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# Validation of a new smartphone app to assess neonatal jaundice in a Mexican population.

Master's thesis in Public Health, specialization in Global Health  
Supervisor: Elisabeth Darj, Anders Aune, Monica Lucía Reyes  
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## **Abstract**

*Background:* Neonatal jaundice is a common and temporary finding in newborns but severe cases can progress to bilirubin encephalopathy and kernicterus which may have serious or fatal consequences. Early detection can be accurately done through a total serum bilirubin measurement with a blood test or a transcutaneous bilirubinometer, which are not available in most health centres because their high cost. Neonatal jaundice related mortality is still high in the poorest regions of the world and is frequently associated with the delay in the diagnosis of hyperbilirubinemia. Therefore, there is a need to a reliable, accurate and affordable method to timely detect high risk newborns. Several mHealth technologies have been developed to address this need, using smartphones and apps that can be used as point-of-care diagnostic devices. A new smartphone app to detect neonatal jaundice has been developed at Norwegian University of Science and Technology which has already been tested in a Caucasian population with good results. The present study aims to test its performance and accuracy in newborns with different skin colour, since melanin can potentially influence the results.

*Design and methods:* A descriptive cross-sectional study was carried out at Hospital Materno-Infantil de Irapuato in Mexico during July and August 2018. Using a calibration card placed on the chest, images of healthy newborns with and without jaundice were obtained using a smartphone camera within 60 minutes of a blood test to measure total serum bilirubin was done. Image analysis was done with the algorithm developed at Norwegian University of Science and Technology. Date and time of birth, birthweight and gestational age were obtained from medical records. Kramer scale of the newborns and Fitzpatrick scale of parents were determined. Correlation between TSB levels and estimated levels of bilirubin obtained with the app and Kramer scale were calculated. The app and Kramer scale sensitivity, specificity and predictive values for screening jaundice were also calculated.

*Results:* The correlation between TSB levels and the app estimated levels was 0.87 and between TSB and Kramer scale 0.80. For TSB cut off value of 255  $\mu\text{mol/l}$  and app value of 186 and 200  $\mu\text{mol/l}$ , sensitivity was 100% and 90% and specificity 79.5% and 80.1% respectively. Kramer scale sensitivity to detect jaundice was 72% with 87% specificity.

*Conclusion:* The new smartphone app provided accurate estimates of TSB levels in a Mexican population of newborns. It can have a role as an affordable, available and accurate supporting diagnosis tool to screen NNJ and closely follow-up newborns with risk to develop dangerous levels of bilirubin in different health care settings.

## **Dedication**

This thesis is dedicated to you, my lovely dad and mom. You have been my inspiration during all my life and although you are not present anymore in this dimension of the world, I am sure that you are very happy and proud to see how well I learned from you one of the most important lessons in life: never give up, no matter age, time and distance.

I also dedicate this work to my dear children, Dany, Gaby e Isaac. You are my motors to go further every moment of my life and I really hope that I can be a good example to follow. Feeling your love and unconditional support during all this time have been invaluable to me. I never felt alone even in the long distance. I love you so much!

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Thanks a lot to Anders Aune for giving me the opportunity to participate in this project which besides of being very interesting and promising, can contribute to improve health of newborns in the most vulnerable places helping to reduce inequalities among world population.

This work could not have been done without the support of my dear lifelong friend and thesis external supervisor Monica Reyes Berlanga, who facilitated all the conditions in Mexico to carry out this study and gave me accommodation and good company during my stay.

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## **Abbreviations**

AAP	American Academy of Pediatrics
ABE	Acute bilirubin encephalopathy
BIND	Bilirubin Induced Neurologic Dysfunction
DALYs	Disability-Adjusted Life Years
eHealth	Electronic Health
GA	Gestational Age
GBD	Global Burden of Disease
GDP	Gross Domestic Product
GOe	Global Observatory for eHealth
ICT	Information and Communication Technologies
IVIG	Intravenous Immunoglobulin
LED	Light Emitting Diode
LMICs	Low- and Middle-Income Countries
mHealth	Mobile Health
NCDs	Non- Communicable Diseases
NICU	Neonatal Intensive Care Unit
NMR	Neonatal Mortality Rate
NNJ	Neonatal Jaundice
PPP	Purchasing Power Parity
RBC	Red Blood Cells
TcB	Transcutaneous bilirubinometry/bilirubinometer
TSB	Total serum bilirubin
UDPGT	Uridine-Diphosphate-Glucuronosyl-Transferase
WHO	World Health Organization

## **Introduction**

Neonatal jaundice (NNJ) is a common transitory finding during the first week of life and it usually resolves without consequences. However, under certain conditions, NNJ can progress and cause damage to the brain better known as acute bilirubin encephalopathy (ABE). If such damage persists, brain damage can be permanent and manifests as cerebral palsy, deafness, language disorders and in the worst cases be fatal.

