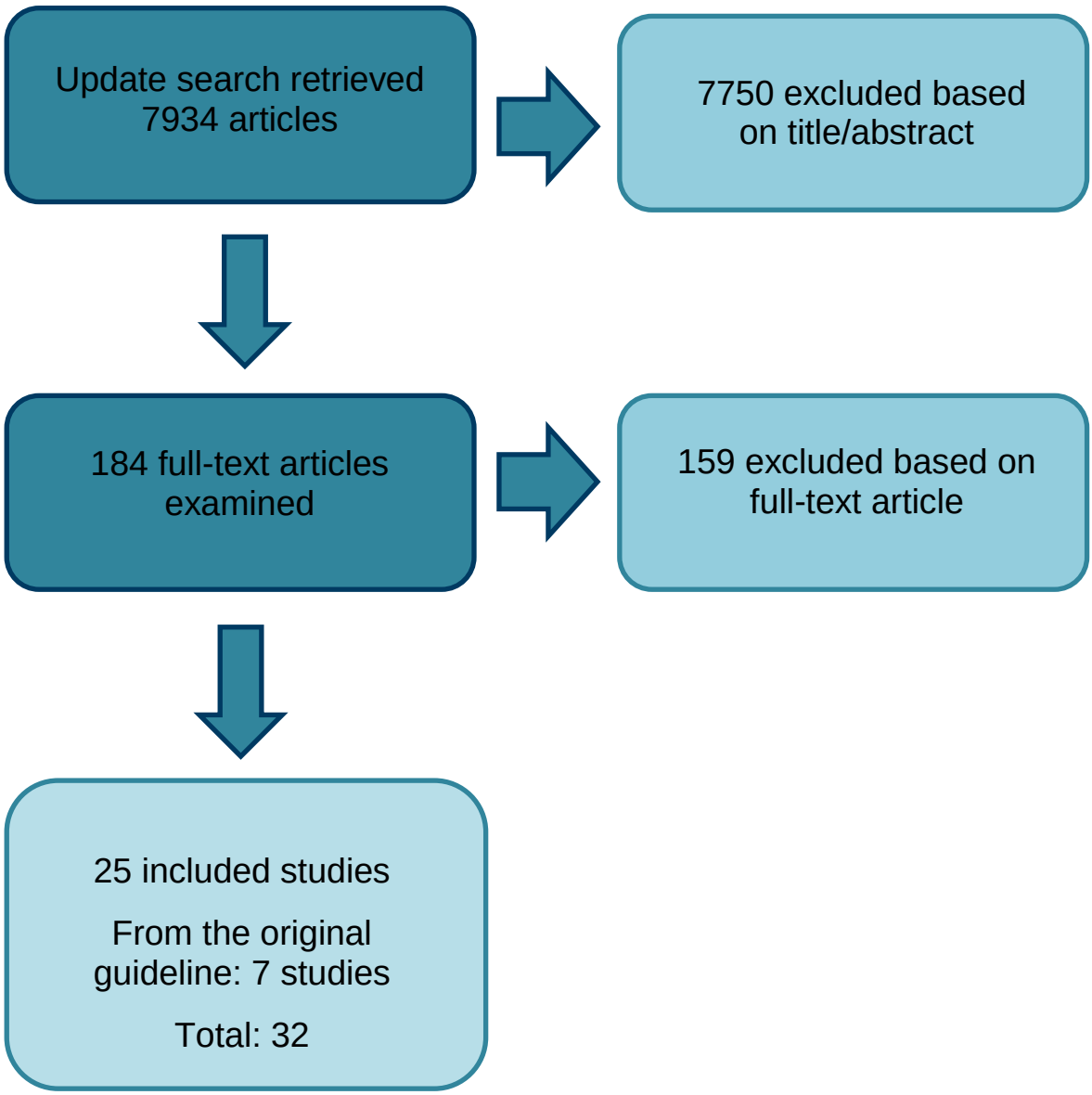
Database	Date searched	Number retrieved
MEDLINE (Ovid)	13/08/2015	1189
MEDLINE In-Process (Ovid)	13/08/2015	73
EMBASE (Ovid)	13/08/2015	1406
Cochrane Central Register of Controlled Trials (CENTRAL)	13/08/2015	118
Cochrane Database of Systematic Reviews (CDSR)	13/08/2015	24
Database of Abstracts of Reviews of Effectiveness (DARE)	13/08/2015	0
Health Technology Assessment (HTA)	13/08/2015	0
PubMed	13/08/2015	54

3 **Table 17: Clinical search strategy (Medline)**

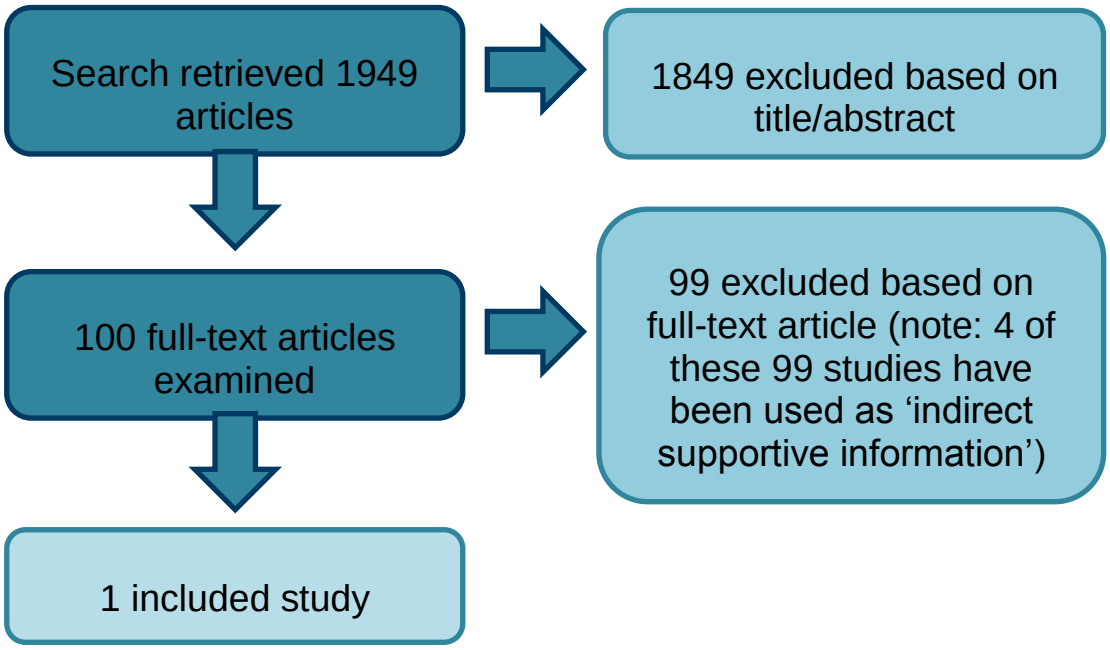
Line number/Search term/Number retrieved
Search Strategy: 1 exp Infant, Newborn/ 519024 2 (newborn* or neonat* or baby or babies).tw. 327823 3 1 or 2 669286 4 Hyperbilirubinemia/ 4000 5 exp Jaundice/ 12215 6 Kernicterus/ 1065 7 (bilirubin* or hyperbilirubin* or jaundice* or kernicterus* or icterus*).tw. 55565 8 exp Bilirubin/ 22256 9 or/4-8 68726 10 Jaundice, Neonatal/ 5479 11 Hyperbilirubinemia, Neonatal/ 599 12 10 or 11 5999 13 3 and 9 12009 14 12 or 13 13310 15 Risk Assessment/ 190637 16 (risk* adj3 (assess* or index or model*)).tw. 80583 17 (total adj3 serum adj3 bilirubin*).tw. 2032 18 (serum adj3 bilirubin* adj3 level*).tw. 2551 19 tsb.tw. 866 20 (bilirubin* adj3 (hour* or day* or age*)).tw. 651 21 threshold*.tw. 166002 22 or/15-21 409993 23 14 and 22 1384 24 Animals/ not Humans/ 3998271 25 23 not 24 1347 26 limit 25 to english language 1210

Appendix E: Review flowchart

E.1 Review question 3



E.2 Review question 4



1 Appendix F:Excluded studies

F.12 Review question 3

Reference	Reason for Exclusion
Conseil d'Evaluation des Technologies de la Sante. (2008) Transcutaneous bilirubinometry in the context of early postnatal discharge. Health Technology Assessment Database.	Narrative review
Is visual assessment a reliable way to estimate bilirubin levels? (2008) Journal of Family Practice. 57: 504.	Commentary
Transcutaneous bilirubinometry for the screening of neonatal hyperbilirubinemia ?35 weeks' gestation (2013) Health Technology Assessment Database. 155.	Unable to supply (abstract only)
Acosta-Torres,S.M., Torres-Espina,M.T., Colina-Araujo,J.A., Colina-Chourio,J.A. (2012) Usefullness of the Kramer's index in the diagnosis of hyperbilirubinemia of the newborn. Investigacion Clinical. 53: 148-156.	Study not in English
Afanetti,M., Eleni dit,Trolli S., Yousef,N., Jrad,I., Mokhtari,M. (2014) Transcutaneous bilirubinometry is not influenced by term or skin color in neonates. Early Human Development. 90: 417-420.	Retrospective study
Akahira-Azuma,M., Yonemoto, N., Ganzorig,B.. Mori,R., Hosokawa,S., Matsushita,T., Bavuusuren,B., Shonkhuuz,E. (2013) Validation of a transcutaneous bilirubin meter in Mongolian neonates: comparison with total serum bilirubin, BMC pediatrics. 13: 151.	Index test and reference standard not within one hour of each other but 3 hours.
Akman,Y., ArIkan,C., Bylgen,H., Kalaca,S., Ozek,E. (2002) Transcutaneous measurement of bilirubin by icterometer during phototherapy on a bilibeds. Turkish Journal of Medical Sciences. 32: 165-168.	Evaluation of transcutaneous bilirubin during phototherapy; tests would perform differently in this situation.
Amato,M., Huppi,P., Markus,D. (1990) Assessment of neonatal jaundice in low birth weight infants comparing transcutaneous, capillary and arterial bilirubin levels. European journal of pediatrics. 150: 59-61.	Device studied is JM-101; not of interest
Bauchner,H. (2009) Predicting hyperbilirubinemia in newborns. Archives of Disease in Childhood: Education and Practice. 94: 192.	Unable to source study
Beck,M., Kau,N., Schlebusch,H. (2003) Transcutaneous bilirubin measurement in newborn infants: evaluation of a new spectrophotometric method. Archives of disease in childhood. 88: F350-F351.	Study is a letter
Bental,Y.A., Shiff,Y., Dorsht,N., Litig,E., Tuval,L., Mimouni,F.B. (2009) Bhutani-based nomograms for the prediction of significant hyperbilirubinaemia using transcutaneous measurements of bilirubin. Acta paediatrica. 98: 1902-1908.	Reference standard not current
Bertini,G., Pratesi,S., Cosenza,E., Dani,C. (2008) Transcutaneous bilirubin measurement: evaluation of Bilitest. Neonatology. 93: 101-105.	Reference standard not current - TSB levels were measured by 2 different methods (1. radiometer 2. GB 13/A bilirubinometer), one of which is not the current reference standard. It is unclear how many subjects TSB levels were measured by the current reference standard.
Bhardwaj,H.P., Narang,A., Bhakoo,O.N. (1989) Evaluation of Minolta	Reference standard not

Reference	Reason for Exclusion
jaundicemeter and icterometer for assessment of neonatal jaundice. Indian pediatrics. 26: 161-165.	current
Bhat,V., Srinivasan,S., Usha,T.S., Puri,R.K. (1987) Correlation of transcutaneous bilirubinometry with serum bilirubin in south Indian neonates. The Indian journal of medical research. 86: 49-52.	Device studied is JM-101; not of interest
Bhutani,V.K., Gourley,G.R., Adler,S., Kreamer,B., Dalin,C., Johnson,L.H. (2000) Noninvasive measurement of total serum bilirubin in a multiracial predischarge newborn population to assess the risk of severe hyperbilirubinaemia. Pediatrics. 106: E17	Reference standard not current
Bhutani,V.K., Johnson,L.H. (2001) Jaundice technologies: prediction of hyperbilirubinemia in term and near-term newborns. Journal of perinatology :official journal of the California Perinatal Association. 21: S76-S77.	Narrative review
Bhutta,Z.A., Yusuf,K. (1991) Transcutaneous bilirubinometry in Pakistani newborns: a preliminary report. The Journal of the Pakistan Medical Association. 41: 155-156.	Device studied is JM-101; not of interest
Bilgen,H., Ince,Z., Ozek,E., Bekiroglu,N., Ors,R. (1998) Transcutaneous measurement of hyperbilirubinaemia: comparison of the Minolta jaundice meter and the Ingram icterometer. Annals of tropical paediatrics. 18: 325-328.	Reference standard not current
Boo,NY., Bakar,A.A. (1984) Transcutaneous bilirubinometry in Malay, Chinese and Indian term neonates. The Medical journal of Malaysia. 39: 35-37.	Device studied is JM-101; not of interest
Bosschaart,N., Kok,Joke H., Newsum,Astrid M., Ouweneel,Dagmar M., Mentink,R., van Leeuwen,Ton G., Aalders,Maurice C.G. (2012) Limitations and opportunities of transcutaneous bilirubin measurements. Pediatrics, 129: 689-694.	Reference standard not current.
Bourchier,D., Cull,A.B., Oettli,P.E. (1987) Transcutaneous bilirubinometry: 22 months experience at Waikato Women's Hospital. The New Zealand medical journal. 100: 599-600.	Unclear timing of tests and reference standard not current
Brown,L.P., Arnold,L., Allison,D., Jacobsen,B., Klein,M.E., Charsha,D. (1990) Transcutaneous bilirubinometer: intermeter reliability. Journal of perinatology : official journal of the California Perinatal Association. 10: 167-169.	Reference standard not current
Carbonell,X., Botet,F., Figueras,J., Riu-Godo,A. (2001) Prediction of hyperbilirubinaemia in the healthy term newborn. Acta paediatrica. 90: 166-170.	Reference standard not current
Chaibva,N.T., Fenner,A., Wolfsdorf,J. (1974) Reliability of an icterometer in Black neonates with hyperbilirubinaemia. South African medical journal. 48: 1533-1534.	Reference standard not current
Chang,Y.H., Hsieh,W.-S., Chou,H.C., Chen,C.Y., Wu,J.Y., Tsao,P.N. (2006) The effectiveness of a noninvasive transcutaneous bilirubin meter in reducing the need for blood sampling in Taiwanese neonates. Clinical Neonatology. 13: 60-63.	Reference standard not current
Chawla,D., Jain,S., Kaur,G., Sinhmar,V., Guglani,V. (2014) Accuracy of transcutaneous bilirubin measurement in preterm low-birth-weight neonates. European journal of pediatrics. 173: 173-179.	Reference standard not current
Christo,G.G., Kamath,S., Aroor,A.R., Venkatesh,A. (1988) Transcutaneous bilirubinometry in newborns. Indian pediatrics. 25: 1073-1077.	Reference standard not current
Coda Zabetta,C.D., Iskander,I.F., Greco,C., Bellarosa,C., Demarini,S., Tiribelli,C., Wennberg,R.P. (2013) Bilistick: a low-cost point-of-care system to measure total plasma bilirubin. Neonatology. 103: 177-181.	Unclear timing of tests
Conceicao,CM., Dornaus,M., Portella,MA., Deutsch,Alice D.A.,	Unclear timing of tests and

Reference	Reason for Exclusion
Rebello,CM. (2014) Influence of assessment site in measuring transcutaneous bilirubin. Einstein. 12: 11-15.	method used to measure serum bilirubin not reported
Crawford-Faucher, A. (2010) Transcutaneous bilirubin nomogram can predict significant hyperbilirubinaemia. American Family Physician. 82: 427-428.	No relevant data; TcB nomogram for assessing the risk of subsequent hyperbilirubinaemia
Crofts,D.J., Michel,V.J., Rigby,A.S., Tanner,M.S., Hall,D.M., Bonham,J.R. (1999) Assessment of stool colour in community management of prolonged jaundice in infancy. Acta paediatrica 88: 969-974.	Project report (non-diagnostic study)
De Luca,D., Zecca,E., Corsello,M., Tiberi,E., Semeraro,C., Romagnoli,C. (2008) Attempt to improve transcutaneous bilirubinometry: a double-blind study of Medick BiliMed versus Respironics BiliCheck. Archives of disease in childhood: Fetal and neonatal edition. 93: F135-F139.	Reference standard not current
De Luca,D., Zecca,E., de Turris,P., Barbato,G., Marras,M., Romagnoli,C. (2007) Using BiliCheck for preterm neonates in a sub-intensive unit: diagnostic usefulness and suitability. Early human development. 83: 313-317.	Reference standard not current
De Luca,D., Zecca,E, Zuppa,A., Romagnoli,C. (2008) The joint use of human and electronic eye: visual assessment of jaundice and transcutaneous bilirubinometry. The Turkish journal of pediatrics. 50: 456-461.	Reference standard not current
Donzelli,G., Pratesi,S. (2000) Transcutaneous bilirubinometry in healthy preterm newborns. Clinical biochemistry. 33: 505-508.	Reference standard not current
Ebbesen,F., Rasmussen,L.M., Wimberley,P.D. (2002) A new transcutaneous bilirubinometer, BiliCheck, used in the neonatal intensive care unit and the maternity ward. Acta paediatrica. 91: 203-211.	Unclear timing of tests
Fakhraee,S.H., Haji-Ebrahim-Tehrani,F., Amid,M.H., Kazemian,M. (2002) Results of urine and blood cultures in healthy jaundiced newborns: Making the correct choice. Archives of Iranian Medicine. 5: 88-90.	Study assesses the incidence of various infections in neonates with jaundice; no relevant data
Felc,Zlata. (2005) Improvement of conventional transcutaneous bilirubinometry results in term newborn infants. American journal of perinatology. 22: 173-179.	Device studied is JM-101; not of interest
Fok,T.F., Lau,S.P., Hui,C.W., Fung,K.P., Wan,C.W. (1986) Transcutaneous bilirubinometer: its use in Chinese term infants and the effect of haematocrit and phototherapy on the TcB index. Australian paediatric journal. 22: 107-109.	Reference standard not current
Fonseca,R., Kyralessa,R., Malloy,M., Richardson,J., Jain,S.K. (2012) Covered skin transcutaneous bilirubin estimation is comparable with serum bilirubin during and after phototherapy. Journal of Perinatology. 32: 129-131.	Accuracy of tests during and after phototherapy
Ford,Karen L. (2010) Detecting neonatal jaundice. Community practitioner: the journal of the Community Practitioners' & Health Visitors' Association. 83: 40-42.	Summary of NICE guidance
Furlan,D., Zalec,L., Pavlin,T., Gradecki,M., Mevzelj,D.O., Bratanic,B. (2013) Prediction of hyperbilirubinemia by noninvasive methods in full-term newborns. Zdravniski Vestnik. 82: 158-163.	Study not in English
Goldman,S.L., Penalver,A., Penaranda,R. (1982) Jaundice meter: evaluation of new guidelines. The Journal of pediatrics. 101: 253-256.	Reference standard not current
Grabenhenrich,J., Grabenhenrich,L., Buhrer,C., Berns,M. (2014) Transcutaneous bilirubin after phototherapy in term and preterm infants. Pediatric. 134: e1324-e1329.	Study examines accuracy of tests after the course of phototherapy

Reference	Reason for Exclusion
Gupta,P.C., Kumari,S., Mullick,D.N., Lal,U.B. (1991) Icterometer: a useful screening tool for neonatal jaundice. Indian pediatrics. 28: 473-476.	Reference standard not current
Hamel,B.C. (1982) Usefulness of icterometer in black newborns with jaundice. Tropical doctor. 12: 213-214.	Reference standard not current
Hannemann,R.E., Schreiner,R.L., DeWitt,D.P., Norris,S.A., Glick,M.R. (1982) Evaluation of the Minolta bilirubin meter as a screening device in caucasian and black infants. Pediatrics. 69: 107-109.	Unclear timing of tests. Also, TSB was measured by 2 different methods, one of which is not the current reference standard (unclear how many subjects were tested using the current method).
Harish,R., Sharma,D.B. (1998) Transcutaneous bilirubinometry in neonates: evaluation of Minolta Air shields jaundicemeter. Indian pediatrics. 35: 264-267.	Reference standard not current
Harkness,R.A., Lawrence,C.R., Renshaw,A., Barr,I.C., Brown,S.S., Rinsler,M.G. (1983) Assessment of the performance and clinical utility of a ward side-room bilirubinometers. Annals of clinical biochemistry. 20: 149-152.	No relevant data
Hartshorn,D., Buckmaster,A. (2010) 'Halving the heel pricks': evaluation of a neonatal jaundice protocol incorporating the use of a transcutaneous bilirubinometers. Journal of paediatrics and child health. 46: 595-599.	Study aims to assess the impact of a new jaundice protocol incorporating the use of transcutaneous meters in a post-natal ward.
Hatzenbuehler,L., Zaidi,A.K.M., Sundar,S., Sultana,S., Abbasi,F., Rizvi,A., Darmstadt,G.L. (2010) Validity of neonatal jaundice evaluation by primary health-care workers and physicians in Karachi, Pakistan. Journal of perinatology : official journal of the California. 30: 616-621.	Unclear timing of tests
HAYES. Transcutaneous bilirubin measurement (Structured abstract), Health Technology Assessment Database, 2010	Unable to supply
Hegyi,T., Hiatt,I.M., Gertner,I., Indyk,L. (1981)Transcutaneous bilirubinometry. The cephalocaudal progression of dermal icterus. American journal of diseases of children. 135: 547-549.	No relevant data
Hegyi,T., Hiatt,I.M., Indyk,L. (1981) Transcutaneous bilirubinometry. I. Correlations in term infants. The Journal of pediatrics. 98: 454-457.	Reference standard not current
Hemmati,F., Kiyani Rad,N.A. (2013) The value of bilicheck as a screening tool for neonatal jaundice in the South of Iran. Iranian Journal of Medical Sciences. 38: 122-128.	Reference standard not current
Ho,E.Y.W., Lee,S.Y.R., Chow,C.B., Chung,J.W.Y. (2006) BiliCheck transcutaneous bilirubinometer: a screening tool for neonatal jaundice in the Chinese population. Hong Kong medical journal. 12: 99-102.	Reference standard not current - TSB levels were measured by 2 different methods, one of which is not the current reference standard. It is unclear how many subjects TSB levels were measured by the current reference standard.
Ho,H.T., Ng,T.K., Tsui,K.C., Lo,Y.C. (2006) Evaluation of a new transcutaneous bilirubinometer in Chinese newborns. Archives of disease in childhood. 91: F434-F43.	Reference standard not current
Jafarzadeh,M., Mohammadzadeh,A. (2009) Should urine culture be considered in the hyperbilirubinemia workup of neonate. Journal of Chinese Clinical Medicine. 4: 136-138.	No relevant outcomes; study does not assess the correlation between urine culture results and TSB

Reference	Reason for Exclusion
	levels
Janjindamai,W., Tansantiwong,T. (2005) Accuracy of transcutaneous bilirubinometer estimates using BiliCheck in Thai neonates. Journal of the Medical Association of Thailand. 88: 187-190.	Reference standard not current
Kaplan,M., Shchors,I., Algur,N., Bromiker,R., Schimmel,Michael S., Hammerman,C. (2008) Visual screening versus transcutaneous bilirubinometry for predischarge jaundice assessment. Acta paediatrica. 97: 759-763.	Reference standard not current
Karolyi,L., Pohlandt,F., Muche,R., Franz,A.R., Mihatsch,W.A. (2004) Transcutaneous bilirubinometry in very low birthweight infants. Acta paediatrica. 93: 941-944.	Method for measuring TSB not reported
Karon,Brad S., Wickremasinghe,Andrea C., Lo,Stanley F., Saenger,Amy K., Cook,Walter J. (2010) BiliChek transcutaneous bilirubin meter overestimates serum bilirubin as measured by the Doumas reference method. Clinical biochemistry. 43: 1009-1012.	Study aims to test the acccuracy of a recalibration scheme by comparing relationship between TcB and TSB before and after reassignment of calibrator setpoints.
Karrar,Z., al Habib,S., al Basit,O.B., Ashong,F., Osundwa,V. (1989) Transcutaneous bilirubin measurements in Saudi infants: the use of the jaundice meter to identify significant jaundice. Annals of tropical paediatrics. 9: 59-61.	Reference standard not current
Kazmierczak,Steven C., Robertson,Alex F., Briley,Kimberly P., Kreamer,Bill, Gourley,Glenn R. (2004) Transcutaneous measurement of bilirubin in newborns: comparison with an automated Jendrassik-Grof procedure and HPLC. Clinical chemistry. 50: 433-435.	Results not extractable; in graph format without accompanying numbers
Keren,R. Tremont,K. Luan,X. Cnaan,A. (2009) Visual assessment of jaundice in term and late preterm infants. Archives of disease in childhood. 94: F317-F322.	Index test and reference standard were not performed within an hour but 8 hours of each other. Also, visual assessment was compared to bilirubin obtained as a TcB or TSB therefore comparator not met.
Kitsommart,R., Pornladnun,P., Chomchai,C., Urujchutchairut,P., Paes,B. (2013) Accuracy and precision of transcutaneous bilirubinometry in postdischarge Asian neonates. European journal of pediatrics. 172: 781-786.	Unclear timing of tests and number who previously received phototherapy unclear.
Knudsen,A. (1995) Predicting the need for phototherapy in healthy mature neonates using transcutaneous bilirubinometry on the first postnatal day. Biology of the neonate. 68: 398-403.	Tests not within one hour of each other and method for measuring plasma bilirubin not reported
Knudsen,A. (1990) Measurement of the yellow colour of the skin as a test of hyperbilirubinemia in mature newborns. Acta paediatrica. 79: 1175-1181.	Device studied is JM-101; not of interest
Knudsen,A. (1990) The cephalocaudal progression of jaundice in newborns in relation to the transfer of bilirubin from plasma to skin. Early human development. 22: 23-28.	Device studied is JM-101; not of interest
Knudsen,A., Brodersen,R. (1989) Skin colour and bilirubin in neonates, Archives of disease in childhood. 64: 605-609.	Study uses JM-101- device not of interest
Knudsen,A., Ebbesen,F. (1996) Transcutaneous bilirubinometry in neonatal intensive care units, Archives of disease in childhood. 75: F53-F56.	No relevant data; study examines the influence of different factors on the association between jaundice meter readings

Reference	Reason for Exclusion
	and plasma bilirubin concentration.
Knudsen,A., Kruse,C., Ebbesen,F. (1993) Detection of hyperbilirubinemia by skin color measurements in icteric newborn infants at 5 to 14 days of age. Acta paediatrica. 82: 510-513.	Study design and timing of test unclear
Kumar,A. (1992) Micro-invasive management of neonatal bilirubinemia. Indian pediatrics. 29: 1101-1106.	Study examines JM-101; device not of interest
Kumar,A., Faridi,M.M., Singh,N., Ahmad,S.H. (1994) Transcutaneous bilirubinometry in the management of bilirubinemia in term neonates. Indian journal of medical research. 99: 227-230.	Secondary publication of Kumar 1992.
Lacaze-Masmonteil,T., Tyrrell,J., Watts,R., Kimak,C., Etches,P., Chinnery,H. (2012) The Use of Transcutaneous Bilirubinometry for Monitoring Jaundiced Newborns in the Community Reduces the Need for Blood Sampling with No Increased Risk of Severe Hyperbilirubinemia: A Cluster Randomized Controlled Trial. Pediatric Academic Societies Annual Meeting.	Conference abstract
Laeeq,A., Yasin,M., Chaudhry,A.R. (1993) Transcutaneous bilirubinometry: clinical application. The Journal of the Pakistan Medical Association. 43: 28-30.	Device studied is JM-101; not of interest
Lam,Tommy S.K., Tsui,K.L., Kam,C.W. (2008) Evaluation of a point-of-care transcutaneous bilirubinometer in Chinese neonates at an accident and emergency department. Hong Kong medical journal. 14: 356-360.	Reference standard not current
Liang,I.S., Lin,J.H., Chen,S.H., Eitzman,D.V. (1983) Transcutaneous bilirubinometry in Chinese term infants. Acta Paediatrica. 24: 8-13.	Reference standard not current
Lin,Y.J., Ju,S.H., Lin,C.H. (1993) The clinical application of transcutaneous bilirubinometry in full-term Chinese infants. Zhonghua Minguo xiao er ke yi xue hui za zhi. 34: 69-76.	Reference standard not current
Luu,M.N., Le,L.T., Tran,B.H., Duong,T.K., Nguyen,H.T., Le,V.T., Partridge,J.C. (2014) Home-use icterometry in neonatal hyperbilirubinaemia: Cluster-randomised controlled trial in Vietnam. Journal of paediatrics and child health. 50: 674-679.	Cluster RCT to assess the use of home based icterometry to improve parental recognition of jaundice; no comparison to serum bilirubin
Maconi,M., Perathoner,C., Tonetto,P., Garzena,E., Prandi,G., Martano,C. (2002) The effectiveness of the BiliCheck method in roomed-in newborns. Italian journal of pediatrics. 28: 191-192.	Letter
Madlon-Kay,D.J. (1997) Recognition of the presence and severity of newborn jaundice by parents, nurses, physicians, and icterometer. Pediatrics. 100: E3.	Method used to measure TSB not reported
Madlon-Kay,D.J. (2001) Home health nurse clinical assessment of neonatal jaundice: comparison of 3 methods. Archives of pediatrics & adolescent medicine. 155: 583-586.	Method used to measure TSB not reported
Madlon-Kay,Diane J. (2002) Maternal assessment of neonatal jaundice after hospital discharge. The Journal of family practice. 51: 445-448.	Unclear timing of tests - nurse obtained bilirubin measurements within 7 days of discharge of infant. Also, method used to measure TSB not reported.
Mah,Michael P., Clark,Steven L., Akhigbe,E., Englebright,J., Frye,Donna K., Meyers,Janet A., Perlin,Jonathan B., Rodriguez,M., Shepard,A. (2010) Reduction of severe hyperbilirubinemia after institution of predischarge bilirubin screening, Pediatrics, 125: e1143-e1148.	Study looks at the efficacy of a universal predischarge neonatal bilirubin screening program in reducing potentially dangerous hyperbilirubinaemia; no relevant data

Reference	Reason for Exclusion
Mahajan,G., Kaushal,R.K., Sankhyan,N., Sharma,R.L., Nakra,M. (2005) Transcutaneous bilirubinometer in assessment of neonatal jaundice in northern India. Indian pediatrics. 42: 41-45.	Reference standard not current
Maisels,M.J., Ostrea,Enrique M.J., Touch,S., Clune,Sarah E., Cepeda,E., Kring,E., Gracey,K., Jackson,C., Talbot,D., Huang,R. (2004) Evaluation of a new transcutaneous bilirubinometers. Pediatrics. 113: 1628-1635.	Reference standard not current
Merritt,K.A., Coulter,D.M. (1994) Application of the Gosset icterometer to screen for clinically significant hyperbilirubinemia in premature infants. Journal of perinatology. 14: 58-65.	Method used to measure TSB not reported
Michaelsson,M. (1972) Evaluation of a method for determination of bilirubin in serum using direct spectrophotometry. Scandinavian journal of clinical and laboratory investigation. 30: 387-390.	Intervention not as specified in protocol
Mohamed,I., Blanchard,A.C., Delvin,E., Cousineau,J., Carceller,A. (2014) Plotting transcutaneous bilirubin measurements on specific transcutaneous nomogram results in better prediction of significant hyperbilirubinemia in healthy term and near-term newborns: a pilot study. Neonatology. 105: 306-311.	Retrospective study and timing of tests not within one hour of each other
Mohieldeen Alsafadi,T.R., Abdullah,Alsaedi S. (2015) The accuracy of transcutaneous bilirubin measurements in preterm infants. Journal of Clinical Neonatology. 4: 18-21.	Reference standard not current
Moyer,V.A., Ahn,C., Sneed,S. (2000) Accuracy of clinical judgment in neonatal jaundice. Archives of pediatrics & adolescent medicine. 154: 391-394.	Method used to measure TSB not reported
Moyer,V.A., Ahn,C., Sneed,S. (2000) Clinical examination could not accurately predict neonatal jaundice. Evidence-Based Medicine. 5: 187.	Commentary
Mussavi,M., Niknafs,P., Bijari,B. (2013) Determining the correlation and accuracy of three methods of measuring neonatal bilirubin concentration. Iranian Journal of Pediatrics. 23: 333-339.	Insufficient details of the reference standard used in the study
Nagar,G., Vandermeer, B., Campbell,S., Kumar,M. (2013) Reliability of transcutaneous bilirubin devices in preterm infants: a systematic review. Pediatrics. 132: 871-881.	Criteria used in this systematic review is not the same as the protocol for this question therefore studies included in this review have been assessed on an individual basis.
Namba,F., Kitajima,H. (2007) Utility of a new transcutaneous jaundice device with two optical paths in premature infants. Pediatrics international: official journal of the Japan Pediatric Society. 49: 497-501.	Reference standard not current
Nanjundaswamy,S., Petrova,A., Mehta,R., Hegyi,T. (2005) Transcutaneous bilirubinometry in preterm infants receiving phototherapy. American journal of perinatology. 22: 127-131.	Accuracy of tests in infants receiving phototherapy; tests would perform differently in this situation
Narang,A., Buche,V.B. (1983) Evaluation of the Minolta Jaundice Meter as a screening device in Indian babies: a preliminary communication. Indian pediatrics. 20: 583-585.	Reference standard not current
Narayanan,I., Banwalikar,J., Mehta,R., Ghorpade,M., Peesay,M.R., Nanda,S., Seth,H.N. (1990) A simple method of evaluation of jaundice in the newborn. Annals of tropical paediatrics. 10: 31-34.	Reference standard not current and unclear timing of tests
Neocleous,C., Adramerina,A., Limnaios,S., Symeonidis,S., Spanou,C., Malakozi,M., Mpampalis,E. (2014) A comparison between transcutaneous and total serum bilirubin in healthy-term greek neonates with clinical jaundice. Prague medical report. 115:	Reference standard not current

Reference	Reason for Exclusion
33-42.	
Palmer,D.C., Zenner,E.M., Drew,J.H. (1982) Transcutaneous bilirubinometry: use in Australia. Australian paediatric journal. 18: 273-276.	Device studied is JM-101; not of interest
Panburana,J., Boonkasidach,S., Rearkyai,S. (2010) Accuracy of transcutaneous bilirubinometry compare to total serum bilirubin measurement. Journal of the Medical Association of Thailand. 93: S81-S86.	Unable to source
Poland,Ronald L., Hartenberger,C., McHenry,H., Hsi,A. (2004) Comparison of skin sites for estimating serum total bilirubin in in-patients and out-patients: chest is superior to brow. Journal of perinatology: official journal of the California. 24: 541-543.	Retrospective study
Raimondi,F., Lama,S., Landolfo,F., Sellitto,M., Borrelli,AC., Maffucci,R., Milite,P., Capasso,L. (2012) Measuring transcutaneous bilirubin: a comparative analysis of three devices on a multiracial population. BMC pediatrics. 12: 70.	Reference standard not current
Randeberg,L., Roll,EB., Nilsen,L.T.N., Christensen,T., Svaasand,L.O. (2005) In vivo spectroscopy of jaundiced newborn skin reveals more than a bilirubin index. Acta paediatrica. 94: 65-71.	Ways to improve algorithm for calculating transcutaneous bilirubin index
Reyes,Christine A., Stednitz,Donald R., Hahn,Carol, Mutchie,Kelly D., McCullough,Steven R., Kronberg,Kent. (2008) Evaluation of the BiliChek being used on hyperbilirubinemic newborns undergoing home phototherapy. Archives of pathology & laboratory medicine. 132: 684-689.	Evaluation of transcutaneous bilirubinometer during phototherapy; tests would perform differently in this situation.
Riskin,A., Kugelman,A., Kuglman,A., Abend-Weinger,M., Green,M., Hemo,M., Bader,D. (2003) In the eye of the beholder: how accurate is clinical estimation of jaundice in newborns?, Acta paediatrica. 92: 574-576.	Reference standard not current
Riskin,A., Tamir,A., Kugelman,A., Hemo,M., Bader,D. (2008) Is visual assessment of jaundice reliable as a screening tool to detect significant neonatal hyperbilirubinemia? The Journal of pediatrics. 152: 782-782.	Reference standard not current
Romagnoli,C., Catenazzi,P., Barone,G., Giordano,L., Riccardi,R., Zuppa,A.A., Zecca,E. (2013) BiliCheck vs JM-103 in identifying neonates not at risk of hyperbilirubinaemia. Italian Journal of Pediatrics. 39 (1)	Reference standard not current
Romagnoli,C., Tiberi,E., Barone,G., De Curtis,M., Regoli,D., Paolillo,P., Picone,S., Anania,S., Finocchi,M., Cardiello,V., Zecca,E. (2012) Validation of transcutaneous bilirubin nomogram in identifying neonates not at risk of hyperbilirubinaemia: a prospective, observational, multicenter study. Early human development. 88: 51-55.	Reference standard not current
Romagnoli,C., Zecca,E., Catenazzi,P., Barone,G., Zuppa,A. (2012) Transcutaneous bilirubin measurement: comparison of Respironics BiliCheck and JM-103 in a normal newborn population. Clinical biochemistry. 45: 659-662.	Reference standard not current
Rubaltelli,F.F., Gourley,G.R., Loskamp,N., Modi,N., Roth-Kleiner,M., Sender,A., Vert,P. (2001) Transcutaneous bilirubin measurement: a multicenter evaluation of a new device. Pediatrics. 107: 1264-1271.	Reference standard not current
Rubegni,P., Cevenini,G., Sbano,P., Perrone,S., Buonocore,G., Lazzeri,L., Vanni,M., Fimiani,M. (2005) Cutaneous colorimetric evaluation of serum concentrations of bilirubin in healthy term neonates: a new methodological approach. Skin Res Technol. 11: 70-75.	No indication that population was suspected of jaundice and method used to measure TSB also not reported.

