Title:

Validating a sclera-based smartphone application for screening jaundiced newborns in Ghana

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Abbreviations: CI – confidence interval, TcB – transcutaneous bilirubinometer, TSB – Total Serum Bilirubin, SCB – Scleral-Conjunctival Bilirubin, neoSCB - neonatal Scleral-Conjunctival Bilirubin, G6PD - glucose-6-phosphate dehydrogenase, AUC - area under the curve, ROC - receiver operating characteristic

Article Summary (25 words): This study validates a sclera-based smartphone app for screening jaundiced newborns in Ghana, showing its diagnostic accuracy comparable to that of a validated transcutaneous bilirubinometer.

What's Known on This Subject (33 words): Visual assessment for screening jaundiced newborns is subjective and unreliable but commonly practiced in low-resource settings where access to validated transcutaneous bilirubinometers is limited. Non-invasive screening methods are preferable to invasive blood sampling.

What This Study Adds (40 words): Smartphone applications based on the yellowness of the sclera can objectively identify jaundiced newborns and is acceptable to mothers. Using the same population, a sclera-based app has been shown to have a similar diagnostic accuracy as a well-established transcutaneous bilirubinometer.

Contributors' Statement

Dr Enweronu-Laryea conceptualized and designed the study, coordinated, and supervised data collection, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr Leung conceptualized and designed the study, developed the software, carried out the analyses, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr Outlaw carried out the initial analyses, developed the software and reviewed and revised the manuscript.

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Mrs Nixon-Hill developed the software.

Dr Meek conceptualized and designed the study and reviewed and revised the manuscript.

All authors reviewed the draft and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

ABSTRACT

Objectives

Reducing the burden of bilirubin-induced neurological complications in low-resource countries requires reliable and accessible screening tools. This study sought to optimize and validate a sclera-based smartphone app, neoSCB app, for screening neonatal jaundice.

Methods

Using a cross-sectional design, consecutive eligible infants (0-28 days, in hospital, not critically ill) were enrolled in Ghana from March 2019 to April 2020. Jaundice screening was performed with neoSCB app (Samsung S8) to quantify scleral bilirubin (SCB) and JM-105 (Drager) for transcutaneous bilirubin (TcB). Screening values were compared with total serum bilirubin (TSB) measured at the point of care.

Results

Overall, 724 infants participated in the optimization and validation phases of the study. Of the 595 analysed for validation, 336 had no prior treatment for jaundice, 231 had phototherapy within 24 hours, and 28 infants <35weeks gestational age were excluded from analysis. Among the 336, single neoSCB image captures identified infants with TSB >14.62 mg/dL (250 µmol/L) with reasonably high sensitivity, specificity, and AUC of the ROC curve at 0.94 (95% CI 0.91-0.97), 0.73 (95% CI 0.68-0.78) and 0.90, respectively. This was comparable to the sensitivity and specificity of JM-105, at 0.96 (95% CI 0.90-0.99) and 0.81 (95% CI 0.76-0.86), respectively. The TcB/TSB had a larger correlation coefficient ($r=0.93$, $p<0.01$) than SCB/TSB ($r=0.78$, $p<0.01$). Performance of both devices was lower in infants with prior phototherapy.

Conclusion

The diagnostic performance of neoSCB app was comparable to JM105. The neoSCB app is a potential affordable contact-free screening tool for neonatal jaundice.

Keywords: neonatal jaundice, sclera, smartphone app, screening, transcutaneous bilirubinometer

INTRODUCTION

Neonatal hyperbilirubinemia is a major global health problem. Bilirubin-induced neurological complications still occur in industrialized countries and severe neonatal jaundice remains an important cause of mortality and long-term impairment in countries with low sociodemographic index values (1–3). Infants in sub-Saharan Africa are at greater risk because of the high prevalence of glucose-6-phosphate dehydrogenase (G6PD) deficiency, a genetic disorder associated with increased risk of haemolysis and hyperbilirubinemia (4,5).

Poor health outcomes associated with neonatal hyperbilirubinemia are largely preventable if affected infants are identified early and given appropriate and timely treatment to avert bilirubin neurotoxicity (6). Most cases of hyperbilirubinemia occur in the first week after birth and policies on routine screening during birth hospitalization and post-discharge monitoring in industrialized countries has significantly reduced bilirubin encephalopathy (6,7). Most countries with high burden of disease do not have the capacity to provide these services and many infants present with severe neonatal jaundice due to several factors including, high prevalence of home births and early postnatal discharge after hospital birth (1,3,8). In Ghana, neonatal jaundice is the major and most preventable cause of cerebral palsy in children (9).