In high and middle-income countries, the incidence of ABE has decreased due to the early identification of maternal risk factors as well as the timely diagnosis of newborns with the risk to develop complications. In low-income countries, nevertheless, severe NNJ and ABE burden remain elevated and related mortality is higher in the poorest regions such as Sub-Saharan Africa and South Asia.

To avoid the presentation of ABE, it is necessary to timely detect infants with severe NNJ, therefore it is essential to have a reliable and accurate method for such detection. The gold standard is the total serum bilirubin (TSB) level measurement, however laboratory facilities are required to process the blood sample. Since visual assessment does not meet the requirements of reliability and accuracy, transcutaneous bilirubinometers (TcB) were developed in order to fulfil this need. However, TcB are not available in most health units due to high costs.

Therefore, the persistence of the need for an accurate, reliable and affordable detection method had led to the development of new technologies including mobile devices, such as smartphones, which can be used as point-of-care diagnostic tools.

A new smartphone app was developed at Norwegian University of Science and Technology (NTNU) in Trondheim which has been tested in Norway in a Caucasian population showing a high correlation with TSB levels. The purpose of this study was to test this novel diagnostic tool in a Mexican population, in order to evaluate its performance in different colour skin types.

Chapter 1 is divided in three parts. A thorough review of NNJ is done in the first part, including bilirubin metabolism, NNJ description, causes, epidemiology, clinical presentation, diagnosis and treatment, with special emphasis on epidemiology in poor regions and diagnostic methods.

In the second part, eHealth and mHealth are addressed to provide an outline of the rapid emergence of both technologies in the recent years and how they have contributed to globally improving health, with a final review of other smartphones-based diagnostic tools for NNJ detection.

An overview of the current situation in Mexico and in the city of Irapuato is presented in the third part. Demographic data, economic, development and health system status are mentioned to put the reader in context about the setting where this study was carried out.

In chapters 2 and 3 the rationale of the study, aims, hypothesis and research question are described.

Chapter 4 addresses the methodology and is divided in different sections which explain in detail all the procedures carried out during this study and the statistical analysis performed.

Main findings and results obtained by statistical analysis are presented in chapter 5. Tables and figures are displayed for a better visualization and understanding of the results.

In chapter 6, the results are interpreted, discussed and compared with previous reports in order to define the performance, accuracy, advantages and disadvantages of the new app. The limitations and strengths of this study are also addressed.

Chapter 7 and 8 include implications and conclusion, pointing out the relevant consequences of the study findings in order to fulfil the need of an affordable and reliable method to accurately screen NNJ and future implications for the app use.

In chapter 9 bibliography supporting this study is found.

## **1 Background**

### **1.1 Neonatal jaundice**

Neonatal jaundice (NNJ) or hyperbilirubinemia, is a one of the most common syndromes occurring in newborns during the first week of life. It was first described 1000 years ago in a Chinese textbook. During the 18<sup>th</sup> and 19<sup>th</sup> centuries, discussions about the causes and treatment of neonatal jaundice can be found in theses, essays and textbooks, which also describe a lethal course in some infants. Jaques Hervieux described jaundice of the brain in 31 autopsies of jaundiced infants in 1847. Later, in 1875, Johannes Orth published his findings of an intense yellow staining of the basal ganglia, the third ventricle wall, the hippocampus and central parts of cerebellum in a jaundiced term newborn autopsy, but it was until 1903, when Christian Schmorl coined the term kernicterus (jaundice of the basal ganglia) after presenting the results of 120 autopsies of jaundiced infants to the German Society of Pathology (1,2).

NNJ is considered a transitional self-limiting physiologic phenomenon, not a singular disease in itself, usually without severe consequences (3,4). It affects approximately 60 to 70% of term and up to 80% of preterm newborns and it is associated with multiple causes and risk factors, both maternal (blood type incompatibility, drug use, gestational diabetes) and neonatal (prematurity, obstetric trauma, poor diet, breastfeeding, siblings with the same disorder, sepsis) (5,6). The yellow coloration observed in the neonates, indicates that bilirubin is outside the circulation and present in the skin, sclera and other tissues, particularly those with lipid fat content. Bilirubin accumulation is due to an imbalance between its production and elimination with multiple factors and conditions affecting these processes in the setting of an immature conjugation/excretion hepatic system during this life stage (3,4).