Reference	Reason for Exclusion
Ruskandi,M., Garna,H., Alisjahbana,A. (1978) The use of icterometer in assessing neonatal jaundice. Paediatrica Indonesian. 18: 158-163.	Reference standard not current
Sajjadian,N., Shajari,H., Saalehi,Z., Esphahani,F., Alizadeh Taheri,P. (2012) Transcutaneous bilirubin measurement in preterm neonates. Acta medica Iranica. 50: 765-770.	Although a TcB device (JH 20- 1A) is examined, study aims to assess the influence of health state (ill vs healthy) and treatment status on accuracy of tests; unclear whether results presented for healthy infants includes those with phototherapy in which case population is not as specified in protocol.
Samiee-Zafarghandy,S., Feberova,J., Williams,K., Yasseen,A.S., Perkins,S.L., Lemyre,B. (2014) Influence of skin colour on diagnostic accuracy of the jaundice meter JM 103 in newborns. Archives of Disease in Childhood: Fetal and Neonatal Edition. 99 (6): F480-F484.	Reference standard not current
Sanpavat,S., Nuchprayoon,I. (2004) Noninvasive transcutaneous bilirubin as a screening test to identify the need for serum bilirubin assessment. Journal of the Medical Association of Thailand. 87: 1193-1198.	Unable to supply study
Sanpavat,S., Nuchprayoon,I. (2005) Comparison of two transcutaneous bilirubinometers--Minolta AirShields Jaundice Meter JM103 and Spectrx Bilicheck--in Thai neonates. The Southeast Asian journal of tropical medicine and public health. 36: 1533-1537.	Reference standard not current
Sanpavat,S., Nuchprayoon,I. (2007) Transcutaneous bilirubin in the pre-term infants. Journal of the Medical Association of Thailand. J Med Assoc Thai. 90: 1803-1808.	Reference standard not current
Sarici,S.U., Koklu,E., Babacan,O. (2014) Comparison of two transcutaneous bilirubinometers in term and near-term neonates. Neonatal Network - Journal of Neonatal Nursing. 33: 138-142.	No comparison against total serum bilirubin
Schlebusch,H., Axer,K., Schneider,C., Liappis,N., Rohle,G. (1990) Comparison of five routine methods with the candidate reference method for the determination of bilirubin in neonatal serum. Journal of clinical chemistry and clinical biochemistry. 28: 203-210.	Comparison of 5 laboratory methods of determining TSB therefore intervention not as specified in protocol
Schumacher,R.E., Thornbery,J.M., Gutcher,G.R. (1985) Transcutaneous bilirubinometry: a comparison of old and new methods. Pediatrics. 76: 10-14.	Reference standard not current
Sharma,J.N., Singh,R.N., Lodha,A., Singh,J. (1988) Transcutaneous bilirubinometry in newborns. Indian pediatrics. 25: 757-760.	Reference standard not current
Sheridan-Pereira,M., Gorman,W. (1982) Transcutaneous bilirubinometry: an evaluation. Archives of disease in childhood. 57: 708-710.	Short report: unclear which device was used to measure TcB as details are not well described
Singh,Kh, Singh,M.A., Shartsho,J.T. (2009) A study of neonatal jaundice (0-14 days). Journal of Medical Society. 23 (1): 11-14.	No relevant outcomes are reported
Siu,L., Kwong,N. (2010) Minolta JM-103 jaundice meter: A screening tool for neonatal jaundice in Chinese Neonates in Maternal and Child Health Centres. Hong Kong Journal of Paediatrics.15 (3): 204-213.	Retrospective study
Siu,L.Y., Siu,L.W., Au,S.K., Li,K.W., Tsui,T.K., Chang,Y.Y., Lee,G.P., Kwong,N.S. (2010) Evaluation of a transcutaneous bilirubinometer with two optical paths in Chinese preterm infant. Hong Kong Journal of Paediatrics. 15 (2): 132-140.	Reference standard not current
Slusher,Tina M., Angyo,Ishaya A., Bode-Thomas,Fidela,	Reference standard not

Reference	Reason for Exclusion
Akor,Francis, Pam,Sunday D., Adetunji,Adedotun A., McLaren,Donald W., Wong,Ronald J., Vreman,Hendrik J., Stevenson,David K. (2004) Transcutaneous bilirubin measurements and serum total bilirubin levels in indigenous African infants. Pediatrics. 113: 1636-1641.	current
Stein,H., Wolfsdorf,J., Buchanan,N. (1975) The use of the icterometer in assessing neonatal jaundice. The Journal of tropical pediatrics and environmental child health. 21: 67-68.	Unclear timing of tests and method used to measure TSB not reported
Stein,S.M., McKinley,I., Horn,D.B., Keay,A.J. (1974) Total neonatal bilirubin: an assessment of the photo-ictometer. International journal of clinical chemistry. 54: 107-113.	Timing of tests and whether study was prospective is unclear; methods not well described.
Stillova,L., Matasova,K., Zibolen,M., Stilla,J., Kolarovszka,H. (2009) Transcutaneous bilirubinometry in preterm neonates. Indian pediatrics. 46: 405-408.	Reference standard not current
Stillova,L., Matasova,K., Mikitova,T., Stilla,J., Kolarovszka,H., Zibolen,M. (2007) Evaluation of transcutaneous bilirubinometry in preterm infants of gestational age 32-34 weeks. Biomedical papers of the Medical Faculty of the University Palacky. 151: 267-271.	Reference standard not current
Stokowski,Laura A. (2002) Early recognition of neonatal jaundice and kernicterus. Advances in neonatal care: official journal of the National Association of Neonatal Nurses. 2: 101-109.	Narrative review
Szabo,P., Wolf,M., Bucher,H.U., Haensse,D., Fauchere,J.C., Arlettaz,R. (2004) Assessment of jaundice in preterm neonates: comparison between clinical assessment, two transcutaneous bilirubinometers and serum bilirubin values. Acta paediatrica. 93: 1491-1495.	Reference standard not current
Szabo,P., Wolf,M., Bucher,HU., Fauchere,JC., Haensse,D., Arlettaz,R. (2004) Detection of hyperbilirubinaemia in jaundiced full-term neonates by eye or by bilirubinometer? European journal of pediatrics. 163: 722-727.	Reference standard not current
Taha,S.A., Karrar,Z.A., Dost,S.M. (1984)Transcutaneous bilirubin measurement in evaluating neonatal jaundice among Saudi newborns. Annals of tropical paediatrics. 4: 229-231.	Reference standard not current
Tan,K.L. (1982) Transcutaneous bilirubinometry in fullterm Chinese and Malay infants. Acta paediatrica Scandinavica. 71: 593-59.	Reference standard not current
Tan,K.L. (1985) Transcutaneous bilirubinometry in Chinese and Malay neonates. Annals of the Academy of Medicine. 14: 591-594.	Reference standard not current
Tan,K.L., Chia,H.P., Koh,B.C. (1996) Transcutaneous bilirubinometry in Chinese, Malay and Indian infants. Acta paediatrica. 85: 986-990.	Reference standard not current
Tan,K.L., Dong,F. (2003) Transcutaneous bilirubinometry during and after phototherapy. Acta Paediatrica. 92: 327-331.	Although study reports before phototherapy data, reference standard not current
Tan,K.L., Mylvaganam,A. (1988) Transcutaneous bilirubinometry in preterm very low birthweight infants. Acta paediatrica Scandinavica. 77: 796-801.	Reference standard not current and study assesses plasma bilirubin not serum bilirubin
Tayaba,R., Gribetz,D., Gribetz,I., Holzman,I.R. (1998) Noninvasive estimation of serum bilirubin. Pediatrics. 102: E28.	Reference standard not current and unclear timing of tests
Thong,Y.H., Rahman,A.A., Choo,M., Tor,S.T., Robinson,M.J. (1976) Dermal icteric zones and serum bilirubin levels in neonatal jaundice. Singapore medical journal. 17: 184-185.	Reference standard not current
Tsai,L.T., Lu,C.C. (1988) Clinical evaluation of transcutaneous	Unable to supply

Reference	Reason for Exclusion
jaundice meter in full-term newborns. Zhonghua Minguo xiao er ke yi xue hui za zhi. 29: 376-382.	
Tudehope,D.I., Chang,A. (1982) Multiple site readings from a transcutaneous bilirubinometers. Australian paediatric journal. 18: 102-105.	Reference standard not current
Tudehope,D.I., Chang,A. (1982) Non-invasive method of measuring bilirubin levels in newborn infants. The Medical journal of Australia. 1: 165-168.	Reference standard not current
Wainer,S., Bolton,K.D., Cooper,P.A., Rothberg,A.D. (1989) Transcutaneous bilirubinometry in black infants: Improved reliability after correction for the background signal. Pediatric Reviews and Communications. 4: 93-99.	Study assesses the importance of background signal in improving the accuracy of transcutaneous bilirubin measurements
Wainer,S., Parmar,SM., Allegro,D., Rabi,Y., Lyon,ME. (2012) Impact of a transcutaneous bilirubinometry program on resource utilization and severe hyperbilirubinaemia. Pediatrics. 129: 77-86.	Study aims to assess the impact of programmatic and coordinated use of a TcB program by using validated nomograms; no relevant correlation data to TSB reported
Waterston,T., Taputaira,M. (1983) Reliability of icterometer. The Central African journal of medicine. 29: 242-244.	Details of method used to measure TSB not reported and unclear timing of tests
Wickremasinghe,Andrea C., Karon,Brad S., Cook,Walter J. (2011) Accuracy of neonatal transcutaneous bilirubin measurement in the outpatient setting. Clinical pediatrics. 50: 1144-1149.	Index test and reference standard not performed within one hour of each other due to constraints (laboratory located on lower level of clinic building)
Williams,R.A., Pitts,L.L., Weinerth,J.L., Dimmette,R.M. (1971) Clinical laboratory evaluation of the American optical Bilirubinometer. The Journal of pediatrics. 79: 671-674.	Reference standard not current
Yamanouchi,I., Yamauchi,Y., Igarashi,I. (1980) Transcutaneous bilirubinometry: preliminary studies of noninvasive transcutaneous bilirubin meter in the Okayama National Hospital. Pediatrics. 65: 195-202.	Reference standard not current.
Yamauchi,Y., Yamanouchi,I. (1988) Transcutaneous bilirubinometry. Evaluation of accuracy and reliability in a large population. Acta paediatrica Scandinavica. 77: 791-795.	Reference standard not current
Yamauchi,Y., Yamanouchi,I. (1989) Transcutaneous bilirubinometry: serum bilirubin measurement using transcutaneous bilirubinometer (TcB). A preliminary study. Biology of the neonate. 56: 257-262.	Study assesses the use of 3 types of cuvettes to improve the reliability of a transcutaenous device (i.e no comparison to serum bilirubin).
Yamauchi,Y., Yamanouchi,I. (1989) Transcutaneous bilirubinometry in normal Japanese infants. Acta paediatrica Japonica. 31: 65-72.	Retrospective study and reference standard not current
Yap,S.H., Mohammad,I., Ryan,C.A. (2002) Avoiding painful blood sampling in neonates by transcutaneous bilirubinometry. Irish journal of medical science. 171: 188-190.	Serum bilirubin measured only when Bilicheck measurements exceeded the phototherapy line of a recognised phototherapy guideline chart; unclear timing of tests.
Yaser,A., Tooke,L., Rhoda,N. (2014) Interscapular site for	Method used to measure

Reference	Reason for Exclusion
transcutaneous bilirubin measurement in preterm infants: a better and safer screening site. Journal of perinatology: official journal of the California Perinatal Association. 34: 209-212.	TSB not reported.
Yasuda,S., Itoh,S., Isobe,K., Yonetani,M., Nakamura,H., Nakamura,M., Yamauchi,Y., Yamanishi,A. (2003) New transcutaneous jaundice device with two optical paths. Journal of perinatal medicine. 31: 81-88.	Reference standard not current
Yip,W.C., Teo,J., Tay,J.S. (1983) Transcutaneous bilirubinometry. Acta paediatrica Scandinavica. 72: 289.	Letter
Zecca,E., Barone,G., De Luca,D., Marra,R., Tiberi,E., Romagnoli,C. (2009) Skin bilirubin measurement during phototherapy in preterm and term newborn infants. Early human development. 85: 537-540.	Reference standard not current and results before phototherapy are not reported.

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F.22 Review question 4

Reference	Reason for exclusion
Anon (2004) Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics.114 (1) (pp 297-316), 2004.Date of Publication: July 2004. 297-316.	Unclear guideline development process and methods.
Anon (2010) Screening of infants for hyperbilirubinemia to prevent chronic bilirubin encephalopathy: Recommendation statement. American Family Physician.82 (4) (pp 408-410), 2010.Date of Publication: August 15, 2010. 408-10.	Not relevant – about universal screening programme.
Agarwal R, Kaushal M, Aggarwal R et al. (2002) Early neonatal hyperbilirubinemia using first day serum bilirubin level. Indian Pediatrics 39: 724-30.	Not relevant – TSB levels not linked to outcomes.
Ahlfors CE (1994) Criteria for exchange transfusion in jaundiced newborns. Pediatrics.93 (3) (pp 488-494), 1994.Date of Publication: 1994. 488-94.	Not relevant – about the distribution of different groups of babies with different TSB, no link to outcomes.
Akinpelu OV, Waissbluth S, Daniel SJ (2013) Auditory risk of hyperbilirubinemia in term newborns: A systematic review. International Journal of Pediatric Otorhinolaryngology.77 (6) (pp 898-905), 2013.Date of Publication: June 2013. 898-905.	Not relevant – about auditory assessment.
Akman I, Ozek E, Kulekci S et al. (2004) Auditory neuropathy in hyperbilirubinemia: is there a correlation between serum bilirubin, neuron-specific enolase levels and auditory neuropathy? International Journal of Audiology 43: 516-22.	Not relevant – about auditory assessment and auditory neuropathy.
AlOtaibi SF, Blaser S, MacGregor DL (2005) Neurological complications of kernicterus. Canadian Journal of Neurological Sciences 32: 311-5.	Not relevant – aetiology of kernicterus.
Alpay F, Sarici SU, Tosuncuk HD et al. (2000) The value of first-day bilirubin measurement in predicting the development of significant hyperbilirubinemia in healthy term newborns. Pediatrics 106: E16.	Not relevant – no usable data that linked to outcomes.
American Academy of Pediatrics Subcommittee on Hyperbilirubinemia (2004) Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation.[Erratum appears in Pediatrics. 2004 Oct;114(4):1138]. Pediatrics 114: 297-316.	Unclear guideline development process and methods.
Atkinson M, Budge H (2011) Review of the NICE guidance on neonatal jaundice. Archives of Disease in Childhood: Education and Practice Edition.96 (4) (pp 136-140), 2011.Date of Publication: August 2011. 136-40.	Not relevant.

Reference	Reason for exclusion
Awasthi S, Rehman H (1998) Early prediction of neonatal hyperbilirubinemia. Indian Journal of Pediatrics 65: 131-9.	Mixed population with pre-term babies, cannot separate the data.
Barak M, Berger I, Dollberg S et al. (2009) When should phototherapy be stopped? A pilot study comparing two targets of serum bilirubin concentration. Acta Paediatrica 98: 277-81.	Not relevant – about when to stop phototherapy.
Barton M, Calonge N, Petitti DB et al. (2009) Screening of infants for hyperbilirubinemia to prevent chronic bilirubin encephalopathy: US Preventive Services Task Force recommendation statement. Pediatrics.124 (4) (pp 1172-1177), 2009.Date of Publication: 2009. 1172-7.	Not relevant – about universal screening programme.
Behjati-Ardakani S, Nikkhah A, Ashrafi MR et al. (2006) Association between total serum bilirubin level and manifestations of kernicterus. Acta Medica Iranica.44 (6) (pp 405-408), 2006.Date of Publication: 2006. 405-8.	Unclear baseline characteristics of the study population.
Bhutani VK, Johnson LH (2000) Managing the assessment of neonatal jaundice: importance of timing. Indian Journal of Pediatrics 67: 733-7.	Single case report.
Bhutani VK, Johnson LH, Keren R (2004) Diagnosis and management of hyperbilirubinemia in the term neonate: for a safer first week. [Review] [23 refs]. Pediatric Clinics of North America 51: 843-61.	Commentary paper – not primary study or guideline.
Bhutani VK, Johnson LH, Schwoebel A et al. (2006) A systems approach for neonatal hyperbilirubinemia in term and near-term newborns. JOGNN - Journal of Obstetric, Gynecologic, & Neonatal Nursing 35: 444-55.	Not relevant – about discharge strategy.
Bhutani VK, Johnson L (2009) Kernicterus in the 21st century: Frequently asked questions. Journal of Perinatology.29 (SUPPL.) (pp S20-S24), 2009.Date of Publication: 2009. S20-S24.	Not relevant – aetiology of kernicterus.
Bhutani VK (2009) Screening for severe neonatal hyperbilirubinemia. Pediatric Health.3 (4) (pp 369-379), 2009.Date of Publication: 2009. 369-79.	Commentary paper – not a primary study or full guideline.
Bhutani VK, Vilms RJ, Hamerman-Johnson L (2010) Universal bilirubin screening for severe neonatal hyperbilirubinemia. [Review]. Journal of Perinatology 30: Suppl-15.	Commentary paper – not primary study.
Bhutani VK, Stark AR, Lazzeroni LC et al. (2013) Predischarge screening for severe neonatal hyperbilirubinemia identifies infants who need phototherapy. Journal of Pediatrics 162: 477-82.	Not relevant – about universal screening programme.
Bhutani VK, Wong RJ, Vreman HJ et al. (2015) Bilirubin production and hour-specific bilirubin levels. J Perinatol	Not relevant – about end-tidal carbon monoxide concentrations.
Birchwood G, Mehta R, Petrova A (2010) Normal distribution of pre-discharge total serum bilirubin in a culturally diverse cohort of healthy term newborn infants. Journal of Neonatal-Perinatal Medicine.3 (3) (pp 223-227), 2010.Date of Publication: 2010. 223-7.	Discharge TSB levels not linked to any outcomes – no usable data.
Boo NY, Oakes M, Lye MS et al. (1994) Risk factors associated with hearing loss in term neonates with hyperbilirubinaemia. Journal of Tropical Pediatrics 40: 194-7.	Not relevant – about clinical risk factors.
Broberger U, Aperia A (1979) Renal function in infants with hyperbilirubinemia. Acta Paediatrica Scandinavica 68: 75-9.	No usable data, no liked-datai between TSB levels and renal function.
Burgos AE, Flaherman VJ, Newman TB (2012) Screening and follow-up for neonatal hyperbilirubinemia: a review. [Review]. Clinical Pediatrics 51: 7-16.	Commentary paper – not primary study.
Carbonell X, Botet F, Figueras J et al. (2001) Prediction of	Not relevant – about TcB.

Reference	Reason for exclusion
hyperbilirubinaemia in the healthy term newborn. Acta Paediatrica 90: 166-70.	
Christensen RD, Lambert DK, Henry E et al. (2013) Unexplained extreme hyperbilirubinemia among neonates in a multihospital healthcare system. Blood Cells Molecules & Diseases 50: 105-9.	TSB thresholds not linked to outcomes.
Crawford-Faucher A (2010) Universal screening effective in identifying severe hyperbilirubinemia. American Family Physician.82 (4) (pp 433), 2010.Date of Publication: August 15, 2010. 433.	Not relevant – about universal screening programme.
Dwarampudi GS, Ramakrishna N (2015) Cord blood albumin and bilirubin levels as predictors in neonatal hyperbilirubinemia. International Journal of Pharma and Bio Sciences.6 (3) (pp B273-B279), 2015.Date of Publication: 2015. B273-B279.	Not relevant – about cord blood albumin.
Ebbesen F, Andersson C, Verder H et al. (2005) Extreme hyperbilirubinaemia in term and near-term infants in Denmark. Acta Paediatrica 94: 59-64.	No usable data, no linked-data between TSB and outcomes.
Ebbesen F, Bjerre JV, Vandborg PK (2012) Relation between serum bilirubin levels >450 mmicromole/L and bilirubin encephalopathy; a Danish population-based study. Acta Paediatrica 101: 384-9.	Not relevant – about the epidemiology of babies with different TSB levels, not linked to any outcomes.
Fay DL, Schellhase KG, Suresh GK (2009) Bilirubin screening for normal newborns: A critique of the hour-specific bilirubin nomogram. Pediatrics.124 (4) (pp 1203-1205), 2009.Date of Publication: 2009. 1203-5.	Commentary paper – not a primary study.
Flaherman VJ, Ferrara A, Newman TB (2008) Predicting significant hyperbilirubinaemia using birth weight. Archives of Disease in Childhood Fetal & Neonatal Edition 93: F307-F309.	Not relevant – about clinical factor (birth weight).
Flaherman VJ, Kuzniewicz MW, Escobar GJ et al. (2012) Total serum bilirubin exceeding exchange transfusion thresholds in the setting of universal screening. Journal of Pediatrics 160: 796-800.	Not relevant – about universal screening programme.
Gamaleldin R, Iskander I, Seoud I et al. (2011) Risk factors for neurotoxicity in newborns with severe neonatal hyperbilirubinemia. Pediatrics 128: e925-e931.	Combination of TSB and clinical risk factors prediction, cannot separate out TSB data.
Gkoltsiou K, Tzoufi M, Counsell S et al. (2008) Serial brain MRI and ultrasound findings: relation to gestational age, bilirubin level, neonatal neurologic status and neurodevelopmental outcome in infants at risk of kernicterus. Early Human Development 84: 829-38.	Not relevant – about neurodevelopment and no link data with TSB levels.
Goncalves A, Costa S, Lopes A et al. (2011) Prospective validation of a novel strategy for assessing risk of significant hyperbilirubinemia. Pediatrics 127: e126-e131.	Some measurements of bilirubin were collected by using TcB.
Gotink MJ, Benders MJ, Lavrijsen SW et al. (2013) Severe neonatal hyperbilirubinemia in the Netherlands. Neonatology 104: 137-42.	Not relevant.
Heimler R, Sasidharan P (2010) Neurodevelopmental and audiological outcome of healthy term newborns with moderately severe non-haemolytic hyperbilirubinemia. Journal of Paediatrics & Child Health 46: 588-91.	Not relevant – re-admitted population.
Heydarian F, Majdi M (2010) Severe neonatal hyperbilirubinemia; causes and contributing factors leading to exchange transfusion at Ghaem Hospital in Mashhad. Acta Medica Iranica 48: 399-402.	Not relevant – about causes of severe hyperbilirubinaemia.
Huang HC, Yang HI, Chang YH et al. (2012) Model to predict hyperbilirubinemia in healthy term and near-term newborns with exclusive breast feeding. Pediatrics & Neonatology 53: 354-8.	Not relevant – about clinical risk factors.
Hulya B, Eren O, Ahmet T (2008) Is the hour-specific bilirubin nomogram suitable for predicting hyperbilirubinemia. Indian Journal of Pediatrics 75: 447-50.	Not relevant – no usable data, no predicted endpoint time.

Reference	Reason for exclusion
Ip S, Chung M, Kulig J et al. (2004) An evidence-based review of important issues concerning neonatal hyperbilirubinemia. [Review] [164 refs]. Pediatrics 114: e130-e153.	Not relevant.
Iskander I, Gamaleldin R, El HS et al. (2014) Serum bilirubin and bilirubin/albumin ratio as predictors of bilirubin encephalopathy. Pediatrics 134: e1330-e1339.	Inappropriate population – babies with ABO incompatibility, G6PD, Rh incompatibility and sepsis.
Jodeiry B, Fakhraee S-H, Kazemian M et al. (2013) Rebound hyperbilirubinaemia in neonates admitted to Mofid Children's Hospital, Tehran, Iran. SAJCH South African Journal of Child Health.7 (1) (pp 22-24), 2013.Date of Publication: 2013. 22-4.	Not relevant – about rebound jaundice.
Johnson L, Bhutani VK (1998) Guidelines for management of the jaundiced term and near-term infant. Clinics in Perinatology.25 (3) (pp 555-574), 1998.Date of Publication: 1998. 555-74.	Commentary review, not a full guideline.
Kern S, Reuter S (2015) Neonatal hyperbilirubinemia--an update for South Dakota physicians. [Review]. South Dakota Medicine: The Journal of the South Dakota State Medical Association 68: 23-7.	Commentary paper – not primary study.
Kim HJ, Kim CR, Oh JW et al. (1998) Comparison of Phototherapy Guidelines for Neonatal Jaundice in Healthy Term Newborns. Journal of the Korean Pediatric Society 41: 606-13.	Not in English.
Kuzniewicz MW, Escobar GJ, Wi S et al. (2008) Risk factors for severe hyperbilirubinemia among infants with borderline bilirubin levels: a nested case-control study. Journal of Pediatrics 153: 234-40.	Combination of TSB and clinical risk factors prediction, cannot separate out TSB data.
Kuzniewicz MW, Escobar GJ, Newman TB (2009) Impact of universal bilirubin screening on severe hyperbilirubinemia and phototherapy use. Pediatrics 124: 1031-9.	Not relevant – about universal screening programme.
Lee YK, Daito Y, Katayama Y et al. (2009) The significance of measurement of serum unbound bilirubin concentrations in high-risk infants. Pediatrics International 51: 795-9.	No usable data, TSB levels not linked to outcomes.
Lunsing RJ, Pardoen WF, Hadders-Algra M (2013) Neurodevelopment after moderate hyperbilirubinemia at term. Pediatric Research 73: 655-60.	Not relevant – about neurodevelopment of babies.
Maisels MJ, Gifford K, Antle CE et al. (1988) Jaundice in the healthy newborn infant: a new approach to an old problem. Pediatrics 81: 505-11.	Not relevant – about universal screening programme.
Maisels MJ, Bhutani VK, Bogen D et al. (2009) Hyperbilirubinemia in the newborn infant > or =35 weeks' gestation: an update with clarifications. [Review] [26 refs]. Pediatrics 124: 1193-8.	Not relevant – about correlation of clinical risk factors.
Maisels MJ (2015) Managing the jaundiced newborn: a persistent challenge. [Review]. CMAJ Canadian Medical Association Journal 187: 335-43.	Opinion, not research evidence.
Malan JE, Ransome OJ, Reinach SG (1990) Predicting the need for phototherapy early in idiopathic neonatal hyperbilirubinemia. Pediatric Reviews and Communications.5 (1) (pp 39-44), 1990.Date of Publication: 1990. 39-44.	Unclear what TSB threshold was used to initiate phototherapy.
Mamtani M, Patel A, Renge R et al. (2007) Prognostic value of direct bilirubin in neonatal hyperbilirubinemia. Indian Journal of Pediatrics 74: 819-22.	Population included pre-term babies, unable to separate the data.
Mayer I, Gursoy T, Hayran M et al. (2014) Value of twelfth hour bilirubin level in predicting significant hyperbilirubinemia in preterm infants. Journal of Clinical Medicine Research 6: 190-6.	Population included pre-term babies, unable to separate the data.
Mazahy MM, Elkhalegy HA, Emran TM et al. (2014) Value of first-day serum bilirubin measurement in predicting the development of neonatal hyperbilirubinemia. Trends in Medical Research.9 (2) (pp	No usable data – no timeframe for the measurement of TSB and

Reference	Reason for exclusion
98-106), 2014.Date of Publication: 2014. 98-106.	when the outcome were predicted.
Moll M, Goelz R, Naegele T et al. (2011) Are recommended phototherapy thresholds safe enough for extremely low birth weight (ELBW) infants? A report on 2 ELBW infants with kernicterus despite only moderate hyperbilirubinemia. Neonatology 99: 90-4.	2 case reports of very low birth weight babies.
Nakamura H, Yonetani M, Uetani Y et al. (1992) Determination of serum unbound bilirubin for prediction of kernicterus in low birthweight infants. Acta Paediatrica Japonica 34: 642-7.	Not relevant – about very low birth weight babies.
Narang A, Kumar P, Kumar R (2001) Neonatal jaundice in very low birth weight babies. Indian Journal of Pediatrics 68: 307-9.	Not relevant – specific population of babies with very low birth weight.
Newman TB, Xiong B, Gonzales VM et al. (2000) Prediction and prevention of extreme neonatal hyperbilirubinemia in a mature health maintenance organization. Archives of Pediatrics & Adolescent Medicine 154: 1140-7.	Not relevant – about clinical risk factors.
Newman TB, Liljestrand P, Escobar GJ (2002) Jaundice noted in the first 24 hours after birth in a managed care organization. Archives of Pediatrics & Adolescent Medicine 156: 1244-50.	Not relevant – about notation of jaundice.
Newman TB, Liljestrand P, Escobar GJ (2003) Infants with bilirubin levels of 30 mg/dL or more in a large managed care organization. Pediatrics 111: t-11.	Case reports.
Newman TB, Liljestrand P, Jeremy RJ et al. (2006) Outcomes among newborns with total serum bilirubin levels of 25 mg per deciliter or more. New England Journal of Medicine 354: 1889-900.	Unclear outcome measurement – unclear when TSB was measured (between day-1 to day-30 of birth).
Nickisch A, Massinger C, Ertl-Wagner B et al. (2009) Pedaudiologic findings after severe neonatal hyperbilirubinemia. European Archives of Oto-Rhino-Laryngology 266: 207-12.	Population included pre-term babies, unable to separate the data.
Ogunlesi TA, Dedeke IO, Adekanmbi AF et al. (2007) The incidence and outcome of bilirubin encephalopathy in Nigeria: a bi-centre study. Nigerian Journal of Medicine: Journal of the National Association of Resident Doctors of Nigeria 16: 354-9.	Not relevant – about causes for bilirubin encephalopathy.
Oktay R, Satar M, Atici A (1996) The risk of bilirubin encephalopathy in neonatal hyperbilirubinemia. Turkish Journal of Pediatrics 38: 199-204.	Population included pre-term babies, unable to separate the data.
Osborn LM, Reiff MI, Bolus R (1984) Jaundice in the full-term neonate. Pediatrics 73: 520-5.	Not relevant – about correlation of different risk factors.
Pathak U, Chawla D, Kaur S et al. (2013) Bilirubin nomogram for prediction of significant hyperbilirubinemia in north Indian neonates. Indian Pediatrics 50: 383-9.	Bilirubin of some babies was measured by TcB instead of TSB.
Prasarnphanich T, Somlaw S (2007) The value of routine bilirubin screening to detect significant hyperbilirubinemia in Thai healthy term newborns. Journal of the Medical Association of Thailand 90: 925-30.	Not relevant – about universal screening programme.
Randev S, Grover N (2010) Predicting neonatal hyperbilirubinemia using first day serum bilirubin levels. Indian Journal of Pediatrics 77: 147-50.	Not relevant – no usable data, unclear of the predicted time and endpoint.
Romagnoli C, De LD, Zuppa AA et al. (2005) Could early serum bilirubin measurement be useful in predicting non physiologic hyperbilirubinemia? Italian Journal of Pediatrics.31 (1) (pp 52-60), 2005.Date of Publication: February 2005. 52-60.	Not relevant – included pre-term babies and babies with low birth weight, cannot separate out the data.

Reference	Reason for exclusion
Romagnoli C, Barone G, Pratesi S et al. (2014) Italian guidelines for management and treatment of hyperbilirubinaemia of newborn infants > 35 weeks' gestational age. Italian Journal of Pediatrics.40 (1) , 2014.Article Number: 11.Date of Publication: 31 Jan 2014.	An amalgamation of the NICE guideline and AAP guideline, no usable data.
Sabatino G, Verrotti A, Ramenghi LA et al. (1996) Newborns with hyperbilirubinemia: usefulness of brain stem auditory response evaluation. Neurophysiologie Clinique 26: 363-8.	Not relevant – about brain stem auditory assessment.
Sakha SH, Gharehbaghi MM (2010) Exchange transfusion in severe hyperbilirubinemia: An experience in northwest Iran. Turkish Journal of Pediatrics.52 (4) (pp 367-371), 2010.Date of Publication: July-August 2010. 367-71.	Not relevant – about causes of jaundice and adverse effects of exchange transfusion.
Salas AA, Mazzi E (2008) Exchange transfusion in infants with extreme hyperbilirubinemia: an experience from a developing country. Acta Paediatrica 97: 754-8.	Not relevant – no data on the relationship between TSB and exchange transfusion.
Sciuto M, Bertino G, Zocco M et al. (2009) Incidence and causes of neonatal hyperbilirubinemia in a center of Catania. Therapeutics & Clinical Risk Management 5: 247-50.	Not relevant – about causes of hyperbilirubinaemia.
Seidman DS, Ergaz Z, Paz I et al. (1999) Predicting the risk of jaundice in full-term healthy newborns: a prospective population-based study. Journal of Perinatology 19: t-7.	Not relevant – very low TSB threshold was used for significant hyperbilirubinaemia.
Sharma R, Grover N, Sankhyan N et al. (2006) Auditory brainstem responses in neonatal hyperbilirubinemia and effect of therapy. Indian Journal of Otolaryngology & Head & Neck Surgery 58: 340-2.	Not relevant – about auditory brainstem assessment.
Slaughter J, Annibale D, Suresh G (2009) False-negative results of pre-discharge neonatal bilirubin screening to predict severe hyperbilirubinemia: a need for caution. European Journal of Pediatrics 168: 1461-6.	Not relevant – about discharge strategy.
Soorani-Lunsing I, Woltil HA, Hadders-Algra M (2001) Are moderate degrees of hyperbilirubinemia in healthy term neonates really safe for the brain? Pediatric Research 50: 701-5.	TSB thresholds not linked to outcomes.
Surjono A, Triasih R, Haksari EL (2003) The first 24 hours bilirubin level as a predictor of hyperbilirubinemia in healthy term newborns. Perinatology.5 (4) (pp 159-166), 2003.Date of Publication: July/August 2003. 159-66.	TSB thresholds not linked to outcomes.
Tiker F, Gulcan H, Kilicdag H et al. (2006) Extreme hyperbilirubinemia in newborn infants. Clinical Pediatrics 45: 257-61.	TSB thresholds not linked to outcomes.
Trikalinos TA, Chung M, Lau J et al. (2009) Systematic review of screening for bilirubin encephalopathy in neonates. Pediatrics.124 (4) (pp 1162-1171), 2009.Date of Publication: 2009. 1162-71.	Not relevant – about the combination of TSB and other clinical risk factors.
van de Bor M, Ens-Dokkum M, Schreuder AM et al. (1992) Hyperbilirubinemia in low birth weight infants and outcome at 5 years of age. Pediatrics 89: 359-64.	Inappropriate population – very low birth weight babies.
Walsh SA, Murphy JF (2010) Neonatal jaundice--are we over-treating? Irish Medical Journal 103: 28-9.	Unclear methodology of the research, narrative summary of findings with no usable data.
Weng YH, Chiu YW, Cheng SW et al. (2011) Risk assessment for adverse outcome in term and late preterm neonates with bilirubin values of 20 mg/dL or more. American Journal of Perinatology 28: 405-12.	Inappropriate population – babies with ABO incompatibility, G6PD, Rh incompatibility and sepsis.
Wennberg RP, Ahlfors CE, Aravkin AY (2009) Intervention guidelines for neonatal hyperbilirubinemia: An evidence based quagmire. Current Pharmaceutical Design.15 (25) (pp 2939-2945), 2009.Date of	Commentary review, not a full guideline.

Reference	Reason for exclusion
Publication: September 2009. 2939-45.	
Wong V, Chen W-X, Wong K-Y (2006) Short- and long- term outcome of severe neonatal nonhemolytic hyperbilirubinemia. Journal of Child Neurology.21 (4) (pp 309-315), 2006.Date of Publication: April 2006. 309-15.	Not relevant – about demographic risk factors, not about TSB thresholds.
Yetman RJ, Parks DK, Huseby V et al. (1998) Rebound bilirubin levels in infants receiving phototherapy. Journal of Pediatrics 133: 705-7.	Not relevant – about rebound jaundice.
Yeung CY (1985) Kernicterus in term infants. Australian Paediatric Journal 21: 273-4.	Unclear what TSB threshold were used for the study, no usable data.
Yu Z-B, Han S-P, Chen C (2014) Bilirubin nomograms for identification of neonatal hyperbilirubinemia in healthy term and late-preterm infants: a systematic review and meta-analysis. World Journal of Pediatrics.10 (3) (pp 211-218), 2014.Date of Publication: 01 Aug 2014. 211-8.	A qualitative review on nomograms, does not meet review protocol criteria, used as cross-checking for references.
Zhu J, Xu Y, Zhang G et al. (2012) Total serum bilirubin levels during the first 2 days of life and subsequent neonatal morbidity in very low birth weight infants: a retrospective review. European Journal of Pediatrics 171: 669-74.	Not relevant – about babies with very low birth weight.

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1 Appendix G: Evidence tables

G.1 2 Review question 3

Bibliographic reference	**Rylance (2014)** **Can transcutaneous bilirubinometry safely guide phototherapy treatment of neonatal jaundice in Malawi?**
Study type	Prospective cohort study
Aim	To assess the correlation between total serum bilirubin (TSB) and transcutaneous bilirubin (TcB) values in Malawian newborn infants, and to investigate whether TcB can be used safely to guide phototherapy treatment in the absence of TSB results.
Patient characteristics	**Inclusion criteria** - All visibly jaundiced infants <14 days old admitted to the neonatal nursery during the study period (subjects were recruited by convenience sampling based on availability of staff and unit workload) **Exclusion criteria** - Infants deemed too unwell to participate i.e. the extremely premature or very sick in whom the extra handling and blood sampling might have been inappropriate and poorly tolerated **Other characteristics** *Sex, n (%)* Male: 71 (55) *Birthweight category in kg* Normal (>2.5): 47 (37) Low (1.5 to 2.5): 64 (50) Very low (<1.5): 17 (13) *Gestational age in weeks, n (%)* ≥37: 51 (40) 32 – 36: 71 (55) <32: 6 (5) *Breastfeeding, n (%)* 128 (100)

<table>
<tr><th>Bibliographic reference</th><th>Rylance (2014)
Can transcutaneous bilirubinometry safely guide phototherapy treatment of neonatal jaundice in Malawi?</th></tr>
<tr><td></td><td>Age at first bilirubin sample, days, n (%)
1: 3 (2)
2: 14 (11)
3: 36 (28)
4 days or more: 75 (59)

Ethnicity
All African newborns</td></tr>
<tr><td>Number of patients</td><td>n=128 infants (132 eligible, 129 mothers consented to take part, 1 excluded due to missing data)
n= 296 TSB samples analysed; 167 from infants not under phototherapy; 129 from infants undergoing phototherapy

60% (77/128) born prematurely (<37 weeks)</td></tr>
<tr><td>Index test</td><td>TcB measurement

<u>Details</u>
- Performed on both sternum and forehead using Drager JM-103 jaundice meter
- Mean of 3 readings used for analysis</td></tr>
<tr><td>Reference standard (or Gold standard)</td><td>TSB measurement

<u>Details</u>
- Heel prick blood samples taken by 2 medical staff for a maximum of 3 days
- Analysed daily by a timed endpoint diazo method, using a Synchron CX5 Pro machine (Beckman Coutler)
- Machine uses two control solutions and is calibrated every 14 days</td></tr>
<tr><td>Time between testing & treatment</td><td>- Index test and reference standard measured concomitantly
- The results were not obtained in time to influence treatment; phototherapy was commenced if the TcB exceeded the relevant treatment threshold (WHO thresholds), taking into account of the infant’s age, gestation, size and clinical condition as summarised in table below.

<table>
<tr><th colspan="3">Threshold to start phototherapy, mmol/L</th></tr>
<tr><th></th><th>Healthy term baby</th><th>Preterm or any risk factors*</th></tr>
</table>
</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Rylance (2014)
Can transcutaneous bilirubinometry safely guide phototherapy treatment of neonatal jaundice in Malawi?</td></tr>
<tr><td></td><td>
<table>
<tr><td>Day 1</td><td>Any visible jaundice</td><td></td></tr>
<tr><td>Day 2</td><td>255</td><td>220</td></tr>
<tr><td>Day 3</td><td>305</td><td>270</td></tr>
<tr><td>Day 4 and thereafter</td><td>340</td><td>290</td></tr>
</table>
* Risk factors include small size (2.5 kg at birth or born before 37 weeks gestation), haemolysis and sepsis.
</td></tr>
<tr><td>Length of follow-up</td><td>6 month period</td></tr>
<tr><td>Location</td><td>Malawi</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>
<u>Correlation of TcB levels (forehead or sternum) with TSB levels for infants not under phototherapy</u>
Preterm infants: r=0.71 (n=101)
Term infants: r=0.83 (n=53)

<u>Bland Altman plot analysis - mean bias in micromole/l (95% limits of agreement) of TcB measurements compared with TSB values for infants not under phototherapy*</u>
Term infants: 25 (+/-72 i.e. -46 to +97)
Preterm infants: 37 (+/-73 i.e. -36 to 110)

*only possible when TSB and TcB values were less than 340micromole/l as the JM-103 does not report a numerical value for levels ≥340micromole/l.

<u>Diagnostic accuracy measures of using the lowest TcB reading to decide whether to start phototherapy or continue observation</u>

Sensitivity: 91%
Specificity: 90%
Positive predictive value: 59%
Negative predictive value: 98%

<u>Diagnostic accuracy measures of using the highest TcB reading</u>

Sensitivity: 100%
Specificity: 72%
Positive predictive value: 35%
</td></tr>
</table>

Bibliographic reference	**Rylance (2014)** **Can transcutaneous bilirubinometry safely guide phototherapy treatment of neonatal jaundice in Malawi?**
	Negative predictive value: 100%
Source of funding	Not reported
Comments	<u>Study limitations</u> - Consecutive/random sampling of subjects not employed – instead participants were recruited by convenience sampling based on availability of staff and unit workload - 296 TSB samples analysed, 5 samples lost (unclear whether this was from group receiving phototherapy or not) - Method used for TSB measurement not described in detail eg: unclear whether it was calibrated to SRM 916a bilirubin as stated in review protocol. - Unclear within what time of blood drawing the sample analysed - Results by site of measurement not reported <u>Setting</u> Neonatal nursery of a tertiary referral hospital <u>Statistical methods</u> - Data analysed using linear regression and Bland-Altman plots - Bias calculated as a mean of the differences between paired TSB and TcB values; only possible when both TSB and TcB values were <340micromole/L as the JM-103 does not report a numerical value for levels ≥340micromole/L. - Standard 2 x 2 contingency table analysis to calculate diagnostic accuracy measures <u>Other info</u> - Data for infants undergoing phototherapy has not been extracted as this is a separate review question not due for an update

1

Bibliographic reference	**Qualter (2011)** **Transcutaneous bilirubin – comparing the accuracy of BiliChek and JM-103 in a regional postnatal unit**
Study type	Prospective cohort study
Aim	To correlate TcB measurements from the BiliChek and JM-103 devices against TSB measurements in a population of otherwise well term and near term infants in a regional postnatal unit. To also carry out a survey regarding the use of TcB in postnatal units.
Patient characteristics	**Inclusion criteria** - Infants ≥35 weeks of gestation who had TSB levels measured as part of routine clinical assessment of jaundice

Bibliographic reference	Qualter (2011) **Transcutaneous bilirubin – comparing the accuracy of BiliChek and JM-103 in a regional postnatal unit**
	Exclusion criteria - Phototherapy prior to the evaluation of each TcB device under study **Other characteristics** *Sex, %* Bilichek: male – 41.9; female – 58.1 JM-103: male – 53.7; female – 46.3 *Birthweight in g, mean (range)* Bilichek: 3439 (2260 to 4250) JM-103: 3449 (2460 to 4680) *Gestational age in weeks, mean (range)* Bilichek: 39.4 (35.7 to 41.6) JM-103: 39.7 (36.4 to 41.7) *Feeding method at time of TcB measurement (%)* Bilichek: breast (exclusively) – 23.3; formula (exclusively) – 32.6; both – 44.1 JM-103: breast (exclusively) – 17.1; formula (exclusively) – 26.8; both – 56.1 *Postnatal age in hours at 1st TcB measurement mean (range)* Bilchek: 56.1 (18 to 124) JM-103: 56.6 (28 to 122) *Ethnicity, %* Bilichek: Caucasian – 97.7; Non-Caucasian – 2.3 JM-103: Caucasian – 95.1; Non-Caucasian – 4.9 *Mean TSB in micromole/l (range)* BiliChek: 215.3 (136 to 370) JM-103: 206.4 (124 to 286)

Bibliographic reference	**Qualter (2011)** **Transcutaneous bilirubin – comparing the accuracy of BiliChek and JM-103 in a regional postnatal unit**
	Mean TcB in micromole/l (range) BiliChek:205 (115 to 321) JM-103: 176.5 (86 to 236)
Number of patients	84 term and near term infants enrolled in the study; 43 with Bilichek and 41 with JM-103
Index test	**TcB measurement** Details - Measured using BiliChek or JM-103 on the infant's forehead - BiliChek was calibrated prior to each measurement using a disposable probe (BiliCal) and the JM-103 on a daily basis - Average of 5 measurements in tandem
Reference standard (or Gold standard)	**TSB measurement** Details - TSB samples performed using venesection by medical practitioners - TSB measured by a standard diazo laboratory method on the Roche/Hitachi analyser
Time between testing & treatment	TSB performed within 30 minutes of acquisition of a TcB (only single paired TcB-TSB measurements used for each infant and repeat measurements excluded)
Length of follow-up	Not reported; study date between November 2007 and December 2008
Location	Ireland
Diagnostic accuracy measures (2 x 2 table)	Pearson correlation coefficient between TSB and TcB BiliChek: r=0.88; p<0.0001 JM-103: r=0.70; p<0.0001 Bland-Altman analysis, mean bias (95%limits of agreement*) BiliChek: -10.3micromole/l (+/-55.076 i.e. -65.4 to 44.8) JM-103: -29.9micromole/l (+/-56.056 i.e. -85.956 to 26.156) *calculated by analyst based on data reported in the article
Source of funding	Not reported

Bibliographic reference	**Qualter (2011)** **Transcutaneous bilirubin – comparing the accuracy of BiliChek and JM-103 in a regional postnatal unit**
Comments	Study limitations - Sampling technique used to recruit subjects not reported - Unclear if subjects were clinically jaundiced - Method for TSB measurement not described in detail – eg: was it calibrated as stated in review protocol. - Unclear within what time of blood drawing the sample analysed and whether it was protected from light. Setting Postnatal ward of a hospital Statistical methods - Pearson correlation coefficient and Bland Altman tests performed

1

Bibliographic reference	**Kaynak-Turkmen (2011)** **Transcutaneous measurement of bilirubin in Turkish newborns: comparison with total serum bilirubin**
Study type	Diagnostic study (cross sectional)
Aim	To determine whether TcB measurement as performed using BiliCheck, correlates with TSB levels measured with HPLC and wth standard laboratory methods. Also to determine BiliCheck cut-off points with desirable sensitivity and specificity values for various clinically relevant TSB levels by HPLC.
Patient characteristics	**Inclusion criteria** - Healthy infants of at least 30 weeks of gestational age **Exclusion criteria** - Infants who had known skin disorders, receiving phototherapy or who had exchange transfusions **Other characteristics** *Sex, n (%)* Female: 23 (43) Male: 31 (57) *Birthweight in g, mean (SD)* 2979 (656)

Bibliographic reference	**Kaynak-Turkmen (2011)** **Transcutaneous measurement of bilirubin in Turkish newborns: comparison with total serum bilirubin**
	Gestational age in weeks, n (%) 30 to 37: 17 (32%) 38 to 42: 37 (68%) *Breastfeeding* Not reported *Postnatal age in days, mean (SD)* 6.67 (4.14) *Ethnicity* Caucasian newborn infants *TSB in mg/dl, mean (SD)* 13.85 (6.21)
Number of patients	54 infants
Index test	**TcB measurement** <u>Details</u> - Performed on the forehead using BiliCheck (SpectRx, Inc) while the infant was a in a quiet state - A location free of any bruising, local nevus, hemangioma or melanotic patch was chosen - Before each measurement, device was calibrated to a standard reference placed in direct contact with the fibreoptic probe tip - Mean of 5 readings used for analysis
Reference standard (or Gold standard)	**TSB measurement** <u>Details</u> - TSB collected by heel stick after warming of heel and lancet puncture incision - Venous samples for TSB measurement were obtained if capillary bilirubin level was >12 mg/dl or if it was necessary for other medical reasons such as screening test for congenital hypothyroidism at 4 to 6 days - TSB in venous samples measured by a diazo method using Architect c8000 automatic analyser in the hospital laboratory