Reliable screening methods that are accessible to all people everywhere are needed for early diagnosis of neonatal hyperbilirubinemia. Early diagnosis is one of the important steps to reducing the burden of deaths and impairment associated with neonatal hyperbilirubinemia (10). It is well known that yellowing of the sclera (the white part of the eye) is an early sign of neonatal jaundice and that visual inspection of the eye, the traditional method for diagnosis, is unreliable for quantifying the severity of jaundice (11-13). Leung *et al* investigated the possibility of using sclera colour as a quantitative tool for jaundice detection in 110 newborns and found a linear correlation of 0.75 ($p<0.01$) between the sclera colour captured by a digital camera and total serum bilirubin (14). They investigated different colour spaces to optimally quantify the yellowness of the jaundiced newborns' sclera, and developed a sclera-based smartphone app, known as the neoSCB (neonatal Scleral-Conjunctival Bilirubin) app (15). The aim of this study was to validate the methodology and optimize the neoSCB app for screening jaundiced infants in clinical settings. This paper reports the process of optimizing and validating the smartphone app as a screening tool for neonatal jaundice in Ghana.

METHODS

Design

Using a cross-sectional design, we consecutively enrolled hospitalized newborns who met the inclusion criteria after written informed consent from parent(s). The study protocol was reviewed and approved by three ethics committees (University College London - United Kingdom, Noguchi Memorial Institute of Medical Research - University of Ghana, and Ghana Health Service).

Setting

The study was conducted in Ghana, a lower middle-income country in West Africa with a population of approximately 30 million. Ghana has 16 administrative regions and the capital city, Accra, is in the Greater Accra region. By 2018, about 82.4% of the total population and 67.3% of rural communities had access to electricity (16). In 2020, 46.1% of the population owned a smartphone and there was increasing use of mobile health technologies (17,18). The study was conducted in a regional hospital in the Greater Accra Region and a district hospital in the Eastern Region from March 2019 to April 2020. The regional hospital, a referral centre for maternal-newborn services, attends to about 10,000 deliveries yearly. The district hospital provides primary and secondary level obstetric and paediatric services for nearby urban and rural communities and attends to about 4,000 deliveries yearly. To assess the acceptability of neoSCB app by primary care providers and parents in rural settings, three rural communities in the Eastern region were included in the study.

Participants

Infants aged 0 – 28 days were eligible. Infants in the neonatal ward were enrolled if they had a clinical indication for a blood test as recommended by the attending clinician. Infants in the postnatal ward were enrolled if the parents gave additional consent for a blood test (a heel prick). Infants who were critically ill, required immediate care, very low birth weight or had congenital abnormalities of the eye and skin were excluded. Frontline healthcare workers and mothers of infants provided feedback on the procedure of screening for jaundice with the app.

Sampling

Sample size calculation was based on the prevalence of neonatal hyperbilirubinemia in low- and middle-income countries (7). We also considered enrolling newborns with total serum bilirubin (TSB) across a wide range below and above 14.62 mg/dL (250 µmol/L), the threshold for referral for a blood test when using transcutaneous devices in standard care (19). Consecutive sampling approach was applied. Newborns who met the inclusion criteria were eligible irrespective of the presence or severity of clinical jaundice. There were 13 eligible community healthcare workers in the rural districts, 11 were available to participate.

Procedures

After obtaining written informed consent from parent(s), we documented the environmental lighting source at the point of care, parental/clinician visual assessment of neonatal jaundice based on scleral colour, the infant's characteristics (age, gestational age, sex, birth weight and prior treatment for neonatal jaundice) and other variables of interest. Thereafter, digital images of the opened eye of the infant were obtained with the neoSCB app followed by transcutaneous bilirubin (TcB) measurement with Drager Jaundice Meter (JM-105) and finally the heel prick or venepuncture procedure for blood samples. All procedures were conducted indoors in hospital wards with ceiling light and/or varying levels of natural light during the day.

After opening the neoSCB app on the smartphone, the mother or the health worker facilitated the process of opening the baby's eye for an image capture of the sclera. The app takes two images, with flash on and without flash, automatically. During the early phase of the study, images were observed to be obtained from varying distances from the infant's eye resulting in insufficient flash illumination of the eye. The early phase dataset was used to optimize the neoSCB app by establishing an appropriate subtracted signal-to-noise ratio (SSNR) for quality control (15), displaying real-time SSNR on the app to make it easier to operate, and providing the option for the operator to zoom in on the captured image and manually choose an area of interest on the sclera using a small square for real time calculated SCB value (Figure 1).