In the majority of newborns with uncomplicated vaginal delivery, NNJ commonly manifests 48 hours after birth and resolves in 3 to 5 days (7). However, in some infants, bilirubin can progressively increase and reach high levels that cross blood brain barrier and cause irreversible damage to brain basal ganglia, with neurologic development impairment. ABE is the acute manifestations of bilirubin toxicity seen during the first week of life and the term kernicterus is reserved for the chronic and permanent sequelae that can manifest as cerebral palsy, deafness, language disorders and in the worst cases be fatal (1,8,9).

In addition, in 2011 Johnson and Buthani described the syndrome of bilirubin-induced neurologic dysfunction (BIND) stating that it is characterized by impairment of audiologic, speech, and language processing, disturbances in visual-motor and cognitive functions associated with failure

of fine neuromotor control that are apparent among vulnerable infants who have experienced an exposure to bilirubin of lesser degree than generally described previously (10).

### **1.1.1 Bilirubin metabolism**

Normal bilirubin metabolism includes the following sequential events: production, transport, hepatic uptake, conjugation, excretion and enterohepatic circulation (11).

Bilirubin production arises from the heme degradation process as a result of the normal red blood cell (RBC) turnover (6). In a healthy individual RBC lifespan is around 115 days (70-140 days) (12). Once its membrane becomes fragile, most of the RBC are destroyed in the spleen and release hemoglobin, which is phagocytized almost immediately by macrophages in different parts of the body, especially in the liver, spleen and bone marrow.

Later on, macrophages release iron into the bloodstream which goes back to the bone marrow for the production of new RBC or to iron storages in different tissues. The porphyrin portion of the hemoglobin molecule containing heme is converted by macrophages in bilirubin, which is release into the bloodstream and removed from the body through the secretion of bile by the liver (13).

In a more detailed description of this process, it should be mentioned that heme is the iron compound of protoporphyrin and constitutes the pigment portion and protein free part of hemoglobin. It binds and carries oxygen in the red blood cells releasing it later to tissues (14,15). After RBC destruction, heme degradation takes place through a 2-step process. In a first step, the IX-methane bridge is broken after a series of oxidations and reductions by the action of the enzyme heme oxygenase, releasing carbon monoxide and ferrous iron and giving rise to biliverdin. In a second step, biliverdin is reduced to bilirubin by the action of biliverdin reductase. (4,6).

Once bilirubin is produced, it is transported in the bloodstream mostly bound to albumin, which constitutes the non-conjugated or indirect water-insoluble bilirubin, and then is actively transported to the liver. Inside the hepatocytes it binds to ligandin and then conjugates with glucuronic acid in the endoplasmic reticulum by the action of the enzyme uridine diphosphoglucuronyltransferase (UDPGT) giving rise to bilirubin glucuronide, known as conjugated or direct bilirubin. This step is critical because it transforms bilirubin in a water-soluble molecule which allows it to incorporate into the bile, pass through to the biliary tree and reach the gut lumen for its excretion (6). Ligandin concentrations and UDPGT activity are low at birth but reach adult values by age 4 to 8 weeks, however they contribute partially to the physiologic jaundice in newborns. Once bilirubin reaches the proximal small intestine some

deconjugation occurs through the action of B-glucuronidases, and unconjugated bilirubin can be reabsorbed into the circulation giving rise to the “enterohepatic circulation”. This process can also increase the total plasma bilirubin and it may be extensive in neonates secondary to limited intake during the first days of life (1).

The daily amount of bilirubin production in humans is approximately 250 to 400 mg (16). If indirect bilirubin is not bound to albumin, it can move from the circulation into tissues, including skin, causing clinical jaundice and into the brain which can be permanently damaged (4).

### **1.1.2 Physiopathology**

Jaundice is the most frequent condition requiring medical attention and readmission to hospitals in newborns and in almost all the cases, it is considered a normal physiologic phenomenon during this transitional period (1). It is the result of the simultaneous occurrence of an elevated bilirubin production secondary to increased breakdown of RBC (shortened lifespan and higher amount in newborns), and a decreased hepatic excretory capacity secondary to low concentrations of the binding protein ligandin and to the low activity of UDPGT which is responsible for bilirubin binding to glucuronic acid. Both phenomena are increased in premature infants so transitional hyperbilirubinemia can be exacerbated in them (1,4,6).

When additional conditions accompany the mechanisms described above, pathologic neonatal jaundice can occur. Some examples which imply increased RBC destruction are immune or nonimmune hemolytic anemia, polycythemia and the presence of hematomas or other extravasation of blood. (1).