Bibliographic reference	**Kaynak-Turkmen (2011)** **Transcutaneous measurement of bilirubin in Turkish newborns: comparison with total serum bilirubin**
	- Standard precautions used to protect samples from exposure to light to prevent photoconversion of bilirubin in the blood
Time between testing & treatment	- TcB measurement was performed 30 minutes or less before blood collection for TSB assay - Time between testing and treatment not reported
Length of follow-up	Not reported
Location	Turkey
Diagnostic accuracy measures (2 x 2 table)	Correlation coefficient between Diazo TSB and TcB r (95%CI): 0.83 (0.73 to 0.90) Bland-Altman plot analysis, mean bias (95% limits of agreement) 4.08mg/dl (-2.88 to 11.03) --> 69.8 micromole/l (-49.2 to 188.6)
Source of funding	Supported by a grant from Adnan Menderes University Research Foundation
Comments	Study limitations - Sampling technique used to recruit subjects not reported - Method used for TSB measurement not described in detail eg: unclear whether it was calibrated to SRM 916a bilirubin as stated in review protocol - Unclear within what time of blood drawing the sample analysed. - Indirect population: healthy infants but no indication of a clinical diagnosis of jaundice Setting Well baby nurseries and the neonatal intensive care unit Statistical methods - Correlation coefficients calculated using linear regression between each pair of methods - Limits of agreement assessed by Bland and Altman tests - Sensitivity and specificity of TcB and TSB to predict HPLC-B estimated at a range of values and plotted on ROC curves

1

Bibliographic reference	**Willems (2004)** **Transcutaneous bilirubinometry with the Bilicheck in very premature newborns**
Study type	Cross sectional

Bibliographic reference	**Willems (2004)** **Transcutaneous bilirubinometry with the Bilicheck in very premature newborns**
Aim	To investigate the potential advantages of use of the Bilicheck in the very preterm population with special emphasis on the effect of possible adverse skin conditions on the accuracy of the measurements.
Patient characteristics	**Inclusion criteria** - Admission to the NICU - Gestational age of <30 weeks - Indication for determination of TSB **Exclusion criteria** - Gestational age of 30 weeks or more - Skin measurements were not performed when the patient's condition was assessed as unstable (peripheral edema/poor peripheral circulation or both), when the skin showed signs of lesions at the location of the measurement or when the patient had received phototherapy within 12 hours prior to the measurements **Other characteristics** *Sex, n/N* Female: 13/24 Male: 11/24 *Birthweight in g, mean (SD)* 1078 (370) *Gestational age in weeks, mean (SD)* *28 (1^{+1})* *Breastfeeding* Not reported *Peripheral edema, n* 15 Poor peripheral circulation, n 5

Bibliographic reference	**Willems (2004)** **Transcutaneous bilirubinometry with the Bilicheck in very premature newborns**
	Peripheral edema and poor peripheral circulation, n 4 *Postnatal age in days* Not reported *Ethnicity* All but 3 infants were of Caucasian origin
Number of patients	24 preterm infants enrolled from which 93 datasets were obtained; only one dataset per patient analysed; 12 infants with good skin condition, 12 with poor skin condition
Index test	**TcB measurement** <u>Details</u> - Performed on infant's forehead by 2 investigators minimally 12 hours after phototherapy had been stopped using BiliCheck (SpectRx, Inc) - Two skin measurements were performed on each occasion. One skin measurement consisted of 5 scans.
Reference standard (or Gold standard)	**TSB measurement** <u>Details</u> - Blood samples collected by heel stick, arterial or venous sampling - Blood analysed for TSB within an hour of sample being obtained - TSB levels determined by a 2 wavelength measurement with Vitros slides; analysis based on the classical diazo reaction; after incubation for 5 min at 37 degrees, TSB is determined by reflection of the azo bilirubins at 540nm and 460nm.
Time between testing & treatment	- TcB measurement performed within 30 minutes of blood sampling for TSB - Time between testing and treatment not reported - The cut off levels for TSB analysis were set at 70% of the intervention lines for phototherapy and exchange transfusion; therefore a TcB value above the 70% cutoff level for initiation of phototherapy will be followed by determination of TSB.
Length of follow-up	Not reported, study period March to June 2001
Location	The Netherlands

Bibliographic reference	**Willems (2004)** **Transcutaneous bilirubinometry with the Bilicheck in very premature newborns**
Diagnostic accuracy measures (2 x 2 table)	Correlation between TSB and TcB All infants: r=0.86; p<0.001 Those with good skin conditions: r=0.89; p<0.001 Those with poor skin conditions (peripheral edema, poor peripheral circulation or both): r=0.87; p<0.001 Bland Altman plot analysis, mean difference in micromole/l (95% limits of agreement)* All infants: -4.92 (-59.22 to 49.38) Those with good skin conditions: 2.42 (-36.7 to 41.54) Those with poor skin conditions: -12.25 (-76.81 to 52.31) *calculated by analyst based on data reported in article
Source of funding	Not reported
Comments	Study limitations - Indirect population: unclear if population was clinically jaundiced - Postnatal age of subjects not reported - TcB measurement was performed minimally 12 hours after phototherapy had been stopped – unclear if this would interfere with TcB measurement and number who received phototherapy not reported - Sampling technique used to recruit population not reported. - Unclear if sample was protected from light although analysed within one hour to avoid photoconversion - Method used for TSB measurement not described in detail eg: unclear whether it was calibrated to SRM 916a bilirubin as stated in review protocol. Setting Neonatal intensive care unit Statistical methods - Bland and Altman tests of agreement using one dataset per patient - Impression of the reliability (agreement between TcB and TSB values and imprecision) obtained - Correlation coefficients with p<0.001 defined as statistically significant

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Bibliographic reference	**Campbell (2011)** **Transcutaneous bilirubin measurement at the time of hospital discharge in a multi-ethnic newborn population**
Study type	Prospective cohort
Aim	To compare the accuracy of the TSB measurement with the TCB measurement using a BiliChek meter (Respironics Inc)
Patient characteristics	**Inclusion criteria** - Neonates older than 35 weeks completed gestational age who were deemed jaundiced by medical staff and cared for the in the postpartum ward of the hospital before initial discharge **Exclusion criteria** - Those who had undergone phototherapy - Admitted to the neonatal intensive care unit - Major congenital anomalies or birth marks - Under the care of child protective services - Language barriers from parents **Other characteristics** *Male sex, n (%)* 236 (55) *Birthweight in g, mean (SD)* 3289 (458) *Gestational age in weeks, mean (SD)* *38.8 (1.4)* *Exclusive breastfeeding, n (%)* 280 (65) *Postnatal age in days* Not reported *Ethnicity, n (%)* Asian: 146 (34)

Bibliographic reference	**Campbell (2011)** **Transcutaneous bilirubin measurement at the time of hospital discharge in a multi-ethnic newborn population**
	Caucasian: 140 (33) Latino: 43 (10) Indian: 36 (8) Black: 34 (8) Middle Eastern: 17 (4) Other or unknown: 14 (3) *TSB in micromole/l, mean (SD)* 194 (60) *TcB in micromole/l, mean (SD)* 206 (55)
Number of patients	430 term and near term newborns
Index test	**TcB measurement** <u>Details</u> - Performed on infant's forehead by the patient's postpartum nurse using the BiliCheck meter - Average of 5 readings
Reference standard (or Gold standard)	**TSB measurement** <u>Details</u> - Blood samples collected via a standard heel prick by nursing staff - Analysed by spectrophotometry for total and direct bilirubin levels using a diazo method with the Synchron LX20 clinical chemistry system (Beckman Coulter).
Time between testing & treatment	- TcB measured within 30 minutes of obtaining TSB - Phototherapy initiated on TSB values according to the AAP guidelines
Length of follow-up	Not reported, study period July 2005 to March 2007
Location	Canada

Bibliographic reference	**Campbell (2011)** **Transcutaneous bilirubin measurement at the time of hospital discharge in a multi-ethnic newborn population**

Diagnostic accuracy measures (2 x 2 table)

Correlation of TCB values to TSB values at different levels of hyperbilirubinaemia

TSB value	Measurements, n	Pearson's correlation coefficient (r)	Lin's concordance coefficient (95%CI)	Minimum, maximum difference (TCB – TSB, micromole/l)
All	430	0.83	0.81 (0.77 to 0.84)	-156, 98
TSB≤200micromole/l	266	0.75	0.59 (0.53 to 0.65)	-45, 98
TSB>200micromole/l	164	0.52	0.58 (0.48 to 0.68)	-156, 69
TSB≤250micromole/l	362	0.79	0.72 (0.68 to 0.76)	-89, 98
TSB>250micromole/l	68	0.23	0.20 (-0.01 to 0.38)	-156, 68

Correlation of TCB values to TSB values based on ethnicity

Ethnicity	Measurements, n	Pearson's correlation coefficient (r)	Lin's concordance coefficient (95%CI)	Minimum, maximum difference (TCB – TSB, micromole/l)
All	430	0.83	0.81 (0.77 to 0.84)	-156, 98
Asian	146	0.84	0.81 (0.75 to 0.86)	-156, 77
Caucasian	140	0.82	0.78 (0.72 to 0.84)	-85, 98
Latino	43	0.86	0.85 (0.74 to 0.92)	-89, 70
Black	34	0.80	0.79 (0.62 to 0.89)	-96, 80
Other	67	0.82	0.79 (0.68 to 0.86)	-104, 70

Bland-Altman plot analysis, mean bias in micromole/l (95% limits of agreement)
12.7 (+/-64.5 i.e. -52 to 77)

Diagnostic accuracy measures
To detect a TSB value of 200micromole/l, a TCB value of 180micromole/l would provide 96% sensitivity, 55% specificity, positive predictive value 64%, negative predictive value 96%.

To detect a TSB value of 250micromole/l, a TCB value of 200micromole/l would provide 96% sensitivity and 57% specificity, positive predictive value 34% and negative predictive value 97%.

Bibliographic reference	**Campbell (2011)** **Transcutaneous bilirubin measurement at the time of hospital discharge in a multi-ethnic newborn population**
	To detect a TSB value of 300micromole/l, TCB measurements of 200micromole/l, 220micromole/l and 250micromole/l provided decreasing levels of sensitivity – 95%, 86% and 81% respectively. Area under ROC curve for TCB predicting a TSB >200micromole/l=0.8976 Area under ROC curve for TCB predicting a TSB >250micromole/l=0.9230
Source of funding	Not reported
Comments	<u>Study limitations</u> - Sampling technique not reported. Assumption that population was otherwise well given subjects admitted in NICU were excluded. - Unclear if sample was protected from light to avoid photoconversion and analysed within an acceptable period of time - Method used for TSB measurement not described in detail eg: unclear whether it was calibrated to SRM 916a bilirubin as stated in review protocol. <u>Setting</u> Academic hospital <u>Statistical methods</u> - Agreement between TSB and TCB assessed using Pearson's correlation and Lin's concordance coefficients - Modified Bland Altman technique used to assess TSB and TCB variability - Sensitivity and specificity analyses estimated at two outcomes of interest (200micromole/L and 250 micromole/L) because they are important clinically important values at 24 hours and 48 hours of age for healthy term infants ready for discharge

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Bibliographic reference	**Engle (2002)** **Assessment of a transcutaneous device in the evaluation of neonatal hyperbilirubinaemia in a primarily Hispanic population**
Study type	Diagnostic
Aim	To compare estimates of serum bilirubin as determined by a transcutaneous device (Bilicheck) with laboratory measured total serum bilirubin in a predominantly Hispanic population in which a significant number of TSB values ≥15mg/dl was anticipated

Bibliographic reference	**Engle (2002)** **Assessment of a transcutaneous device in the evaluation of neonatal hyperbilirubinaemia in a primarily Hispanic population**
Patient characteristics	**Inclusion criteria** - Infants with clinically apparent jaundice necessitating serum bilirubin determination (including inpatients and outpatients although 64% were inpatients) – no patients were receiving phototherapy at time of measurement **Exclusion criteria** - Not reported although no infants were receiving phototherapy when TCB or TSB measurements were taken **Other characteristics** *Sex,male/female n* Hispanic: 146/102 Non-Hispanic: 22/34 *Birthweight in g, mean (SD)* Hispanic: 3304 (5.74) Non-Hispanic: 3239 (455) *Gestational age in weeks, mean (SD)* Hispanic: 38.9 (1.7) Non-Hispanic: 38.7 (1.4) *Exclusive breastfeeding, (%)* Hispanic: 30 Non-Hispanic: 16 *Postnatal age in hours, %*

	Hispanic		Non-Hispanic	
	Initial n=248	Subsequent n=87	Initial n=56	Subsequent n=12
≤24 hours (%)	13	1	27	0
25 to 48 hours (%)	15	7	30	33
49 to 72 hours (%)	25	14	11	17

Bibliographic reference	**Engle (2002)** **Assessment of a transcutaneous device in the evaluation of neonatal hyperbilirubinaemia in a primarily Hispanic population**
	73 to 96 hours (%): 15 / 26 / 14 / 17 >96 hours (%): 32 / 52 / 18 / 33 *Ethnicity, n* Hispanic: 248 Non-Hispanic: 56 *TSB ≥15mg/dl (%)* Hispanic infants: 31 Non-Hispanic infants: 9
Number of patients	404 comparisons in 304 term infants; only first reading used for analysis therefore 304 comparisons in 304 infants
Index test	**TcB measurement** Details - Measured by 1 investigator on infant's forehead using BiliChek while infant was in a quiet state - Device calibrated before each measurement - For each infant, readings were obtained with 2 of the 4 BiliChek devices used in the study and the first reading was used for data analysis
Reference standard (or Gold standard)	**TSB measurement** Details - Blood drawn by heel puncture - Serum bilirubin analysed using the diazo Jendrassik-Grof with blank method (Olympus AU600)
Time between testing & treatment	- TcB reading performed within 30 minutes of blood sampling for TSB - Time between testing and treatment not reported
Length of follow-up	Not reported
Location	USA
Diagnostic accuracy measures (2 x 2 table)	Correlation coefficient between TSB and TcB r=0.84

Bibliographic reference	**Engle (2002)** **Assessment of a transcutaneous device in the evaluation of neonatal hyperbilirubinaemia in a primarily Hispanic population**

Predictive indices of different TcB cutoff values for TSB >10mg/dl (171micromole/l) in Hispanic neonates, n=335 comparisons in 268 infants

TcB cutoff (mg/dl)	Sensitivity	Specificity	PPV	NPV	LR+	LR-
>5 (85.5micromole/l)	1.0	0.10	0.80	1.0	1.1	0
>7 (119.7micromole/l)	1.0	0.40	0.86	1.0	1.7	0
>8 (136.8micromole/l)	0.98	0.51	0.88	0.90	2.0	0.04
>9 (153.9micromole/l)	0.92	0.77	0.93	0.73	4.0	0.10
>10 (171micromole/l)	0.83	0.88	0.96	0.59	6.9	0.19
>11 (188.1micromole/l)	0.73	0.97	0.99	0.50	24.3	0.28

Predictive indices of different TcB cutoff values for TSB >15mg/dl (256.5micromole/l) in Hispanic neonates, n=335 comparisons in 268 infants

TcB cutoff (mg/dl)	Sensitivity	Specificity	PPV	NPV	LR+	LR-
>5 (85.5micromole/l)	1.0	0.03	0.33	1.0	1.0	0
>7 (119.7micromole/l)	1.0	0.13	0.36	1.0	1.1	0
>8 (136.8micromole/l)	0.99	0.17	0.37	0.98	1.1	0.06
>9 (153.9micromole/l)	0.98	0.33	0.42	0.97	1.5	0.06
>11	0.92	0.59	0.52	0.94	2.2	0.14

Bibliographic reference	**Engle (2002)** **Assessment of a transcutaneous device in the evaluation of neonatal hyperbilirubinaemia in a primarily Hispanic population**

(188.1micromole/l)						
>12 (205.2micromole/l)	0.85	0.74	0.62	0.91	3.3	0.20
>13 (222.3micromole/l)	0.76	0.84	0.71	0.88	4.8	0.29
>15 (256.5micromole/l)	0.33	0.96	0.82	0.75	8.3	0.70

Source of funding	Funded in part by Respironics, Inc
Comments	Study limitations - Sampling technique not reported - Exclusion criteria not reported; unclear if subjects were otherwise well - 6 patients included in analysis were studied 8 to 22 hours after phototherapy and skin sites were not patched during phototherapy; unclear if this could have interfered with measurements taken - Unclear within what time after collection, blood sample was analysed - Unclear if blood sample was protected from light - Method used to measure TSB not well described eg: was it calibrated to the current method? Setting Newborn nursery of a hospital Statistical methods - Comparisons between TCB and TSB determinations made for all infants and within ethnic groups usng the Bradley Blackwood test - For TSB >10mg/dl and >15mg/dl in Hispanic neonates, sensitivity, specificity, predictive values and likelihood ratios associated with various Bilichek cutoff levels were determined and ROC curves plotted

1

Bibliographic reference	**Barko (2006)** **Evaluation of point of care direct spectrophotometric method for measurement of total serum bilirubin in term and near term neonates**
Study type	Diagnostic study (cross sectional study)

Bibliographic reference	**Barko (2006)** **Evaluation of point of care direct spectrophotometric method for measurement of total serum bilirubin in term and near term neonates**
Aim	To evaluate point of care measurement of TSB in the management of neonatal jaundice
Patient characteristics	**Inclusion criteria** - Term and near term neonates (35 to 42 weeks) admitted to the newborn nursery with jaundice who were having blood drawn for TSB determination as well as neonates who were not recognised as having clinically significant jaundice but who were having blood drawn for the state newborn metabolic screen at approximately 34 to 38 hours and prior to hospital discharge - Neonates evaluated because of clinical jaundice were studied either before hospital discharge or as outpatients within the first 6 days of life for follow up of clinical jaundice **Exclusion criteria** - Not reported **Other characteristics** *Sex,male/female %* 46/54 *Birthweight in g, median (range)* 3335 (2145 to 4495) *Gestational age in weeks, median (range)* 39 (35 to 42) *Exclusive breastfeeding, (%)* 58 *Postnatal age in hours , median (range)* *37 (25 to 141)* *Ethnicity, %* Hispanic: 79 Black: 11 Caucasian: 3

Bibliographic reference	**Barko (2006)** **Evaluation of point of care direct spectrophotometric method for measurement of total serum bilirubin in term and near term neonates**
	East Asian: 2 Asian (other): 3 Other: 2 *Prior phototherapy, %* 2.5 *TSB in mg/dl, median (range)* 9.0 (1.1 to 23.5) --> 153.9micromole/l (18.81micromole/l to 401.85)
Number of patients	120 term/near term neonates; clinically jaundiced n=60; no significant clinical jaundice n=60
Index test	**TcB measurement** <u>Details</u> - Measured using Konica Minolta/Drager AirShields JM-103 jaundice meter - A single reading taken over the sternum recorded by one investigator
Reference standard (or Gold standard)	**TSB measurement** <u>Details</u> - Measured by diazo Jendrassik-Grof with blank method, Olympus AU640E analyser - Blood samples obtained by heelstick (n=110) or venepuncture (n=10) - Blood collected in a tube containing Gel Z, protected from light and transported to lab within approximately 15 mins of collection
Time between testing & treatment	- TcB measured within 30 mins of blood sampling for TSB - Time between testing and treatment not reported
Length of follow-up	Not reported; study date between January and June 2005
Location	USA
Diagnostic accuracy measures (2 x 2 table)	<u>Correlation between JM and diazo TSB</u> All infants: r=0.93 (n=113) Infants with clinical jaundice: r=0.90

Bibliographic reference	**Barko (2006)** **Evaluation of point of care direct spectrophotometric method for measurement of total serum bilirubin in term and near term neonates**

Predictive indices for diazo TSB outcomes of interest (>15 to >18mg/dl) and various transcutaneous JM-103 cut off values – all infants*

Diazo TSB (mg/dl)	JM (mg/dl)	Sensitivity	Specificity	PPV	NPV	Blood tests avoided (%)
>15 (256.5micromole/l)	>11 (188.1micromole/l)	0.96	0.82	0.58	0.99	66
	>12 (205.2micromole/l)	0.91	0.87	0.64	0.98	71
	>13 (222.3micromole/l)	0.87	0.91	0.71	0.96	75
>16 (273.6micromole/l)	>12 (205.2micromole/l)	1.0	0.80	0.39	1.0	71
	>13 (222.3micromole/l)	0.92	0.91	0.57	0.99	81
	>14 (239.4micromole/l)	0.92	0.92	0.60	0.99	82
>17 (290.7micromole/l)	>13 (222.3micromole/l)	1.0	0.81	0.31	1.0	74
	>14*(239.4micromole/l)	1.0	0.86	0.38	1.0	79
	>15 (256.5micromole/l)	0.67	0.93	0.46	0.97	88
>18 (307.8micromole/l)	>14 (239.4micromole/l)	1.0	0.84	0.29	1.0	79
	>15 (256.5micromole/l)	0.71	0.92	0.38	0.98	88
	>16 (273.6micromole/l)	0.57	0.98	0.67	0.97	95

*Restricting the analysis to clinically jaundiced neonates only, using a JM cutoff value>14mg/dl to predict diazo TSB >17mg/dl, sensitivity was still 1.0 however % of blood tests that could be avoided decreased to 59%.

Source of funding	Not reported
Comments	Study limitations - Method used to measure TSB not well described eg: was it calibrated to the current method? - 2.5% prior phototherapy - Blood sample transported to lab within approximately 15 mins of collection; unclear if analysed within an acceptable period of time Setting

Bibliographic reference	**Barko (2006)** **Evaluation of point of care direct spectrophotometric method for measurement of total serum bilirubin in term and near term neonates**
	Newborn nursery of a large public hospital <u>Statistical analysis</u> - Correlations between TCB and TSB both for all patients as well as those with clinical jaundice were determined - The ability of various JM cutoff values to predict selected diazo/TSB values was analysed using standard 2x2 tables

1

Bibliographic reference	**Nanjundaswamy (2004)** **The accuracy of transcutaneous bilirubin measurements in neonates: a correlation study**
Study type	Cross sectional
Aim	A correlation study to evaluate the accuracy of the BiliCheck measurements in neonates with different birth weight, race/ethnic background and serum bilirubin values
Patient characteristics	**Inclusion criteria** - Neonates born between 24 and 42 weeks of gestation who required blood sampling to determine TSB in the first week of life **Exclusion criteria** - Infants previously exposed to phototherapy and/or exchange transfused **Other characteristics** *Sex,male/female %* Not reported *Birthweight, n (%)* >2000g: 165 (77.8) <1500g: 26 (12.3) 1500 to 2000g: 21 (9.9) *Gestational age in week, range* 24 to 42 weeks *Exclusive breastfeeding, (%)*

Bibliographic reference	**Nanjundaswamy (2004)** **The accuracy of transcutaneous bilirubin measurements in neonates: a correlation study**
	Not reported *Postnatal age in days , mean (SD)* 2.5 (1.6) *Ethnicity, n (%)* Caucasian: 106 (50) Black: 34 (16) Hispanic: 25 (11.8) Other: 47 (22.2) *TSB in mg/dl, n (%)* ≤10mg/dl: 152 (71.7) 10.1 to 14.9mg/dl: 51 (24.1) >15mg/dl: 9 (4.2)
Number of patients	212 term and preterm infants
Index test	TcB measurement <u>Details</u> - Measured using BiliCheck (SpectRx Inc) on the infant's forehead on an area of skin without visible bruising - Device calibrated before each measurement as per the manufacturer's instructions - The same BiliCheck unit was used for all the measurements, and measurements were made by the same operator to avoid interoperator imprecision - Average of 5 readings used for analysis; all measurements done with the same room illumination
Reference standard (or Gold standard)	TSB measurement <u>Details</u> - Measured by the Aeroser system, a direct spectrophotometric assay from Abbott Laboratories in the chemistry lab
Time between testing & treatment	- TcB measured within 30 minutes of a blood sample being drawn for serum bilirubin - Time between testing and treatment not reported - One paired measurement

Bibliographic reference	**Nanjundaswamy (2004)** **The accuracy of transcutaneous bilirubin measurements in neonates: a correlation study**
Length of follow-up	Not reported
Location	USA
Diagnostic accuracy measures (2 x 2 table)	<u>Correlation between TSB and TcB</u> All: r=0.78; p<0.0001 Infants with TSB <10mg/dl (171micromole/l): r=0.72, p<0.0001 Infants with TSB between 10.1mg/dl (172.71micromole/l) and 14.9mg/dl (254.79micromole/l): r=0.54, p<0.0001 Infants with TSB ≥15mg/dl (256.5micromole/l): r=-0.30, p>0.05 Negative non-significant correlation appeared when TSB levels were more than 11mg/dl: 11-12mg/dl (188.1micromole/l – 205.2micromole/l); n=18; r=-0.29 12-13mg/dl (205.2micromole/l – 222.3micromole/l); n=8; r=-0.65 13-14mg/dl (222.3micromole/l – 239.4micromole/l); n=6; r=-0.46 >14mg/dl (239.4micromole/l);n=12; r=-0.18 <u>Correlation between TSB and TcB in terms of race</u> Caucasian (n=106): 0.84, p<0.0001 Black (n=34): 0.65, p<0.001 Hispanic (n=25): 0.75, p<0.0001 Other (n=47): 0.85, p<0.0001
Source of funding	Not reported
Comments	<u>Study limitations</u> - Sampling technique not described - Population not well described; unclear if clinically jaundiced - Method used to measure TSB not well described eg: was it calibrated to the current method? - Unclear if blood sample was analysed within an acceptable period of time - Unclear if sample was protected from light <u>Setting</u> Nursery and neonatal intensive care unit of a university hospital <u>Statistical methods</u>

Bibliographic reference	**Nanjundaswamy (2004)** **The accuracy of transcutaneous bilirubin measurements in neonates: a correlation study**
	- Data stratified by birth weight and bilirubin levels before assessing correlation between TSB and TcB - Correlation analysis performed

1

Bibliographic reference	**Ebbesen (2012)** **Comparison of the transcutaneous bilirubinometers BiliCheck and Minolta JM-103 in preterm neonates**
Study type	Diagnostic
Aim	To investigate the trueness and uncertainty of two transcutaneous bilirubinometers BiliCheck and Minolta JM-103 in preterm infants, establish cut-off values for the transcutaneous bilirubin level, indicating the need for total serum bilirubin measurement and estimate how many blood samples could be saved
Patient characteristics	**Inclusion criteria** - All preterm infants with a gestational age from 28 to 34 weeks - >24 hours and <14 days old and TsB measured for clinical reasons **Exclusion criteria** - Infants <24 hours old as they always need to have the TSB measured - Neonates who received exchange transfusion or had Rhesus haemolytic disease, hepatic disease or generalised skin disease **Other characteristics** *Sex,male/female n* 77/56 *Birthweight in g, median (5 to 95 percentiles)* 1998 (1110 to 2764) *Gestational age in weeks, median (5 to 95 percentiles)* 33 (28 to 34) *Exclusive breastfeeding, (%)* Not reported *Postnatal age in hours , median (5 to 95 percentiles)*

Bibliographic reference	**Ebbesen (2012)** **Comparison of the transcutaneous bilirubinometers BiliCheck and Minolta JM-103 in preterm neonates**
	101 (35 to 253) *Ethnicity, n, (%)* Africans: 6 (5) Middle Easterns: 2 (2) *Median TSB in micromole/l (5 to 95 percentiles)* 160 (89 to 266)
Number of patients	133 preterm infants, in whom 1 to 7 measurements performed; total of 239 bilirubin analyses
Index test	**TcB measurement** <u>Details</u> - Measured using BiliCheck or JM-103 on the forehead in a skin area without purpura or bruising when the infant was in a quiet state - Two BiliCheck and two JM-103 devices were used - TcB was never determined during phototherapy and the subsequent 24 hours - Average of 3 or 5 readings for JM-103 ad BiliCheck devices respectively (according to manufacturer's instructions) - JM-103 calibrated once daily against a standard produced by manufacturer and BiliCheck calibrated before each measurement with a disposable tip (BiliCap)
Reference standard (or Gold standard)	**TSB measurement** <u>Details</u> - Capillary blood drawn by heel puncture for determination of TSB - TSB determined by reflection densitometry on Vitros 5.1 (Ortho Clinical Diagnostic, Rochester) - TSB was calculated as the sum of measured unconjugated and conjugated bilirubin (Vitros BuBc slide) - Instrument calibration verified using an instrument specific verifier supplied by the provider
Time between testing & treatment	- Index test and reference standard within 15 minutes of each other - 1 to 7 measurements performed; total of 239 bilirubin analyses - For infants in NICU, phototherapy was given if TsB was greater than 300micromole/l or greater than 10% of the infant's birth weight in grams as expressed in micromole/l. Phototherapy was not given if the value was below 100micromole/l.
Length of follow-up	Not reported; study performed during a 18 month period from May 2008
Location	Denmark

<table>
<tr><th>Bibliographic reference</th><th>Ebbesen (2012)
Comparison of the transcutaneous bilirubinometers BiliCheck and Minolta JM-103 in preterm neonates</th></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>
<u>Correlation coefficients</u>
Bilicheck: r=0.83
JM-103: r=0.86
P<0.001

<u>Multivariate analysis</u>
Results for BiliCheck using TcB as the dependent variable
TSB micromole/l - coefficient (95%CI): 0.71 (0.63 to 0.79); p<0.001
Gestational age in days - coefficient (95%CI): -0.34 (-0.69 to 0.02); p=0.06
Non-Caucasian – coefficient (95%CI): 10.02 (-6.51 to 26.54); p=0.24
Caucasian – 0.00 (reference)

Results for JM-103 using TcB as the dependent variable
TSB micromole/l – 0.73 (0.66 to 0.81); p<0.001
Gestational age in days – 0.20 (-0.12 to 0.53); p=0.22
Non-Caucasian – 29.60 (14.48 to 44.73); p<0.001
Caucasian – 0.00 (reference)

<u>Accuracy of TcB (BiliCheck) ≥210micromole/l in predicting TSB above the phototherapy limit (≥300micromole/l); n=239</u>

<table>
<tr><th>Adjusted decision limits</th><th><phototherapy limit (n=181)</th><th>≥phototherapy limit (n=58)</th><th>Total (n)</th></tr>
<tr><td>TcB*
≥210micromole/l
<210micromole/l</td><td>
94
87</td><td>
55
3</td><td>
149
90</td></tr>
</table>
*Sensitivity 95%, specificity 48%

<u>Accuracy of TcB (JM-103) ≥105micromole/l in predicting TSB above the phototherapy limit (≥300micromole/l); n=239</u>

<table>
<tr><th>Adjusted decision limits</th><th><phototherapy limit (n=181)</th><th>≥phototherapy limit (n=58)</th><th>Total (n)</th></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Ebbesen (2012)** **Comparison of the transcutaneous bilirubinometers BiliCheck and Minolta JM-103 in preterm neonates**
	<table><tr><td>TcB*</td><td></td><td></td><td></td></tr><tr><td>≥105micromole/l</td><td>123</td><td>56</td><td>179</td></tr><tr><td><105micromole/l</td><td>58</td><td>2</td><td>60</td></tr></table> *Sensitivity 97%, specificity 32%
Source of funding	Funding not reported
Comments	<u>Study limitations</u> - Unclear if subjects were clinically jaundiced; TSB measured for clinical reasons so possible this was the case - Sampling technique not reported - Ethnicity of all subjects not reported - Method used to measure TSB not well described eg: was it calibrated to the current method? - Unclear if blood sample was analysed within an acceptable period of time - Unclear if sample was protected from light - Bland Altman plot analysis not extractable <u>Setting</u> NICU of a university hospital <u>Statistical methods</u> - Relationship between TCB and TSB assessed using Pearson's correlation coefficient, Passing Bablok non-parametric regression analysis or Bland Altman difference plot. Regression analysis of the Bland-Altman plot performed using ordinary linear regression. - Comparison between TCB and TSB for TSB values <180micromole/l as well as values >=180micromole/l was examined using t- test - Multivariate analysis using either Bilicheck or Minolta as dependent variables were performed by including TSB, gestational age, gender, postnatal age, ethnicity and severe illness as predictors being able to assess factors influencing the TcB measurement besides TsB. <u>Other</u> TcB never determined during phototherapy and the subsequent 24 hours; therefore results shown are before treatment commencing

1

Bibliographic reference	**Kosarat (2013)** **Accuracy of transcutaneous bilirubin measurement in terms newborns**
Study type	Cross sectional study
Aim	To evaluate the accuracy of transcutaneous bilirubin compared with serum bilirubin in full term infants, to compare the accuracy of TcB reading from two, three and four measurements and to compare the accuracy of TcB measured at the forehead and sternum
Patient characteristics	**Inclusion criteria** - Full term newborns who were diagnosed neonatal jaundice by the attending physician and underwent blood tests for TSB level in neonatal ward **Exclusion criteria** - Gestational age less than 37 weeks - Clinically unstable - Previously received phototherapy or exchange transfusion **Other characteristics** *Sex,male %* 48 *Birthweight in g, mean (SD)* 3.043 (473.98) *Gestational age in weeks, mean (SD)* 38.44 (1.29) *Exclusive breastfeeding* Not reported *Postnatal age at time of bilirubin measurement in hours , mean (SD)* 59.67 (18.38) *Ethnicity* Not reported

<table>
<tr><td>Bibliographic reference</td><td>Kosarat (2013)
Accuracy of transcutaneous bilirubin measurement in terms newborns</td></tr>
<tr><td></td><td>TSB in mg/dl, mean (SD)
11.03 (2.73)</td></tr>
<tr><td>Number of patients</td><td>294 measurements obtained from 257 term infants</td></tr>
<tr><td>Index test</td><td>TcB measurement

<u>Details</u>
- Measured using JM-103 by trained personel
- Device calibrated according to manufacturer’s recommendations
- Device’s optical probe cleaned and placed on infant’s forehead and sternum
- Two, three and four measurements performed on each site
- Average value displayed by device in mg/dl</td></tr>
<tr><td>Reference standard (or Gold standard)</td><td>TSB measurement

<u>Details</u>
- Blood taken by heel prick and collected in sodium-heparinzed capillary tubes, shielded from light exposure and analysed by Roche/Hitachi Automatic analyser 902</td></tr>
<tr><td>Time between testing & treatment</td><td>- TcB measurement performed within 30 minutes before or after blood sampling
- Time between testing and treatment not reported</td></tr>
<tr><td>Length of follow-up</td><td>Not reported, study dates June to December 2009</td></tr>
<tr><td>Location</td><td>Thailand</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td><u>Correlation coefficients between TsB and TcB measured at forehead and sternum</u>
<table>
<tr><td>Number of measurements</td><td>R for forehead</td><td>R for sternum</td></tr>
<tr><td>2</td><td>0.812</td><td>0.829</td></tr>
<tr><td>3</td><td>0.800</td><td>0.844</td></tr>
<tr><td>4</td><td>0.800</td><td>0.823</td></tr>
</table>

<u>Bland Altman plot analysis, mean bias in mg/dl (95%limits of agreement*)</u>
Forehead (2 measurements): 0.9260 (+/-3.31 i.e. -2.38 to 4.24) -->15.83micromole/l (-40.70 to 72.50)
Sternum (2 measurements): 0.97 (+/-3.038 i.e. -2.07 to 4.01) -->16.59micromole/l (-35.40 to 68.57)</td></tr>
</table>

Bibliographic reference	**Kosarat (2013)** **Accuracy of transcutaneous bilirubin measurement in terms newborns**
	*Calculated by analyst based on data reported in the article
Source of funding	Not reported
Comments	Study limitations - Sampling technique not reported - Although those who had prior phototherapy/exchange transfusion were excluded, 61 infants received phototherapy during admission and one received exchange transfusion; unclear if this was before/after measurement and whether it could have interfered with measurement of bilirubin - Unclear if subjects otherwise well - Method used to measure TSB not well described eg: was it calibrated to the current method? - Unclear if blood sample was analysed within an acceptable period of time Setting Neonatal ward of a hospital Statistical methods - Pearson correlation coefficients calculated by using linear regression techniques - Error distribution performed by Bland Altman method

1

Bibliographic reference	**Wong (2002)** **A comparison of transcutaneous bilirubinometers: SpectRx BiliCheck versus Minolta AirShields**
Study type	Prospective cohort
Aim	To measure how well the readings produced by these devices agree with SBR measured in the laboratory, to estimate for each device, the proportion of infants with clinical jaundice who would require blood sampling if the device was used as a screening tool to detect infants with SBR ≥250micromole/l
Patient characteristics	**Inclusion criteria** - Neonates who required blood sampling for TSB; clinically jaundiced but otherwise well **Exclusion criteria** - Infants who received phototherapy or exchange transfusion

Bibliographic reference	**Wong (2002)** **A comparison of transcutaneous bilirubinometers: SpectRx BiliCheck versus Minolta AirShields**
	Other characteristics *Sex* Not reported *Birthweight in g, mean (SD)* All: 2920.8 (755.5) Term: 3258.9 (605.4) Preterm: 2120.0 (373.1) *Gestational age in weeks, mean (SD)* All: 37.4 (3.0) Term: 39.1 (1.4) Preterm: 33.4 (1.2) *Exclusive breastfeeding* Not reported *Postnatal age in days , mean (SD)* All: 4.6 (3.4) Term: 3.6 (2.5) Preterm: 7 (4.0) *Ethnicity* 6 infants in total were non-caucasian *Serum bilirubin in micromole/l, mean (SD)* All: 207.3 (68.8) Term: 212.1 (72.5) Preterm: 195.9 (59.4)
Number of patients	64 enrolled, 19 preterm (31 to 35 weeks)
Index test	**TcB measurement**

Bibliographic reference	**Wong (2002)** **A comparison of transcutaneous bilirubinometers: SpectRx BiliCheck versus Minolta AirShields**
	<u>Details</u> - Performed by one author on infant's forehead using JM-102 and the new SpectRx BiliCheck (designated A and B) with the infant lying supine - Forehead was not exposed to direct sunlight and care was taken to avoid skin areas that were bruised, excessively hairy or hypermelanotic
Reference standard (or Gold standard)	**TSB measurement** <u>Details</u> - Blood taken by venepuncture or heel lance - TSB samples analysed by automated Hitachi 911 multichannel analyser; laboratory participates in the External Qualiy Assessment Scheme (EQA) and shows a mean of +2.4% bias for SBR analysis
Time between testing & treatment	- TcB measured within 30 minutes of blood sample - Time between testing and treatment not reported
Length of follow-up	Not reported
Location	UK
Diagnostic accuracy measures (2 x 2 table)	<u>Bland-Altman plot analysis, mean difference in micromole/l (95% limits of agreement)</u> *JM-102* All: 0.0 (+/-66.7 i.e -66.7 to +66.7), n=64 Term: -9.6 (+/-65.1 i.e -74.7 to 55.5), n=45 Preterm: 22.7 (+/-46.0 i.e -23.3 to 68.7), n=19 *SpectRx BiliCheck A* All: -4.0 (+/-67.9 i.e -71.9 to 63.9) n=64 Term: -5.5 (+/-67.2 i.e -72.7 to 61.7) n=45 Preterm: -0.5 (+/-71.1 i.e -71.6 to 70.6) n=19 *SpectRx BiliCheck B* All: -8.6 (+/-66.4 i.e -75 to 57.8) n=64 Term: -12.8 (+/-62.9 i.e -75.7 to 50.1) n=45 Preterm: 1.3 (+/-72.0 i.e -70.7 to 73.3) n=19

Bibliographic reference	**Wong (2002)** **A comparison of transcutaneous bilirubinometers: SpectRx BiliCheck versus Minolta AirShields**

Correlation in non-caucasian infants

JM-102, Bilicheck A, BiliCheck B: r=0.94, 0.95 and 0.99 respectively (n=6 hence no tests of statistical agreement performed by authors)

Specificity and positive predictive values for respective devices when sensitivity is set to 100%

	SBR≥250micromole/l	SBR<250micromole/l	Totals	PPV
JM-102 TcB ≥170micromole/l TcB <170micromole/l Totals	 17 0 17 100 (sensitivity)	 32 15 47 31.9 (specificity)	 49 15 64	34.7
BiliCheck A TcB ≥150micromole/l TcB <150micromole/l Totals	 17 0 17 100 (sensitivity)	 37 10 47 21.3 (specificity)	 54 10 64	31.5
BiliCheck B TcB ≥150micromole/l TcB <150micromole/l Totals	 17 0 17 100 (sensitivity)	 34 13 47 27.7 (specificity)	 51 13 64	33.3

Source of funding	Not reported
Comments	Study limitations - Sampling technique not reported - Method used to measure TSB not well described eg: was it calibrated to the current method? - Unclear if blood sample was analysed within an acceptable period of time and protected from light Setting

Bibliographic reference	**Wong (2002)** **A comparison of transcutaneous bilirubinometers: SpectRx BiliCheck versus Minolta AirShields**
	Maternity Pavillion <u>Statistical methods</u> - Each patient assessed only once - Pearson correlation coefficients calculated using original Minolta index readings - For measurement of agreement by Bland-Altman tests, Minolta index readings were transformed into micromole/l using linear regression of SBR on TcB readings

1

Bibliographic reference	**Roberston (2002)** **Improved transcutaneous bilirubinometry: comparison of SpectRx BiliCheck and Minolta Jaundice Meter JM-102 for estimating total serum bilirubin in a normal newborn population**
Study type	Cross sectional
Aim	To compare a new transcutaneous bilirubinometer which uses multiple wavelength analysis of reflectance data (BiliCheck system) and the commonly used two wavelength bilirubinometer (JM-102) to estimate serum bilirubin
Patient characteristics	**Inclusion criteria** - Infants from the normal newborn nursery for whom the physician had ordered a total serum bilirubin for clinical purposes **Exclusion criteria** - Receiving phototherapy **Other characteristics** *Sex* Not reported *Birthweight in g, mean (SD)* 3179 (723) *Gestational age in weeks, mean (SD)* 37.7 (2.2) *Exclusive breastfeeding*

Bibliographic reference	**Roberston (2002)** **Improved transcutaneous bilirubinometry: comparison of SpectRx BiliCheck and Minolta Jaundice Meter JM-102 for estimating total serum bilirubin in a normal newborn population**
	Not reported *Age at time of study in hours , mean (SD)* 50 (18) *Ethnicity, n* Caucasians: 70 African-Americans: 21 Hispanics: 6 Asians: 4
Number of patients	N=101 samples from 101 term infants
Index test	**TcB measurement** <u>Details</u> - TcB measured on the forehead using the Bilicheck meter and JM-102 according to manufacturer's instructions - Both instruments and supplies were provided without charge - The order of the use of 2 instruments was randomised
Reference standard (or Gold standard)	**TSB measurement** <u>Details</u> - Blood sample was obtained by heel stick by one medical technologist - Bilirubin was determined by the colorometric diazonium salt method using the Olympus AU600 instrumentation (Olymplus America)
Time between testing & treatment	- Tests within 15 minutes of each other - One paired measurement for each infant - Time between testing and treatment not reported
Length of follow-up	Not reported, study dates January 2000 to December 2000
Location	USA
Diagnostic accuracy measures (2 x 2	<u>Regression coefficeints, SE, p value</u>