Figure 1. The neoSCB app showing digital images

The neoSCB app used the rear LED flash (equipped with an optical diffuser to lower the light intensity) and camera of Samsung 8 galaxy smartphones to capture images of the infant's eye. For each capture, two images were taken, one with LED on and one with the LED off, so that ambient subtraction can be performed to minimize the effect of ambient lighting (15). To ensure different smartphones provide similar numerical results despite inter-phone variation in the cameras, a one-time calibration was performed on the study smartphones by taking a photo of a standardised color checker which allowed the characteristics of the smartphone camera to be measured and calibrated (20).

Transcutaneous measurement of bilirubin with JM-105 was performed according to the manufacturer's protocol (21). Blood sample collection by venepuncture was performed by doctors and heel prick samples were obtained by nurses according to local guidelines. A sample of blood (about 0.1ml) was centrifuged (SciSpin Haematocrit Micro Centrifuge) and the supernatant used to obtain the total serum bilirubin (TSB) (Pfaff Bilimeter) at the point of care.

Mothers of infants referred to hospital because of jaundice were asked about how their infant's jaundice was first diagnosed before referral to hospital. Mothers' assessment of the presence of jaundice during the procedure for digital eye image data collection and her feedback on the procedure were documented. Rural community health workers were trained to use the neoSCB app and were given the smartphones to use (but not for clinical decision making) for a period of two weeks and provide feedback on their experience and acceptability by mothers.

Data management and analysis

The neoSCB app provides a Scleral-Conjunctival Bilirubin (SCB) value which is a measure of bilirubin concentration based on the sclera colour (15). The screening threshold for neoSCB app and JM105 was TSB above 14.62 mg/dL (250 µmol/L). Digital images were analysed at study-defined intervals and the user interface of the neoSCB app was regularly improved as previously described. Analysis was offline, the scleral region was traced manually for each eye image. The SCB was estimated by taking the mean of up to three captures and the SCB predictive algorithm was optimised with a large dataset. The correlation between SCB error - the difference between SCB and TSB values, and participants characteristics was analysed. For validation, the SCB value was compared to the ground truth TSB value, and the screening performance of the neoSCB app was compared against the well-established TcB measurements with JM-105. We selected datasets that met both JM-105 manufacturer's recommendations (21) and optimal performance of neoSCB app (15). Only datasets from infants who were older than 35 weeks of gestational age, and with subtracted signal to noise ratio (SSNR) greater than 3.4 (15) were included in the validation analysis.

RESULTS

Of the 724 infants enrolled, 568 and 156 were from the regional and district hospital, respectively, and 416 had not received prior treatment (phototherapy) for jaundice. Participants' characteristics are summarized in Table 1. Infants without documented gestational age or birth weight were enrolled based on clinical assessment at the hospital. Of the 804 data capture occasions when mothers assessed the eye of their infant for jaundice, the mother's assessment was similar to health workers' assessment in most (92.4%) cases.

Table 1. Characteristics of newborns enrolled for validation of the neoSCB app.

Overall, 847 datasets were collected during the study as summarized in Figure 2. Most of the datasets excluded from the validation analysis were obtained during the early stages of the study before the optimization of the neoSCB app with real-time SSNR display.

Figure 2. Description of segments of the whole dataset for neoSCB app optimization and validation

Among the 416 infants who had not received phototherapy before enrolment, 111 (26.7%) had serum bilirubin level above 14.62 mg/dL, and JM-105 did not return a numerical value in 50.4% (56/111) of these cases. Out of the 416, the 347 infants with sufficient SSNR had no significant correlation between SCB error, that is SCB-TSB difference, and postnatal age ($p=0.07$) or birth weight ($p=0.11$). There was no significant difference in the mean SCB error between male ($n=192$) and female ($n=155$) groups (unpaired two-sample t test, $p=0.31$). However, there was a significant correlation coefficient of 0.2 (95% CI 0.1 - 0.3, $p<0.01$)

between the SCB error and gestational age, indicating that neoSCB tended to underestimate bilirubin value in infants with shorter gestational ages. The SCB error for preterm infants (≤37 weeks gestation, n=46) was significantly biased compared to the term infant with a mean relative offset value of -2.57 mg/dL (95% CI [-1.46 mg/dL, -3.74 mg/dL]).