Risk factors associated with higher incidence of neonatal jaundice are:

- a. Race: East Asians and American Indians attributed to genetic polymorphisms linked to ethnicity. Although lower NNJ incidence is found among Africans and African Americans, severe neonatal jaundice is more common in African ethnicity due to lack of detection and treatment.
- b. Genetics: Infants with mutation/polymorphisms in the genes coding for enzymes and proteins required in bilirubin metabolism, with homozygous or heterozygous glucose-6-phosphatase dehydrogenase deficiency and other hemolytic anemias.
- c. Familial: Infants with siblings who had significant neonatal jaundice (linked to genetics).
- d. Geography: It has been suggested that in infants living at high altitude there is a hematologic response to decreased oxygen availability which results in increased bilirubin production and delayed clearance.



- e. Nutrition: Infants who are breastfed (breast feeding jaundice and breast milk jaundice) or with inadequate nutritional intake, due to increased enterohepatic circulation.
- f. Low birthweight and prematurity
- g. Congenital infections, obstetric traumas
- h. Maternal factors: Gestational diabetes, use of some drugs, intake of herbal remedies during breastfeeding, blood type incompatibility (1,5,17).

Hyperbilirubinemia in the first 1-3 days reflects an increased production of the unconjugated form. It is usually associated to hemolysis secondary to minor blood-type incompatibilities such as Rh or Kell or intrauterine infections. Less frequently it can be due to a large hematoma. From day 3 to 10, jaundice reflects more increased production, and may be associated to ABO incompatibilities or maternal diabetes. Additionally, it is the time when problems in the conjugation process can appear as Gilbert's disease or G-6-PD deficiency, which can lead to rapid rise in bilirubin levels and have severe consequences. In the so-called breast-feeding jaundice, decreased food intake and thus prolonged intestinal transit with decreased stooling, increases enterohepatic circulation of bilirubin with a higher risk of develop jaundice. When hyperbilirubinemia starts after the first week of life it should be considered secondary to decreased bilirubin excretory ability, rather than to increased production, and it is crucial to recognize this transition. If jaundice persists beyond 10 -14 days, conjugated hyperbilirubinemia must be suspected (6).

As unconjugated bilirubin is considered a neurotoxin, monitoring its levels during the first week of life is effective to prevent most bilirubin-induced morbidity and mortality. It has been observed in cell cultures that early bilirubin exposure of developing neurons leads to neuritic atrophy, cell death, decreased neuronal arborization, arrested neuritic growth and neuritic hypoplasia. In newborns it can cause permanent neural damage (kernicterus) if total bilirubin levels reaches levels between 428 to 513  $\mu\text{mol/l}$  depending on age, but even with lower levels, exposure to moderate to severe hyperbilirubinemia with varying duration in infants with bilirubin-albumin binding alterations, some degree of damage can occur (10).

### **1.1.3 Epidemiology**

Along with respiratory distress, NNJ is one of the two most frequent diseases during neonatal period and one of the first ten causes of morbidity and readmission to intermediate care in

neonatal units (5), however its contribution to the global burden of disease (GBD) remains still unknown.

Since most cases of NNJ resolve in 3 to 5 days without consequences, reports concerning morbidity and mortality focus mainly in severe cases and complications. A global estimation reported that extreme NNJ (up to 428  $\mu\text{mol/l}$  or 25 mg/dl) affected 481,000 late-preterm and term newborns during 2010. Failure to detect and manage it, resulted in 114,100 avoidable neonatal deaths and 63,000 infants with severe disabilities. The global burden was extremely higher for the poorest countries: 11-fold higher for infants born in countries with neonatal mortality rate (NMR)  $> 15$  compared to those with  $\text{NMR} < 5$ . Seventy-five percent of mortality occurred in Sub-Saharan Africa and South Asia, attributing this outcome to lack of preventive services and care (18).

Another systematic review reported higher rates of exchange transfusion, BIND and kernicterus among low and middle-income countries (LMICs) when compared to high-income countries (HIC) and found that the risk of severe hyperbilirubinemia in those countries is associated with maternal and neonatal factors that are now preventable in HIC (19).

According to the 2016 GBD study, NNJ caused 1309 deaths per 100,000 in the early neonatal period (0-6 days) and 187 deaths per 100,000 in the late-neonatal period (7-27 days), ranking 7<sup>th</sup> and 9<sup>th</sup> leading causes of mortality globally in these age groups. Since 1990, NNJ has ranked 16<sup>th</sup> from up to 100 possible causes of under-5 mortality with a higher burden in Sub-Saharan Africa and South Asia (3).