Bibliographic reference	**Roberston (2002)** **Improved transcutaneous bilirubinometry: comparison of SpectRx BiliCheck and Minolta Jaundice Meter JM-102 for estimating total serum bilirubin in a normal newborn population**
table)	JM meter: 0.704; 0.069; 0.000 Skin colour: -0.771; 0.240; 0.002 BiliCheck: 0.937; 0.043; 0.000 Skin colour: 0.019; 0.134; 0.890
Source of funding	Not reported
Comments	Study limitations - Sampling technique not reported - Population: unclear if children were clinically jaundiced (but otherwise well) - Method used to measure TSB not well described eg: was it calibrated to the current method? - Unclear if blood sample was analysed within an acceptable period of time and protected from light - Bland-Altman plot analysis not extractable Setting Normal newborn nursery of a hospital Statistical methods - Analysis of data generated by the BiliChek and TSB was by the method of Bland and Altman which compares the mean of two measurement methods to the difference in the measured values - For the JM meter values which are read as reflectance units, a transformation was performed using linear regression; the differences (transformed JM meter reading – TSB) are plotted against the JM meter values for comparison to the Bland Altman plot Other - Skin colour defined as light (score readings 1 to 4) or dark (skin readings 5 to 8)

1

Bibliographic reference	**Kolman (2007)** **A comparison of transcutaneous and total serum bilirubin in newborn Hispanic infants at 35 or more weeks of gestation**
Study type	Diagnostic

Bibliographic reference	**Kolman (2007)** **A comparison of transcutaneous and total serum bilirubin in newborn Hispanic infants at 35 or more weeks of gestation**
Aim	To evaluate the accuracy of TcB measurments for assessing jaundice in the general population of Hispanic neonates by using TSB as the reference standard and to determine the TcB level that can be used to identify neonates who are at risk for clinically significant jaundice with risk defined as a TSB level above the 95th percentile.
Patient characteristics	**Inclusion criteria** - Infant of Hispanic ethnicity - Infant had not previously had a TSB level measured as part of this study - A trained nursery nurse was available to check a TcB measurement within 30 minutes of drawing a TSB level *this newborn nursery admits all healthy infants born at the hospital who are more than 35 weeks gestation and weigh more than 2267g. **Exclusion criteria** - Those of non-Hispanic ethnicity were excluded **Other characteristics** *Sex* Not reported *Birthweight in g, mean (SD)* 3368 (489.4) *Gestational age in weeks, mean (SD)* 39 (1.5) *Exclusive breastfeeding* Not reported *Age at time of study in hours , mean (SD)* 40 (13.4) *Ethnicity* Hispanic

<table>
<tr><td>Bibliographic reference</td><td>Kolman (2007)
A comparison of transcutaneous and total serum bilirubin in newborn Hispanic infants at 35 or more weeks of gestation</td></tr>
<tr><td></td><td>TSB in mg/dl (range)
1.7 to 13.9</td></tr>
<tr><td>Number of patients</td><td>N=198 enrolled; 6 excluded (non Hispanic) therefore 192 included</td></tr>
<tr><td>Index test</td><td>TcB measurement

<u>Details</u>
- Measured using BiliCheck; all performed with a single device in accordance with manufacturer’s recommendations
- All nurses obtaining TcB measurements received one-one instructions
- Device calibrated before each measurement according to manufacturer’s recommendations
- 3 TcB measurements obtained from infant’s forehead and averaged</td></tr>
<tr><td>Reference standard (or Gold standard)</td><td>TSB measurement

<u>Details</u>
- Blood obtained by venous puncture
- Analysed using Irtho Vitros 950 or the Ortho Vitros 5.1 FS Chemistry system; these analysers measure TSB using a modified diazo reaction
- Calibrated daily according to manufacturer’s recommendations
- Obtained only one TSB level</td></tr>
<tr><td>Time between testing & treatment</td><td>- TcB measured within 30 minutes of TSB
- Time between testing and treatment not reported
- One paired measurement used for analysis</td></tr>
<tr><td>Length of follow-up</td><td>Not reported, study dates January to April 2006</td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td><u>Predictive indices using >95th percentile TSB and ≥75th percentile TcB</u>
<table>
<tr><td></td><td>TSB>95th percentile</td><td>TSB ≤95th percentile</td></tr>
<tr><td>TcB ≥75th percentile</td><td>12</td><td>61</td></tr>
<tr><td>TcB <75th percentile</td><td>0</td><td>119</td></tr>
<tr><td>Total (n=192)</td><td>12</td><td>180</td></tr>
</table>
*For all values, sensitivity: 100%, specificity: 66.1%, PPV: 16.4%, NPV: 100%
*None of 119 infants with TcB below the 75th percentile for age had clinically significant hyperbilirubinaemia (TSB above the 95th</td></tr>
</table>

Bibliographic reference	**Kolman (2007)** **A comparison of transcutaneous and total serum bilirubin in newborn Hispanic infants at 35 or more weeks of gestation**
	percentile for age). The sensitivity of TcB measurements for detecting this level of hyperbilirubinaemia was thus 100%. Correlation coefficient between TSB and TcB r=0.87 (0.84 to 0.89)
Source of funding	None
Comments	Study limitations - Method used to measure TSB not well described eg: was it calibrated to the current method? - Indirect population: subjects don't seem to be clinically jaundiced as in this newborn nursery, all infants admitted routinely undergo TSB measurement before discharge - Prior phototherapy not reported - Unclear if blood sample was analysed within an acceptable period of time and protected from light - Bland Altman plot analysis not extractable Setting Newborn nursery Statistical methods - Overall relationship between the TcB and TSB was assessed using the Pearson product moment correlation, regression slope and Bland and Altman error plots - Sensitivity, specificity, positive and negative predictive values calculated

1

Bibliographic reference	**Rodriguez-Capote (2009)** **Clinical implication of the difference between trasncutaenous bilirubinometry and total serum bilirubin for the classification of newborns at risk of hyperbilirubinaemia**
Study type	Cross sectional
Aim	To determine whether transcutaneous bilirubin measurements performed using BiliCheck and the Minolta Air Shields (JM -103) meter correlate with TSB measured in the laboratory (Vitros 950) and to evaluate the predictive accuracy of the TcB measurements pertinent to the risk classification of infants with jaundice based on a nomagram
Patient characteristics	**Inclusion criteria** - Healthy neonates greater than 35 weeks gestational age and less than 10 days of life - Not undergoing phototherapy or recently exposed to phototherapy

Bibliographic reference	Rodriguez-Capote (2009) Clinical implication of the difference between trasncutaenous bilirubinometry and total serum bilirubin for the classification of newborns at risk of hyperbilirubinaemia
	- Absence of generalised skin diseases (newborn skin rashes were acceptable) and extensive head bruising - No assisted ventilation - Weight greater than 2500g at study entry **Exclusion criteria** - Not reported **Other characteristics** *Sex, n(%)* Bilicheck-Vitros: male – 29 (48); female – 31 (52) JM-103-Vitros: male - 45 (48); female - 49 (52) *Birthweight in g, mean (SD)* Not reported; weight at the time when measurements were taken: 3391.6 (487.7) *Gestational age in weeks, n (%)* Bilicheck-Vitros: <37: 5 (8) 37-38: 16 (27) 39-40: 25 (42) >40: 14 (23) JM-103-Vitros <37: 4 (4) 37-38: 27 (29) 39-40: 31 (33) >40: 32 (34) *Exclusive breastfeeding* Not reported

Bibliographic reference	**Rodriguez-Capote (2009)** **Clinical implication of the difference between trasncutaenous bilirubinometry and total serum bilirubin for the classification of newborns at risk of hyperbilirubinaemia**
	Age at measurement in hours, n (%) Bilicheck-Vitros: <18: 5 (8) 18-24: 10 (16) 25-48: 28 (44) 49-72: 13 (21) 73-96: 4 (6) >96: 3 (5) JM-103-Vitros <18: 1 (1) 18-24: 4 (4) 25-48: 73 (76) 49-72: 14 (15) 73-96: 3 (3) >96: 1 (1) *Ethnicity, n (%)* Bilicheck-Vitros Caucasian: 42 (70) Non-Caucasian: 18 (30) JM-103-Vitros Caucasian: 63 (67) Non-Caucasian: 31 (33)
Number of patients	N=154 healthy term/near term infants; 94 for JM-103; 60 for Bilicheck comparison
Index test	**TcB measurement** <u>Details</u> - Measured using BiliCheck or JM-103; device placed on infant's forehead - 6 nurses trained in the use of both instruments

Bibliographic reference	**Rodriguez-Capote (2009)** **Clinical implication of the difference between trasncutaenous bilirubinometry and total serum bilirubin for the classification of newborns at risk of hyperbilirubinaemia**
	- Only one device provided for each study and calibrated prior to each measurement - Total of three measurements obtained from each infant and averaged
Reference standard (or Gold standard)	**TSB measurement** <u>Details</u> - TSB measured using BuBc SLIDE Ortho Vitros 950 (Ortho Clinical Diagnostics) according to manufacturer's recommendations
Time between testing & treatment	- TcB measured within 30 minutes of serum sampling - Time between testing and treatment not reported - Only one measurement from each infant used for analysis
Length of follow-up	Not reported; study dates July- August 2003 (Bilicheck); December 2003 to February 2004 (JM-103* *JM-103 was available in Canada at the end of 2003
Location	Canada
Diagnostic accuracy measures (2 x 2 table)	<u>Correlation, r</u> BiliCheck: 0.93 JM-103: 0.92 <u>Bland-Altman plot analysis in micromole/l, mean bias (95%CI)</u> BiliCheck: -5.2 (-50.8 to 40.4) JM-103: -38.3 (-78.4 to 1.8)
Source of funding	Not reported
Comments	<u>Study limitations</u> - Unclear whether all subjects were clinically jaundiced; prior to discharge nurses visually inspected neonates for jaundice and blood sample taken; in patients without clinical suspicion of jaundice, extra 200uL of blood was taken at the time of newborn screening to prevent unnecessary heel stick procedures. - Method used to measure TSB not well described eg: was it calibrated to the current method? - Unclear if blood sample was analysed within an acceptable period of time and protected from light <u>Setting</u> Nursery of a children's hospital

Bibliographic reference	**Rodriguez-Capote (2009)** **Clinical implication of the difference between trasncutaenous bilirubinometry and total serum bilirubin for the classification of newborns at risk of hyperbilirubinaemia**
	<u>Statistical methods</u> - Correlation between TcB and TSB assessed using concordance correlation efficient, regression slope and Bland and Altman plots - 2x2 tables using Vitros as the gold standard <u>Other</u> No indication of phototherapy; therefore results shown must be before treatment commencing

1

Bibliographic reference	**Knupfer (2001)** **Transcutaneous bilirubinometry in preterm infants**
Study type	Diagnostic
Aim	To measure serum and transcutaneous bilirubin concentrations simultaneously using the transcutaneous measurement analyser BiliCheck to characterise more precisely the possibilities of transcutaneous bilirubinometry for recognising clinically relevant hyperbilirubinaemia and to detect factors influencing the use of this method in preterm infants
Patient characteristics	**Inclusion criteria** - Preterm babies born in the Department of obstetrics and admitted to the NICU - Serum bilirubin requested by attending physician because of visible jaundice **Exclusion criteria** - Missing data - Rhesus haemolytic disease **Other characteristics** *Sex, n* 60 females 75 males *Birthweight in g, mean (SD)* 1805 (684)

Bibliographic reference	**Knupfer (2001)** **Transcutaneous bilirubinometry in preterm infants**
	Gestational age in weeks, mean (SD) 31.9 (3.3) *Exclusive breastfeeding* Not reported *Age at measurement in hours, n (%)* Not reported Ethnicity Caucasians: 128 Asians: 7 *Serum bilirubin values, micromole* 17 to 371
Number of patients	145 preterm infants, 10 excluded therefore n=135
Index test	**TcB measurement** <u>Details</u> - Measured over forehead using BiliCheck (no other details)
Reference standard (or Gold standard)	**TSB measurement** <u>Details</u> - Serum bilirubin requested by attending physician because of visible jaundice (capillary, venous or arterial blood) - Blood samples stored in dark tubes until measurement of bilirubin values which were determined with a standard DPD method using an automatic analyser (HITACHI) according to the protocol of the manufacturer (Roche Diagnostics)
Time between testing & treatment	- Index test and reference standard within one hour of each other - Phototherapy started if serum bilirubin was higher than a value which was calculated by the following method: borderline concentration of bilirubin= birthweight x 0.1. Children with a birthweight greater than 3000g were given phototherapy at a level of 300micromole/l.
Length of follow-up	Not reported, study dates March and October 1999
Location	Germany

<table>
<tr><td>Bibliographic reference</td><td>Knupfer (2001)
Transcutaneous bilirubinometry in preterm infants</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td>
<u>Correlation between serum bilirubin and TcB for newborns without phototherapy</u>

r=0.73; p<0.001

<u>Influence of gestational age on correlation of serum bilirubin and TcB for children without phototherapy</u>

<table>
<tr><td>Gestational age</td><td>R</td><td>P value</td></tr>
<tr><td>23 to 28 weeks</td><td>0.47</td><td><0.05</td></tr>
<tr><td>29 to 30 weeks</td><td>0.67</td><td><0.0001</td></tr>
<tr><td>31 to 32 weeks</td><td>0.78</td><td><0.0001</td></tr>
<tr><td>33 to 34 weeks</td><td>0.85</td><td><0.0001</td></tr>
<tr><td>35 to 36 weeks</td><td>0.81</td><td><0.0001</td></tr>
</table>

<u>Predictive accuracy of TcB values in predicting the need for phototherapy for all Caucasians without phototherapy</u>

<table>
<tr><td>Sensitivity (%)</td><td>Specificity (%)</td><td>PPV (%)</td><td>NPV (%)</td><td>Efficiency (%)</td></tr>
<tr><td>86.8</td><td>72.6</td><td>37.9</td><td>96.6</td><td>74.9</td></tr>
</table>
</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Comments</td><td>
<u>Study limitations</u>
- Sampling technique not reported
- Postnatal age of infants not reported
- Method used to measure TSB not well described eg: was it calibrated to the current method?
- Unclear if blood sample was analysed within an acceptable period of time and protected from light

<u>Setting</u>
Department of obstetrics at the Univeristy of Leipzig and admitted to NICU

<u>Statistical methods</u>
- Pearson’s correlation coefficient and linear correlation analyses and a multiple linear regression analysis were used to detect
</td></tr>
</table>

Bibliographic reference	**Knupfer (2001)** **Transcutaneous bilirubinometry in preterm infants**
	associations between serum bilirubin and transcutaneous bilirubin

1

Bibliographic reference	**Holland (2009)** **Implementing and validating transcutaneous bilirubinometry for neonates**
Study type	Cross sectional
Aim	To evaluate the use of a transcutaneous spectrophotometer that allows noninvasive measurement of bilirubin levels
Patient characteristics	**Inclusion criteria** - More than 36 weeks gestation - Not receiving phototherapy - Between 1 and 5 days old - Admitted to a well-baby nursery **Exclusion criteria** - Not reported **Other characteristics** Postnatal age in hours, mean (range) 38 (25 to 104)
Number of patients	343 term neonates from 3 hospitals
Index test	**TcB measurement** <u>Details</u> - All hospitals used BiliCheck - Measurements were taken on the forehead or sternum
Reference standard (or Gold standard)	**TSB measurement** <u>Details</u> - Each institution used a different chemistry analyser: Dimension RXL (Dade Behring); Synchron LX20 (Beckman Coulter) or Vitros 950 (Ortho-Clinical Diagnostics) - Specimens grossly haemolysed were not included ; bilirubin results performed on the Synchron LX20 also included a

<table>
<tr><td>Bibliographic reference</td><td>Holland (2009)
Implementing and validating transcutaneous bilirubinometry for neonates</td></tr>
<tr><td></td><td>haemolytic index and those with a index >5 were considered to have significant hemolysis and excluded</td></tr>
<tr><td>Time between testing & treatment</td><td>- TcB within 10 minutes of obtaining blood sample
- Time between testing and treatment not reported</td></tr>
<tr><td>Length of follow-up</td><td>Not reported, study dates not reported</td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td><u>Correlation between TSB and TcB by measurement site for the 3 instruments used in the study</u>
<table>
<tr><td>Instrument</td><td>N</td><td>Site</td><td>r</td></tr>
<tr><td>Dimension XL</td><td>35</td><td>Forehead</td><td>0.91</td></tr>
<tr><td>Synchron LX20</td><td>70
146</td><td>Forehead
Sternum</td><td>0.85
0.91</td></tr>
<tr><td>Vitros</td><td>52
40</td><td>Forehead
Sternum</td><td>0.88
0.91</td></tr>
</table>
<u>Influence of race or ethnicity and measurement site on the bias and correlation between serum bilirubin and TcB</u>
<table>
<tr><td></td><td colspan="2">African American</td><td colspan="2">Caucasian</td><td colspan="2">Hispanic</td></tr>
<tr><td></td><td>TcB forehead N=14</td><td>TcB sternum N=17</td><td>TcB forehead N=15</td><td>TcB sternum N=32</td><td>TcB forehead N=42</td><td>TcB sternum N=58</td></tr>
<tr><td>Correlation</td><td>0.88 (0.59 to 0.97)</td><td>0.89 (0.71 to 0.96)</td><td>0.94 (0.76 to 0.98)</td><td>0.93 (0.87 to 0.97)</td><td>0.83 (0.70 to 0.90)</td><td>0.92 (0.86 to 0.95)</td></tr>
</table></td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Comments</td><td><u>Study limitations</u>
- A number of baseline characteristics not reported
- Exclusion criteria not reported
- Indirect population: all infants are screened before discharge regardless of visual presence or absence of jaundice
- Method used to measure TSB not well described eg: was it calibrated to the current method?
- Unclear if blood sample was analysed within an acceptable period of time and protected from light

<u>Setting</u></td></tr>
</table>

Bibliographic reference	**Holland (2009)** **Implementing and validating transcutaneous bilirubinometry for neonates**
	Hospitals <u>Statistical methods</u> - Regression equations - R converted to z scores before comparison to normalise for effect of varying numbers of partiipants in each study

1

Bibliographic reference	**Stoniene (2009)** **The value of transcutaneous method of bilirubin measurement in newborn population with the risk of ABO haemolytic disease**
Study type	Diagnostic
Aim	To evaluate the correlation between TSB and transcutaneous bilirubin in newborn infants at risk of ABO haemolytic disease
Patient characteristics	**Inclusion criteria** - Healthy full term (≥37 weeks) newborns with ABO incompatability born at the Clinic of obstetric and gynecology **Exclusion criteria** - Full term infants of mothers with RhD antibodies **Other characteristics** *O-B incompatibility, n (%)* 44 (33.6) *O-A incompatability, n (%)* 86 (66.1) *ABO haemolytic disease, n(%)* 6 (4.8) *Hyperbilirubinaemia diagnosis, n(%)* 12 (9.5) *Physiological jaundice, n(%)*

<table>
<tr><td>Bibliographic reference</td><td>Stoniene (2009)
The value of transcutaneous method of bilirubin measurement in newborn population with the risk of ABO haemolytic disease</td></tr>
<tr><td></td><td>108 (85.7)</td></tr>
<tr><td>Number of patients</td><td>N=130 full term infants, 387 paired measurements performed between 6 and 78 hours of age</td></tr>
<tr><td>Index test</td><td>TcB measurement

<u>Details</u>
- Measured using a noninvasive bilirubinometer BiliCheck on forehead following the manufacturer’s instructions</td></tr>
<tr><td>Reference standard (or Gold standard)</td><td>TSB measurement

<u>Details</u>
- Blood sample taken from the peripheral vein
- Analysed by the Jendrassik Grof method</td></tr>
<tr><td>Time between testing & treatment</td><td>- TcB measured within 30 mins of getting a blood sample
- Time between testing and treatment not reported
- 387 paired measurements in total performed between 6 and 78 hours of age</td></tr>
<tr><td>Length of follow-up</td><td>78 hours</td></tr>
<tr><td>Location</td><td>Lithuania</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td><u>Correlation between TSB and TcB at different newborn’s age</u>
<table>
<tr><th>Newborn’s age in hours</th><th>N</th><th>Mean TSB (SD) in micromole/l</th><th>Mean TcB (SD) in micromole/l</th><th>r</th><th>p value</th></tr>
<tr><td>6</td><td>130</td><td>65.00 (20.01)</td><td>59.42 (24.99)</td><td>0.72</td><td><0.001</td></tr>
<tr><td>30</td><td>119</td><td>128.13 (40.48)</td><td>126.94 (40.01)</td><td>0.77</td><td><0.001</td></tr>
<tr><td>54</td><td>103</td><td>174.55 (48.54)</td><td>171.63 (51.60)</td><td>0.87</td><td><0.001</td></tr>
<tr><td>78</td><td>35</td><td>225.46 (54.99)</td><td>218.09 (50.93)</td><td>0.83</td><td><0.001</td></tr>
<tr><td>6 to 78 (overall)</td><td>387</td><td>114.83 (62.85)</td><td>111.51 (61.31)</td><td>0.92</td><td><0.001</td></tr>
</table>
<u>Mean values of TSB and TcB differences at different newborn’s age</u>
<table>
<tr><th>Newborn’s age in hours</th><th>N</th><th>Mean difference of TSB and TcB value in micromole/l (95%CI)</th><th>p value</th></tr>
<tr><td>6</td><td>130</td><td>5.58 (2.55 to 8.61)</td><td><0.001</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Stoniene (2009)** **The value of transcutaneous method of bilirubin measurement in newborn population with the risk of ABO haemolytic disease**
	30 | 119 | 1.19 (-3.68 to 6.06) | NS 54 | 103 | 2.92 (-2.04 to 7.89) | NS 78 | 35 | 7.37 (-3.30 to 18.04) | NS 6 to 78 | 387 | 3.31 (0.70 to 5.93) | <0.05
Source of funding	Not reported
Comments	Study limitations - Sampling technique not reported - Unclear whether subjects were clinically jaundiced; seems like TSB measured at specified time intervals as part of routine management - Prior phototherapy not reported - Method used to measure TSB not well described eg: was it calibrated to the current method? - Unclear if blood sample was analysed within an acceptable period of time and protected from light Setting Clinic of Obstetric and Gynecology Statistical methods - Coefficient of correlation evaluated Other comments - Once hyperbilirubinaemia was diagnosed and subsequent medical care was provided, further pair tests were not performed. Therefore, results shown are before treatment commencing.

1

Bibliographic reference	**Jangaard (2006) Estimation of bilirubin using BiliChek and trade: a transcutaneous bilirubin measurement device: effects of gestational age and use of phototherapy**
Study type	Prospective cohort
Aim	To correlate bilirubin measurements using the transcutaneous device BiliChek with gold standard serum measurements in well term infants and in ill term and preterm infants admitted to the neonatal intensive care unit

Bibliographic reference	Jangaard (2006) Estimation of bilirubin using BiliChek and trade: a transcutaneous bilirubin measurement device: effects of gestational age and use of phototherapy
Patient characteristics	Inclusion criteria - All healthy term infants - Preterms in NICU Exclusion criteria - Refusal of either newborn screening or consent Other characteristics *Sex* Not reported *Birthweight in g, mean (SD)* Term: 3523 (560) n=99 Preterm:1565 (482) n=33 *Gestational age in weeks, mean (SD)* Term: 39.4 (1.4) Preterm: 30.8 (2.5) *Exclusive breastfeeding* Not reported *Age at measurement in hours, n (%)* Not reported *Ethnicity, n (%)* Caucasian: term – 92 (93), preterm – 28 (85) African Canadian: term – 3 (3), preterm – 1 (3) First Nations: term – 1 (1), preterm – 1 (3) Other: term – 3 (3), preterm – 3 (9) *Median serum bilirubin level (range)*

Bibliographic reference	Jangaard (2006) Estimation of bilirubin using BiliChek and trade: a transcutaneous bilirubin measurement device: effects of gestational age and use of phototherapy
	144micromole/l (17micromole/l to 294micromole/l)
Number of patients	N=99 healthy terms plus 56 in NICU (only data relating to the accuracy of tests before phototherapy has been extracted)
Index test	**TcB measurement** Details - Recorded immediately before and after the heel puncture using BiliCheck placed on the baby's forehead as recommended by the manufacturer - All measurements performed by a single research assistant who was unaware of the serum bilirubin level - Average of 5 readings
Reference standard (or Gold standard)	**TsB measurement** Details - When heel puncture was performed for routine screening of thyroid stimulating hormone and phenylketonuria, 250ul of extra blood was drawn for serum bilirubin analysis - Analysed by the Vitros BuBc method (Ortho-Clinical Diagnostics)
Time between testing & treatment	- Tests performed within one hour of each other - Time between testing and treatment not reported
Length of follow-up	Not reported
Location	Canada
Diagnostic accuracy measures (2 x 2 table)	Bland-Altman plot analysis in micromole/l Term infants not receiving phototherapy, mean bias (95% limits of agreement): -0.5 (-32.2 to 31.2), n=99 Preterm infants with or without phototherapy, mean bias (95% limits of agreement): -3.8 (-69.6 to 62.0), n=65
Source of funding	IWK Research Services
Comments	Study limitations - Indirect population: no indication of clinical diagnosis of jaundice; 31% of the samples had serum bilirubin less than 85micromole/l, the level deemed by the authors to be necessary to produce visible jaundice. - Convenience sample - Postnatal age of infants not reported - Method used to measure TSB not well described eg: was it calibrated to the current method? - Unclear if blood sample was analysed within an acceptable period of time and protected from light - Data for preterm group includes those with and without phototherapy

Bibliographic reference	Jangaard (2006) Estimation of bilirubin using BiliChek and trade: a transcutaneous bilirubin measurement device: effects of gestational age and use of phototherapy
	Setting Health centre Statistical methods Bland-Altman plot analysis Other Study had multiple arms: only data for those not receiving phototherapy has been extracted

1

Bibliographic reference	Maisels (2011) Transcutaneous bilirubin levels in an outpatient and office population
Study type	Diagnostic
Aim	To evaluate whether TcB screening is accurate in outpatient settings, whether TcB screening should be used when TSB levels are >15mg/dl^{-1}and whether fewer false negative TcB measurements occur if three independent measurements are performed and the maximum TcB measurement is used rather than the average of those measurements
Patient characteristics	**Inclusion criteria** - Jaundiced infants in two hospital based outpatient clinics, one Regional Public Health Nurse Follow up Program and two pediatric office practices - ≥35 weeks gestation **Exclusion criteria** - Not reported **Other characteristics** *Sex, n (%)* Male – 64 (53) Female – 56 (47) *Birthweight* Not reported

Bibliographic reference	Maisels (2011) Transcutaneous bilirubin levels in an outpatient and office population
	Gestational age in weeks, n (%) *35 -37: 24 (20)* *>38: 91 (76)* *Unknown: 5 (4)* *Feeding, n (%)* Breast: 57 (47.5) Bottle: 15 (12.5) Both: 45 (37.5) Unknown: 3 (2.5) *Age at measurement in hours, mean (SD)* 90.4 (32.9) *Ethnicity, n (%)* Caucasian: 42 (35) African-American: 11 (9) Asian: 19 (16) Hispanic: 37 (31) Middle Eastern: 3 (3) Native Canadian: 4 (3) Unknown: 4 (3) *TSB level, mean (SD)* 15.1 (3.1)
Number of patients	N=120
Index test	**TcB measurement** <u>Details</u> - Measured with JM-103 by nursing staff in the offices

<table>
<tr><th>Bibliographic reference</th><th>Maisels (2011) Transcutaneous bilirubin levels in an outpatient and office population</th></tr>
<tr><td></td><td>- In the regional home visit follow up program, measurements were obtained by Publc Health Nurses
- 3 individual TcB readings obtained from the mid-sternum – average and maximum values recorded; unless otherwise indicated, each TcB value is the maximum from the 3 readings</td></tr>
<tr><td>Reference standard (or Gold standard)</td><td>TSB measurement

<u>Details</u>
- Obtained on clinical indication when a jaundiced infant presented during an outpatient follow-up visit
- TSB measurements performed in each location using the following methods:
1) Royal Oak and Sterling Heights – Synchron Diazo
2) Dallas – Olympus Diazo
3) Calgary – Roche Modular, Htachi 912 and 917
4) Iowa – Siemens Dimension</td></tr>
<tr><td>Time between testing & treatment</td><td>- TcB measured within half an hour of TSB
- Time between testing and treatment not reported</td></tr>
<tr><td>Length of follow-up</td><td>Not reported</td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td><u>Correlation coefficient from linear regression* plot</u>
r=0.78, p=0.0

*this regression analysis excludes 2 obvious outliers; in one the TcB was 6.7, TSB 15.6mg dl^{-1} and in the other the TcB was 18.2, TSB 11.1mg dl^{-1}

<u>Predictive indices for TSB levels ≥13 to ≥18mg/dl^{-1}at various JM-103 cut off values (maximum of three readings), n=118</u>

<table>
<tr><th>TSB, mg/dl</th><th>TcB, mg/dl</th><th>Sensitivity</th><th>Specificity</th><th>PPV</th><th>NPV</th><th>False negative (TcB readings less than cut-off value)</th></tr>
<tr><td>≥13mg/dl (222.3micromole/l)</td><td>≥9 (153.9micromole/l)
≥10</td><td>1
1
1</td><td>0.04
0.07
0.19</td><td>0.78
0.78
0.81</td><td>1
1
1</td><td>0
0
0</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Maisels (2011) Transcutaneous bilirubin levels in an outpatient and office population						
		(171micromole/l) ≥11 (188.1micromole/l) ≥12 (205.2micromole/l) ≥13 (222.3micromole/l)	0.99 0.96	0.52 0.74	0.87 0.93	0.94 0.83	1 4
	≥14mg/dl (239.4micromole/l)	≥10 (171micromole/l) ≥11 (188.1micromole/l) ≥12 (205.2micromole/l) ≥13 (222.3micromole/l) ≥14 (239.4micromole/l)	1 1 1 0.98 0.91	0.05 0.12 0.37 0.54 0.63	0.66 0.68 0.75 0.8 0.82	1 1 1 0.92 0.79	0 0 0 2 7
	≥15mg/dl (256.5micromole/l)	≥11 (188.1micromole/l) ≥12 (205.2micromole/l) ≥13 (222.3micromole/l) ≥14 (239.4micromole/l) ≥15 (256.5micromole/l)	1 1 0.99 0.92 0.79	0.1 0.29 0.44 0.54 0.7	0.58 0.64 0.69 0.72 0.76	1 1 0.96 0.85 0.72	0 0 1 5 14
	≥16 (273.6micromole/l)	≥12 (205.2micromole/l) ≥13 (222.3micromole/l) ≥14 (239.4micromole/l)	1 0.98 0.96 0.86 0.78	0.22 0.33 0.45 0.62 0.75	0.48 0.51 0.55 0.62 0.69	1 0.96 0.94 0.86 0.83	0 1 2 7 11

Bibliographic reference	Maisels (2011) Transcutaneous bilirubin levels in an outpatient and office population						
		≥15 (256.5micromole/l) ≥16 (273.6micromole/l)					
	≥17 (290.7micromole/l)	≥13 (222.3micromole/l) ≥14 (239.4micromole/l) ≥15 (256.5micromole/l) ≥16 (273.6micromole/l) ≥17 (290.7micromole/l)	1 1 0.92 0.81 0.6	0.3 0.41 0.58 0.69 0.84	0.39 0.44 0.5 0.55 0.63	1 1 0.94 0.89 0.82	0 0 3 7 15
	≥18 (307.8micromole/l)	≥14 (239.4micromole/l) ≥15 (256.5micromole/l) ≥16 (273.6micromole/l) ≥17 (290.7micromole/l) ≥18 (307.8micromole/l)	1 0.95 0.85 0.75 0.6	0.34 0.5 0.61 0.8 0.9	0.24 0.28 0.31 0.43 0.55	1.0 0.98 0.95 0.94 0.92	0 1 3 5 8
Source of funding	Dr Maisels has been a consultant for Draeger Medical Inc and has received funding from Drager Medical Inc for previous studies of JM-103						
Comments	Study limitations - Sampling technique not reported - Exclusion criteria not reported – population otherwise well? - Method used to measure TSB not well described eg: was it calibrated to the current method? - Unclear if blood sample was analysed within an acceptable period of time and protected from light Setting						

Bibliographic reference	Maisels (2011) Transcutaneous bilirubin levels in an outpatient and office population
	Two hospital based outpatient clinics, one Regional Public Health Nurse Follow up Program and two pediatric office practices <u>Statistical methods</u> - Data analysed by regression of TcB against TSB and prediction of TSB by TcB was assessed for various cutoff values for TSB and TcB using standard sensitivity, specificity, and positive and negative value calculations - The number of blood tests potentially avoided by use of TcB was calculated as: (false negatives + true negatives)/total number of comparisons

1

Bibliographic reference	Wainer (2009) Impact of skin tone on the performance of a transcutaneous jaundice meter
Study type	Cross sectional (diagnostic)
Aim	To evaluate the performance of the JM-103 jaundice meter on the basis of infant skin tone during the early neonatal period
Patient characteristics	**Inclusion criteria** - Infants ≥37 weeks gestation born at a single regional centre between December 1 2004 and 31 December 2005 **Exclusion criteria** - Home address outside of the geographical area served by the designated study Public Health nurses - Born with any major malformation - Received phototherapy prior to recruitment - Admitted to neonatal intensive care unit for more than 24 hours for any reason - Infants with missing skin tone categorisation **Other characteristics** *Sex, n (%)* Male: 377 (48.7) Female: 397 (51.3) *Birthweight in g, mean (SD)* 3166 (447) *Gestational age in weeks, mean (SD)*

Bibliographic reference	Wainer (2009) Impact of skin tone on the performance of a transcutaneous jaundice meter
	39.1 (1.2) *Exclusive breastfeeding* Not reported *Age at measurement in hours* Mean not reported, TSB drawn at around 24 hours of age *Ethnicity,%* Caucasian: 41.7 Asian: 41.3 Middle-Eastern: 9.5 Black: 4.6 Aboriginal: 3.0
Number of patients	938 full term infants enrolled; 774 TSB/TcB pairs met the criteria for analysis
Index test	**TcB measurement** <u>Details</u> - TcB performed on forehead of all infants at approximately 12, 24, 48 and 72 hours and 7 days of age using JM-103 - Performed by study nurses or public health nurses - Average of 3 readings - 4 TcB devices were used in the community and one device in the hospital - Devices calibrated according to the manufacturer's specifications
Reference standard (or Gold standard)	**TSB measurement** <u>Details</u> - TSB samples were protected from light after collection. - TSB samples drawn along with routine metabolic studies at approximately 24 hours of age - Analysed using the diazonium method with the same instrumentation, analytical method and calibrators within a single regional laboratory system (Roche Modular, Hitachi 912 and 917 instruments)

<table>
<tr><td>Bibliographic reference</td><td>Wainer (2009) Impact of skin tone on the performance of a transcutaneous jaundice meter</td></tr>
<tr><td></td><td>- During the course of the study, there was a change in approved calibrators used with Roche instrumentation which resulted in a phased 9.0% decrease in TSB concentrations. This adjustment was accounted for in the data analysis.</td></tr>
<tr><td>Time between testing & treatment</td><td>- TcB and TSB measurements paired only if tests within 60 minutes of each other
- Time between testing and treatment not reported
- Although 8.4% of infants had more than one TSB/TcB pair captured, only the TSB/TcB pair with the highest TSB concentration for each infants was used in the regression analysus to avoid bias resulting from multiple measurements in a single infant</td></tr>
<tr><td>Length of follow-up</td><td>Not reported</td></tr>
<tr><td>Location</td><td>Canada</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td><u>Multivariate linear regression analysis of skin tone on TSB vs TcB</u>
TcB - coefficient (95%CI): 0.93 (0.90 to 0.96); p<0.001
Light skin tone - coefficient (95%CI): 12.20 (9.27 to 15.12); p<0.001
Medium skin tone - coefficient (95%CI): reference
Dark skin tone- coefficient (95%CI): - 31.20 (-41.57 to -20.83); p<0.001

<u>Device performance at various TSB concentrations</u>
<table>
<tr><th>TcB</th><th>Sensitivity (%)</th><th>Specificity (%)</th><th>PPV (%)</th><th>NPV (%)</th><th>Blood tests avoided (%)</th><th>AUC (95%CI)</th></tr>
<tr><td colspan="6">All infants (n=774)</td><td></td></tr>
<tr><td colspan="6">TSB >150micromole/l</td><td>0.953 (0.937 to 0.9369)</td></tr>
<tr><td>70</td><td>100</td><td>24.9</td><td>27.4</td><td>100</td><td>19.4</td><td></td></tr>
<tr><td>80</td><td>99.4</td><td>34.3</td><td>30.0</td><td>99.5</td><td>26.9</td><td></td></tr>
<tr><td>190</td><td>38.6</td><td>99.7</td><td>97.1</td><td>85.1</td><td>91.2</td><td></td></tr>
<tr><td>200</td><td>31.6</td><td>100</td><td>100</td><td>83.8</td><td>93.0</td><td></td></tr>
<tr><td colspan="6">TSB >200micromole/l</td><td>0.987 (0.979 to 0.996)</td></tr>
<tr><td>130</td><td>100</td><td>80.8</td><td>32.7</td><td>100</td><td>73.9</td><td></td></tr>
<tr><td>140</td><td>98.5</td><td>85.7</td><td>39.2</td><td>99.8</td><td>78.6</td><td></td></tr>
<tr><td>220</td><td>54.5</td><td>99.7</td><td>94.7</td><td>95.9</td><td>95.1</td><td></td></tr>
<tr><td>230</td><td>45.5</td><td>100</td><td>100</td><td>95.2</td><td>96.1</td><td></td></tr>
<tr><td colspan="6">TSB >250micromole/l</td><td>0.993 (0.987 to 0.999)</td></tr>
<tr><td>160</td><td>100</td><td>90.1</td><td>31.1</td><td>100</td><td>86.3</td><td></td></tr>
</table></td></tr>
</table>

Bibliographic reference	Wainer (2009) Impact of skin tone on the performance of a transcutaneous jaundice meter						
	170	97.0	91.8	34.4	99.9	88.0	
	240	60.6	99.7	90.9	98.3	97.2	
	250	57.6	100	100	98.1	97.5	
	Light tone (n=347)						
	TSB >150micromole/l						0.966 (0.950 to 0.983)
	100	100	72.0	51.3	100	55.6	
	110	97.5	81.0	60.2	99.1	63.1	
	150	53.2	99.3	95.5	87.8	87.3	
	160	45.6	100	100	86.2	89.6	
	TSB >200micromole/l						0.991 (0.980 to 1.00)
	130	100	85.4	33.8	100	79.5	
	140	95.8	90.4	42.6	99.7	84.4	
	200	62.5	99.7	93.8	97.3	95.4	
	210	54.2	100	100	96.7	96.3	
	TSB >250micromole/l						0.999 (0.998 to 1.00)
	160	100	92.8	33.3	100	89.6	
	170	91.7	94.0	35.5	99.7	91.1	
	230	50.0	99.7	85.7	98.2	98.0	
	240	41.7	100	100	98.0	98.6	
	Medium tone (n=412)						
	TSB >150micromole/l						0.961 (0.939 to 0.984)
	70	100	17.1	25.5	100	13.3	
	80	98.9	24.9	27.2	98.8	19.7	
	170	62.6	99.1	95.0	90.3	85.4	
	180	54.9	100	100	88.7	87.9	
	TSB >200micromole/l						Not reported
	140	100	82.2	38.9	100	73.8	
	150	95.2	87.6	46.5	99.4	79.1	
	220	61.9	99.5	92.9	95.8	93.2	

Bibliographic reference	Wainer (2009) Impact of skin tone on the performance of a transcutaneous jaundice meter

230	54.8	100	100	95.1	94.4	
TSB >250micromole/l						0.989 (0.979 to 0.999)
190	100	94.1	47.7	100	89.3	
200	95.2	95.4	52.6	99.7	90.8	
240	71.4	99.7	93.8	98.5	96.1	
250	66.7	100	100	98.2	96.6	

Source of funding

Not reported

Comments

Study limitations

- No indication of clinical jaundice
- Convenience sample
- Method used to measure TSB not well described eg: was it calibrated to the current method?
- Unclear if blood sample was analysed within an acceptable period of time
- Categorisation of skin colour not performed by the same person - study coordinator for 79% of infants, with balance being performed by study nurses

Setting

Single regional centre

Statistical methods

- Impact of skin tone on agreement between TcB and TSB measurements assessed using a multivariate linear regression analysis with medium skin tone designated as the reference group
- Bradley-Blackwood analyses based on the Bland Altman analysis were performed
- Precision and accuracy of the TcB measurements were calculated using the Lin concordance correlation coefficient
- The concordance correlation coefficient is the product of the Peaston correlation coefficient and a bias correction factor that estimates accuracy by assessing deviation from the line of equality (TSB=TcB)
- Utility of meter assessed using ROC curves and Sens analyses for skin tone
- Bland Altman plot analysis: mean differences not extractable as numbers not reported

Other info

- Categorisation of skin colour (light, medium, dark) relative to two reference consmetic colours. Infants categorised as light if skin colour less than or equal to light reference colour, dark if greater than or equal to dark reference colour and medium between the two.

Bibliographic reference	Wainer (2009) Impact of skin tone on the performance of a transcutaneous jaundice meter
	- Results shown are before phototherapy as those receiving phototherapy excluded

1

Bibliographic reference	Ahmed (2010) Comparison between transcutaneous bilirubinometry and total serum bilirubin measurements in preterm infants <35 weeks gestation
Study type	Prospective cohort
Aim	To look at the agreement between 2 different methods of measuring total bilirubin using BiliCheck and TSB in babies <35 weeks gestation with or without phototherapy
Patient characteristics	**Inclusion criteria** - All babies less than 35 weeks gestation admitted to the neonatal unit during the study period **Exclusion criteria** - Infants requiring exchange transfusion **Other characteristics** *Sex* Not reported *Birthweight in g, mean (SD)* Not reported *Gestational age in weeks, range* From 26 to 34 weeks *Exclusive breastfeeding* Not reported *Age at measurement* Not reported *Ethnicity, n* Caucasian: 50

Bibliographic reference	Ahmed (2010) Comparison between transcutaneous bilirubinometry and total serum bilirubin measurements in preterm infants <35 weeks gestation
	Indian: 4 Mixed: 3
Number of patients	57 preterm infants
Index test	**TcB measurement** Details - Measured using BiliChek on the infants forehead with the infant lying supine - Disposable probe tips calibrated as per the manufacturer's instructions before each measurement - Average of 5 readings in either micromole/l or mg/dl
Reference standard (or Gold standard)	**TSB measurement** Details - Clinical decision made to undertake TSB - Analysed using a standard diazo method (Olympus AU640)
Time between testing & treatment	- TcB within 15 minutes of blood collection for TSB - Decision to commence phototherapy based on TSB result; threshold used depends on gestational age – threshold for 35 week gestation infant would be 250micromole/l. TSB repeated in 6-8 hours then 12-24 hours for those on phototherapy - One paired measurement data (before phototherapy) extracted
Length of follow-up	Study period one year; July 2007 to June 2008
Location	UK
Diagnostic accuracy measures (2 x 2 table)	Correlation coefficient for first observation dataset i.e. before phototherapy commenced r=0.8775, p<0.005
Source of funding	No external finanaical support received for this project (BiliCheck probe tips financed from the R&D project)
Comments	Study limitations - Unclear if population clinically jaundiced; most admitted here require blood tests on admission and then routinely on a weekly basis or based on clinical judgement - Sampling technique not reported - Method used to measure TSB not well described eg: was it calibrated to the current method?