Out of the 347 infants with sufficient SSNR, 336 were born at gestational age of 35 weeks and higher, the recommended gestational age for using JM105. The analysis of single image captures in this group showed reasonably high sensitivity, specificity, and the area under the curve (AUC) of the receiver operating characteristic (ROC) at 0.94, 0.73, and 0.90, respectively with a cut-off SCB threshold of 11.58 mg/dL (Figure 4). When the average of 3 captures were used (n=179), the sensitivity and specificity increased further to 1.00 and 0.76, respectively, with a cut-off SCB threshold of 11.52 mg/dL. These were comparable to JM-105 with sensitivity at 0.97 and specificity 0.79 in the same population (Table 2). For the JM-105, some TcB measurements, all with corresponding TSB above 19.88 mg/dL, returned warning messages instead of numerical values. These were included in the TcB data for the purpose of estimating sensitivity and specificity but excluded in the scatter plot for the single capture results in Figure 4. The sensitivity and specificity of the optimized neoSCB app improved compared to the prototype used in an earlier study (14) and were comparable to other smartphone skin colour-based jaundice apps (22-24) as shown in Table 2

Figure 3. Receiver Operating Characteristic curves of neoSCB app for screening infants at TSB>14.62 mg/dL threshold.

Table 2. Summary of comparative accuracy of neoSCB and other skin-based methodologies

Figure 4. Association between total serum bilirubin, scleral and transcutaneous bilirubin

The TcB/TSB had a larger correlation coefficient (r=0.93) than that of the SCB/TSB (r=0.78), with both being statistically significant ($p<0.01$). In general, the SCB/TSB data points had a higher error variance, especially when TSB >14.62 mg/dL (Figure 4). In Figure 5, the Bland-Altman plot (25) for SCB against TSB depicts the mean bias of 0.11 mg/dL (95% CI: -0.09 – 0.31 mg/dL) and the lower and upper limits of agreement of -7.13 mg/dL (95% CI: -7.48 - -6.78 mg/dL) and 7.36 mg/dL (95% CI: 7.01–7.70 mg/dL), respectively. It shows that SCB tends to be increasingly smaller than TSB as TSB gets larger.

Figure 5. The Bland-Altman plot for Scleral-Conjunctival Bilirubin (SCB) against the Total Serum Bilirubin (TSB).

Among the 231 datasets of infants with prior phototherapy, sufficient SSNR and gestational age higher than 35 weeks, the neoSCB app's sensitivity was 0.72 (95% CI 0.59-0.80), specificity 0.73 (95% CI 0.66-0.79), and AUC of the ROC curve 0.80 at cut-off SCB threshold of 13.27 mg/dL (Figure 3).

Overall, the procedure was acceptable to mothers in hospital and in rural settings. Two mothers refused to give consent; the reason being that the infants' fathers were unavailable to give permission for enrolment. Mothers easily devised ways to enable the infant to open the eyes, most often by breastfeeding. It took an average of 30 minutes (range: 10 – 60 minutes) to teach rural community health workers how to use the app.

DISCUSSIONS

Yellow discoloration of the sclera was the most common diagnostic criteria for hospital referral in the study population. The neoSCB app showed similar diagnostic accuracies to JM-105 but had a higher error variance when TSB >14.62 mg/dL. The neoSCB app underestimated bilirubin at higher values of TSB while the JM-105 gave no numerical values under similar conditions. These findings are not clinically relevant for devices intended for use as threshold detectors for onward referral for further clinical assessment and blood test.

JM-105 is not recommended for use in infants who have received prior phototherapy (21); these infants were excluded in the validation analysis.

The diagnostic accuracy of the neoSCB app is reasonably high, and comparable to JM-105 and other skin colour-based jaundice apps, namely, BiliCam (22) and Picterus (23) though the diagnostic results were based on higher screening thresholds (Table 2). The diagnostic accuracy of neoSCB app increased when three captures were considered because processing multiple images tends to minimize random noise, but there was no significant difference between single and triple capture data in this study. The optimized neoSCB app in the Ghana study performed better than the prototype in the United Kingdom study (15) which used a different smartphone (LG Nexus 5X), a front facing camera and screen lighting for illumination.

There was high level of concordance between mothers' and health workers' subjective visual assessment of neonatal jaundice, although mothers' assessment may have been influenced by their participation in the study. The ability of mothers to assess scleral yellowness indicates that, given the right tool and regulatory framework, mothers may play a vital role in settings with limited healthcare workforce. The high acceptability of neoSCB app procedure was probably because it was similar to local practice of visual sclera assessment for neonatal jaundice. Training of community health workers was straightforward because of their previous experience with other phone-based healthcare programs. Documenting acceptability of new healthcare interventions is useful for implementation at scale (26).

For clinical use, the neoSCB app would have additional advantages, such as storing and transferring information between hospitals, prompts for healthcare workers and/or parents to recognise 'red flags' for healthcare seeking, and information for parents if approved for use by the general population. However, the app cannot be recommended for use in infants less than 37 weeks gestation because it underestimates the scleral yellowness in preterm infants. This could be due to the relatively thin and immature sclera of the late preterm which may allow underlying choroidal pigment to counteract yellowing due to bilirubin (27). A correction factor for gestational age may improve the app estimation accuracy in future versions.

For populations that depend on subjective visual assessment of the sclera for diagnosing neonatal hyperbilirubinemia, the neoSCB app may be an objective tool for screening. Although universal screening for neonatal jaundice is standard care in high-resource settings, most high burden countries, including Ghana, do not have similar policy, possibly due to limited capacity of the health system including limited access to reliable screening tools. With increasing penetration of smartphone technology and integrated healthcare pathways the capacity to screen newborns in low-resource populations may improve.

The neoSCB app was easy to use but the SCB value is dependent on the quality of the digital photo and selection of the scleral segment of interest. These limitations can be reduced by training healthcare workers to: (a) increase the SSNR by moving the smartphone closer to the infant's face during photo capture, (b) recognize and discard a blurred photo image, and (c) avoid the eyelid and iris when selecting the scleral segment of interest. Many health systems provide training to healthcare workers whenever a new clinical tool is provided for service delivery (28).

Smartphones with similar specifications to Samsung 8 galaxy are increasing available but cost could be a drawback for the uptake of neoSCB app in low-resource settings. The Covid-19 pandemic has impacted methods for delivering health services globally. With increasing penetration of smartphone technologies into rural communities (17), the prospects for applying new health technologies in most settings are high.

CONCLUSION

The neoSCB app was validated as a potential contact-free screening tool for neonatal jaundice. It requires no consumables or extra utility costs to the health system and was acceptable to mothers. To reduce unnecessary hospital referrals for blood tests and delays in clinical decision-making, the neoSCB app may be considered a feasible tool for neonatal jaundice screening of term infants in settings similar to Ghana.

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REFERENCE

1. Olusanya BO, Kaplan M, Hansen TWR. Neonatal hyperbilirubinemia: a global perspective. *Lancet Child Adolesc Health.* 2018;2(8):610-620.
2. Wang H, Abajobir AA, Abate KH, et al. Global, regional, and national under-5 mortality, adult mortality, age-specific mortality, and life expectancy, 1970-2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet.* 2017;390(10100):1084-1150.
3. Slusher TM, Zamora TG, Appiah D, et al. Burden of severe neonatal jaundice: a systematic review and meta-analysis. *BMJ Paediatr Open.* 2017;1(1):e000105.
4. Olusanya BO, Ogunlesi TA, Slusher TM. Why is kernicterus still a major cause of death and disability in low-income and middle-income countries? *Arch Dis Child.* 2014;99(12):1117-21.
5. Cappellini MD, Fiorelli G. Glucose-6-phosphate dehydrogenase deficiency. *Lancet.* 2008;371(9606):64-74.
6. Smitherman H, Stark AR, Bhutani VK. Early recognition of neonatal hyperbilirubinemia and its emergent management. *Semin Fetal Neonatal Med.* 2006;11(3):214-24.
7. Bhutani VK, Zipursky A, Blencowe H, et al. Neonatal hyperbilirubinemia and Rhesus disease of the newborn: incidence and impairment estimates for 2010 at regional and global levels. *Pediatr Res*. 2013;74(Suppl 1):86-100.
8. Olusanya BO, Emokpae AA, Zamora TG, *et al.* Addressing the burden of neonatal hyperbilirubinaemia in countries with significant glucose-6-phosphate dehydrogenase deficiency. Acta Paediatr 2014;103:1102–9.doi:10.1111/apa.12735

9. Adei-Atiemo E, Rodrigues O, Badoe E. Classification and risk factors for cerebral palsy in the Korle Bu Teaching Hospital, Accra: A case-control study. *Pediatrics.* 2015;135(Suppl 1):S7

10. Bhutani, V., Johnson, L. A proposal to prevent severe neonatal hyperbilirubinemia and kernicterus. *J Perinatol*. 2009;29:S61–S67.