Bibliographic reference	Ahmed (2010) Comparison between transcutaneous bilirubinometry and total serum bilirubin measurements in preterm infants <35 weeks gestation
	- Unclear if blood sample was analysed within an acceptable period of time Setting Neonatal unit of a district hospital Statistical methods - Linear regression analysis and difference plots Other Data during phototherapy including ROC curve analysis not extracted as aim of this question is not to examine accuracy of tests in monitoring response to treatment

1

Bibliographic reference	Mielsch (2010) Point of care determination of neonatal bilirubin with the blood gas analyser RapidLab 1265
Study type	Cross sectional
Aim	To evaluate the comparability of the new neonatal bilirubin method on the RapidLab 1265 blood gas analyser
Patient characteristics	**Inclusion criteria** - Consecutive newborns from the pediatric newborn ward **Exclusion criteria** - Newborns with a birth weight below 2500g and/or with lung immaturity as well as preterm infants <32 weeks of gestation **Other characteristics** *Sex* Not reported *Birthweight* Not reported *Gestational age* Not reported

Bibliographic reference	Mielsch (2010) Point of care determination of neonatal bilirubin with the blood gas analyser RapidLab 1265
	Exclusive breastfeeding Not reported *Age at measurement* Not reported *Ethnicity* Not reported
Number of patients	N=232 infants >32 weeks gestation
Index test	**TcB measurement** Details - Measured using JM-103 – no other details reported
Reference standard (or Gold standard)	**TSB measurement** Details - Vitros 350 chemistry system with BuBc slide
Time between testing & treatment	- TcB within one hour of blood collection - Time between testing and treatment not reported
Length of follow-up	Not reported
Location	Germany
Diagnostic accuracy measures (2 x 2 table)	Correlation coefficient r=0.87 (0.84 to 0.90) Bland Altman plot analysis, mean difference in mg/dl (95% limits of agreement) -1.558mg/dl (-4.614 to 1.499) --> -26.64micromole/l (-78.90 to 25.63)
Source of funding	Supported by Siemens Healthcare Diagnostics

Bibliographic reference	Mielsch (2010) Point of care determination of neonatal bilirubin with the blood gas analyser RapidLab 1265
Comments	Study limitations - No indication of clinical jaundice - Baseline characteristics of population not reported - Index test not well described – eg: where was it TcB measured? - Method used to measure TSB not well described eg: was it calibrated to the current method? - Unclear if blood sample was analysed within an acceptable period of time - Prior phototherapy not reported Setting Pediatric newborn ward Statistical methods - Correlation coefficients calculated according to Pearson - Bland Altman plot analysis

1

Bibliographic reference	Grohmann (2006) Bilirubin measurement for neonates: comparison of 9 frequently used methods
Study type	Diagnostic
Aim	To compare 9 frequently used methods for bilirubin determination for newborns under routine conditions, to define their sequence of use.
Patient characteristics	**Inclusion criteria** - Gestational age ≥32 weeks and a birth weight of ≥1500g **Exclusion criteria** - Infants receiving phototherapy before blood sampling **Other characteristics** *Sex, n* 58 males, 64 females

Bibliographic reference	Grohmann (2006) Bilirubin measurement for neonates: comparison of 9 frequently used methods
	Birthweight in g, mean (range) 3433 (2260 to 4510) *Gestational age in weeks, mean (range)* 39 (35 to 42) *Exclusive breastfeeding* Not reported *Age at time of blood sampling in days, mean (range)* 3 (0 to 8) *Ethnicity* All caucasian *Plasma bilirubin concentration in micromole/l, range* 9 to 388; 9 infants (7%) had concentrations above 257micromole/l
Number of patients	124 samples obtained from 122 term or near term infants
Index test	TcB measurement <u>Details</u> - JM-102, JM-103 and BiliCheck measurements - Performed at lower end of sternum - For JM-102 and JM-103, 2 measurements performed and mean obtained - With BiliCheck, 1 determination performed
Reference standard (or Gold standard)	TSB measurement <u>Details</u> - Venous blood obtained - Analysed using Hitachi 912, Dimension RxI and Vitros 250 – Hitachi 912 and Dimension RxL analysers are diazo methods, Vitros

<table>
<tr><td>Bibliographic reference</td><td>Grohmann (2006) Bilirubin measurement for neonates: comparison of 9 frequently used methods</td></tr>
<tr><td></td><td>analyser a direct spectrophotometric assay
- The measurements of samples with the 3 standard methods above correlated strongly with each other. Therefore, and because of no standard test for bilirubin determination is available, the mean of Hitachi 912, Dimension RxL and Vitros 250 measurements were used for comparison with the index test</td></tr>
<tr><td>Time between testing & treatment</td><td>- Both tests performed simultaneously at the time of routine metabolic screening or if there was a clinical indication for bilirubin determination
- Time between testing and treatment not reported</td></tr>
<tr><td>Length of follow-up</td><td>Not reported; study dates July 2003 to Febraury 2004</td></tr>
<tr><td>Location</td><td>Germany</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td><u>Correlation coefficient</u>
JM-102: r=0.962
JM-103: r=0.961
BiliCheck: r=0.966

<u>Bland-Altman plot analysis, mean difference in micromole/l (95%limits of agreement)</u>
JM-102: 0.31 (+/-43.98 i.e. -43.67 to 44.29)
JM-103: -10.78 (+/-42.77 i.e. -53.55 to 31.99)
BiliCheck: 10.81 (+/-38.85 i.e. -28.04 to 49.66)

<u>Biliruin concentration that results in 100% sensitivity and corresponding specificity, positive predictive value, and area under ROC curve for each test</u>
<table>
<tr><th></th><th>JM-102</th><th>JM-103</th><th>BiliCheck</th></tr>
<tr><td colspan="4">Cutoff value of 222micromole/l</td></tr>
<tr><td>Sensitivity of 100% at level, micromole/l
Specificity, %
PPV, %
AUC</td><td>190
81
53
0.963</td><td>170
70
41
0.949</td><td>180
64
34
0.961</td></tr>
<tr><td colspan="4">Cutoff value of 257micromole/l</td></tr>
<tr><td>Sensitivity of 100% at level,</td><td>224</td><td>209</td><td>222</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Grohmann (2006) Bilirubin measurement for neonates: comparison of 9 frequently used methods
	micromole/l: 91 / 90 / 89 Specificity, %: 47 / 45 / 38 PPV, %: 0.982 / 0.983 / 0.998 AUC
Source of funding	Supported in part by Roche Diagnostics
Comments	Study limitations - Sampling technique not reported - Unclear if population clinically jaundiced – tests performed at time of routine metabolic screening or if there was a clinical indication for bilirubin determination - Method used to measure TSB not well described eg: was it calibrated to the current method? - Unclear if blood sample was analysed within an acceptable period of time Setting Women's hospital Statistical methods Passing-Bablok regression analyses, Bland-Altman plots and ROC curves Other comments Comparison of 9 different methods for bilirubin determination: only methods of interest (as speicified in review protocol) have been extracted

1

Bibliographic reference	Riskin (2003) How accurate are neonataologists in identifying clinical jaundice in newborns?
Study type	Diagnostic
Aim	To evaluate the ability of the experienced clinician to identify clinical jaundice as well as on its role as a screening tool.
Patient characteristics	**Inclusion criteria** - Term infants undergoing venous blood sampling for bilirubin determination before discharge (along with routine screening) **Exclusion criteria**

Bibliographic reference	Riskin (2003) How accurate are neonataologists in identifying clinical jaundice in newborns?
	- Not reported **Other characteristics** *Sex, male to female ratio* 1.3:1 *Birthweight in g, mean (SD)* 3213 (558) *Gestational age in weeks, mean (SD)* 39.2 (2) *Exclusive breastfeeding* Not reported *Age at time of blood sampling in hours, mean (SD)* 60 (24) *Ethnicity, n* All caucasian; 260 Jewish; 110 Arabs (no babies of Asian or African origin included as rare minority) *Mean bilirubin concentration in micromole/l (SD)* 127.5 (51.0)
Number of patients	371 term infants; one paired measurement per infant
Index test	Visual assessment <u>Details</u> - A certified neonatologist examined baby and was asked to assess whether the newborn was clinically jaundiced – question presented as dichotomous yes/no clinical jaundice - None of the neonatologists were told about the study ahead of time and the TSB level was unkown before a clinical impression

<table>
<tr><td>Bibliographic reference</td><td>Riskin (2003) How accurate are neonataologists in identifying clinical jaundice in newborns?</td></tr>
<tr><td></td><td>was provided
- Three neonataologists included in study but only 1 clinical impression of jaundice per baby was given by physician assigned to the baby on discharge day
- Double blinded study</td></tr>
<tr><td>Reference standard (or Gold standard)</td><td>TSB measurement

<u>Details</u>
- Venous blood sample drawn before discharge along with routine phenylketonuria screening
- Sample immediately sent to lab
- TSB levels measured in less than 30 minutes using the conventional diazo method</td></tr>
<tr><td>Time between testing & treatment</td><td>- Both tests performed at same time
- Time between testing and treatment not reported</td></tr>
<tr><td>Length of follow-up</td><td>Not reported</td></tr>
<tr><td>Location</td><td>Israel</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td><u>Diagnostic accuracy measures for different bilirubin thresholds</u>
<table>
<tr><td>Bilirubin (mg/dl)</td><td>Group A – no clinical jaundice (N)</td><td>Group B – clinical jaundice (N)</td><td>PPV %</td><td>NPV%</td><td>Sensitivity %</td><td>Specificity %</td><td>x^2</td></tr>
<tr><td>>4.0 (>68micromole/l)
≤4.0 (≤68.0micromole/l)</td><td>200
52</td><td>117
2</td><td>98.3</td><td>20.6</td><td>36.9</td><td>96.3</td><td>23.4
P<0.001</td></tr>
<tr><td>>7.5 (>127.5micromole/l)
≤7.5 (≤127.5micromole/l)</td><td>93
159</td><td>97
22</td><td>81.5</td><td>63.1</td><td>51.0</td><td>87.8</td><td>64.6
P<0.001</td></tr>
<tr><td>>12.0 (>204.0micromole/l)
≤12.0</td><td>4
248</td><td>17
102</td><td>14.3</td><td>98.4</td><td>80.9</td><td>70.9</td><td>24.4
P<0.001</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Riskin (2003) How accurate are neonataologists in identifying clinical jaundice in newborns?**
	(≤204.0micromole/l)
Source of funding	Not reported
Comments	Study limitations - Exclusion criteria not reported - All infants underwent tests as part of common practice in this hospital as opposed to those clinically jaundiced - Method used to measure TSB not well described eg: was it calibrated to the current method? Setting Newborn nursery Statistical methods Diagnostic accuracy measures for various cut-offs calculated. Chi square analyses.

1

Bibliographic reference	**Karen (2009) Comparison of a new transcutaneous bilirubinometers (Bilimed) with serum bilirubin measurements in preterm and full term infants**
Study type	Cross sectional
Aim	To determine the accuracy and agreement of a new transcutaneous device with serum bilirubin concentration in newborn infants of different gestational ages and different skin colour.
Patient characteristics	**Inclusion criteria** - Healthy term and preterm infants of different skin colours - No infant had been treated with phototherapy until enrolment **Exclusion criteria** - Not reported **Other characteristics** *Sex* Not reported *Birthweight in g, median (range)* Group 1 (term infants): 3300 (2510 to 4950)

Bibliographic reference	Karen (2009) Comparison of a new transcutaneous bilirubinometers (Bilimed) with serum bilirubin measurements in preterm and full term infants
	Group 2 (premature infants $34^{0/7}$ to $36^{6/7}$ weeks gestation): 2362.2 (1570 to 3020) Group 3 (premature infants $28^{0/7}$ to $33^{6/7}$ weeks gestation): 1360 (1160 to 1790) *Gestational age in weeks, median (range)* Group 1 (term infants): 39.1 (37 to 42.3) Group 2 (premature infants $34^{0/7}$ to $36^{6/7}$ weeks gestation): 36 (34.1 to 36.5) Group 3 (premature infants $28^{0/7}$ to $33^{6/7}$ weeks gestation): 30.3 (29 to 32.2) *Exclusive breastfeeding* Not reported *Age at time of blood sampling, median (range)* Group 1 (term infants): 4 (2 to 12) Group 2 (premature infants $34^{0/7}$ to $36^{6/7}$ weeks gestation): 4 (2 to 7) Group 3 (premature infants $28^{0/7}$ to $33^{6/7}$ weeks gestation): 5 (2 to 11) *Ethnicity, n* Caucasian: 90 Non-caucasian: 60; 36 Hispanic or middle eastern; 9 African and 15 Asian origin *Mean bilirubin concentration in micromole/l (SD)* Group 1 (term infants): 223 (35 to 349) Group 2 (premature infants $34^{0/7}$ to $36^{6/7}$ weeks gestation): 181 (95 to 262) Group 3 (premature infants $28^{0/7}$ to $33^{6/7}$ weeks gestation): 195 (81 to 224)
Number of patients	150 infants in total: Group 1 (term infants): n=99 Group 2 (premature infants $34^{0/7}$ to $36^{6/7}$ weeks gestation): n=38 Group 3 (premature infants $28^{0/7}$ to $33^{6/7}$ weeks gestation): n=13 111 measurements performed in group1; 47 measurements in group 2; 21 measurements in group 3.
Index test	TcB measurement

Bibliographic reference	Karen (2009) Comparison of a new transcutaneous bilirubinometers (Bilimed) with serum bilirubin measurements in preterm and full term infants
	Details - Measured using Bilimed (Nufer Medical) – a microprocessor controlled device with 10 LEDs which do not move during measurement - In order to keep the measurement distance between the LEDs and the skin constant, a soft ring provided by the manufacturer was used - BiliMed applied on sternum - Mean of three readings taken for analysis
Reference standard (or Gold standard)	TSB measurement Details - Capillary blood sample taken and analysed by the diazo method (total bilirubin special COBAS integra) by same investigator taking TcB measurement
Time between testing & treatment	- Tests done within 15 minutes of each other - Time between testing and treatment not reported
Length of follow-up	Not reported
Location	Switzerland
Diagnostic accuracy measures (2 x 2 table)	Pearson correlation coefficient Group 1: 0.722; p<0.001 Group 2: 0.370; p=0.01 Group 3: 0.521; p=0.016 Bland Altman plot analysis by gestational age, mean difference in micromole/l (95% limits of agreement) Group 1: -14 (+/-144 i.e -158 to 130) Group 2: 16 (+/-91 i.e -75 to 107) Group 3: -8 (+/-76 i.e -84 to 68) Bland Altman plot analysis by ethnicity, mean difference in micromole/l (95% limits of agreement) Caucasian infants: 16 (+/-121 i.e -105 to 137) Non-Caucasian infants: 10 (+/-174 i.e -164 to 184)

Bibliographic reference	**Karen (2009) Comparison of a new transcutaneous bilirubinometers (Bilimed) with serum bilirubin measurements in preterm and full term infants**
Source of funding	Not reported
Comments	Study limitations - Sampling technique not reported - Exclusion criteria not reported - No indication of clinical jaundice - No infants had been treated with phototherapy 'until enrolment' – unclear if any subjects received phototherapy before measurements took place - Method used to measure TSB not well described eg: was it calibrated to the current method? - Unclear if blood sample was analysed within an acceptable period of time Setting Maternity ward (term infants) and neonatal intensive care unit of University Hospital Statistical methods Pearson correlation coefficient calculated and agreement between methods assessed using Bland Altman tests.

1

Bibliographic reference	**Briscoe L, Clark S, and Yoxall CW. Can transcutaneous bilirubinometry reduce the need for blood tests in jaundiced full term babies? Archives of Disease in Childhood Fetal and Neonatal Edition 2002; 86:(3)F190-F192** ***[included in CG98]***
Study type	Diagnostic study
Aim	To evaluate the accuracy of TcB as a method of determining the need for serum bilirubin measurements in full term babies and to quantify the magnitude of any benefit
Patient characteristics	**Inclusion criteria** - Babies > 34 weeks who were having blood taken for any reason, mostly done for clinical jaundice in 94% of infants (measurements from non-jaundiced babies were used to investigate the correlation between the 2 methods but not for assessing the effectiveness of TcB as a screening test. **Exclusion criteria** - Babies who had previously received phototherapy **Other characteristics** *Sex*

Bibliographic reference	**Briscoe L, Clark S, and Yoxall CW. Can transcutaneous bilirubinometry reduce the need for blood tests in jaundiced full term babies? Archives of Disease in Childhood Fetal and Neonatal Edition 2002; 86:(3)F190-F192 *[included in CG98]***
	Not reported *Median birthweight in g (range)* 3267 (1800–5008) *Median gestational age in weeks (range)* 39 (34–42) *Breastfeeding* Not reported *Median age at presentation in days (range)* 3 (0 to 13) *Ethnicity, % caucasian* *94.7* *Prevalence of serum bilirubin, n/N (%)* Serum bilirubin <50micromole/l: 3/303 (% Serum bilirubin 50-100micromole/l: 15/303 (%) Serum bilirubin 101 to 150micromole/l: 70/303 (%) Serum bilirubin 151 to 200micromole/l: 102/303 (%) Serum bilirubin 201 to 250micromole/l: 63/303 (%) Serum bilirubin 251 to 300micromole/l: 40/303 (%) Serum bilirubin 301 to 351micromole/l: 8/303 (%) Serum bilirubin 351 to 409micromole/l: 2/303 (%)
Number of patients	N=303
Index test	**TcB measurement** <u>Details</u> - Reading made by the phlebotomist using Minolta JM-102 at the forehead

Bibliographic reference	**Briscoe L, Clark S, and Yoxall CW. Can transcutaneous bilirubinometry reduce the need for blood tests in jaundiced full term babies? Archives of Disease in Childhood Fetal and Neonatal Edition 2002; 86:(3)F190-F192 *[included in CG98]***
	- Mean of 3 readings used for analysis
Reference standard (or Gold standard)	**Serum bilirubin measurement** Details - Blood taken by same phlebotomist - Analysed using a standard diazo method (Cobas Integra 700; Roche Diagnostics)
Time between testing & treatment	- TcB measurement made concurrently with blood test - Indication for starting phototherapy was a serum bilirubin ≥250micromole/l on the 2nd day of life, or ≥300micromole/l thereafter.
Length of follow-up	Not reported
Location	UK
Diagnostic accuracy measures (2 x 2 table)	Correlation of JM-102 with lab TSB levels (Pearson correlation coefficient, n = 303) r = 0.76, P < 0.0001 Diagnostic accuracy of JM-102 for detecting significant jaundice i.e. TSB > 249 micromol/litre 53/285 babies for whom SBR was measured to evaluate clinically apparent jaundice had TSB >249micromole/l. Area under ROC curve of TcB to detect serum bilirubin >249micromole/l = 0.89 Predictive accuracy of JM-102 value 19.9 to detect SBR>249micromole/l (highest accuracy from ROC curve) Sensitivity: 86% (81–89%) Specificity: 78% (73–83%) PPV: Not reported NPV: Not reported The TcB value that gave 100% sensitivity was 18 which gave a specificity of 45% (39% to 51%)

Bibliographic reference	**Briscoe L, Clark S, and Yoxall CW. Can transcutaneous bilirubinometry reduce the need for blood tests in jaundiced full term babies? Archives of Disease in Childhood Fetal and Neonatal Edition 2002; 86:(3)F190-F192 *[included in CG98]***
	In this study a reading of > 18 reflectance units was taken as an indicator for serum bilirubin, resulting in a reduction of 34% in the number of blood samples taken
Source of funding	Not reported
Comments	Study limitations - Sampling technique not reported - Method used for TSB measurement not described in detail eg: unclear whether it was calibrated to SRM 916a bilirubin as stated in review protocol. - Unclear within what time of blood drawing the sample analysed Setting Postnatal wards Statistical methods - The relation between TcB values and all SBR measurements was investigated using simple linear regression analysis - ROC curve constructed to determine which TcB value had the greatest overall predictive power in babies in whom the blood test had been performed to evaluate clinical jaundice - The lowest TcB value to give 100% sensitivity for detecting jaundice also determined

1

Bibliographic reference	**Engle WD, Jackson GL, Stehel EK et al. Evaluation of a transcutaneous jaundice meter following hospital discharge in term and near-term neonates. Journal of Perinatology 2005; 25:(7)486-90 *[included in CG98]***
Study type	Diagnostic study
Aim	To evaluate performance of the JM-103 as a predictor of total serum bilirubin in outpatient neonates during the first week postnatal and to estimate the number of TSB determinations that might be avoided in clinical use.
Patient characteristics	**Inclusion criteria** - Term and near term neonates who had been discharged from the hospital and evaluated during first week postnatally in a follow-up centre - study patients were referred for follow up of TSB because of clinical jaundice prior to hospital discharge or were jaundiced during outpatient evaluation - No prior phototherapy - Only initial comparison between JM-103 and TSB included (as some patients evaluated more than once) **Exclusion criteria** - Not reported

Bibliographic reference	Engle WD, Jackson GL, Stehel EK et al. Evaluation of a transcutaneous jaundice meter following hospital discharge in term and near-term neonates. Journal of Perinatology 2005; 25:(7)486-90 *[included in CG98]*
	Other characteristics *Gender, % males* 56.2% *Median birthweight in grams (range)* 3280 (2265 to 4590) *Median gestational age in weeks (range)* 40 (35 to 41) *Feedings, %* Breast: 33 Formula: 22 Both: 45 *Median age at time of study in hours (range)* 91 (51 to 166) *Ethnicity, %* Hispanic = 92, Black = 3, Asian = 3, Caucasian = 2 TSB (mg/dl), median (range) 14.8 (9.2 to 22.1) TSB ≥15mg/dl = 47%
Number of patients	N=121
Index test	**TcB measurement** Details

<table>
<tr><td>Bibliographic reference</td><td>Engle WD, Jackson GL, Stehel EK et al. Evaluation of a transcutaneous jaundice meter following hospital discharge in term and near-term neonates. Journal of Perinatology 2005; 25:(7)486-90 [included in CG98]</td></tr>
<tr><td></td><td>- Measured using minolta JM-103 from the sternum – single measurements taken.</td></tr>
<tr><td>Reference standard (or Gold standard)</td><td>TSB measurement

<u>Details</u>
- Blood drawn by heelstick
- Analysed by diazo Jendrassik-Grof with blank method (Olympus AU600)</td></tr>
<tr><td>Time between testing & treatment</td><td>- TcB measured within 30 minutes of blood collection
- Time between testing and treatment not reported</td></tr>
<tr><td>Length of follow-up</td><td>Not reported</td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td><u>Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, n = 121)</u>
r = 0.77, P < 0.001 --> all infants
r = 0.76, P <0.001 --> Hispanic infants only

Bland Altman analysis for difference between TSB and TcB
Mean difference = -1.6 mg/dl (27.36micromole/l); CIs not reported

<u>Predictive indices for TSB levels >15 to >18mg/dl and various JM cutoff values</u>
<table>
<tr><th>TSB (mg/dl)</th><th>JM (mg/dl)</th><th>Sensitivity</th><th>Specificity</th><th>PPV</th><th>NPV</th></tr>
<tr><td>>15 (256.5micromole/l)</td><td>>11 (188.1micromole/l)
>12 (205.2micromole/l)
>13 (222.3micromole/l)
>14 (239.4micromole/l)
>15 (256.5micromole/l)</td><td>1.00
0.91
0.79
0.58
0.40</td><td>0.34
0.53
0.77
0.95
0.97</td><td>0.58
0.63
0.75
0.92
0.92</td><td>1.00
0.87
0.80
0.72
0.65</td></tr>
<tr><td>>16</td><td>>12</td><td>0.91</td><td>0.42</td><td>0.39</td><td>0.92</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Engle WD, Jackson GL, Stehel EK et al. Evaluation of a transcutaneous jaundice meter following hospital discharge in term and near-term neonates. Journal of Perinatology 2005; 25:(7)486-90 *[included in CG98]***					
	(273.6micromole/l)	(205.2micromole/l) >13 (222.3micromole/l) >14 (239.4micromole/l) >15 (256.5micromole/l) >16 (273.6micromole/l)	0.86 0.63 0.43 0.26	0.65 0.84 0.88 0.94	0.50 0.61 0.60 0.64	0.92 0.85 0.79 0.76
	>17 (290.7micromole/l)	>13 (222.3micromole/l) >14 (239.4micromole/l) >15 (256.5micromole/l) >16 (273.6micromole/l) >17 (290.7micromole/l)	1.00 0.94 0.75 0.56 0.31	0.58 0.80 0.88 0.95 0.95	0.27 0.42 0.48 0.64 0.50	1.00 0.99 0.96 0.93 0.90
	>18 (307.8micromole/l)	>14 (239.4micromole/l) >15 (256.5micromole/l) >16 (273.6micromole/l) >17 (290.7micromole/l) >18 (307.8micromole/l)	1.00 0.73 0.55 0.36 0.36	0.77 0.85 0.93 0.98 1.00	0.31 0.32 0.43 0.67 1.00	1.00 0.97 0.95 0.94 0.94
Source of funding	Not reported					
Comments	Study limitations - Sampling technique not reported					

Bibliographic reference	**Engle WD, Jackson GL, Stehel EK et al. Evaluation of a transcutaneous jaundice meter following hospital discharge in term and near-term neonates. Journal of Perinatology 2005; 25:(7)486-90 *[included in CG98]***
	- Exclusion criteria not reported - Method used for TSB measurement not described in detail eg: unclear whether it was calibrated to SRM 916a bilirubin as stated in review protocol. - Unclear within what time of blood drawing the sample analysed <u>Setting</u> Newborn nursery of a large public hospital <u>Statistical methods</u> - Data analysed using linear regression and Bland Altman plot - Ability of various JM cut off values to predict elevated TSB values analysed standard 2x2 tables - % of TSB determinations that might be avoided calculated on the assumption that in clinical practice, only neonates with a JM determination greater than a chosen cut off value would have a TSB measurement

1

Bibliographic reference	**Schmidt ET, Wheeler CA, and Jackson GL. Evaluation of transcutaneous bilirubinometry in preterm neonates. Journal of Perinatology 2009; 29:564-9 *[included in CG98]***
Study type	Diagnostic study
Aim	To determine the accuracy and precision of transcutaneous measurements in preterm neonates
Patient characteristics	<u>Inclusion criteria</u> - Preterm neonates ≤ 34 weeks in a NICU of 1 hospital - TSB ordered as part of routine management <u>Exclusion criteria</u> - Hydrops fetalis - Severe haemolytic disease - Non-viable - Had receive or were receiving phototherapy or an exchange transfusion - Considered to be non-viable <u>Other characteristics</u> *Gender, M:F*

Bibliographic reference	**Schmidt ET, Wheeler CA, and Jackson GL. Evaluation of transcutaneous bilirubinometry in preterm neonates. Journal of Perinatology 2009; 29:564-9 *[included in CG98]***
	24 to 28 weeks – 21:9 29 to 31 weeks – 15:14 32 to 34 weeks – 15:16 *Birthweight in grams, median (range)* 24 to 28 weeks – 940 (370 to 1530) 29 to 31 weeks – 1481 (890 to 2030) 32 to 34 weeks – 2033 (980 to 2989) *Gestational age in weeks, median (range)* 24 to 28 weeks – 26 (24 to 28) 29 to 31 weeks – 30 (29 to 31) 32 to 34 weeks – 33.5 (32 to 34) *Breastfeeding* Not reported *Age TSB obtained in hours, median (range)* 24 to 28 weeks – TSB_1: 24 (6 to 49); TSB_{2*}: 25 (13 to 61) 29 to 31 weeks – TSB_1: 36 (15 to 93); TSB_{2*}: 55 (23 to 132) 32 to 34 weeks - TSB_1: 53 (12 to 88); TSB_{2*}: 64 (25 to 142) *9 in Group 1, 14 in Group 2 and 18 in Group 3 *Ethnicity (%)* 24 to 28 weeks – Hispanic: 66, African American: 17, Caucasian/other: 17 29 to 31 weeks – Hispanic: 70, African American: 20, Caucasian/other: 10 32 to 34 weeks – Hispanic: 75, African American: 19, Caucasian/other: 6
Number of patients	N=90
Index test	**TcB measurement** <u>Details</u>

<table>
<tr><td>Bibliographic reference</td><td>Schmidt ET, Wheeler CA, and Jackson GL. Evaluation of transcutaneous bilirubinometry in preterm neonates. Journal of Perinatology 2009; 29:564-9 [included in CG98]</td></tr>
<tr><td></td><td>- TcB using Minolta JM-103 from the sternum, and included a single determination and a device calculated mean of 5 determinations; values shown in results are for single determination</td></tr>
<tr><td>Reference standard (or Gold standard)</td><td>TSB measurement

<u>Details</u>
- Diazo Jendrassik Grof with blank method (Olympus AU640)</td></tr>
<tr><td>Time between testing & treatment</td><td>- TcB was carried out within 45 minutes of TSB
- Time between testing and treatment not reported</td></tr>
<tr><td>Length of follow-up</td><td>Not reported; study dates June 2007 to June 2008</td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Diagnostic accuracy measures (2 x 2 table)</td><td><u>Correlation of TcB levels with lab TSB_1 levels</u>
All groups R = 0.88, P < 0.001
Group 1 GA 24 – 28 weeks: r = 0.92
Group 2 GA 29 – 31 weeks: r = 0.90
Group 3 GA 32 –34 weeks: r = 0.79

<u>Bland-Altman analysis for mean difference in micromole/l (95% limits) between TcB and TSB</u>
Group 1 GA 24 – 28 weeks: -18.81 (+/-63.68 i.e -82.49 to 44.87)
Group 2 GA 29 – 31 weeks: -13.68 (+/-43.57 i.e -57.25 to 29.89)
Group 3 GA 32 –34 weeks: -17.1 (± 53.63 i.e -70.73 to 36.53)

<u>Ability of TcB value >4, >6 or >8 to predict a TSB of >6, >8 or >10mg per 100ml</u>

<table>
<tr><td></td><td>Sensitivity</td><td>Specificity</td><td>PPV</td><td>NPV</td><td>Blood tests avoided (%)</td></tr>
<tr><td colspan="6">Ability of TcB >4mg per 100ml (68.4micromole/l) to predict TSB >6mg per 100ml (102.6micromole/l)</td></tr>
<tr><td>Group 1</td><td>1.0</td><td>0.76</td><td>0.78</td><td>1.0</td><td>41</td></tr>
<tr><td>Group 2</td><td>0.94</td><td>0.38</td><td>0.87</td><td>0.60</td><td>12</td></tr>
<tr><td>Group 3</td><td>0.98</td><td>0.29</td><td>0.89</td><td>0.67</td><td>6</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Schmidt ET, Wheeler CA, and Jackson GL. Evaluation of transcutaneous bilirubinometry in preterm neonates. Journal of Perinatology 2009; 29:564-9 *[included in CG98]***
	Ability of TcB >6mg per 100ml (102.6micromole/l) to predict TSB >8mg per 100ml (136.8micromole/l) Group 1: 0.88 / 0.81 / 0.54 / 0.96 / 67 Group 2: 0.92 / 0.58 / 0.73 / 0.85 / 30 Group 3: 0.97 / 0.70 / 0.82 / 0.93 / 31 Ability of TcB >8mg per 100ml (136.8micromole/l) to predict TSB >10mg per 100ml (171micromole/l) Group 1: 0.67 / 0.81 / 0.22 / 0.97 / 77 Group 2: 1.0 / 0.70 / 0.50 / 1.0 / 53 Group 3: 0.93 / 0.74 / 0.59 / 0.96 / 57
Source of funding	JM-103 loaned by Draeger AirShields, none of the authors had a financial relationship with Draeger Airshields
Comments	Study limitations - Sampling technique not reported - No indication of clinical jaundice - Method used for TSB measurement not described in detail eg: unclear whether it was calibrated to SRM 916a bilirubin as stated in review protocol. - Unclear within what time of blood drawing the sample analysed Setting Neonatal intensive care unit Statistical methods - Linear regression and Bland-Altman plots - Predictive indices using target TSB values >6, >8 and >10mg per 100ml.

1

Bibliographic reference	**Karon BS, Teske A, Santrach PJ et al. Evaluation of the BiliChek noninvasive bilirubin analyzer for prediction of serum bilirubin and risk of hyperbilirubinemia. American Journal of Clinical Pathology 2008; 130:(6)976-82 *[included in CG98]***
Study type	Diagnostic study
Aim	To identify clinical and laboratory variables that impact the relationship between TcB and TSB and to define the sensitivity and specificity of the BiliChek TcB for predicting high-intermediate (>75th percentile for age) and/or high (>95th percentile for age) TSB values in a population of term and near term infants in a well infant nursery
Patient	**Inclusion criteria**

Bibliographic reference	**Karon BS, Teske A, Santrach PJ et al. Evaluation of the BiliChek noninvasive bilirubin analyzer for prediction of serum bilirubin and risk of hyperbilirubinemia. American Journal of Clinical Pathology 2008; 130:(6)976-82 *[included in CG98]***
characteristics	- Babies in a well-infant nursery were eligible if a serum bilirubin was ordered to assess risk of hyperbilirubinaemia - Only the first bilirubin measurement for any infant was used **Exclusion criteria** Not reported **Other characteristics** *Sex* Not reported *Median birthweight* Not reported *Median gestational age in weeks, median (IQR)* $39^{0/7}$ ($38^{0/7}$to $39^{6/7}$) *Breastfeeding* Not reported *Postnatal age in hours, median (IQR)* 48 (42 to 55) *Ethnicity, n* 146 Caucasian 19 Asian 9 Hispanic 3 African American
Number of patients	N=177
Index test	**TcB measurement** <u>Details</u>

Bibliographic reference	**Karon BS, Teske A, Santrach PJ et al. Evaluation of the BiliChek noninvasive bilirubin analyzer for prediction of serum bilirubin and risk of hyperbilirubinemia. American Journal of Clinical Pathology 2008; 130:(6)976-82 *[included in CG98]***
	- TcB reading from the forehead using BiliChek; performed by nurses - Mean of 5 measurements taken for data analysis - Calibrated with disposable tip before each measurement
Reference standard (or Gold standard)	**TSB measurement** <u>Details</u> - Serum samples obtained by capillary puncture or venepuncture - TSB measured using 1) modification of the diazo method and 2) The Vitros method – vitros 250 analyser
Time between testing & treatment	- TcB obtained within 30 minutes of blood collection for TSB measurement - Time between testing and treatment not reported
Length of follow-up	Not reported, study dates August 2006 to July 2007
Location	USA
Diagnostic accuracy measures (2 x 2 table)	<u>Correlation of TcB levels with TSB levels (Pearson correlation coefficient, n = 177)</u> Diazo: r = 0.81 VITROS: r = 0.81 <u>Diagnostic accuracy of various TcB cutoffs</u> Sensitivity and specificity of high or high-intermediate TcB for predicting a high or high-intermediate diazo/vitros TSB (high defined as bilirubin levels exceeding 95th percentile for age and high-intermediate defined as bilirubin levels exceeding the 75th percentile for age on Bhutani nomogram): *Diazo* Sensitivity: 56/57 (98.2%) Specificity: 48/120 (40%) PPV: 56/127 (43.7%) NPV: 48/49 (98%) *Vitros* Sensitivity: 63/67 (94%)

Bibliographic reference	**Karon BS, Teske A, Santrach PJ et al. Evaluation of the BiliChek noninvasive bilirubin analyzer for prediction of serum bilirubin and risk of hyperbilirubinemia. American Journal of Clinical Pathology 2008; 130:(6)976-82 *[included in CG98]***
	Specificity: 35/64 (54.7%) PPV: 63/92 (68.5%) NPV: 35/39 (89.7%)
Source of funding	Not reported
Comments	<u>Study limitations</u> - Not consecutive as not all physicians practicing in the nursery were involved in the study - No indication of clinical jaundice - Exclusion criteria not reported - Method used for TSB measurement not described in detail eg: unclear whether it was calibrated to SRM 916a bilirubin as stated in review protocol. - Unclear within what time of blood drawing the sample analysed <u>Setting</u> Well infant nursery <u>Statistical methods</u> - Median bias (TcB minus TSB) calculated for the diazo and vitros TsB data sets with 95%Cis - Bland-Altman plots (data not extractable) - Standard 2x2 for diagnostic accuracy measures

1

Bibliographic reference	**Maisels MJ and Conrad S. Transcutaneous bilirubin measurements in full-term infants. Pediatrics 1982; 70:(3)464-7 *[included in CG98]***
Study type	Diagnostic study
Aim	Not reported
Patient characteristics	**Inclusion criteria** - Full term Caucasian babies in a well-baby nursery - Standard practice to obtain a serum bilirubin on all infants on third day of life or at other times if clinically indicated - None of the infants received phototherapy **Exclusion criteria** - Not reported

Bibliographic reference	**Maisels MJ and Conrad S. Transcutaneous bilirubin measurements in full-term infants. Pediatrics 1982; 70:(3)464-7 *[included in CG98]***
	Other characteristics *Sex* Not reported *Birthweight* Not reported *Gestational age* Not reported *Breastfeeding* Not reported *Age* Not reported *Ethnicity* All caucasian *Mean serum bilirubin in mg (SD)* All infants: 6.4 (3.6) mg/100ml For 11 infants in whom bilirubin obtained on clinical grounds: 4.7 (3.4) mg/100ml
Number of patients	N=157
Index test	**TcB measurement** <u>Details</u> - Minolta JM-102 from the forehead and the sternum - Measurements routinely made on the 3rd day except in 11 infants where earlier sampling done based on clinical indication
Reference standard (or Gold	**TSB measurement**

Bibliographic reference	**Maisels MJ and Conrad S. Transcutaneous bilirubin measurements in full-term infants. Pediatrics 1982; 70:(3)464-7 *[included in CG98]***
standard)	Details - Measured by modified diazo method using the DuPont automatic clinical analyser (ACA III instruction manual)
Time between testing & treatment	- TcB obtained at same time of blood collection - Time between testing and treatment not reported
Length of follow-up	Not reported
Location	USA
Diagnostic accuracy measures (2 x 2 table)	Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient) At forehead (157 observations) r = 0.93, P < 0.0001 At mid-sternum (135 observations) r = 0.93, P < 0.0001 Diagnostic accuracy of TcB measurements in predicting infants with serum bilirubin concentrations >10mg/100ml (171micromolees/litre) *Forehead* TP: 20 FP: 14 FN: 2 TN: 121 Sensitivity: 91% Specificity: 90% PPV: 59% NPV: 98% Prevalence: 14% *Sternum* TP: 11 FP: 19 FN: 0 TN: 105 Sensitivity: 100%

Bibliographic reference	Maisels MJ and Conrad S. Transcutaneous bilirubin measurements in full-term infants. Pediatrics 1982; 70:(3)464-7 *[included in CG98]*
	Specificity: 85% PPV: 37% NPV: 100% Prevalence: 8.1% <u>Diagnostic accuracy of TcB measurements in predicting infants with serum bilirubin concentrations >12.9mg/100ml (221micromolees/litre)</u> *Forehead* TP: 7 FP: 5 FN: 0 TN: 145 Sensitivity: 100% Specificity: 97% PPV: 58% NPV: 100% Prevalence: 4.5% *Sternum* TP: 4 FP: 5 FN: 0 TN: 126 Sensitivity: 100% Specificity: 96% PPV: 44% NPV: 100% Prevalence: 3%
Source of funding	Not reported
Comments	<u>Study limitations</u> - Indirect population: no indication of clinical jaundice – standard practice to obtain serum bilirubin on all infants on the third day of

Bibliographic reference	**Maisels MJ and Conrad S. Transcutaneous bilirubin measurements in full-term infants. Pediatrics 1982; 70:(3)464-7 *[included in CG98]***
	life or at other times if clinically indicated (in 11 instances, serum bilirubin determined on clinical indication). - Postnatal age of infants not reported - Exclusion criteria not reported - Sampling technique not reported - Method used for TSB measurement not described in detail eg: unclear whether it was calibrated to SRM 916a bilirubin as stated in review protocol. - Unclear within what time of blood drawing the sample analysed <u>Setting</u> Well baby nursery <u>Statistical methods</u> Linear regression, standard 2 x2 tables

1

Bibliographic reference	**Boo NY and Ishak S. Prediction of severe hyperbilirubinaemia using the Bilicheck transcutaneous bilirubinometer. Journal of Paediatrics and Child Health 2007; 43:(4)297-302 *[included in CG98]***
Study type	Diagnostic study
Aim	To determine the sensitivity and specificity of different levels of bilirubin measured by the transcutaneous bilirubinometers BiliCheck on the forehead and sternum for predicting severe hyperbilirubinaemia of TSB >300micromole/l in Malay, Chinese and Indian infants
Patient characteristics	**Inclusion criteria** - Healthy term Malaysian babies with hyperbilirubinaemia **Exclusion criteria** - Infants who had received phototherapy or exchange transfusion - Congenital anomalies, severely ill, foreigners - Those with conjugated hyperbilirubinaemia **Other characteristics** *Sex, male n (%)* 207 (60)

Bibliographic reference	**Boo NY and Ishak S. Prediction of severe hyperbilirubinaemia using the Bilicheck transcutaneous bilirubinometer. Journal of Paediatrics and Child Health 2007; 43:(4)297-302 *[included in CG98]***
	Birthweight in grams (SD) 3056 (487) *Gestational age in weeks, median (50%CI)* 38 (37, 39) *Breastfeeding* Not reported *Age when serum measured in hours, median (50%CI)* 70 (46, 103.5) *Ethnicity, %* Malays = 63.8%, Chinese = 30.7%, Indians = 5.5%, *Total serum bilirubin in micromole/l, median (range)* 223 (108 to 589)
Number of patients	N=345; 95 had severe hyperbilirubinaemia (≥300micromole/l)
Index test	**TcB measurement** <u>Details</u> - Using BiliChek from the forehead and midpoint of sternum – number of measurements from each site not specified - Prior to measurement, device calibrated using a disposable standard reference placed in direct contact with its probe - Probe placed away from infant's hairline and at a site free of bruises, hematoma and local nevus
Reference standard (or Gold standard)	**TSB measurement** <u>Details</u> - Venous blood collected, protected from light - Analysed by the diazo method using the Cobas Integra system (Roche Diagnostics) - Technicians who measured the TSB had no knowledge of the TcB readings of the infants

Bibliographic reference	**Boo NY and Ishak S. Prediction of severe hyperbilirubinaemia using the Bilicheck transcutaneous bilirubinometer. Journal of Paediatrics and Child Health 2007; 43:(4)297-302 *[included in CG98]***
Time between testing & treatment	- Laboratory TSB levels within 30 minutes of TcB measurement - Time between testing and treatment not reported
Length of follow-up	Not reported, study dates January 2003 to January 2005
Location	Malaysia
Diagnostic accuracy measures (2 x 2 table)	Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, n = 345) *Forehead* All babies r = 0.80, P < 0.0001 Malays: r = 0.79, P < 0.0001 Chinese: r = 0.84, P < 0.0001 Indians: r = 0.83, P < 0.0001 *Sternum* All babies r = 0.86, P < 0.0001 Malays: r = 0.86, P < 0.0001 Chinese: r = 0.86, P < 0.0001 Indians: r = 0.94, P < 0.0001 Correlation of TcB levels with lab TSB levels at >80 hours of age in 75 infants (79%) with severe hyperbilirubinaemia, TSB ≥ 300micromole/l At ≤ 80 hours of age r = 0.85, P < 0.0001 At > 80 hours of age r = 0.71, P < 0.0001 Diagnostic accuracy of TcB for detecting TSB ≥ 300 micromol/litre *Forehead (threshold 250 micromol/litre)* Sensitivity: 100% Specificity: 39.2% *Forehead (threshold 260 micromol/litre)* Sensitivity: 75.8% Specificity: 84.8%

Bibliographic reference	**Boo NY and Ishak S. Prediction of severe hyperbilirubinaemia using the Bilicheck transcutaneous bilirubinometer. Journal of Paediatrics and Child Health 2007; 43:(4)297-302 *[included in CG98]***
	Sternum (threshold 200 micromol/litre) Sensitivity: 100% Specificity: 33.6% *Sternum (threshold 280 micromol/litre)* Sensitivity: 92.6% Specificity: 84% <u>ROC curve analyses</u> Area under curve when TSB ≥300micromole/l Forehead: 0.89 (0.85 to 0.92) Sternum: 0.93 (0.90 to 0.96) Area under curve when TSB ≥280micromole/l Forehead: 0.87 (0.83 to 0.91) Sternum: 0.94 (0.91 to 0.97) Area under curve when TSB ≥250micromole/l Forehead: 0.89 (0.85 to 0.92) Sternum: 0.93 (0.90 to 0.96)
Source of funding	Supported by research grant from the Faculty of Medicine
Comments	<u>Study limitations</u> - Data not given for the mean difference and SD from Bland Altman analysis for TSB – TcB - Sampling technique not reported - Method used for TSB measurement not described in detail eg: unclear whether it was calibrated to SRM 916a bilirubin as stated in review protocol. - Unclear within what time of blood drawing the sample analysed <u>Setting</u> Postnatal wards and neonatal intensive care unit

Bibliographic reference	**Boo NY and Ishak S. Prediction of severe hyperbilirubinaemia using the Bilicheck transcutaneous bilirubinometer. Journal of Paediatrics and Child Health 2007; 43:(4)297-302 *[included in CG98]***
	Statistical methods Diagnostic accuracy of TcB (various thresholds) calculated for detecting TSB > 250, > 280, and > 300 micromol/litre.