11. Riskin A, Tamir A, Kugelman A, et al. Is visual assessment of jaundice reliable as a screening tool to detect significant neonatal hyperbilirubinemia? *J Pediatr*. 2008;152(6):782-7

12. Moyer VA, Ahn C, Sneed S. Accuracy of clinical judgment in neonatal jaundice. *Arch Pediatr Adolesc Med.* 2000;154(4):391-4.

13. Keren R, Tremont K, Luan X, et al. Visual assessment of jaundice in term and late preterm infants. *Arch Dis Child Fetal Neonatal Ed*. 2009;94(5):F317-22.

14. Leung TS, Kapur K, Guilliam A, et al. Screening neonatal jaundice based on the sclera color of the eye using digital photography. *Biomed Opt Express*. 2015;6(11):4529-4538.

15. Outlaw F, Nixon M, Odeyemi O, et al. Smartphone screening for neonatal jaundice via ambient-subtracted sclera chromaticity. *PLoS ONE*. 2020;15(3): e0216970.

16. World Bank. Access to electricity (% of population) – Ghana. 2019

17. National Communications Authority and Ghana Statistical Service. Household Survey on ICT in Ghana. 2020. https://statsghana.gov.gh/infobankdetails.php?infobank=MTI0MDM5Njc1Ny42OTU1/infodesk/n1r7pr567p

18. Hampshire K, Mwase-Vuma T, Alemu K, et al. Informal mhealth at scale in Africa: Opportunities and challenges. World Development. Volume 140, 2021,105257, https://doi.org/10.1016/j.worlddev.2020.105257.

19. NICE clinical guideline 98: Chapter 5: Recognition. In: Welsh A, ed. Neonatal Jaundice. Royal College of Obstetricians and Gynaecologists. 2010:84-86

20. Nixon M, Outlaw F, Leung TS. Accurate device-independent colorimetric measurements using smartphones. *PLoS One*. 2020;15(3):e0230561.

21. Drager. JM105 Sample Usage Protocol. https://www.draeger.com/Library/Content/jm-105-sample-usage-ifu-9071391-ca.pdf

22. Taylor JA, Stout JW, de Greef L, et al. Use of a Smartphone App to Assess Neonatal Jaundice. *Pediatrics.* 2017;140(3):e20170312.

23. Aune A, Vartdal G, Bergseng H, et al. Bilirubin estimates from smartphone images of newborn infants' skin correlated highly to serum bilirubin levels. *Acta Paediatr.* 2020;109(12):2532-2538.

24. Ren Y, Huang D, Yang B, et al. The effects on accuracy of image-based estimating neonatal jaundice with a smartphone APP in the different conditions. *Pediatr Med.* 2020;3:AB036.

25. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet.* 1986;1(8476):307-10.

26. Diepeveen S, Ling T, Suhrcke M, Roland M, Marteau TM. Public acceptability of government intervention to change health-related behaviours: a systematic review and narrative synthesis. BMC Public Health. 2013;13(1):756.

27. Read S, Alonso-Caneiro D, Vincent S, *et al.* Anterior eye tissue morphology: Scleral and conjunctival thickness in children and young adults. *Sci Rep.* 2016;6:33796.

28. Asgary R, Cole H, Adongo P, et al. Acceptability and implementation challenges of smartphone-based training of community health nurses for visual inspection with acetic acid in Ghana: mHealth and cervical cancer screening. *BMJ Open*. 2019;9(7):e030528.

LIST OF FIGURES AND TABLES

Table 1. Characteristics of infants for validation of neoSCB app for screening jaundice.

Criteria	Characteristics	Cases (n)	Proportion (%)
Sex	Male	404	55.8
	Female	320	44.2
Gestational age	32 - 34	34	4.7
	35 - 37	165	22.8
	38 - 42	510	70.4
	No data	15	2.1
Birth weight	1500 - 2500g	93	12.8
	≥ 2500g	626	86.5
	No data	5	0.7
Postnatal age at enrolment	< 24 hours	272	37.6
	24 – 72 hours	222	30.7
	4 – 7 days	165	22.8
	8 – 14 days	27	3.7
	>14days	9	1.2
	Incomplete data	29	4
Phototherapy	No exposure before enrolment	416	57.5
Referred with clinical diagnosis of neonatal jaundice (n = 467)	Diagnosed by yellow discoloration of the eye	364	77.9
	Diagnosed by yellow discoloration of skin	66	14.1
	Not sure	47	8
Total serum bilirubin value in mg/dL (n=804)	Less than 8.77	209	26.0
	8.77 – 14.59	366	45.5
	14.60 – 20.41	159	19.8
	More than 20.41	70	8.7
Comparing parental and frontline health worker subjective assessment of neonatal jaundice (n = 804, each time, we asked if eye was yellow)	Concordance: eye not yellow	213	26.5
	Concordance: eye yellow	530	65.9
	No concordance	51	6.3
	Incomplete data	10	1.2

Table 2. Diagnostic accuracies of sclera-based and skin colour or transcutaneous-based methodologies for screening jaundiced newborns without prior phototherapy.