1

Bibliographic reference	**Samanta S, Tan M, Kissack C et al. The value of Bilicheck as a screening tool for neonatal jaundice in term and near-term babies. Acta Paediatrica 2004; 93:(11)1486-90 *[included in CG98]***
Study type	Diagnostic study
Aim	To determine the accuracy of BiliCheck as a measure of serum bilirubin, to evaluate its effectiveness as a screening tool in term and near term infants with clinically detectable jaundice and to estimate the magnitude of the reduction in serum bilirubin measurements which the routine use of this device would lead to.
Patient characteristics	**Inclusion criteria** - All jaundiced babies > 33 weeks in the postnatal ward of a regional teaching hospital who were due to have blood taken for TSB estimation **Exclusion criteria** - Babies who had previously received phototherapy **Other characteristics** *Sex, male* 1:1 *Birthweight in grams, median (range)* 3295 (1972 to 4720) *Gestational age in weeks, median (range)* 39 (33, 42) *Breastfeeding* Not reported *Age in days, median (range)* 3 (1 to 11)

Bibliographic reference	**Samanta S, Tan M, Kissack C et al. The value of Bilicheck as a screening tool for neonatal jaundice in term and near-term babies. Acta Paediatrica 2004; 93:(11)1486-90 *[included in CG98]***
	Ethnicity Not reported *Total serum bilirubin in micromole/l, median (range)* 200 (40 to 399)
Number of patients	N=300
Index test	**TcB measurement** Details - TcB using BiliChek (site not specified) – single measurement taken.
Reference standard (or Gold standard)	**TSB measurement** Details - Blood taken for serum bilirubin by heel prick - Serum bilirubin measured in the laboratory using a standard diazo method (Cobas Integra 700)
Time between testing & treatment	- Laboratory TSB levels taken concurrently with TcB measurement - Indication for starting phototherapy was serum bilirubin concentration of 250micromole/l and above on the second day of life or 300micromole/l and above thereafter. Hyperbilirubinaemia defined as serum bilirubin ≥250micromole/l.
Length of follow-up	Not reported
Location	UK
Diagnostic accuracy measures (2 x 2 table)	Correlation of TcB levels with lab TSB levels (Pearson correlation coefficient, n = 300) r = 0.77, P < 0.0001 Bland Altman analysis for difference between lab TSB and TcB in micromole/l MD = -10.6 (95% CI -80.0 to +60.0) SD = Not reported Diagnostic accuracy of TcB (threshold value > 195 micromol/litre) for detecting significant jaundice TSB >250 micromol/litre

Bibliographic reference	**Samanta S, Tan M, Kissack C et al. The value of Bilicheck as a screening tool for neonatal jaundice in term and near-term babies. Acta Paediatrica 2004; 93:(11)1486-90 *[included in CG98]***
	Sensitivity: 50/55 (90.9%) Specificity: 162/245 (66.1%) PPV: 50/133 (37.6%) NPV: 162/167 (97%)
Source of funding	Not reported
Comments	Study limitations - Method used for TSB measurement not described in detail eg: unclear whether it was calibrated to SRM 916a bilirubin as stated in review protocol. - Unclear within what time of blood drawing the sample analysed Setting Postnatal wards of Liverpool Women's Hospital Statistical methods - Pearson's correlation coefficient - Bland-Altman plot analysis - ROC curve for detecting significant hyperbilirubinaemia

1

G.2 Review question 4

Clinical evidence table

Bibliographic reference	**Argent (1985)** **Threshold for initiation of phototherapy in infants with nonhaemolytic hyperbilirubinaemia**
Study type	Cohort study
Aim	To investigate the effect of phototherapy at three different bilirubin thresholds in term neonates with physiological hyperbilirubinaemia.
Patient characteristics	Inclusion criteria: • Infants delivered at term (> 37 weeks, > 2500 g) through normal pregnancy, labour and delivery, with evidence of clinical jaundice.

Bibliographic reference	**Argent (1985)** **Threshold for initiation of phototherapy in infants with nonhaemolytic hyperbilirubinaemia**
	Exclusion criteria: • The babies were investigated further if jaundice persisted or reached levels> 257 micromole/l and were excluded with: • History of birth asphyxia • A positive Coombs reaction • Any clinical or laboratory evidence of infection • Polycythaemia (Hct > 65%).
Number of patients	Total = 92 (group A = 32; group B = 32; group C = 28) Mean weight (g, SD): group A = 3200 (40); group B = 3300 (40); group C = 3300 (50) Gender (male/female): group A = 21/11; group B = 17/15; group C = 14/14
Intervention	The infants were observed in the postnatal wards for clinical evidence of jaundice. When jaundiced, babies were randomly allocated to one of three study groups Group A: started on phototherapy when TSB reached 170 micromole/l and continued until bilirubin levels had decreased to < 170 micromole/l. Group B: started on phototherapy when TSB reached 257 micromole/l and continued until bilirubin levels had decreased to < 257 micromole/l. Group C: started on phototherapy when TSB reached 300 micromole/l and continued until bilirubin levels had decreased to < 257 micromole/l. Phototherapy was administered continuously by standard phototherapy units which delivered > 770 uW/cm^2. All the babies in the study had their bilirubin levels and Hct checked 12-hourly until 24 hours after discontinuation of phototherapy or until bilirubin had decreased in the case of those who did not qualify for phototherapy.
Outcomes	Number of infants in phototherapy: Group A = 31/32 (97%); Group B = 15/32 (47%); Group C = 5/28 (18%) Duration of phototherapy (days, SD): Group A = 1.7 (1.0); Group B = 1.4 (1.1); Group C = 2.4 (0.9); p>0.05

Bibliographic reference	**Argent (1985)** **Threshold for initiation of phototherapy in infants with nonhaemolytic hyperbilirubinaemia**

Peak bilirubin (mean micromole/l)

	Group A	Group B	Group C	Intergroup differences
Total	225.7±37.6	237.7 ± 49.6	215.5± 56.4	NS
Phototherapy	229.1 ±32.5	282.2±20.5	318.1±15.4	A vs. B (p<0.001)
No phototherapy	NA (1 infant)	200.0±32.5	194.9±35.9	NS

Duration of hospitalization (days, SD)

	Group A	Group B	Group C	Intergroup differences
Total	5.8 ± 1.8	5.6± 1.2	5.3 ± 1.4	NS
Phototherapy	5.9 ± 1.3	6.2 ± 1.1	7.2±1.8	NS
No phototherapy	NA (1 infant)	5.1 ± 1.0	4.9±0.9	NS

Two babies in group C suffered complications. One required readmission for further phototherapy, and 1 underwent an exchange transfusion for a bilirubin level of > 340 micromole/l.

Length of follow-up	8-days
Location	Johannesburg Hospital
Source of funding	Not reported.
Comments	For quality assessment, please see GRADE profile.

1 **Below are summaries of additional supportive information to assist the Committee's discussion**

Bibliographic reference	**Bhutani (1999)** **Predictive Ability of a Predischarge Hour-specific Serum Bilirubin for Subsequent Significant Hyperbilirubinemia in Healthy Term and Near-term Newborns**
Study type	Cross-sectional
Aim	To assess the predictive ability of a universal pre-discharge serum bilirubin measurement to screen for risk of subsequent significant hyperbilirubinemia in the direct Coombs negative healthy term and near-term babies during the first postnatal week.

Bibliographic reference	**Bhutani (1999)** **Predictive Ability of a Predischarge Hour-specific Serum Bilirubin for Subsequent Significant Hyperbilirubinemia in Healthy Term and Near-term Newborns**
Patient characteristics	*Inclusion criteria:* • Term or near-term babies with appropriate for gestational age (GA) as defined by a birth weight (BW) ≥2000 g for ≥36 weeks; GA or BW ≥2500 g for ≥35 weeks GA. Newborns who had post-discharge TSB levels obtained over the next 1 to 6 days in a hospital supervised follow-up programme were eligible for inclusion in the nomogram. *Exclusion criteria:* • Admission and treatment in the intensive care nursery for neonatal illness or, positive direct Coombs test. • All newborns whose mothers had blood type O, were Rh-negative, or had a positive indirect Coombs test were evaluated for blood type and direct Coombs test. • TSB values measured after the initiation of phototherapy were excluded from the nomogram. • TSB values not measured at the hospital laboratory were excluded but were replaced by a repeat, hospital based measurement close in time. • Newborns who required phototherapy before age 60 hours to control unexplained rapidly rising TSB levels. • were excluded • Newborns with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency.
Number of patients	Total N=2840 Gender: male = 50.1%; female = 49.9% Mean (SD) age for pre-discharge TSB sampling = 33.7 (14.6) hours. No. of visible jaundice at the time of the first pre-discharge sample = 13.4% had a TSB > 171 micromole/L; 4.3% had > 205.2 micromole/L; 4% (12/2840) had >256.5 micromole/L. • Consecutively discharged newborns, with universal TSB measurements between age 20 to 28 hours. • Subsequent TSB levels were usually obtained within 24 to 48 hours after discharge and as needed thereafter. • Additional follow-up either involved a repeat TSB sample or a visual inspection at physician's discretion. • Resolution of hyperbilirubinemia was confirmed at about age 10 days, usually through contact with the private paediatrician. • *Those received phototherapy = 4.1%*

<table>
<tr><td>Bibliographic reference</td><td>Bhutani (1999)
Predictive Ability of a Predischarge Hour-specific Serum Bilirubin for Subsequent Significant Hyperbilirubinemia in Healthy Term and Near-term Newborns</td></tr>
<tr><td></td><td>• Hospital-based or home-based phototherapy was initiated at the discretion of the based on the American Academy of Paediatrics (AAP) guideline.</td></tr>
<tr><td>Outcomes</td><td>• Among the newborns with a TSB in the high-risk zone pre-discharge (172/2840 or 6.1% of the study population), 68 continue to have subsequent significant hyperbilirubinemia.
• TSB levels of a small but significant number from the intermediate-zone newborns (58/912, 6.4%) moved upwards to the high-risk zone after discharge.
• Of 356 newborns in the upper intermediate-risk zone, 46 jumped to the high-risk zone on follow-up and 310 did not.
• This compared with the 556 newborns in the lower intermediate-risk zone. Of these, 12 jumped tracks into the high-risk zone on follow-up and 544 did not.
• Another 29 of these 556 newborns (5.2%) changed their risk status by moving upwards but only into the upper intermediate-risk zone.

• Follow-up of newborns placed in the low-risk zone at discharge (1756/2840; 61.8%) showed them to be the most predictable. Nearly 93.6% remained in the 40th percentile-risk zone; while, only 6.4% moved up to the intermediate-risk zone. None jumped up to the high-risk zone.

• None of the newborns in the low-risk zone received phototherapy.
• No newborn in the study population required an exchange transfusion or developed a TSB value ≥25 mg/dL.

• None developed acute signs of bilirubin encephalopathy. None are known to have sequelae at about 1 year of age as determined by telephone interviews of parents, pediatric offices or feedback from area hospitals.</td></tr>
<tr><td>Nomogram</td><td>Nomogram in micromole/L
<table>
<tr><th>Age (hrs)</th><th>Low risk</th><th>Low-intermediate risk</th><th>High-intermediate risk</th><th>High risk</th></tr>
<tr><td>0</td><td>--</td><td>--</td><td>--</td><td>--</td></tr>
<tr><td>6</td><td>--</td><td>--</td><td>--</td><td>--</td></tr>
<tr><td>12</td><td><68.40</td><td>68.40 to 78.66</td><td>78.66 to 114.57</td><td>>114.57</td></tr>
<tr><td>18</td><td><76.95</td><td>76.95 to 94.05</td><td>94.05 to 119.70</td><td>>119.70</td></tr>
<tr><td>24</td><td><85.5</td><td>85.50 to 109.44</td><td>109.44 to 131.67</td><td>>131.67</td></tr>
<tr><td>30</td><td><102.60</td><td>102.60 to 128.25</td><td>128.25 to 162.45</td><td>>162.45</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Bhutani (1999)** **Predictive Ability of a Predischarge Hour-specific Serum Bilirubin for Subsequent Significant Hyperbilirubinemia in Healthy Term and Near-term Newborns**

36	<119.70	119.70 to 153.90	153.90 to 188.10	>188.10
42	<133.38	133.38 to 171.00	171.00 to 208.62	>208.62
48	<147.06	147.06 to 184.68	184.68 to 224.01	>224.01
54	<153.90	153.90 to 198.36	198.36 to 239.40	>239.40
60	<164.16	164.16 to 215.46	215.46 to 258.21	>258.21
66	<177.84	177.84 to 222.30	222.30 to 265.05	>265.05
72	<191.52	191.52 to 229.14	229.14 to 273.60	>273.60
78	<194.94	194.94 to 239.40	239.40 to 277.02	>277.02
84	<196.65	196.65 to 249.66	249.66 to 285.57	>285.57
90	<205.20	205.20 to 256.50	256.50 to 290.70	>290.70
96	<212.04	212.04 to 259.92	259.92 to 299.25	>299.25
108	<222.30	222.30 to 259.92	259.92 to 299.25	>299.25
120	<225.72	225.72 to 259.92	259.92 to 299.25	>299.25
132	<225.72	225.72 to 259.92	259.92 to 299.25	>299.25
144	<225.72	225.72 to 259.92	259.92 to 299.25	>299.25

X

Analysis used	• The nomogram database includes all measured hour-specific TSB values except for that relatively small number of values obtained before age 18 hours. • Data were recorded in epochs of 4 hours (or, age 6± 2 hours) for the first 48 hours and in epochs of 12 hours (or age 6± 6 hours) until 96 hours age and at epochs of 24 hours (or age 6± 12 hours) for age 5 to 7 days. • For each epoch at least 300 data points and demonstration of a Gaussian distribution were required for inclusion in the nomogram. From these data, hour-specific TSB percentiles for each of the epochal periods were calculated. • The 5th, 25th, 40th, 50th, 75th, 90th, and 95th percentiles of TSB values were determined from the Gaussian distribution for each epoch and connected as percentile tracks.
Length of follow-up	10-day after birth.
Location	Pennsylvania Hospital during 1993 to 1997, US.
Source of funding	The Newborn Paediatrics Research Fund at Pennsylvania Hospital.
Comments	

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Bibliographic reference	**Sarici (2004)** **Incidence, Course, and Prediction of Hyperbilirubinemia in Near-Term and Term Newborns.**
Study type	Cross-sectional
Aim	To investigate prospectively the incidence of significant hyperbilirubinemia and demographic and laboratory characteristics and pattern of serum bilirubin levels of near-term newborns (35–37 weeks gestation) by comparing them with those of term newborns (38–42 weeks gestation) longitudinally in the first 7 days of life.
Patient characteristics	*Inclusion criteria:* • All newborns with a gestational age between 35 and 42 completed weeks (245–294 days) were consecutively enrolled in the study. • Infants with 35 to 37 weeks gestation were defined as near-term and constituted, whereas those with 38 to 42 weeks gestation were defined as term and constituted the term group. *Exclusion criteria:* • Infants whose mothers could not recall the exact date (first day) of last menstrual period and/or those who had a critical discrepancy (≥2 weeks) between 2 methods on gestational-age determination. • Newborns with a gestational age of <35 weeks and > 42 weeks (preterm and post-term). • Other exclusion criteria were small for gestationa lage and large for gestational age, determined on the basis of Colorado intrauterine growth charts. • Any congenital malformation, respiratory distress, glucose-6-phosphate dehydrogenase deficiency, clinical or culture-proven sepsis, and inability to initiate or maintain oral feedings within 3 hours after birth due to various reasons. • Infants who had any evidence of hemolysis (Rhesus hemolytic disease, anemia, a positive direct antiglobulin test, reticulocytosis, or a peripheral blood smear compatible with hemolysis) and those newborns who had a blood group system of groups A or B born to mothers with blood group O and had a first-day (6th-hour) serum bilirubin level of ≥6 mg/dL were excluded from the study.
Number of patients	Total = 365 newborns (term group = 219; near-term group = 146) *Term group:* Birth weight (g, SD) = 3194 (379) Gestational age (week, SD) = 39.7 (0.9) Gender (male/female) = 113/106 *Near-term group:* Birth weight (g, SD) = 2777 (372) Gestational age (week, SD) = 36.6 (0.8)

<table>
<tr><td>Bibliographic reference</td><td>Sarici (2004)
Incidence, Course, and Prediction of Hyperbilirubinemia in Near-Term and Term Newborns.</td></tr>
<tr><td></td><td>Gender (male/female) = 77/69

Serum total bilirubin measurements were made initially at the 6th hour of life (a postnatal age at which all newborns could be reached at the hospital before discharge) and were repeated daily for the next 4 days; each measurement was performed just 24 hours after the previous measurement, and a last measurement was performed on the 7th day (150th hour) to follow the pattern of serum bilirubin levels in a more longitudinal manner.

Definitions for significant hyperbilirubinemia:
<table>
<tr><td>Postnatal Age, day (h)*</td><td colspan="2">Birth Weight, g</td></tr>
<tr><td></td><td>2000–2500</td><td>>2500</td></tr>
<tr><td>1 (0–24) [6]</td><td colspan="2">85.5 micromole/L and an increase of 8.55 micromole/L/h on 2 consecutive measurements</td></tr>
<tr><td>2 (25–48) [30]
3 (49–72) [54]
4 (73–96) [78]
5 (97–120) [102]
7 (145–168) [150]</td><td>136.8 micromole/L
205.2 micromole/L
239.4 micromole/L
239.4 micromole/L
239.4 micromole/L</td><td>205.2 micromole/L
256.5 micromole/L
290.7 micromole/L
290.7 micromole/L
290.7 micromole/L</td></tr>
</table>
X</td></tr>
<tr><td>Outcomes</td><td>Twenty-three newborns (10.5%) in the term group and 37 newborns (25.3%) in the near-term group had significant hyperbilirubinemia and required phototherapy.</td></tr>
<tr><td>Nomogram</td><td>Nomogram in micromole/L
<table>
<tr><td>Age (hrs)</td><td>Low-risk</td><td>Low-intermediate risk</td><td>Intermediate risk</td><td>High-intermediate risk</td><td>High risk</td></tr>
<tr><td>0</td><td>--</td><td>--</td><td>--</td><td>--</td><td>--</td></tr>
<tr><td>6</td><td><42.75</td><td>42.75 to 51.3</td><td>51.3 to 68.4</td><td>68.4 to 94.05</td><td>>94.05</td></tr>
<tr><td>12</td><td><51.3</td><td>51.3 to 68.4</td><td>68.4 to 85.5</td><td>85.5 to 119.7</td><td>>119.7</td></tr>
<tr><td>18</td><td><59.85</td><td>59.85 to 76.95</td><td>76.95 to 94.05</td><td>94.05 to 136.8</td><td>>136.8</td></tr>
<tr><td>24</td><td><68.4</td><td>68.4 to 87.21</td><td>87.21 to 104.31</td><td>104.31 to 162.45</td><td>>162.45</td></tr>
<tr><td>30</td><td><71.82</td><td>71.82 to 97.47</td><td>97.47 to 119.7</td><td>119.7 to 179.55</td><td>>179.55</td></tr>
<tr><td>36</td><td><76.95</td><td>76.95 to 111.15</td><td>111.15 to 128.25</td><td>128.25 to 205.2</td><td>>205.2</td></tr>
<tr><td>42</td><td><85.5</td><td>85.5 to 119.7</td><td>119.7 to 152.19</td><td>152.19 to 224.01</td><td>>224.01</td></tr>
<tr><td>48</td><td><87.21</td><td>87.21 to 136.8</td><td>136.8 to 162.45</td><td>162.45 to 247.95</td><td>>247.95</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Sarici (2004)** **Incidence, Course, and Prediction of Hyperbilirubinemia in Near-Term and Term Newborns.**
	54 <90.63 90.63 to 145.35 145.35 to 179.55 179.55 to 265.05 >265.05 60 <94.05 94.05 to 153.9 153.9 to 188.1 188.1 to 277.02 >277.02 66 <99.08 99.08 to 159.03 159.03 to 201.78 201.78 to 290.7 >290.7 72 <102.6 102.6 to 162.45 162.45 to 205.2 205.2 to 294.12 >294.12 78 <102.6 102.6 to 169.29 169.29 to 213.75 213.75 to 299.25 >299.25 84 <102.6 102.6 to 171.0 171.0 to 220.59 220.59 to 299.25 >299.25 90 <102.6 102.6 to 172.71 172.71 to 222.3 222.3 to 299.25 >299.25 96 <102.6 102.6 to 174.42 174.42 to 224.01 224.01 to 299.25 >299.25 102 <102.6 102.6 to 174.42 174.42 to 225.72 225.72 to 299.25 >299.25 150 <102.6 102.6 to 188.1 188.1 to 235.98 235.98 to 299.25 >299.25 X
Analysis used	• Serum total bilirubin values measured after the initiation of phototherapy were excluded from additional statistical analysis but were documented and recorded. • A Gaussian distribution curve, the 5th, 30th, 60th, and 95th percentiles, and 4 percentile tracks were obtained from mean serum total bilirubin values.
Length of follow-up	7-day after birth.
Location	Division of Neonatology of Hacettepe University Faculty of Medicine between November 2001 and May 2002.
Source of funding	Not reported.
Comments	

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Bibliographic reference	**Romagnoli (2012)** **Development and validation of serum bilirubin nomogram to predict the absence of risk for severe hyperbilirubinaemia before discharge: a prospective, multicenter study.**
Study type	Cross-sectional
Aim	To elaborate a percentile-based hour specific total serum bilirubin (TSB) nomogram and to assess its ability to predict the absence of risk for subsequent non physiologic severe hyperbilirubinaemia before discharge.
Patient characteristics	*Inclusion criteria:* • Healthy full term infants (gestational age ≥ 37 weeks), appropriate for gestational age (birth weight > 10th centile), delivered by vaginal birth or caesarean section after uneventful pregnancy, without asphyxia (Apgar score ≥ 7 at 1 and 5

Bibliographic reference	**Romagnoli (2012)** **Development and validation of serum bilirubin nomogram to predict the absence of risk for severe hyperbilirubinaemia before discharge: a prospective, multicenter study.**
	minutes). *Exclusion criteria:* • Prematurity, congenital anomalies, Rh or major ABO isoimmunisation indexed by a positive direct antiglobulin test, or the need of intensive care. Infants presenting with delayed meconium emission (> 24 hours), hypoglycemia, • hypothermia, cephalohaematoma, cutaneous bruising, hemorrhagic disease of the newborn (vitamin K deficiency), urinary tract infection, and suspected clinical sepsis were also excluded.
Number of patients	*Phase 1 development: Total = 1708* Mean gestational age = 39.3 ± 1.3 weeks (range: 37-42) Mean birth weight = 3302 ± 432 grams (range: 2580-4720) Gender (male/female) = 943/765 • 89 neonates (5.2%) had TSB value > 256.5 mmol/dl, while only 51 (3.0%) exceeded the value of 290.7 mmol/dl. • The infants were eligible for discharge 72 hours after birth in case of vaginal delivery and 96 hours in case of caesarean section. • TSB was measured at 12 hours of life and then every 12-24 hours during the first three day of life or when clinically indicated. Newborn babies with TSB values > 256.5 mmol/dl were discharged after a TSB decrease at two consecutive samples. In these infants direct acting bilirubin measurement was also performed. • Severe hyperbilirubinemia defined as TSB value > 290.7 mmol/dL, or as need for phototherapy treatment according to AAP guidelines. *Phase 2 validation = 2167* Mean gestational age = 38.9 ± 1.5 weeks (range 2000-5090) Mean birth weight = 3237 ± 471 grams (range 35-42) Gender (male/female) = 1137/1030
Outcomes	• Significant hyperbilirubinaemia, defined as TSB value > 290.7 mmol/dL or as need for phototherapy was diagnosed in 55 newborns (2.5%): 46 neonates required phototherapy while 9 newborn babies reached a TSB value greater than 17 mg/dL but were not treated. • No exchange transfusion was performed and no case of significant hyperbilirubinaemia was documented after discharge.
Nomogram	*Values of TSB corresponding at the 50th, 75th and 90th percentile of the hour-specific nomogram (micromole/L)*

Bibliographic reference	**Romagnoli (2012)** **Development and validation of serum bilirubin nomogram to predict the absence of risk for severe hyperbilirubinaemia before discharge: a prospective, multicenter study.**
	<table><tr><th>Age (hrs)</th><th>50th percentile</th><th>75th percentile</th><th>90th percentile</th></tr><tr><td>0</td><td>--</td><td>--</td><td>--</td></tr><tr><td>24</td><td>104.31</td><td>128.25</td><td>152.19</td></tr><tr><td>30</td><td>119.7</td><td>145.35</td><td>165.87</td></tr><tr><td>36</td><td>136.8</td><td>157.32</td><td>184.68</td></tr><tr><td>42</td><td>147.06</td><td>167.58</td><td>189.81</td></tr><tr><td>48</td><td>153.9</td><td>174.42</td><td>201.78</td></tr><tr><td>54</td><td>159.03</td><td>182.97</td><td>212.04</td></tr><tr><td>60</td><td>162.45</td><td>188.1</td><td>220.59</td></tr><tr><td>66</td><td>164.16</td><td>193.23</td><td>222.3</td></tr><tr><td>72</td><td>169.29</td><td>200.07</td><td>225.72</td></tr><tr><td>78</td><td>174.42</td><td>203.49</td><td>230.85</td></tr><tr><td>84</td><td>181.26</td><td>212.04</td><td>235.98</td></tr><tr><td>90</td><td>184.68</td><td>215.46</td><td>246.24</td></tr><tr><td>96</td><td>196.65</td><td>230.85</td><td>256.5</td></tr></table> X
Analysis used	TSB percentiles for each designated time were calculated, and these data were used for the design of an hour specific nomogram with Microsoft Excel.
Length of follow-up	96-hour plus a validation study.
Location	A multicenter prospective study was conducted in five neonatal units of Rome.
Source of funding	Not reported.
Comments	

1

Bibliographic reference	**Rennie (2009)** **Range of UK practice regarding thresholds for phototherapy and exchange transfusion in neonatal hyperbilirubinaemia**
Study type	Survey questionnaire
Aim	To establish the range of opinion regarding thresholds at which phototherapy and exchange transfusion are used to treat

Bibliographic reference	**Rennie (2009)** **Range of UK practice regarding thresholds for phototherapy and exchange transfusion in neonatal hyperbilirubinaemia**
	neonatal hyperbilirubinaemia in the UK.
Patient characteristics	*Inclusion criteria:* • A copy of the local guideline for the management of jaundice from the lead clinician in each of the 263 neonatal units who are listed as providing neonatal intensive care in the UK was requested. • Stamped addressed envelopes were provided for the reply. The survey was carried out in the first months of 2005. An attempt was made to contact a different individual in units who did not respond but no attempt was made to analyse the nonresponding units in terms of level of unit or geographical location.
Number of patients	Of the 263 hospitals contacted, 163 responded, of which 140 sent information which could be interpreted.
Outcomes	*The range of bilirubin levels chosen for action lines in term babies (initiation of phototherapy):* Range = between 250 and 400 micromole/l, with a median value of 340 micromole/l *Range for exchange transfusion:* Range = between 340 and 510 micromole/l with a median value of 400 micromole/l 20 hospitals chose a value of 350 micromole/l for exchange transfusion in a healthy term baby.
Analysis used	• Bilirubin levels were extracted from each of the graphical charts received, and entered into an Excel spreadsheet. • Each curve was summarised as a series of straight line segments that captured the shape of the curve, by recording the time (in decimal days) and corresponding bilirubin level at the start and end of each segment.
Length of follow-up	N/A
Location	UK
Source of funding	Funding from the Department of Health's NIHR Biomedical Research Centres funding scheme.
Comments	

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Appendix H: GRADE profiles

H.1 Review question 3

Table 18: GRADE profile for studies reporting accuracy data for visual assessment

Quality assessment							No of patients	Effect estimate				Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Measurements/ no. of patients	Sensitivity (95%CI)	Specificity (95%CI)	LR + (95%CI)	LR- (95%CI)	
Outcome: Diagnostic accuracy of visual assessment compared to total serum bilirubin measurement in detecting various bilirubin thresholds:												
TSB>68micromole/l												
1 (Riskin 2003)	Diagnostic	Very serious[1]	Very serious[2]	N/A	Not assessed[3]	No serious	371/371	36.9% (35.3 to 37.4)[4]	96.3% (86.7 to 99.4)[4]	9.965 (2.646 to 57.941)[5]	0.655 (0.630 to 0.747)[5]	Very low
TSB>127.5micromole/l												
1 (Riskin 2003)	Diagnostic	Very serious[1]	Very serious[2]	N/A	Not assessed[3]	No serious	371/371	51.0% (46.6 to 54.7)[4]	87.8% (83.2 to 91.7)[4]	4.200 (2.769 to 6.559)[5]	0.557 (0.494 to 0.642)[5]	To do
TSB>204micromole/l												
1 (Riskin 2003)	Diagnostic	Very serious[1]	Very serious[2]	N/A	Not assessed[3]	No serious	371/371	81.0 (58.2 to 93.7)[4]	70.9 % (69.5 to 71.6)[4]	2.778 (1.906 to 3.300)[5]	0.269 (0.088 to 0.602)[5]	To do

[1] *Very serious risk of bias because study did not satisfy 2 of the 4 criteria (patient selection, index test, reference standard, flow and timing), downgraded 2 levels*
[2] *Very serious indirectness because study did not satisfy 2 of the 3 criteria (patient selection, index test, reference standard), downgraded 2 levels*
3 Imprecision for accuracy data was not assessed given a MID could not be defined
[4] *Confidence intervals calculated by analyst based on data reported in the article*
[5] *LRs and confidence intervals calculated by analyst based on data reported in the article*

Table 19: GRADE profile for studies reporting Bland-Altman difference plots for BiliCheck

Quality assessment							No of patients	Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Measurements/no. of subjects	Mean difference in micromole/l (95% CI)	
Outcome: Bland-Altman test of agreement between total serum bilirubin and transcutaneous bilirubin									
Site of measurement: forehead									
8	Prospective cohort/cross sectional	Serious[1]	Very serious[2]	N/A	Very serious[3]	No serious	Qualter 2011: 43/43	-10.3 (-65.4 to 44.8)	VERY LOW
							Kaynak-Turkmen (2011: 54/54	69.8 (-49.2 to 188.6)	
							Willems (2004): 93/24	All infants: -4.9 (-59.2 to 49.4) Those with good skin conditions: 2.4 (-36.7 to 41.5) Those with poor skin conditions: -12.3 (-76.8 to 52.3)	

Quality assessment							No of patients	Effect estimate	Quality
							Campbell (2011): 430/430	12.7 (-52 to 77)	
							Wong (2002): all - 64/64 Term: 45/45 Preterm: 19/19	BiliCheck A: Term: -5.5 (-72.7 to 61.7) Preterm: -0.5 (-71.6 to 70.6) BiliCheck B Term: -12.8 (-75.7 to 50.1) Preterm: 1.3 (-70.7 to 73.3)	
							Rodriguez-Capote (2009): 60/60	-5.2 (-50.8 to 40.4)	
							Jangaard (2006) Term: 99/99 Preterm: 56/56	Term: -0.5 (-32.2 to 31.2) Preterm: -3.8 (-69.6 to 62.0)	
							Stoniene (2009) 6 hours: 130/130 30 hours: 119/119 54 hours: 103/103	 6 hours: 5.58 (2.55 to 8.61) 30 hours: 1.19 (-3.68 to 6.06) 54 hours: 2.92 (-2.04 to 7.89)	

Quality assessment							No of patients	Effect estimate	Quality
							78 hours: 35/35 6 to 78 hours : 387/387	78 hours: 7.37 (-3.30 to 18.04) 6 to 78 hours: 3.31 (0.70 to 5.93)	
Site of measurement: sternum									
1	Diagnostic	Serious[4]	Very serious[5]	N/A	Serious[6]	No serious	Grohmann (2006): 124/122	10.81 (-28.04 to 49.66)	VERY LOW
Site of measurement: not specified									
1	Diagnostic	Serious[4]	Serious[7]	N/A	Serious[6]	No serious	Samanta (2004): 300/300	-10.6 (-80.0 to +60.0)	VERY LOW

[1]*Serious risk of bias because 7/7 studies did not satisfy 1 of the 4 criteria (patient selection, index test, reference standard, flow and timing), downgraded 1 level*
[2]*Very serious indirectness because 5/7 studies did not satisfy 2 or more of the 3 criteria (patient selection, index test, reference standard), downgraded 2 levels*
[3] *Very serious imprecision as more than 50% of the studies had greater than zero bias, downgraded 2 levels*
[4]*Serious risk of bias because study did not satisfy 1 of the 4 criteria ((patient selection, index test, reference standard, flow and timing), downgraded 1 level*
[5]*Very serious indirectness because study did not satisfy 2 of the 3 criteria (patient selection, index test, reference standard), downgraded 2 levels*
[6]*Serious imprecision as study had greater than zero bias, downgraded 1 level*
[7]*Serious indirectness because study did not satisfy 1 of 3 criteria, (patient selection, index test, reference standard), downgraded 1 level*

Table 20: GRADE profile for studies reporting Bland-Altman difference plots for JM-102

Quality assessment							No of patients	Effect estimate	Quality
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Other considerations**	**Measurements/no. of subjects**	**Mean difference in micromole/l (95% CI)**	
Outcome: Bland-Altman test of agreement between total serum bilirubin and transcutaneous bilirubin									
Site of measurement: forehead									
1	Prospective cohort	Serious[1]	Serious[2]	N/A	Serious[3]	No serious	Wong (2002): 45/45 (term); 19/19 (preterm)	Term: -9.6 (-74.7 to 55.5) Preterm: 22.7 (-23.3 to 68.7)	VERY LOW
Site of measurement: sternum									

Quality assessment							No of patients	Effect estimate	Quality
1	Diagnostic	Serious[1]	Very serious[4]	N/A	Serious[3]	No serious	Grohmann (2006): 124/122	0.31 (-43.67 to 44.29)	VERY LOW

[1] *Serious risk of bias because study did not satisfy 1 of the 4 criteria (patient selection, index test, reference standard, flow and timing), downgraded 1 level*
[2] *Serious indirectness because study did not satisfy 1 of 3 criteria, (patient selection, index test, reference standard), downgraded 1 level*
[3] *Serious imprecision because mean difference had greater than zero bias*
[4] *Very serious indirectness because study did not satisfy 2 of the 3 criteria (patient selection, index test, reference standard), downgraded 2 levels*

Table 21: GRADE profile for studies reporting Bland-Altman difference plots for JM-103

Quality assessment							No of patients	Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Measurements/no. of subjects	Mean difference in micromole/l (95% CI)	
Outcome: Bland-Altman test of agreement between total serum bilirubin and transcutaneous bilirubin									
Site of measurement: sternum and forehead									
1	Prospective cohort	Serious[1]	Serious[2]	N/A	Serious[3]	No serious	Rylance (2014): 167/NR	Term infants: 25 (-46 to +97) Preterm infants: 37 (-36 to 110)	VERY LOW
Site of measurement: forehead									
3	Cross sectional/prospective cohort	Serious[4]	Very serious[5]	N/A	Very serious[6]	No serious	Qualter (2011): 41/41	-29.9 (-85.956 to 26.156)	VERY LOW
							Kosarat (2013): 294/257	15.83(-40.70 to 72.50)	
							Rodriguez-Capote (2009): 94/94	-38.3 (-78.4 to 1.8)	
Site of measurement: sternum									
3	Cross sectional	Serious[4]	Very serious[5]	N/A	Very serious[6]	No serious	Kosarat (2013): 294/257	16.59 (-35.40 to 68.57)	VERY LOW

Quality assessment							No of patients	Effect estimate	Quality
							Grohmann (2006): 124/122	-10.78 (-53.55 to 31.99)	
							Schmidt (2009): 24 to 28 weeks: 30/30 29 to 31 weeks: 29/29 32 to 34 weeks: 31/31	24 – 28 weeks: -18.81 (-82.49 to 44.87) 29 – 31 weeks: -13.68 (-57.25 to 29.89) 32 –34 weeks: -17.1 (-70.73 to 36.53)	
Site of measurement: not specified									
1	Cross sectional	Very serious[7]	Very serious[8]	N/A	Serious[3]	No serious	Mielsch (2010): 230/230	-26.64 (-78.90 to 25.63)	VERY LOW

[1] *Serious risk of bias because study did not satisfy 1 of the 4 criteria (patient selection, index test, reference standard, flow and timing), downgraded 1 level*
[2] *Serious indirectness because study did not satisfy 1 of 3 criteria, (patient selection, index test, reference standard), downgraded 1 level*
[3] *Serious imprecision as mean difference was greater than zero bias, downgraded 1 level*
[4] *Serious risk of bias because 3/3 studies not satisfy 1 of the 4 criteria (patient selection, index test, reference standard, flow and timing), downgraded 1 level*
[5] *Very serious indirectness because 3/3 studies not satisfy 2 of the 3 criteria, (patient selection, index test, reference standard), downgraded 2 levels*
[6] *Very serious imprecision because all 3 studies had greater than zero bias, downgraded 2 levels*
[7] *Very serious risk of bias because study did not satisfy 2 or more of the 4 criteria (patient selection, index test, reference standard, flow and timing), downgraded 2 levels*
[8] *Very serious indirectness because study did not satisfy 2 of the 3 criteria, (patient selection, index test, reference standard), downgraded 2 levels*

Table 22: GRADE profile for studies reporting Bland-Altman difference plots for BiliMed

Quality assessment							No of patients	Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Measurements/no. of subjects	Mean difference in micromole/l (95% CI)	

Quality assessment							No of patients	Effect estimate	Quality
Outcome: Bland-Altman test of agreement between total serum bilirubin and transcutaneous bilirubin									
Site of measurement: sternum									
1	Cross sectional	Very serious[1]	Very serious[2]	N/A	Serious[3]	No serious	Karen (2009): Term -111/99 $34^{0/7}$ to $36^{6/7}$ weeks-47/38 $28^{0/7}$ to $33^{6/7}$ weeks-21/13	<u>By gestational age</u> Term: -14 (-158 to 130) $34^{0/7}$ to $36^{6/7}$ weeks: 16 (-75 to 107) $28^{0/7}$ to $33^{6/7}$ weeks: -8 (-84 to 68)	VERY LOW
								<u>By ethnicity</u> Caucasian infants: 16 (-105 to 137) Non-Caucasian infants: 10 (-164 to 184)	

[1] *Very serious risk of bias because study did not satisfy 2 of the 4 criteria (patient selection, index test, reference standard, flow and timing), downgraded 1 level*
[2] *Very serious indirectness because study did not satisfy 2 of the 3 criteria (patient selection, index test, reference standard), downgraded 2 levels*
[3] *Serious imprecision because study had greater than zero bias, downgraded 1 level*

Table 23: GRADE profile for studies reporting accuracy data for BiliCheck

Quality assessment							No of patients	Effect estimate				Quality
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Other considerations**	**Measurements/no. of patients**	**Sensitivity (95%CI)**	**Specificity (95%CI)**	**LR + (95%CI)**	**LR- (95%CI)**	
Site of measurement: forehead												
Outcome: Accuracy of TcB value of 180micromole/l to detect TSB of 200micromole/l												

Quality assessment							No of patients	Effect estimate				Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Measurements/no. of patients	Sensitivity (95%CI)	Specificity (95%CI)	LR + (95%CI)	LR- (95%CI)	
1 Campbell (2011)	Prospective cohort	Serious[1]	Serious[2]	N/A	NC[3]	Mean age: not reported[4]	430/430	96% (NR)	55% (NR)	NR	NR	VERY LOW
								AUC for TCB predicting TSB>200micromole/l: 0.8976				
Outcome: Accuracy of TcB value of 200micromole/l to detect TSB of 250micromole/l												
1 Campbell (2011)	Prospective cohort	Serious[1]	Serious[2]	N/A	NC[3]	Mean age: not reported[4]	430/430	96% (NR)	57% (NR)	NR	NR	VERY LOW
								AUC for TCB predicting TSB >250micromole/l: 0.9230				
Outcome: Accuracy of various TcB cutoffs for detecting TSB >171micromole/l												
1 Engle (2002)	Diagnostic	Very serious[5]	Very serious[6]	N/A	NC[3]	Mean age: not reported	335/268	*TcB >85.5micromole/l*				VERY LOW
								100% (NR)	10% (NR)	1.1 (NR)	0 (NR)	
								TcB >119.7micromole/l				
								100% (NR)	40% (NR)	1.7 (NR)	0 (NR)	
								TcB >136.8micromole/l				
								98% (NR)	51% (NR)	2.0 (NR)	0.04 (NR)	
								TcB >153.9micromole/l				
								92% (NR)	77% (NR)	4.0 (NR)	0.10 (NR)	
								TcB > 171micromole/l				
								83% (NR)	88% (NR)	6.9 (NR)	0.19 (NR)	
								TcB >188.1micromole/l				