Studies	Sample Size (n)	**Sensitivity (95% CI)** Specificity (95% CI)	Screening Threshold in mg/dL [in µmol/L]	AUC of the ROC
The Ghana validation study: Single image captures neoSCB	336	**0.94 (0.91 -0.97)** 0.73 (0.68 – 0.78)	14.62 [250]	0.90
The Ghana validation study: JM-105 TcB	336	**0.96 (0.90 - 0.99)** 0.81 (0.76 - 0.86)	14.62 [250]	N.A.
The Ghana validation study: Triple image captures neoSCB	179	**1.00 (0.95 – 1.00)** 0.76 (0.70 – 0.82)	14.62 [250]	0.92
The Ghana validation study: JM-105 TcB	179	**0.97 (0.95 - 1.00)** 0.79 (0.73 - 0.85)	14.62 [250]	N.A.
Outlaw et al. (15): Multiple image captures neoSCB prototype	37	**1.00 (0.88 – 1.00)** 0.61 (0.43 – 0.76)	14.62 [250]	0.86
Taylor et al. (22): Multiple image captures BiliCam	530	**1.00** 0.76	17.02 [291]	0.99
Aune et al. (23): Multiple image captures Picterus	185	**1.00** 0.69	14.62 [250]	0.93
Ren et al. (24): BiliScan	247	**0.75** 0.87	14.97 [256]	0.89

CI, confidence interval; AUC: area under the curve; ROC: receiver operating characteristic

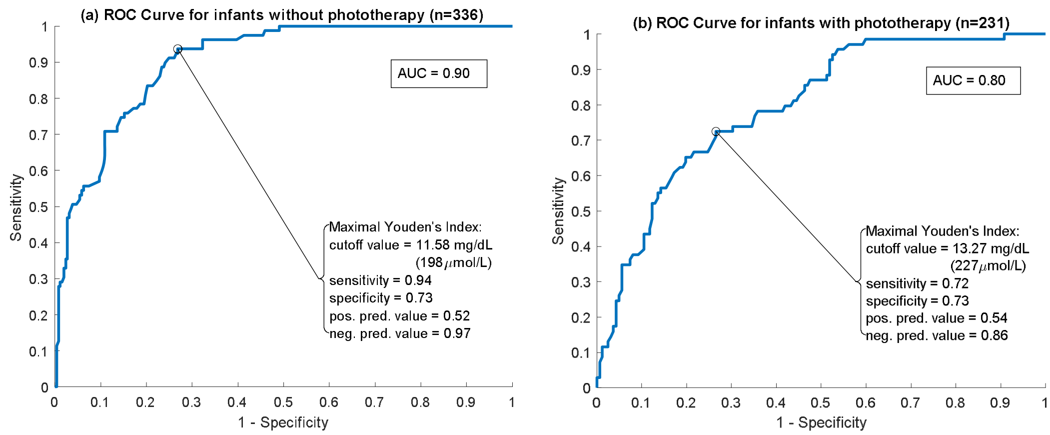

Figure 3. Receiver Operating Characteristic (ROC) curves of neoSCB app for screening infants at TSB>14.62 mg/dL (250 µmol/L) threshold. Infants (a) without prior phototherapy and (b) with phototherapy exposure within 24 hours. AUC: area under the curve

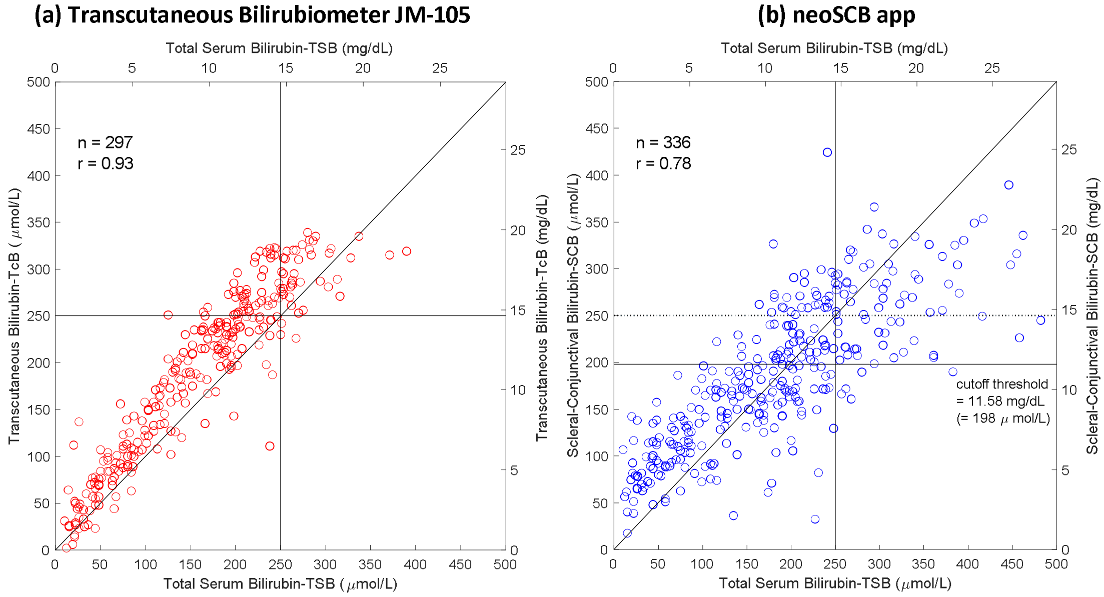

Figure 4. Association between total serum bilirubin, scleral-conjunctival and transcutaneous bilirubin.

Scatter plots for (a) transcutaneous bilirubin (TcB) versus total serum bilirubin (TSB) and (b) scleral-conjunctival bilirubin (SCB) (based on single image capture) versus TSB. Both correlation coefficients (r) are statistically significant with $p<0.01$. While the sample size (n) for the SCB study was 336, only 297 were displayed here for the TcB study since in 39 measurements the TcB returned warning messages instead of numerical values, indicating the values were very high.

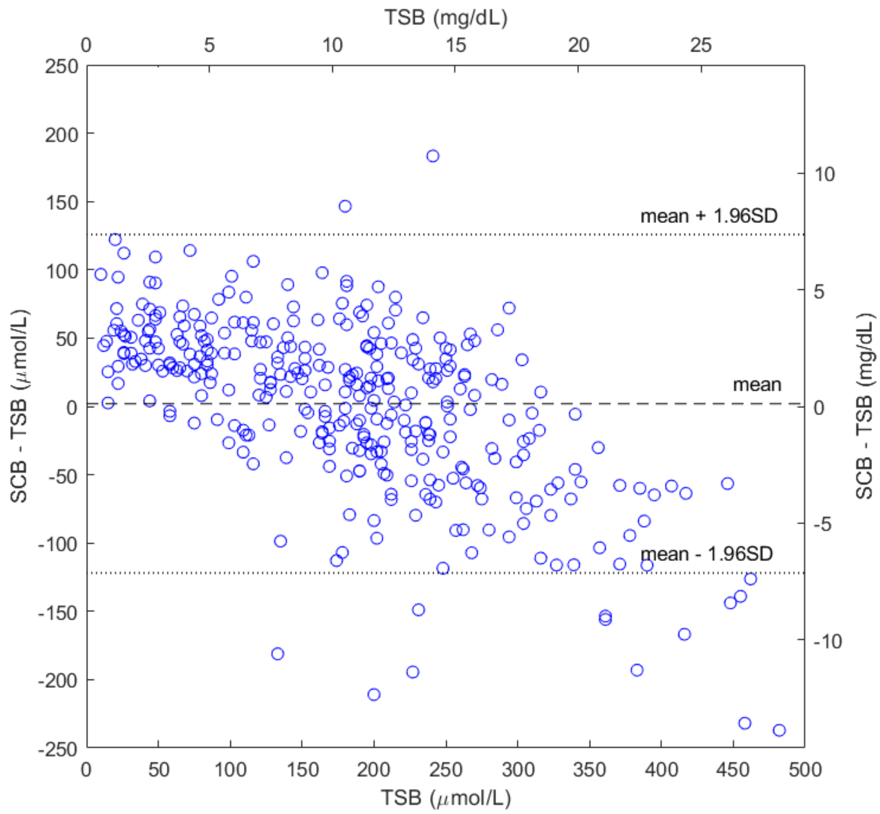

Figure 5. The Bland-Altman plot for Scleral-Conjunctival Bilirubin (SCB) against the Total Serum Bilirubin (TSB): SCB estimated based on single image capture (n=336)