Quality assessment							No of patients	Effect estimate				Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Measurements/no. of patients	Sensitivity (95%CI)	Specificity (95%CI)	LR + (95%CI)	LR- (95%CI)	
								73% (NR)	97% (NR)	24.3 (NR)	0.28 (NR)	
Outcome: Accuracy of various TcB cuttoffs for detecting TSB >256.5micromole/l												
1 Engle (2002)	Diagnostic	Very serious[5]	Very serious[6]	N/A	NC[3]	Mean age: not reported	335/268	TcB >85.5micromole/l				VERY LOW
								100% (NR)	3% (NR)	1.0 (NR)	0 (NR)	
								TcB >119.7micromole/l				
								100% (NR)	13% (NR)	1.1 (NR)	0 (NR)	
								TcB >136.8micromole/l				
								99% (NR)	17% (NR)	1.1 (NR)	0.06 (NR)	
								TcB >153.9micromole/l				
								98% (NR)	33% (NR)	1.5 (NR)	0.06 (NR)	
								TcB >188.1micromole/l				
								92% (NR)	59% (NR)	2.2 (NR)	0.14 (NR)	
								TcB >205.2micromole/l				
								85% (NR)	74% (NR)	3.3 (NR)	0.20 (NR)	
								TcB >222.3micromole/l				
								76% (NR)	84% (NR)	4.8 (NR)	0.29 (NR)	
								TcB >256.5micromole/l				
								33% (NR)	96% (NR)	8.3 (NR)	0.70 (NR)	

Quality assessment							No of patients	Effect estimate				
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Measurements/no. of patients	Sensitivity (95%CI)	Specificity (95%CI)	LR + (95%CI)	LR- (95%CI)	Quality
Outcome: Accuracy of TcB ≥150micromole/l for detecting TSB≥250micromole when sensitivity is set to 100%												
1 Wong (2002)	Prospective cohort	Serious[1]	Serious[2]	N/A	NC[3]	Mean age: 4.6 days	64/64	BiliCheck A 100% (81.7 to 100)[7]	BiliCheck A 21.3% (14.7 to 21.3)[7]	BiliCheck A 1.270 (0.957 to 1.270)[8]	BiliCheck B 0.000(0.000 to 1.248)[8]	LOW
								BiliCheck B 100% (80.9 to 100)[7]	BiliCheck B 27.7% (20.8 to 27.7)[7]	BiliCheck B 1.382 (1.021 to 1.382)[8]	BiliCheck B 0.000 (0.000 to 0.919)[8]	
Outcome: Accuracy of TcB ≥75th percentile to detect clinically significant hyperbilirubinaemia defined as TSB level above 95th percentile on the Bhutani nomagram												
1 Kolman (2007)	Diagnostic	Serious[1]	Very serious[6]	N/A	NC[3]	Mean age: 40 hours	192/192	100% (70.9 to 100)[7]	66.1% (64.2 to 66.1)[7]	2.951 (1.978 to 2.951)[8]	0.000 (0.000 to 0.454)[8]	VERY LOW
Outcome: Accuracy of TcB of various thresholds to detect TSB >256.5micromole/l												
1 Engle (2005)	Diagnostic	Serious[1]	Serious[2]	N/A	NC[3]	Median age: 91 hours	121/121	*TcB >188.1micromole/l*				VERY LOW
								100% (NR)	34% (NR)	NR	NR	
								TcB >205.2micromole/l				
								91% (NR)	53% (NR)	NR	NR	
								TcB >222.3micromole/l				
								79%	77%	NR	NR	

Quality assessment							No of patients	Effect estimate				
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Measurements/no. of patients	Sensitivity (95%CI)	Specificity (95%CI)	LR + (95%CI)	LR- (95%CI)	Quality
								(NR)	(NR)			
								TcB >239.4micromole/l				
								58% (NR)	95% (NR)	NR	NR	
								TcB >256.5micromole/l				
								40% (NR)	97% (NR)	NR	NR	
Outcome: Accuracy of TcB of various thresholds to detect TSB>273.6micromole/l												
1 Engle (2005)	Diagnostic	Serious[1]	Serious[2]	N/A	NC[3]	Median age: 91 hours	121/121	*TcB>205.2micromole/l*				VERY LOW
								91% (NR)	42% (NR)	NR	NR	
								TcB>222.3micromole/l				
								86% (NR)	65% (NR)	NR	NR	
								TcB>239.4micromole/l				
								63% (NR)	84% (NR)	NR	NR	
								TcB>256.5micromole/l				
								43% (NR)	88% (NR)	NR	NR	
								TcB>273.6micromole/l				
								26%	94%	NR	NR	
Outcome: Accuracy of TcB of various thresholds to detect TSB>290.7micromole/l												
1 Engle (2005)	Diagnostic	Serious[1]	Serious[2]	N/A	NC[3]	Median age: 91 hours	121/121	*TcB>222.3micromole/l*				VERY LOW
								100% (NR)	58% (NR)	NR	NR	
								TcB>239.4micromole/l				

Quality assessment							No of patients	Effect estimate				
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Measurements/no. of patients	Sensitivity (95%CI)	Specificity (95%CI)	LR + (95%CI)	LR- (95%CI)	Quality
								94% (NR)	80% (NR)	NR	NR	
								TcB>256.5micromole/l				
								75% (NR)	88% (NR)	NR	NR	
								TcB>273.6micromole/l				
								56% (NR)	95% (NR)	NR	NR	
								TcB>290.7micromole/l				
								31% (NR)	95% (NR)	NR	NR	
Outcome: Accuracy of TcB of various thresholds to detect TSB>307.8micromole/l												
1 Engle (2005)	Diagnostic	Serious[1]	Serious[2]	N/A	NC[3]	Median age: 91 hours	121/121	*TcB>239.4micromole/l*				VERY LOW
								100% (NR)	77% (NR)	NR	NR	
								TcB>256.5micromole/l				
								73% (NR)	85% (NR)	NR	NR	
								TcB>273.6micromole/l				
								55% (NR)	93% (NR)	NR	NR	
								TcB>290.7micromole/l				
								36% (NR)	98% (NR)	NR	NR	
								TcB>307.8micromole/l				
								36% (NR)	100% (NR)	NR	NR	

Quality assessment							No of patients	Effect estimate				
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Measurements/no. of patients	Sensitivity (95%CI)	Specificity (95%CI)	LR + (95%CI)	LR- (95%CI)	Quality
Outcome: Accuracy of high or high-intermediate TcB for predicting a high or high intermediate diazo TSB (defined as >95th percentile for age and >75th percentile for age respectively on Bhutani nomogram												
1 Karon (2008)	Diagnostic	Very serious[5]	Serious[2]	N/A	NC[3]	Median age: 48 hours	177/177	98.2% (90.3 to 99.9)[7]	40% (36.2 to 40.8)[7]	1.637 (1.416 to 1.687)[8]	0.044 (0.002 to 0.268)[8]	VERY LOW
Outcome: Accuracy of TcB of various thresholds to detect TSB ≥300micromole/l												
1 Boo (2007)	Diagnostic	Serious[1]	Serious[2]	N/A	NC[3]	Median age: 70 hours	345/345	*TcB 250micromole/l*				VERY LOW
								100% (NR)	39.2% (NR)	NR	NR	
								TcB 260micromole/l				
								75.8% (NR)	84.8% (NR)	NR	NR	
Outcome: Accuracy of TcB (threshold not reported) in predicting the need for phototherapy												
1 Knupfer (2001)	Diagnostic	Serious[1]	Serious[2]	N/A	NC[3]	Postnatal age not reported	135/135	86.8% (NR)	72.6% (NR)	NR	NR	VERY LOW
Site of measurement: sternum												
Outcome: Accuracy of TcB≥70% of phototherapy limit i.e. 210micromole/l to detect TSB above the phototherapy limit i.e. ≥300micromole/l												
1 Ebbesen (2012)	Diagnostic	Serious[1]	Very serious[6]	N/A	NC[3]	Median age: 101 hours	239/133	51.9% (50.7 to 54.9)[7]	5.2% (1.4 to 14.4)[7]	0.548 (0.514 to 0.642)[8]	9.293 (3.125 to 36.308)[8]	VERY LOW
Outcome: Accuracy of TcB value of various thresholds to detect TSB≥300micromole/l												
1 Boo (2007)	Diagnostic	Serious[1]	Serious[2]	N/A	NC[3]	Median age: 70 hours	345/345	*TcB 200micromole/l*				VERY LOW
								100% (NR)	33.6% (NR)	NR	NR	
								TcB 280micromole/l				

Quality assessment							No of patients	Effect estimate				
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Measurements/no. of patients	Sensitivity (95%CI)	Specificity (95%CI)	LR + (95%CI)	LR- (95%CI)	Quality
								92.6% (NR)	84% (NR)	NR	NR	
Outcome: Accuracy of TcB value of 180micromole/l in detecting TSB of 222micromole/l when sensitivity set at 100%												
1 Grohmann (2006)	Diagnostic	Serious[1]	Very serious[6]	N/A	NC[3]	Mean age: 3 days	124/122	100% (NR)	64% (NR)	NR	NR	VERY LOW
								AUC: 0.961				
Outcome: Accuracy of TcB value of 222micromole/l in detecting TSB of 257micromole/l when sensitivity set at 100%												
1 Grohmann (2006)	Diagnostic	Serious[1]	Very serious[6]	N/A	NC[3]	Mean age: 3 days	124/122	100% (NR)	89% (NR)	NR	NR	VERY LOW
								AUC: 0.998				
Site of measurement: not specified												
Outcome: Accuracy of TcB>195micromole/l to detect significant jaundice defined as TSB>250micromole/l												
1 Samanta (2004)	Diagnostic	Serious[1]	Serious[2]	N/A	NC[3]	Median age: 3 days	300/300	90.9% (80.2 to 96.6)[7]	66.1% (63.7 to 67.4)[7]	2.683 (2.210 to 2.961)[8]	0.137 (0.051 to 0.311)[8]	LOW

[1] *Serious risk of bias because study did not satisfy 1 of the 4 criteria (patient selection, index test, reference standard, flow and timing) – downgrade 1 level*
[2] *Serious indirectness because study did not satisfy 1 of the 3 criteria (applicability of patient selection, index test, reference standard) – downgrade 1 level*
[3] *Imprecision could not be calculated as confidence intervals not reported in study nor could a MID be defined by the committee– downgrade 1 level for studies not reporting confidence intervals*
[4] *Mean age not reported, TSB thresholds chosen by study authors as deemed to clinically important values at 24 hours and 48 hours of age*
[5] *Very serious risk of bias because study did not satisfy 2 or more of the 4 criteria (patient selection, index test, reference standard, flow and timing) – downgrade 2 levels*
[6] *Very serious risk of indirectness because study did not satisfy 2 or more of the 3 criteria (applicability of patient selection, index test, reference standard) – downgrade 2 levels*
[7] *Confidence intervals calculated by analyst*
[8] *LRs and confidence intervals calculated by analyst based on data reported in the article*
[9] *Very serious indirectness because study did not satisfy 2 of the 3 criteria (applicability of patient selection, index test, reference standard) – downgrade 2 levels*
[10] *Very serious risk of bias because study did not satisfy 2 of the 4 criteria (patient selection, index test, reference standard, flow and timing) – downgrade 2 levels*

Table 24: GRADE profile for studies reporting accuracy data for JM-102

Quality assessment							No of patients	Effect estimate				Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Measurements/ no. of patients	Sensitivity (95%CI)	Specificity (95%CI)	LR + (95%CI)	LR- (95%CI)	
Site of measurement: forehead												
Outcome: Accuracy of TcB ≥170micromole/l in detecting TSB≥250micromole when sensitivity is set to 100%												
1 Wong (2002)	Prospective cohort	Serious[1]	Serious[2]	N/A	NC[3]	Mean age: 4.6 days	64/64	100% (80.6 to 100)[4]	31.9 % (24.9 to 31.9)[4]	1.469 (1.073 to 1.469)[5]	0.000 (0.000 to 0.780)[5]	LOW
Outcome: Accuracy of TcB value of 19.9 to detect TSB >249micromole/l (highest accuracy from ROC curve)												
1 Briscoe (2002)	Diagnostic	Serious[1]	Serious[2]	N/A	NC[3]	Median age: 3 days	285/285	86% (81% to 89%)	78% (73% to 83%)	NR	NR	LOW
Outcome: Accuracy of TcB (threshold not reported) in detecting TSB >171micromole/l												
1 Maisels (1982)	Diagnostic	Very serious[6]	Very serious[7]	N/A	NC[3]	Postnatal age not reported	157/157	90.9% (72.1 to 98.4)[4]	89.6 % (86.6 to 90.8)[4]	8.766 (5.364 to 10.748)[5]	0.101 (0.018 to 0.323)[5]	VERY LOW
Outcome: Accuracy of TcB (threshold not reported) in detecting TSB >221micromole/l												
1 Maisels (1982)	Diagnostic	Very serious[6]	Very serious[7]	N/A	NC[3]	Postnatal age not reported	157/157	100% (60.1 to 100)[3]	96.7 % (94.8 to 96.7)[4]	30.00 (11.572 to 30.00)[5]	0.00 (0.00 to 0.421)[5]	VERY LOW
Site of measurement: sternum												
Outcome: Accuracy of TcB value of 190micromole/l in detecting TSB of 222micromole/l when sensitivity set at 100%												
1 Grohma	Diagnostic	Serious[1]	Very serious[7]	N/A	NC	Mean age: 3 days	124/122	100% (NR)	81% (NR)	NR	NR	VERY LOW

Quality assessment							No of patients	Effect estimate				Quality
nn (2006)								AUC:0.963				
Outcome: Accuracy of TcB value of 224micromole/l in detecting TSB of 257micromole/l when sensitivity set at 100%												
1 Grohmann (2006)	Diagnostic	Serious[1]	Very serious[7]	N/A	NC	Mean age: 3 days	124/122	100% (NR)	91% (NR)	NR	NR	VERY LOW
								AUC: 0.982				
Outcome: Accuracy of TcB (threshold not reported) in detecting TSB >171micromole/l												
1 Maisels (1982)	Diagnostic	Very serious[6]	Very serious[7]	N/A	NC[3]	Postnatal age not reported	135/135	100% (69.9 to 100)[3]	84.7% (82 to 84.7)[4]	6.526 (3.886 to 6.526)[5]	0.00 (0.00 to 0.367)[5]	VERY LOW
Outcome: Accuracy of TcB (threshold not reported) in detecting TSB >221micromole/l												
1 Maisels (1982)	Diagnostic	Very serious[6]	Very serious[7]	N/A	NC[3]	Postnatal age not reported	135/135	100% (42.2 to 100)[4]	96.2% (94.4 to 96.2)[4]	26.2 (7.560 to 26.2)[5]	0.00 (0.00 to 0.612)[5]	VERY LOW

[1] *Serious risk of bias because study did not satisfy 1 of the 4 criteria (patient selection, index test, reference standard, flow and timing) – downgrade 1 level*
[2] *Serious indirectness because study did not satisfy 1 of the 3 criteria (applicability of patient selection, index test, reference standard) – downgrade 1 level*
[3] *Imprecision could not be calculated as confidence intervals not reported in study nor could a MID be defined by the committee– downgrade 1 level for studies not reporting confidence intervals*
[4] *Confidence intervals calculated by analyst*
[5] *LRs and confidence intervals calculated by analyst based on data reported in the article*
[6] *Very serious risk of bias because study did not satisfy 2 or more of the 4 criteria (patient selection, index test, reference standard, flow and timing) – downgrade 2 levels*
[7] *Very serious indirectness because study did not satisfy 2 of the 3 criteria (applicability of patient selection, index test, reference standard) – downgrade 2 levels*

Table 25: GRADE profile for studies reporting accuracy data for JM-103

Quality assessment							No of patients	Effect estimate				Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Measurements/ no. of patients	Sensitivity (95%CI)	Specificity (95%CI)	LR + (95%CI)	LR- (95%CI)	
Site of measurement: forehead												

Quality assessment							No of patients	Effect estimate				Qualit
Outcome: Accuracy of TcB of various thresholds to detect TSB >150micromole/l												
1 Wainer (2009)	Diagnostic	Serious[1]	Very serious[2]	N/A	NC[3]	Mean not reported, TSB drawn at around 24 hours of age	774/774	**All infants (n=774)**				VERY LOW
								TcB 70micromole/l				
								100% (NR)	24.9% (NR)	NR	NR	
								TcB 80micromole/l				
								99.4% (NR)	34.3% (NR)	NR	NR	
								TcB 190micromole/l				
								38.6% (NR)	99.7% (NR)	NR	NR	
								TcB 200micromole/l				
								31.6% (NR)	100%(NR)	NR	NR	
								Light tone infants (n=347)				
								TcB 100micromole/l				
								100% (NR)	72% (NR)	NR	NR	
								TcB 110micromole//l				
								97.5% (NR)	81.0% (NR)	NR	NR	
								TcB 150micromole/l				
								53.2% (NR)	99.3% (NR)	NR	NR	
								TcB 160micromole/l				
								45.6% (NR)	100% (NR)	NR	NR	
								Medium tone infants (n=412)				
								TcB 70micromole/l				
								100%	17.1%(NR	NR	NR	

Quality assessment							No of patients	Effect estimate				Qualit
								(NR)	)			
								TcB 80micromole/l				
								98.9% (NR)	24.9% (NR)	NR	NR	
								TcB 170micromole/l				
								62.6% (NR)	99.1% (NR)	NR	NR	
								TcB 180micromole/l				
								54.9% (NR)	100% (NR)	NR	NR	
Outcome: Accuracy of TcB of various thresholds to detect TSB >200micromole/l												
1 Wainer (2009)	Diagnostic	Serious[1]	Very serious[2]	N/A	NC[3]	Mean not reported, TSB drawn at around 24 hours of age	774/774	**All infants (n=774)**				
								TcB 130micromole/l				
								100% (NR)	80.8% (NR)	NR	NR	
								TcB 140micromole/l				
								98.5% (NR)	85.7% (NR)	NR	NR	
								TcB 220micromole/l				
								54.5% (NR)	99.7% (NR)	NR	NR	
								TcB 230micromole/l				
								45.5%(NR)	100%(NR)	NR	NR	
								Light tone infants (n=347)				
								TcB 130micromole/l				
								100% (NR)	85.4% (NR)	NR	NR	
								TcB 140micromole/l				
								95.8%	90.4%	NR	NR	

Quality assessment							No of patients	Effect estimate				Qualit
								(NR)	(NR)			
								TcB 200micromole/l				
								62.5%(NR)	99.7% (NR)	NR	NR	
								TcB 210micromole/l				
								54.2% (NR)	100% (NR)	NR	NR	
								Medium tone infants (n=412)				
								TcB 140micromole/l				
								100% (NR)	82.2% (NR)	NR	NR	
								TcB 150micromole/l				
								95.2%(NR)	87.6% (NR)	NR	NR	
								TcB 220micromole/l				
								61.9% (NR)	99.5% (NR)	NR	NR	
								TcB 230micromole/l				
								54.8%(NR)	100% (NR)	NR	NR	
Outcome: Accuracy of TcB of various thresholds to detect TSB >250micromole/l												
1 Wainer (2009)	Diagnostic	Serious[1]	Very serious[2]	N/A	NC[3]	Mean not reported, TSB drawn at around 24 hours of age	774/774	**All infants (n=774)**				
								TcB 160micromole/l				
								100% (NR)	90.1% (NR)	NR	NR	
								TcB 170micromole/l				
								97% (NR)	91.8% (NR)	NR	NR	
								TcB 240micromole/l				
								60.6%	99.7%	NR	NR	

Quality assessment							No of patients	Effect estimate				Qualit
								(NR)	(NR)			
								TcB 250micromole/l				
								57.6% (NR)	100% (NR)	NR	NR	
								Light tone (n=347)				
								TcB 160micromole/l				
								100% (NR)	92.8% (NR)	NR	NR	
								TcB 170micromole/l				
								91.7% (NR)	94.0%(NR)	NR	NR	
								TcB 230micromole/l				
								50% (NR)	99.7% (NR)	NR	NR	
								TcB 240micromole/l				
								41.7% (NR)	100% (NR)	NR	NR	
								Medium tone (n=412)				
								TcB 190micromole/l				
								100% (NR)	94.1%(NR)	NR	NR	
								TcB 200micromole/l				
								95.2%(NR)	95.4%(NR)	NR	NR	
								TcB 240micromole/l				
								71.4%(NR)	99.7%(NR)	NR	NR	
								TcB 250micromole/l				
								66.7%(NR)	100%(NR)	NR	NR	
Site of measurement: sternum												

Quality assessment							No of patients	Effect estimate				Qualit
Outcome: Accuracy of TcB of various thresholds to detect TSB >256.5micromole/l												
1 Barko (2006)	Diagnostic	Serious[1]	Serious[4]	N/A	NC[3]	Median age: 37 hours	120/120	*TcB > 188.1micromole/l*				VERY LOW
								96% (NR)	82% (NR)	NR	NR	
								TcB > 205.2micromole/l				
								91% (NR)	87% (NR)	NR	NR	
								TcB > 222.3micromole/l				
								87% (NR)	91% (NR)	NR	NR	
Outcome: Accuracy of TcB of various thresholds to detect TSB >273.6micromole/l												
1 Barko (2006)	Diagnostic	Serious[1]	Serious[4]	N/A	NC[3]	Median age: 37 hours	120/120	*TcB > 205.2micromole/l*				VERY LOW
								100% (NR)	80% (NR)	NR	NR	
								TcB > 222.3micromole/l				
								92% (NR)	(91% (NR)	NR	NR	
								TcB > 239.4micromole/l				
								92% (NR)	92% (NR)	NR	NR	
Outcome: Accuracy of TcB of various thresholds to detect TSB >290.7micromole/l												
1 Barko (2006)	Diagnostic	Serious[1]	Serious[4]	N/A	NC[3]	Median age: 37 hours	120/120	*TcB > 222.3micromole/l*				VERY LOW
								100% (NR)	81% (NR)	NR	NR	
								TcB > 239.4micromole/l				
								100% (NR)	86% (NR)	NR	NR	
								TcB > 256.5micromole/l				
								67% (NR)	93% (NR)	NR	NR	

Quality assessment							No of patients	Effect estimate				Qualit
Outcome: Accuracy of TcB of various thresholds to detect TSB >307.8micromole/l												
1 Barko (2006)	Diagnostic	Serious[1]	Serious[4]	N/A	NC[3]	Median age: 37 hours	120/120	*TcB > 239.4micromole/l*				VERY LOW
								100% (NR)	84% (NR)	NR	NR	
								TcB > 256.5micromole/l				
								71% (NR)	92% (NR)	NR	NR	
								TcB > 273.6micromole/l				
								57% (NR)	98% (NR)	NR	NR	
Outcome: Accuracy of TcB ≥35% of phototherapy limit i.e. ≥105micromole/l in detecting TSB above phototherapy limit i.e. ≥300micromole/l												
1 Ebbesen (2012)	Diagnostic	Serious[1]	Very serious[2]	N/A	NC[3]	Median age: 101 hours	239/133	68% (67 to 70.7)[6]	3.4% (0.6 to 12.1)[6]	0.704 (0.675 to 0.804)[7]	9.293 (2.423 to 54.674)[7]	VERY LOW
Outcome: Accuracy of TcB of various thresholds to detect TSB ≥222.3micromole/l												
1 Maisels (2011)	Diagostic	Very serious[5]	Serious[4]	N/A	NC[3]	Mean age: 90.4 hours	118/118	*TcB ≥ 153.9micromole/l*				VERY LOW
								100% (NR)	4% (NR)	NR	NR	
								TcB ≥171micromole/l				
								100% (NR)	7% (NR)	NR	NR	
								TcB ≥ 188.1micromole/l				
								100% (NR)	19% (NR)	NR	NR	
								TcB ≥ 205.2micromole/l				
								99% (NR)	52% (NR)	NR	NR	
								TcB ≥ 222.3micromole/l				
								96%	74%	NR	NR	

Quality assessment							No of patients	Effect estimate				Qualit
								(NR)	(NR)			
Outcome: Accuracy of TcB of various thresholds to detect TSB ≥239.4micromole/l												
1 Maisels (2011)	Diagostic	Very seriou s[5]	Serious[4]	N/A	NC[3]	Mean age: 90.4 hours	118/118	*TcB ≥171micromole/l*				VERY LOW
								100% (NR)	5% (NR)	NR	NR	
								TcB ≥188.1micromole/l				
								100% (NR)	12% (NR)	NR	NR	
								TcB ≥205.2micromole/l				
								100% (NR)	37% (NR)	NR	NR	
								TcB ≥222.3micromole/l				
								98% (NR)	54% (NR)	NR	NR	
								TcB ≥239.4micromole/l				
								91% (NR)	63% (NR)	NR	NR	
Outcome: Accuracy of TcB of various thresholds to detect TSB ≥256.5micromole/l												
1 Maisels (2011)	Diagostic	Very seriou s[5]	Serious[4]	N/A	NC[3]	Mean age: 90.4 hours	118/118	*TcB ≥188.1micromole/l*				VERY LOW
								100% (NR)	10% (NR)	NR	NR	
								TcB ≥205.2micromole/l				
								100% (NR)	29% (NR)	NR	NR	
								TcB ≥222.3micromole/l				
								99% (NR)	44% (NR)	NR	NR	
								TcB ≥239.4micromole/l				
								92% (NR)	54% (NR)	NR	NR	

Quality assessment							No of patients	Effect estimate				Qualit
								TcB ≥256.5micromole/l				
								79% (NR)	70% (NR)	NR	NR	
Outcome: Accuracy of TcB of various thresholds to detect TSB ≥273.6micromole/l												
1 Maisels (2011)	Diagostic	Very seriou s[5]	Serious[4]	N/A	NC[3]	Mean age: 90.4 hours	118/118	*TcB ≥205.2micromole/l*				VERY LOW
								100% (NR)	22% (NR)	NR	NR	
								TcB ≥222.3micromole/l				
								98% (NR)	33% (NR)	NR	NR	
								TcB ≥239.4micromole/l				
								96% (NR)	45% (NR)	NR	NR	
								TcB ≥256.5micromole/l				
								86% (NR)	62% (NR)	NR	NR	
								TcB ≥273.6micromole/l				
								78% (NR)	75% (NR)	NR	NR	
Outcome: Accuracy of TcB of various thresholds to detect TSB ≥290.7micromole/l												
1 Maisels (2011)	Diagostic	Very seriou s[5]	Serious[4]	N/A	NC[3]	Mean age: 90.4 hours	118/118	*TcB ≥222.3micromole/l*				VERY LOW
								100% (NR)	30% (NR)	NR	NR	
								TcB ≥239.4micromole/l				
								100% (NR)	41% (NR)	NR	NR	
								TcB ≥256.5micromole/l				
								92% (NR)	58% (NR)	NR	NR	
								TcB ≥273.6micromole/l				

Quality assessment							No of patients	Effect estimate				Qualit
								81% (NR)	69% (NR)	NR	NR	
								TcB ≥290.7micromole/l				
								60% (NR)	84% (NR)	NR	NR	
Outcome: Accuracy of TcB of various thresholds to detect TSB ≥307.8micromole/l												
1 Maisels (2011)	Diagostic	Very serious[5]	Serious[4]	N/A	NC[3]	Mean age: 90.4 hours	118/118	*TcB ≥239.4micromole/l*				VERY LOW
								100% (NR)	34% (NR)	NR	NR	
								TcB ≥256.5micromole/l				
								95% (NR)	50% (NR)	NR	NR	
								TcB ≥273.6micromole/l				
								85% (NR)	61% (NR)	NR	NR	
								TcB ≥290.7micromole/l				
								75% (NR)	80% (NR)	NR	NR	
								TcB ≥307.8micromole/l				
								60% (NR)	90% (NR)	NR	NR	
Outcome: Accuracy of TcB value of 170micromole/l in detecting TSB of 222micromole/l when sensitivity set at 100%												
1 Grohmann (2006)	Diagnostic	Serious[1]	Very serious[2]	N/A	NC[3]	Mean age: 3 days	124/122	100% (NR)	70% (NR)	NR	NR	VERY LOW
								AUC: 0.949				
Outcome: Accuracy of TcB value of 209micromole/l in detecting TSB of 257micromole/l when sensitivity set at 100%												
1 Grohma	Diagnostic	Serious[1]	Very serious[2]	N/A	NC[3]	Mean age: 3 days	124/122	100%(NR)	90% (NR)	NR	NR	VERY LOW

Quality assessment							No of patients	Effect estimate				Qualit
nn (2006)								AUC: 0.983				
Outcome: Accuracy of TcB >68.4micromole/l to detect TSB >102.6micromole/l												
1 Schmidt (2009)	Diagnostic	Serious[1]	Very serious[2]	N/A	NC[3]	Median age in hours: 24 to 28 weeks - 24 29 to 31 weeks – 36 32 to 34 weeks - 53	24 to 28 weeks: 30/30 29 to 31 weeks: 29/29 32 to 34 weeks: 31/31	Infants with gestational age 24 to 28 weeks				VERY LOW
								100% (NR)	76% (NR)	NR	NR	
								Infants with gestational age 29 to 31 weeks				
								94% (NR)	38% (NR)	NR	NR	
								Infants with gestational age 32 to 34 weeks				
								98% (NR)	29% (NR)	NR	NR	
Outcome: Accuracy of TcB >102.6micromole/l to detect TSB >136.8micromole/l												
1 Schmidt (2009)	Diagnostic	Serious[1]	Very serious[2]	N/A	NC[3]	Median age in hours: 24 to 28 weeks - 24 29 to 31 weeks – 36 32 to 34 weeks - 53	24 to 28 weeks: 30/30 29 to 31 weeks: 29/29 32 to 34 weeks: 31/31	Infants with gestational age 24 to 28 weeks				VERY LOW
								88% (NR)	81% (NR)	NR	NR	
								Infants with gestational age 29 to 31 weeks				
								92% (NR)	58% (NR)	NR	NR	
								Infants with gestational age 32 to 34 weeks				
								97% (NR)	70% (NR)	NR	NR	
Outcome: Accuracy of TcB >136.8micromole/l to detect TSB >171micromole/l												
1 Schmidt (2009)	Diagnostic	Serious[1]	Very serious[2]	N/A	NC[3]	Median age in hours: 24 to 28 weeks - 24 29 to 31 weeks – 36 32 to 34 weeks - 53	24 to 28 weeks: 30/30 29 to 31 weeks: 29/29	Infants with gestational age 24 to 28 weeks				VERY LOW
								67% (NR)	81% (NR)	NR	NR	
								Infants with gestational age 29 to 31 weeks				
								100% (NR)	70% (NR)	NR	NR	
								Infants with gestational age 32 to 34 weeks				

Quality assessment							No of patients	Effect estimate				Qualit
							32 to 34 weeks: 31/31	93% (NR)	74% (NR)	NR	NR	
Site of measurement: forehead and sternum												
Outcome: Accuracy of using lowest TcB reading (threshold not reported) to decide whether to start phototherapy or continue observation												
1 Rylance (2014)	Prospective cohort	Serious[1]	Serious[4]	N/A	NC[3]	Postnatal age - 3 days: 2% 2: 14 days: 11% 3: 36 days: 28% 4 days or more: 59%	167/NR	91% (NR)	90% (NR)	NR	NR	VERY LOW
Outcome: Accuracy of using highest TcB reading (threshold not reported) to decide whether to start phototherapy or continue observation												
1 Rylance (2014)	Prospective cohort	Serious[1]	Serious[4]	N/A	NC[3]	Postnatal age - 3 days: 2% 2: 14 days: 11% 3: 36 days: 28% 4 days or more: 59%	167/NR	100% (NR)	72% (NR)	NR	NR	VERY LOW

[1] *Serious risk of bias because study did not satisfy 1 of the 4 criteria (patient selection, index test, reference standard, flow and timing) – downgrade 1 level*
[2] *Very serious indirectness because study did not satisfy 2 of the 3 criteria (applicability of patient selection, index test, reference standard) – downgrade 2 levels*
[3] *Imprecision could not be calculated as confidence interval not reported in study nor could a MID be defined by the committee– downgrade 1 level for studies not reporting confidence intervals*
[4] *Serious risk of indirectness because study did not satisfy 1 of the 3 criteria (applicability of patient selection, index test, reference standard) – downgrade 1 level*
[5] *Very serious risk of bias because study did not satisfy 2 or more of the 3 criteria (applicability of patient selection, index test, reference standard) – downgrade 2 levels*
[6] *Confidence intervals calculated by analyst*
[7] *LRs and confidence intervals calculated by analyst based on data reported in the article*

H.2 Review question 4

Quality assessment							No of patients in PT			Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	G1: TSB >170micromole/l	G2: TSB >257micromole/l	G3: TSB >300micromole/l	Count	
Outcome: Complications (readmission and/or exchange transfusion)											
1	Cohort	Serious[1]	No serious	N/A	Serious[2]	No serious	31/32 (97%)	15/32 (47%)	5/28 (18%)	G1 = 0/32 G2 = 0/32 G3 = 2/28	Very low

1 Lack of information on baseline characteristics

2 Very small sample size

1 Appendix I: Quality assessment

I.1 2 Review question 3

	Risk of bias				Applicability concerns		
Study	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Rylance (2014)	√	√	?	√	√	√	?
Willems (2004)	√	√	?	√	?	√	?
Qualter (2011)	√	√	?	√	?	√	?
Campbell (2011)	√	√	?	√	√	√	?
Kaynak-Turkmen (2011)	√	√	?	√	?	√	?
Engle (2002)	?	?	?	√	?	?	?
Barko (2006)	√	√	?	√	√	√	?
Nanjundaswamy (2004)	√	√	?	√	?	√	?
Ebbesen (2012)	√	√	?	√	?	√	?
Kosarat (2013)	?	√	?	√	?	√	?
Wong (2002)	√	√	?	√	√	√	?
Robertson (2002)	√	√	?	√	?	√	?
Kolman (2007)	√	√	?	√	?	√	?
Rodra-guez-Capote (2009)	√	√	?	√	?	√	?
Kunpfer (2001)	√	√	?	√	√	√	?
Holland (2009)	?	√	?	√	?	√	?
Stoniene (2009)	√	√	?	√	?	√	?
Jangaard (2006)	√	√	?	√	?	√	?
Maisels (2011)	?	√	?	√	√	√	?
Wainer (2009)	√	√	?	√	?	√	?
Ahmed (2010)	√	√	?	√	?	√	?
Briscoe (2002) – CG98	√	√	?	√	√	√	?
Engle (2005) – CG98	√	√	?	√	√	√	?
Schmidt (2009) – CG98	√	√	?	√	?	√	?

	Risk of bias				Applicability concerns		
Maisels (1982) – CG98	?	√	?	√	?	√	?
Boo (2007) – CG98	√	√	?	√	√	√	?
Mielsch (2010)	?	?	?	√	?	√	?
Grohmann (2006)	√	√	?	√	?	√	?
Samanta (2004) – CG98	√	√	?	√	√	√	?
Karon (2008) – CG98	?	√	?	√	√	√	?
Riskin (2003)	?	√	?	√	?	√	?
Karen (2009)	?	√	?	√	?	√	?

1

2 √ Low risk

3 × High risk

4 ? Unclear risk

Appendix J: Economic search strategy

J.1 Review question 3

Databases that were searched, together with the number of articles retrieved from each database are shown in table 26. The search strategy is shown in table 27. The same strategy was translated for the other databases listed.

Table 26: Economic search summary

Databases	Version/files	No. retrieved
NHS EED (Wiley)	Issue 1 of 4, January 2015	4
HTA (Wiley)	Issue 1 of 4, January 2015	4
MEDLINE (Ovid)	1980 to 2015 Week 07	190
MEDLINE In-Process (Ovid)	February 13, 2015>	9
EMBASE (Ovid)	1980 to 2015 Week 07	338

Table 27: Economic search strategy

Database: Medline Ovid
Database: Ovid MEDLINE(R) <1946 to February Week 2 2015> Search Strategy: --- 1 exp Infant, Newborn/ (500899) 2 (newborn* or neonat* or preterm* or premature).tw. (372689) 3 1 or 2 (688920) 4 Hyperbilirubinemia/ (3896) 5 exp Jaundice/ (11852) 6 Kernicterus/ (1034) 7 (bilirubin* or hyperbilirubin* or jaundice* or kernicterus* or icterus*).tw. (53897) 8 (bilirubin adj2 encephalopath*).tw. (352) 9 or/4-8 (59526) 10 Jaundice, Neonatal/ (5322) 11 Hyperbilirubinemia, Neonatal/ (564) 12 10 or 11 (5810) 13 3 and 9 (11092) 14 12 or 13 (12489) 15 predictive value of tests/ (146769) 16 (sensitiv: or diagnos: or predictive value: or accurac:).mp. or di.fs. (4080163) 17 history*.ti. (61762) 18 Physical Examination/ (29598) 19 ((clinical* or visual* or physical*) adj4 examin*).tw. (118301) 20 Skin Pigmentation/ (5773) 21 ((skin or urine or stool*) adj4 (colo?r* or discol?r*)).tw. (5191) 22 ((urine or stool*) adj4 examin*).tw. (5797) 23 Bilirubin/bl [Blood] (13207) 24 (transcutaneous* adj4 bilirubin*).tw. (280) 25 (jaundice adj4 (meter* or metre*)).tw. (43) 26 (jaundice-meter or jaundice-metre).tw. (41) 27 ((point-of-care or "point of care" or bedside or bed-side or lab*) adj4 test*).tw. (47737) 28 (icterometer or bilicheck or bilirubinometer).tw. (134) 29 or/15-28 (4229441) 30 14 and 29 (6066) 31 animals/ not human/ (3890800) 32 30 not 31 (5971)

Database: Medline Ovid

33 limit 32 to english language (4572)
34 Economics/ (26563)
35 exp "Costs and Cost Analysis"/ (184592)
36 Economics, Dental/ (1856)
37 exp Economics, Hospital/ (19923)
38 exp Economics, Medical/ (13490)
39 Economics, Nursing/ (3911)
40 Economics, Pharmaceutical/ (2549)
41 Budgets/ (9871)
42 exp Models, Economic/ (10453)
43 Markov Chains/ (10104)
44 Monte Carlo Method/ (20522)
45 Decision Trees/ (8962)
46 econom$.tw. (159001)
47 cba.tw. (8752)
48 cea.tw. (16326)
49 cua.tw. (795)
50 markov$.tw. (11791)
51 (monte adj carlo).tw. (21204)
52 (decision adj3 (tree$ or analys$)).tw. (8468)
53 (cost or costs or costing$ or costly or costed).tw. (311382)
54 (price$ or pricing$).tw. (23373)
55 budget$.tw. (17528)
56 expenditure$.tw. (35273)
57 (value adj3 (money or monetary)).tw. (1361)
58 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (2863)
59 or/34-58 (662637)
60 "Quality of Life"/ (122099)
61 quality of life.tw. (141223)
62 "Value of Life"/ (5413)
63 Quality-Adjusted Life Years/ (7279)
64 quality adjusted life.tw. (6085)
65 (qaly$ or qald$ or qale$ or qtime$).tw. (5010)
66 disability adjusted life.tw. (1218)
67 daly$.tw. (1198)
68 Health Status Indicators/ (20168)
69 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (15544)
70 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1002)
71 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (2713)
72 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (21)
73 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (333)
74 (euroqol or euro qol or eq5d or eq 5d).tw. (4000)
75 (qol or hql or hqol or hrqol).tw. (25256)
76 (hye or hyes).tw. (53)
77 health$ year$ equivalent$.tw. (38)
78 utilit$.tw. (113012)
79 (hui or hui1 or hui2 or hui3).tw. (860)
80 disutili$.tw. (212)
81 rosser.tw. (71)
82 quality of wellbeing.tw. (5)
83 quality of well-being.tw. (330)
84 qwb.tw. (171)
85 willingness to pay.tw. (2245)

Database: Medline Ovid	
86	standard gamble$.tw. (646)
87	time trade off.tw. (743)
88	time tradeoff.tw. (201)
89	tto.tw. (594)
90	or/60-89 (323843)
91	59 or 90 (942494)
92	33 and 91 (190)

1

J.2 Review question 4

Table 28: Economic search summary

Database	Date searched	Number retrieved
MEDLINE (Ovid)	18/08/2015	56
MEDLINE In-Process (Ovid)	18/08/2015	7
EMBASE (Ovid)	19/08/2015	126
NHS Economic Evaluation Database - NHS EED (Wiley)	18/08/2015	0
Health Technology Assessment Database (HTA)	18/08/2015	0

Table 29: Economic search strategy

Line number/Search term/Number retrieved
Search Strategy: 1 exp Infant, Newborn/ 519024 2 (newborn* or neonat* or baby or babies).tw. 327823 3 1 or 2 669286 4 Hyperbilirubinemia/ 4000 5 exp Jaundice/ 12215 6 Kernicterus/ 1065 7 (bilirubin* or hyperbilirubin* or jaundice* or kernicterus* or icterus*).tw. 55565 8 exp Bilirubin/ 22256 9 or/4-8 68726 10 Jaundice, Neonatal/ 5479 11 Hyperbilirubinemia, Neonatal/ 599 12 10 or 11 5999 13 3 and 9 12009 14 12 or 13 13310 15 Risk Assessment/ 190637 16 (risk* adj3 (assess* or index or model*)).tw. 80583 17 (total adj3 serum adj3 bilirubin*).tw. 2032 18 (serum adj3 bilirubin* adj3 level*).tw. 2551 19 tsb.tw. 866 20 (bilirubin* adj3 (hour* or day* or age*)).tw. 651 21 threshold*.tw. 166002 22 or/15-21 409993 23 14 and 22 1384 24 Economics/ 26829 25 exp "Costs and Cost Analysis"/ 192502 26 Economics, Dental/ 1879 27 exp Economics, Hospital/ 20669 28 exp Economics, Medical/ 13918 29 Economics, Nursing/ 3932 30 Economics, Pharmaceutical/ 2603 31 Budgets/ 10141 32 exp Models, Economic/ 11035 33 Markov Chains/ 10764 34 Monte Carlo Method/ 21646 35 Decision Trees/ 9289 36 econom$.tw. 166984 37 cba.tw. 8930

Line number/Search term/Number retrieved
38 cea.tw. 16967
39 cua.tw. 817
40 markov$.tw. 12622
41 (monte adj carlo).tw. 22346
42 (decision adj3 (tree$ or analys$)).tw. 9003
43 (cost or costs or costing$ or costly or costed).tw. 328087
44 (price$ or pricing$).tw. 24561
45 budget$.tw. 18180
46 expenditure$.tw. 37118
47 (value adj3 (money or monetary)).tw. 1426
48 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. 2933
49 or/24-48 694577
50 "Quality of Life"/ 129941
51 quality of life.tw. 150784
52 "Value of Life"/ 5498
53 Quality-Adjusted Life Years/ 7915
54 quality adjusted life.tw. 6672
55 (qaly$ or qald$ or qale$ or qtime$).tw. 5455
56 disability adjusted life.tw. 1384
57 daly$.tw. 1343
58 Health Status Indicators/ 20917
59 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. 16468
60 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. 1045
61 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. 2951
62 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. 21
63 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. 340
64 (euroqol or euro qol or eq5d or eq 5d).tw. 4411
65 (qol or hql or hqol or hrqol).tw. 27126
66 (hye or hyes).tw. 54
67 health$ year$ equivalent$.tw. 38
68 utilit$.tw. 120630
69 (hui or hui1 or hui2 or hui3).tw. 913
70 disutili$.tw. 236
71 rosser.tw. 71
72 quality of wellbeing.tw. 5
73 quality of well-being.tw. 346
74 qwb.tw. 176
75 willingness to pay.tw. 2477
76 standard gamble$.tw. 687
77 time trade off.tw. 794
78 time tradeoff.tw. 217
79 tto.tw. 636
80 or/50-79 344177
81 49 or 80 991814
82 23 and 81 68
83 Animals/ not Humans/ 3998271

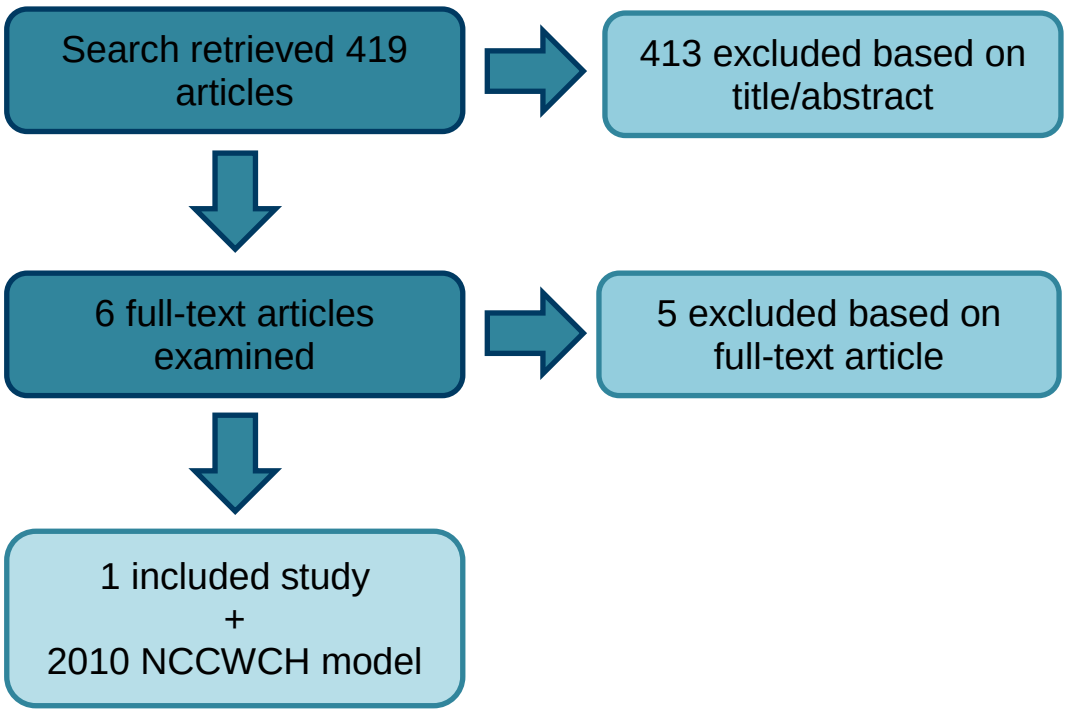
Line number/Search term/Number retrieved			
84	82 not 83	68	
85	limit 84 to english language		57

1

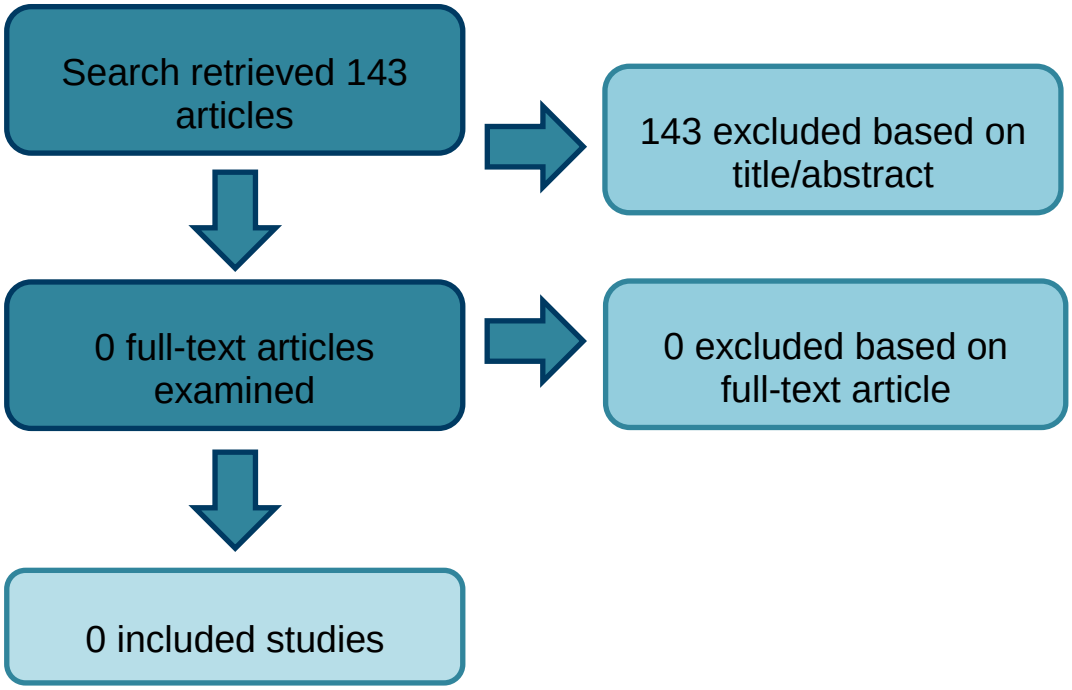
2

Appendix K: Economic review flowchart

K.1 Review question 3



K.2 Review question 4



Appendix L:Economic excluded studies

L.1 Review question 3

Reference	Reason for exclusion
Institute of Health Economics. Transcutaneous Bilirubinometry for the Screening of Hyperbilirubinemia in Neonates ≥35 Weeks' Gestation. Edmonton AB: Institute of Health Economics. 2013.	Systematic review only. Included studies checked against present included/excluded studies.
Conseil d'évaluation des technologies de la santé du Québec. Transcutaneous bilirubinometry in the context of early postnatal discharge. (CETS 99-6 RA). Montréal: CETS, 2000, xvi-50 p.	Systematic review only. Included studies checked against present included/excluded studies.
Hartshorn D, Buckmaster A (2010) 'Halving the heel pricks': evaluation of a neonatal jaundice protocol incorporating the use of a transcutaneous bilirubinometer. Journal of Paediatrics & Child Health 46: 595-9.	Not applicable
HAYES, Inc (2010) Transcutaneous bilirubin measurement (Structured abstract). Health Technology Assessment Database	Could not obtain. Note this is an abstract reference identified by the search.
Xie B, Da SO, Zaric G (2012) Cost-effectiveness analysis of a system-based approach for managing neonatal jaundice and preventing kernicterus in Ontario. Paediatrics and Child Health.17 (1) (pp 11-16), 2012.Date of Publication: January 2012. 11-6.	Not applicable

Appendix M: Economic evidence tables

M.1 Review question 3

Table 30: Full economic evidence table

Bibliographic reference	National Collaborating Centre for Women's and Children's Health. 2010. Neonatal jaundice, NICE clinical guideline 98.	
Evaluation design	**Interventions**	• Total serum bilirubin (TSB) for all babies with a positive visual examination • Transcutaneous bilirubinometer (TcB) for all babies with a positive visual examination followed by a TSB for those babies with a positive TcB
	Comparators	Visual examination followed by TSB in 10% of visually jaundiced babies
	Population	Healthy term infants
	Type of Analysis	Cost analysis
	Structure	Series of scenario analyses rather than a decision analytic model
	Cycle length	Not applicable
	Time horizon	Not applicable
	Perspective	NHS
	Country	United Kingdom
	Currency unit	£
	Cost year	2008
	Discounting	3.5%
	Other comments	Key assumptions: • All strategies were equally effective at detecting hyperbilirubinaemia and preventing kernicterus • Phototherapy rates were the same for all strategies • 60% of babies were visually jaundiced • 25% of the TcBtests were positive and required a TSB test

Bibliographic reference	**National Collaborating Centre for Women's and Children's Health. 2010. Neonatal jaundice, NICE clinical guideline 98.**
Results	

Cost	Total cost per year:
	• Current practice: £1.02 million
	• TSB to all visually jaundiced babies: £10.22 million
	• TCB to all visually jaundiced babies followed by TSB if TcBis positive:
	  ○ BiliChek: £6.26 million plus annual equivalent equipment cost
	  ○ Minolta JM-103: £3.23 million plus annual equivalent equipment cost

Incremental effects	Not applicable (equivalent effectiveness assumed)
Incremental cost effectiveness ratio	Not applicable
Conclusion	• The TcBstrategy using the cheaper meter will cost less than the TSB strategy providing that it can be delivered with fewer than 9200 meters. • 1.52 cases of kernicterus would need to be averted per year for the additional cost of £9.14 million for 9200 meters to be cost effective compared to current practice.

Data sources

Effectiveness data	Not applicable (equivalent effectiveness assumed)
Cost data	• Lifetime cost of kernicterus: based on legal settlement, £5.5 million, range analysed £0 to £10 million • Staff time: Personal Social Services Research Unit's Unit Costs of Health and Social Care 2008 • TSB: £7 from expert advice • TCB equipment: £3400 for the JM-103 and £3600 for the BiliChek from the manufacturers • Calibration tips for the BiliChek: £5.50 from the manufacturer per test
Utility data	QALYs gained per kernicterus case avoided: 25 from approximation, range analysed 0 to 25

Bibliographic reference	**National Collaborating Centre for Women's and Children's Health. 2010. Neonatal jaundice, NICE clinical guideline 98.**
Uncertainty	

One-way sensitivity analysis	• Cost of meters – cost of Minolta varied between £600 and £3600 (base case £3400): As the cost of meters fell, the number of meters had far less impact in determining the incremental cost of the TcBstrategy. For example, at a cost of £2400, the TcBstrategy remains cost saving compared with TSB up to 13000 meters. • Mean number of tests per baby – varied between 1 and 2 (base case 1.33): The incremental cost of the TcBtest strategy relative to the TSB test strategy fell as the average number of tests per baby increased. This reflected that TSB had the higher marginal cost. For example, if just one test per baby were required then the threshold number of meters for cost neutrality was approximately 7000. However, if babies were tested twice on average, the cost neutrality of TcBrose to approximately 14000 meters compared with TSB. • Simultaneously varying the QALY gain and cost per kernicterus case averted – number of kernicterus cases averted varied between 1 and 7 and QALY gain varied between 0 and 25: A high cost of kernicterus implies that a much lower number of cases would need to be averted in order to be cost effective. Increasing the QALY gain associated with an averted case has only a relatively small impact on the threshold cost saving. For example, for a given number of averted cases, a much higher saving and QALY gain is necessary for cost-effectiveness when the TcBstrategy requires 9200 meters compared with when 2000 meters are required.
Probabilistic sensitivity analysis	Not conducted

Applicability	**Directly Applicable**
Limitations	**Potentially Serious Limitations** • Most parameters estimated • Equivalent effectiveness assumed for all strategies
Conflicts	Developed by a National Collaborating Centre and subject to NICE's processes on declaring conflicts of interest

1 *Acronyms*

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; TSB: total serum bilirubin blood test; TcB: transcutaneous bilirubinometer

Bibliographic reference	**Suresh GK, Clark RE. 2004. Cost-effectiveness of strategies that are intended to prevent kernicterus in newborn infants. Pediatrics, Vol. 114, No. 4, 917-924.**
Evaluation design	

Interventions	• Routine predischarge serum bilirubin with selective follow-up and laboratory testing • Routine transcutaneous bilirubin with selective follow-up and laboratory testing (BiliChek)
Comparators	Universal follow-up in the office or at home within 1 to 2 days of early newborn discharge
Population	Healthy term newborns who are eligible for early discharge
Type of Analysis	Cost analysis
Structure	Decision tree
Cycle length	Not applicable
Time horizon	1 year
Perspective	Modified societal
Country	United States
Currency unit	US$
Cost year	2002
Discounting	3%
Other comments	Key assumptions: • Assumed equivalent effectiveness in preventing kernicterus • All strategies prevent 70% of kernicterus cases compared with current practice

Bibliographic reference	**Suresh GK, Clark RE. 2004. Cost-effectiveness of strategies that are intended to prevent kernicterus in newborn infants. Pediatrics, Vol. 114, No. 4, 917-924.**
Results	

Total cost	Cost to prevent one case of kernicterus: • Universal follow-up within 1 or 2 days: US$10,321,463 • Predischarge TSB: US$5,743,905 • Predischarge TcB: US$9,191,352 Total incremental cost for 2,800,000 infants: • Universal follow-up within 1 or 2 days: US$202,300,671 • Predischarge TSB: US$112,580,535 • Predischarge TcB: US$180,150,494
Incremental effects	Not applicable (equivalent effectiveness assumed)
Incremental cost effectiveness ratio	Not applicable
Conclusion	Widespread implementation of these strategies is likely to increase health care costs significantly with uncertain benefits.

Data sources

Base-line data	Literature and expert opinion
Effectiveness data	Literature and expert opinion
Cost data	Costs from providers, manufacturers and estimated
Utility data	Not applicable

Uncertainty

One-way sensitivity analysis	• Incidence of kernicterus varied between 1:10,000 to 1:500,000: ○ Predischarge TSB cost per case prevented ranged from –US$235,610 (cost savings) for 1:10,000 to US$32,319,524 for 1:500,000 ○ Predischarge TcBcost per case prevented ranged from US$109,135 (cost savings) for 1:10,000 to US$49,556,759 for 1:500,000 • Relative risk reduction varied from 1 to 0.1: ○ Predischarge TSB cost per case prevented ranged from US$3,750,733 for a RRR of 1 (100% effective) to US$45,607,334 for a RRR of 0.1 ○ Predischarge TcBcost per case prevented ranged from US$6,163,946 for a RR of 1 to US$69,739,462

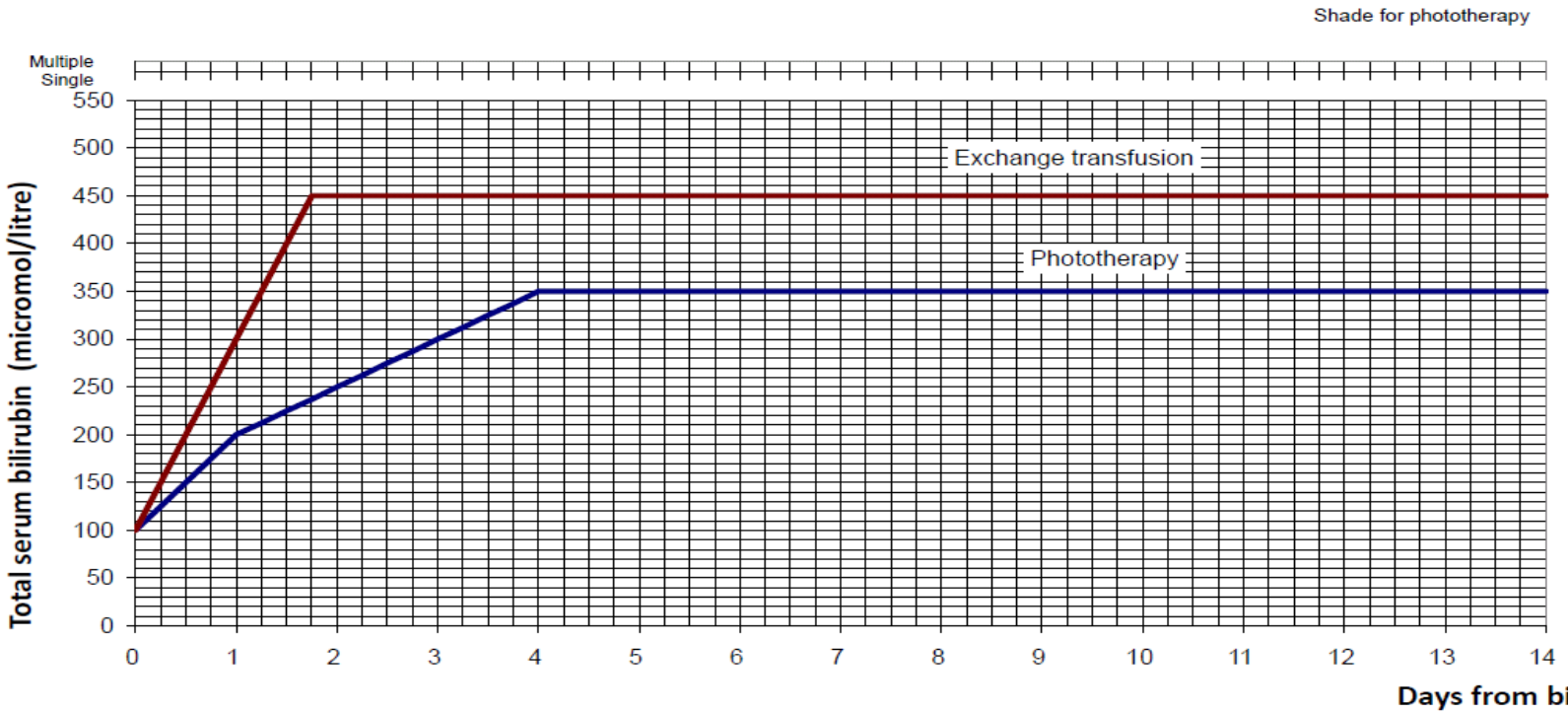
Bibliographic reference	**Suresh GK, Clark RE. 2004. Cost-effectiveness of strategies that are intended to prevent kernicterus in newborn infants. Pediatrics, Vol. 114, No. 4, 917-924.**
	Probabilistic sensitivity analysis: Not conducted
Applicability	**Partially Applicable** • Costs based on the US healthcare system which may not be representative of the costs incurred in the UK • The current guideline is focused on identifying jaundice in infants through visual examination prior to testing rather than the screening strategies used in this analysis.
Limitations	**Potentially Serious Limitations** • Assumed equivalent effectiveness across all strategies • Many parameters were estimated through expert advice
Conflicts	No declaration provided

Acronyms
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; TSB: total serum bilirubin blood test; TcB: transcutaneous bilirubinometers

Appendix N: Original bilirubin threshold chart for phototherapy and exchange transfusion in babies with hyperbilirubinaemia (NICE 2010)

Baby's name _____ Date of birth _____

Hospital number _____ Time of birth _____ Direct Antiglobulin Test _____ >=38 weeks gestation



Baby's blood group _____ Mother's blood group _____

NHS
National Institute for
Health and ClinicalExcellence

Appendix O: Targeted consultation summary

O.1 Rationale

Bilirubin thresholds for the initiation, monitoring and management of hyperbilirubinaemia are crucial to ensure optimal treatments are delivered to neonates with hyperbilirubinaemia. In 2010, when the NICE guideline on Neonatal Jaundice (CG98) was developed, no clinical evidence was identified to assist the development of recommendations in this particular area. The previous guideline development group therefore used their expertise and opinions to reach informal consensus on a table of bilirubin thresholds for management of babies 38 weeks or more gestational age with hyperbilirubinaemia.

During the update of the guideline in 2015, the topic experts recruited to join the Clinical Guidelines Update Committee (CGUC) for this topic expressed concern that the consensus-based bilirubin thresholds are not implemented by clinicians and midwives for the following reasons:

i) some of the bilirubin thresholds relating to retesting and consideration for phototherapy are too conservative

ii) repeat measurements of bilirubin before phototherapy (in 6-12 hours) as recommended by the consensus-based thresholds table are too resource intensive to be implemented, particularly for community midwives and are not used in practice

iii) the public consultation in 2010 did not manage to engage wider stakeholders, clinicians and midwives who would use the thresholds table on a day-to-day basis.

As anticipated, the clinical evidence base in this area has not improved since 2010, and to update the bilirubin thresholds for the management of hyperbilirubinaemia in babies 38 weeks or more gestational age, a consensus based on topic experts' expertise and opinion was required. To ensure the new consensus thresholds were developed with an appropriate group and stakeholder consultation, a targeted consultation was conducted with clinicians working in neonatology and midwives before the public consultation of the updated guideline. (please see Table 13 for the updated threshold table).

O.2 Development and conduct of the survey

The content of the survey was drafted by the technical team members with all committee members including the topic experts involved in the shaping of the questions asked. These were reviewed and signed off by the committee lead at NICE in consultation with the committee chair and members.

The questionnaire was administered by email. Given the short time frame and resource limitations, this was considered to be a fast and straight forward method of administering the survey.

The survey ran from 22nd October to 4th November 2015.

O.3 Recruitment and briefing process

Opportunity sampling was used to recruit participants for the targeted consultation - the 6 original update topic experts were consulted to obtain suggestions for the recruitment of participants. The topic experts proposed to invite neonatal network clinical leads and

midwives across the country – names and contact details were obtained from one of the topic experts.

Relevant organisations from England were then approached with a brief description of the aims and objectives of the targeted consultation. They were were requested to nominate 10 to 15 representatives with good geographical coverage to become participants.

Contact details of the nominated participants were obtained and they were emailed more detailed aims and objectives of the targeted consultation, their role with regards to completing the structured survey and a timeline of key steps.

A total of 55 participants including midwives and clinicians working in neonatology were invited to take part. Following roughly 2 email reminders and a telephone follow-up, 32 participants expressed interest and returned the relevant paperwork (declaration of interests and confidentiality forms) to take part in the survey. Following a few email reminders and telephone follow-up where the telephone number was available, 17 respondents completed the survey by the deadline. Roles of the 17 respondents ranged from neonatal network leads, nurses and largely midwifery specialists from London, Yorkshire, Sheffield and Gloucestershire.

O.47 Summary of main findings

Draft proposal for updated bilirubin thresholds

In babies with a gestational age of 38 weeks or more and more than 24 hours old:

A. Use bilirubin treatment thresholds in the threshold chart when considering the use of phototherapy/exchange transfusion.

B. If bilirubin is within 50µmol/l below the phototherapy threshold;

- repeat bilirubin measurement within 18 hours (instead of the current 6-12 hours) for babies with risk factors (i.e. a previous sibling with neonatal jaundice requiring phototherapy and/or an intention to exclusively breastfeed)

- repeat bilirubin measurement within 24 hours for babies without risk factors

C. If bilirubin measurement is more than 50µmol/l from the phototherapy threshold, no retesting is recommended unless clinically indicated.

D. If baby is within the first 24 hours of birth, follow the original guideline's separate recommendations for this group i.e. NICE proposes no changes to recommendations regarding this group of infants.

Participants were asked to answer yes/no (along with reasons if no) to the following questions:

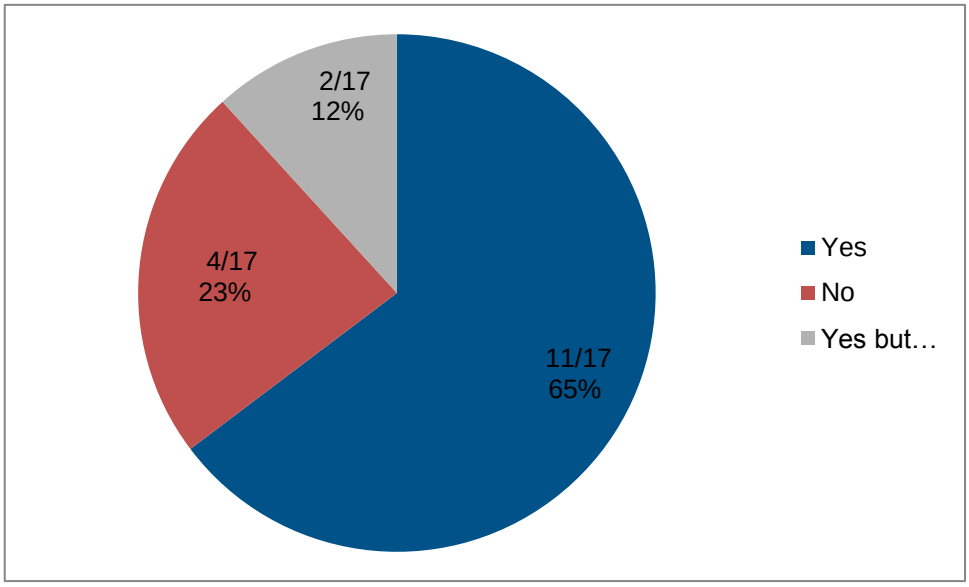
Q1i) This question relates to part A of draft proposal above. Do you agree with NICE's proposal to remove the first 2 columns of the consensus based threshold table for babies with a gestational age of 38 weeks or more with hyperbilirubinaemia?

17/17 (100%) participants responded 'yes' to this question.

Q1ii) If no to i. above, please explain why in the space below

N/A

Q2i) This question relates to part B of the draft proposal above. For babies with risk factors, do you agree with NICE's proposal that the bilirubin measurement should be repeated within 18 hours (instead of the existing 6-12 hours guidance) if bilirubin levels are within 50µmol of the phototherapy threshold and the baby is more than 24 hours old?



Q2ii) If no to i. above, within what time point should the bilirubin measurement be repeated for babies with risk factors with bilirubin levels within 50µmol of the phototherapy threshold and why?

Of the 4 participants that answered 'no', reasons were:

'It would be helpful if the guideline development group could provide evidence of the range of change in bilirubin levels over time for this group to inform a change in practice'

'The flexibility of the 18 hour upper threshold for bilirubin measurement repeat is a very good idea but I believe practitioners will then start questioning when the appropriate minimum threshold for repeat measurement is. If it is not stated within NICE guideline, practitioners will wait until exactly 18 hours and this will create a new problem e.g where the first measurement was taken at 10am. I think it is better to state "Repeat bilirubin measurement to be undertaken between 6 and 18 hours"

'If babies have risk factors then need to repeat test earlier to identify rising level of bilirubin'

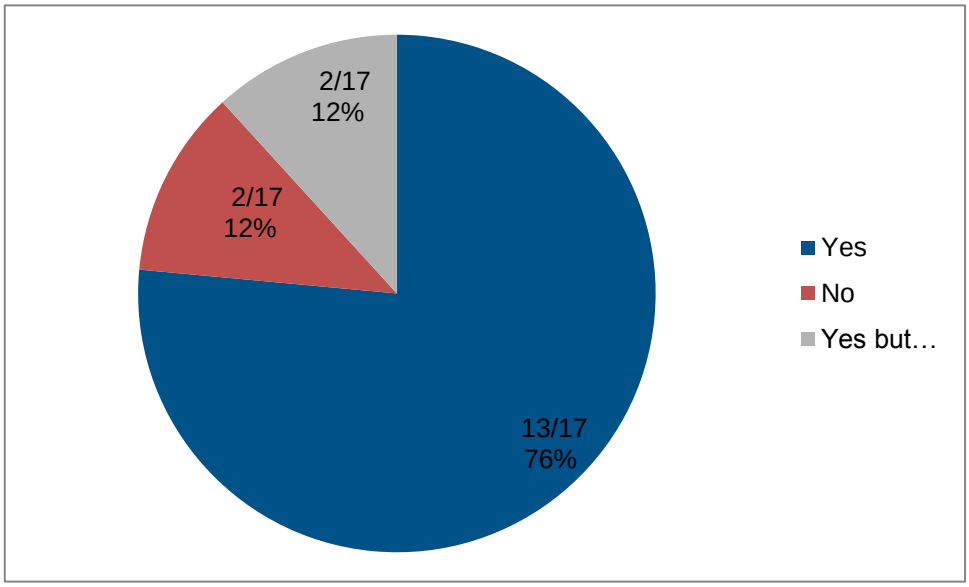
'No repeat at all should be necessary if below the treatment line unless the risk factors are family history of spherocytosis or exchange transfusion for jaundice, poor feeding at initial measurement, or skin pigmentation makes clinical assessment of jaundice uncertain'.

Of the 2 subjects that answered 'yes but…', reasons were:

'Yes but my concern would be if the SBR is doubling (increasing rapidly) this is a long time to wait'.

'Yes, there should be further clarification and a simple statement that a repeat bilirubin can be measured at any point within the 18 hours, dependent on clinical decision making. To avoid the wait until 18 hours and taking into consideration risk factors, or clarity on risk factors and what these are to be more explicit. Previous NNJ, Antibodies, sepsis risk factors, method of feeding , rate of rise etc'.

Q2iii) For babies without risk factors, do you agree with NICE's proposal that the bilirubin measurement should be repeated within 24 hours if bilirubin levels are within 50µmol of the phototherapy threshold?



Q2iv) If no to iii. above, within what time point should the bilirubin be repeated for babies without risk factors with bilirubin levels within 50µmol of the phototherapy threshold and why?

Of the 2 partipants that answered 'no', reasons were:

'it would be helpful if the guideline development group could provide evidence of the range of change in bilirubin levels over time for this group to inform a change in practice'

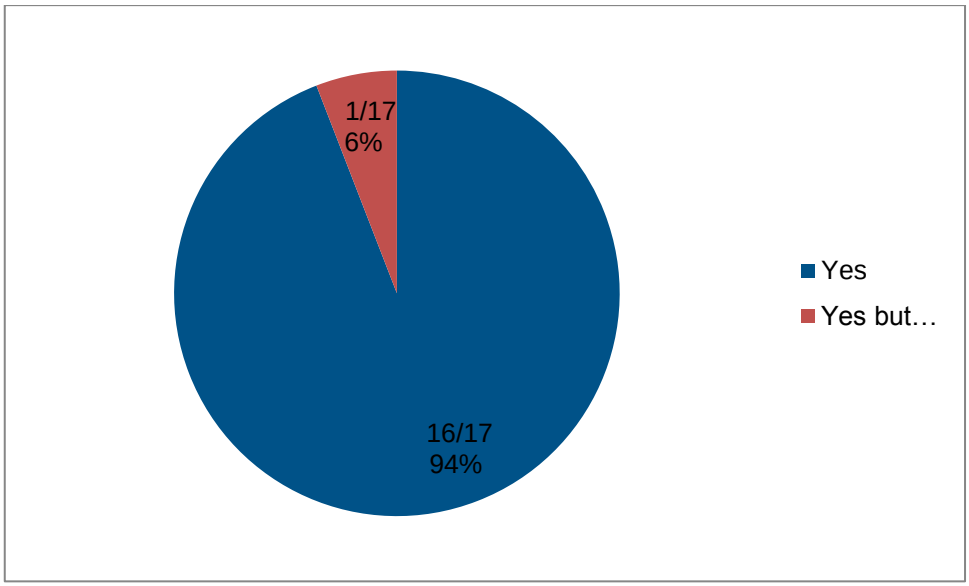
'no repeat test necessary unless midwife concerned regarding complete clinical picture'.

Of the 2 partipants that answered 'yes but…', reasons were:

'similar further clarification to Q2i: ie at any point within dependent on clinical decision making'

'my concern would be if the SBR is doubling (increasing rapidly) this is a long time to wait'.

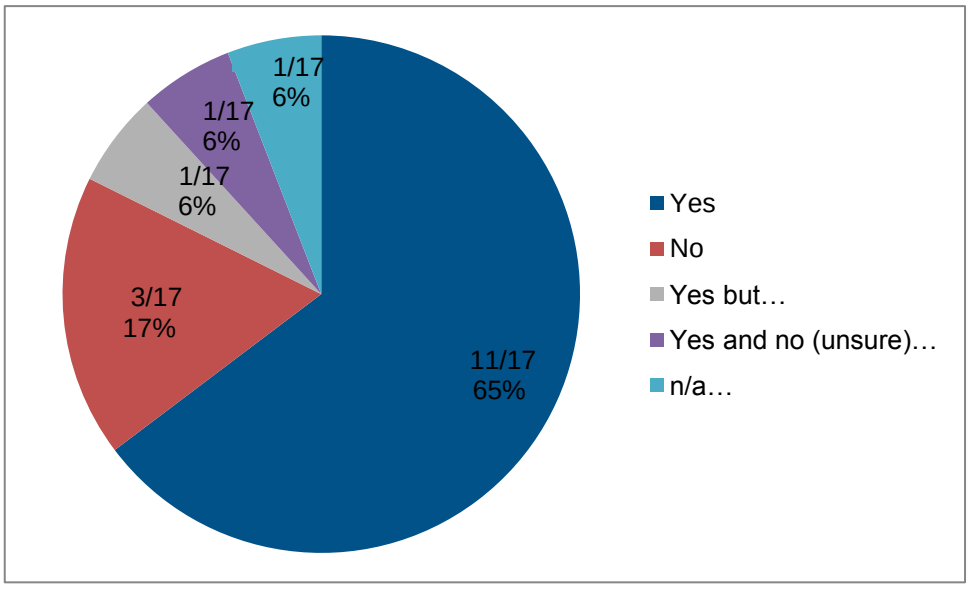
Q3i) This question relates to part C of the updated draft recommendation. If the bilirubin measurement is more than 50µmol/l from the phototherapy threshold and the baby is more than 24 hours old, no retesting is recommended unless clinically indicated. Do you agree with the draft threshold for no retesting that NICE recommends?



Of the 1 subject that answered 'yes but…', reason was:

'yes but rephrased to state that " if no clinical indication and the baby is more than 24 hours old, no retesting is recommended unless there are subsequent clinical indications".

Q3ii) If yes to i. above, would a third line (to be drawn at 50µmol/l from the phototherapy threshold) on the threshold chart be useful?



Q3iii) If no to i. above, please explain why and define what level you think the threshold for no retesting should be with a rationale for the chosen threshold.

Of the 3 participants that answered no, reasons were:

'confusing to staff understanding the charts, will also negate clinical assessment and consideration for further testing if indicated'

'would complicate chart'.

The third participant did not provide a reason.

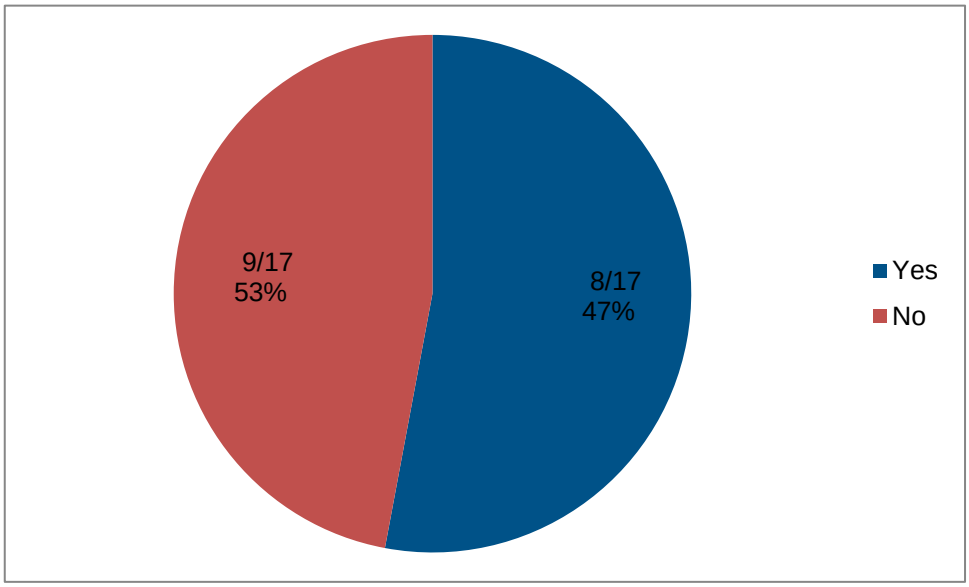
Of the 1 subject that answered,' yes but'…reason was:

'If "Repeat bilirubin measurement in 6-18 hours" added between phototherapy treatment line and 50micromole/l line'.

Of the 1 partipant that answered 'yes and no (uncertain)', reason was:

'We already add a third line guiding colleague about when TC bili acceptable which has been helpful – but more lines make more possibility of misinterpreatation!'

Q4i) Are there any barriers to implementing the draft recommendations?



Q4ii) If yes, please explain what they are and how they could be addressed.

Of the 8 partipants that answered yes, reasons were:

'Midwives who qualified in recent years will have less experience of accessing neonatal jaundice due to selective postnatal visits. This may be associated with a lack of confidence and reliance on 6-12 hourly TCB recordings to inform their clinical judgement'.

'Inconsistency of opinion among neonatologists./lack of acceptance and need to remove all old guidelines/charts/policies'.

'Paediatricians not following NICE guidance and developing their own as a prevention of presumed litigation'.

'Custom and practice and anxiety, a good launch of the guideline and some in house updating'

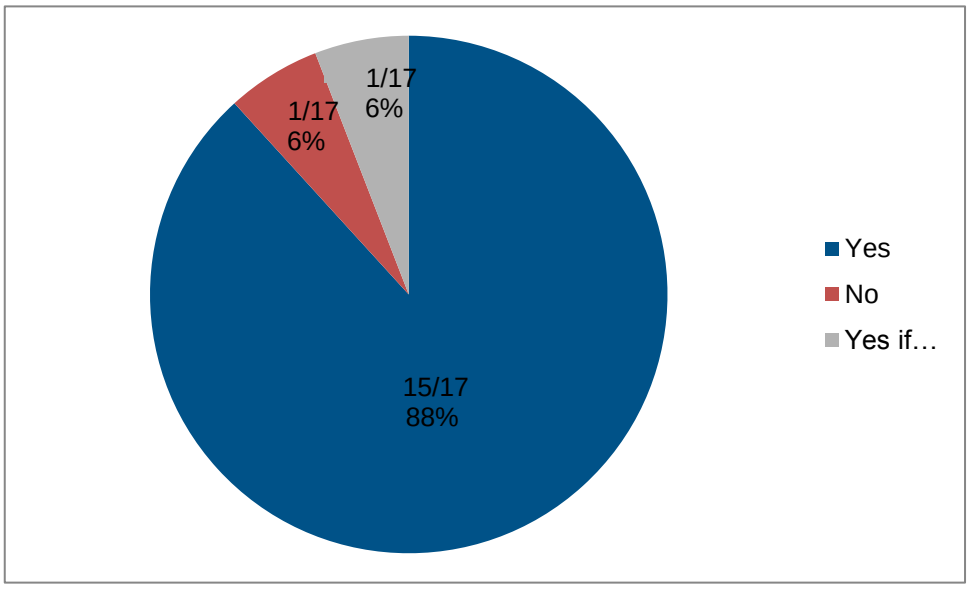
'The proposed draft assumes bilirubin tests is undertaken by community midwives but in many units the babies must be referred to a Paediatrician for testing during working outpatient clinic hours. It does not provide a minimum threshold period for repeating the bilirubin measurement if you simply use the words within 18 hours. In my experience, the repeat testing will be deferred until the stated time on guidelines (in this case 18 hours) which creates further problems if the baby was tested at 12pm for example and would need repeat testing by 6am the following morning. This would create a problem both on the wards and for outpatients. This could be overcome by adding a minimum threshold of 6 hours so that practitioners will clearly understand this is flexible t repeat between 6-18 hours'.

'Dissemination of these recommendations to the key medical personal for each organisation. Presentations/information sessions from NICE to organisations would assist with implementation'.

'Not applicable'.

'With any change there needs to be very good communication stratergy'.

Q5i) Do you agree that the proposed recommendations will result in a more appropriate use of resources?



Q5ii) If no to i. above, please explain why in the space below.

Of the 1 participant who answered no, reason was:

'Community midwives do not perform these blood tests on babies within my organisation. The babies are referred back to hospital for review/testing in order to ensure they receive the appropriate care management following appropriate review'.

Of the 1 partipant that answered 'yes if…', reason was:

'if minimum threshold added'.

Q6) Please express any other comments regarding the updated draft recommendations in the space below.

10 participants responded to this question. Comments were:

'The current reduction in postnatal care should be carefully considered in relation to patient safety and appropriate follow up for babies who are not considered at risk'.

'These changes will be very welcome, currently we are over monitoring health jaundiced babies'

'Are these proposals to be applied equally to invasive and non-invasive methods for biliurmin estimation? Will there be a reporting mechanism to enable staff to report cases where NICE guideance has been followed but the patient has folloewed an unanticipated course, to allow for the possiblity that further refinements may be needed or desirable?'

'I believe that use of transcutaneous bilirubinometers (TBM) would be preferential in the first instance with a baby presenting with jaundice. Unfortunately, Trust managers see only the cost of such equipment and the cost of the blood test is overlooked, despite 75% babies being tested with TBM not requiring SBR blood test. Clinicians have historically used their clinical skills to determine which babies require a blood test but the recent guideline recommends either TBM or blood test for any baby presenting with jaundice. I believe this is resulting in practitioners rejecting the guideline as it results in a significant number of babies having invasive tests unnecessarily and this in turn results in the babies requiring treatment

being missed. This could be overcome by making the use of transcutaneous bilirubinometers (TBM) compulsory for all asymptomatic babies without risk factors'.

'I would value some clarification regarding the use of TcB machines as currently the threshold for these reading levels is much lower than SBR levels. We are currently using TcB machines in the community for babies >38 weeks gestation and <24 hours of age. The threshold values for TcB machines is causing some professional challenge as they do not correlate to the Bilirubin threshold chart'

'The proposed changes are simpler, and in practice more likely to be followed, while remaining safe for babies'.

'Updates seem reasonable'

'I have concerns that the risk factor of exclusive breastfeeding /intention to will cause some clinicians and units to promote mixed feeding in this group. Some parents, on being told that exclusive Bf is placing their baby in the at risk category may choose to introduce formula. The guidelines need to be very clear that the above should not happen and clinicians need to be aware of the risks to infant/maternal health and mother's milk supply…when exclusive BF does not take place and communicate this to parents in a supportive manner'

'Parents and community midwives would be less anxious if retesting on babies with low risk factors increased to 18 hours and less babies having to be rushed to hospital for retesting on the same day of community visit if baby is actively well'.

'Please, stop the chart for phototherapy at 7 days. It is highly unlikely that anyone would start phototherapy at 13 days in a term infant. I think this is also an area for consultation as it causes unnecessary testing, when we need to do prolonged jaundice at 2 weeks and sit tight until then'.

O.5 Data analysis and presentation to the committee

All the information was anonymised. A summary of the survey results as shown in the section above was presented to the committee on the 23rd Novemeber. Statements for which there was no agreement were discussed with the committee and if appropriate, the draft proposal will be tweaked using the participants comments as a guide. Following revisions if any, the technical team prepared the draft updated recommendations for public consultation.

O.6 Conclusions of targeted consultation

Following the close of the targeted consultation on the draft proposal , the committee discussed the survey results and concluded further that:

- No minimum threshold needs to be specified for repeat testing for both babies with and without risk factors: the committee highlighted this would give clinicians and midwives greater flexibility to consider a range of clinical factors, shift patterns and difficulties of undertaking the test during the night. The committee noted the uncertainty around the rate of change of bilirubin levels and felt that within 18 hours is a safe period for the vast majority of babies. Specifying a minimum threshold of 6 hours for example would persuade clinicans to not only keep babies hospitalised for an extra 6 hours and thereby increase the length of stay but also encourage testing earlier than needed.
- No third line needs to be drawn onto the threshold charts to indicate when 'no-retesting' is needed: the committee discussed 3 main reasons for this decision 1) as indicated by the results of the targeted survey, some practices already draw a third line themselves to indicate when transcutaneous measurements are acceptable – further lines could therefore complicate the chart and lead to misinterpretation 2) the

committee wanted to shift the emphasis to not test unless clinically indicated and thereby give clinicians the flexibility to take the full clinical picture into account. A third line would emphasise retesting and encourage more testing than needed especially (for example) by less experienced members of staff 3) this review question addresses clinically well term babies only and so having a third line on term babies charts but no equivalent on preterm charts could lead to confusion.

- The need to take the full clinical picture into account including checking records of maternal antibodies, ensuring that the baby is feeding adequately and has no signs of sepsis. These are addresedin chapter 6 of the full guideline and have now been referred to in this update.

The need to clarify that it is ‘clinically well’ babies this update addresses via this particular review question.