#### **1.1.4 Clinical findings**

Clinical jaundice can be observed in newborns at serum bilirubin levels of 80 to 90  $\mu\text{mol/l}$  (4.6 to 5.2 mg/dl) and is more difficult to detect in dark skin tones and in preterm infants (20). Once NNJ becomes apparent it usually has a cephalocaudal presentation. It is visible first in the face and forehead and then progress to the trunk and extremities and disappears in the opposite direction. This feature is well described even in medical texts from 19<sup>th</sup>-century and is the base for the scale developed by Kramer in 1969. Changes in bilirubin-albumin binding related to pH and different skin temperatures and blood flow have been proposed as an explanation for this phenomenon. It is useful to pressure on the skin to blanch it, so the underlying colour can be seen. Regardless other factors, visible jaundice in lower extremities suggest the need to evaluate bilirubin level (1).

In most cases, yellow colour is the only finding on physical examination, but when severe jaundice is present, symptoms and signs of neurological damage may appear which indicates

progression to ABE. ABE features include drowsiness, progressive changes in mental status, altered cry pattern, seizures, poor feeding, hypotonia and hypertonia specially of extensor muscles, retrocollis, opisthotones, paralysis of upward gaze and “kernicterus facies” (1,10).

Death may occur in 7-10% of cases with severe ABE and is caused by respiratory failure, progressive coma or refractory seizures. This progression depends on the degree of bilirubin increase, hyperbilirubinemia duration, presence of co-morbidities and host susceptibility.

Although the term kernicterus refers strictly to the yellow staining of the brain basal ganglia found by autopsy, is commonly used to describe the irreversible classic sequelae present in patients who survive severe ABE and is characterized by dystonia, athetoid cerebral palsy, paralysis of upward gaze and sensorineural hearing loss. In most cases intellectual capacity is preserved but patients may need occupational and speech therapy, as well as appropriate hearing support (10).

Secondary to increased clinical and technological evidences of damage to narrower neural pathway, BIND related disorders have been described as less severe forms of auditory neuropathy with mild hearing loss associated to minimal fine and/or gross motor disability (10).

### **1.1.5 Diagnosis**

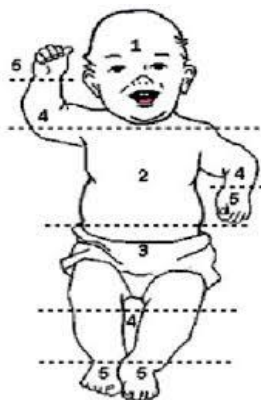
Although most cases of NNJ resolve without complications, severe hyperbilirubinemia can lead to severe ABE, BIND and kernicterus which is completely preventable if such hyperbilirubinemia is early identified and appropriately treated. These pathologies were significantly reduced by the 1970s secondary to laboratory testing for TSB development, phototherapy and exchange transfusions as well as prenatal follow up with blood type testing. However, in the last 15 years a resurgence of this condition has been reported and associated with earlier discharge of newborns (21). In response to kernicterus reappearance clinical guidelines were updated by the American Academy of Pediatrics (AAP) in 2004 and by the American Academy of Pediatrics and European Society for Pediatric Research in 2008 (9,22). In addition, many other professional and clinical organizations have made position statements for kernicterus prevention. Some of the most relevant recommendations regarding to diagnosis are: to establish nursery protocols for the identification and evaluation of jaundice; assessment of the risk of hyperbilirubinemia of all newborns before discharge by universal bilirubin measurements, either transcutaneous or TSB levels and plot the results in a nomogram; interpret all bilirubin levels according to the newborns age in hours; recognize that visual assessment of jaundice is not reliable, particularly in darkly pigmented infants and recognize that infants of <38 weeks of gestation, particularly those who are breastfed, are at higher risk of developing hyperbilirubinemia and require closer surveillance and monitoring (21,22).

The diagnosis of NNJ can be done through different methods. The most important and used ones are describe in the next paragraphs.

**Visual Assessment**

Skin colour depends on the concentration of chromophores including melanin, collagen, hemoglobin and bilirubin. Melanin is the most relevant of these chromophores, and according to its amount in the epidermis, skin can have different colours, from very white to dark brown. Along with the colour, the result of exposure to ultraviolet radiation (tanning) is the base for the Fitzpatrick scale, which classifies skin in six different phototypes, being type I the lighter and VI the darkest. When evaluating the presence of jaundice, skin colour may influence the degree of “yellowness” perceived (23,24).

In 1969, Lloyd I. Kramer developed a 5-point scale based on the previously recognized cephalocaudal progression. Figure 1 shows Kramer’s scale and its correlation with bilirubin levels (25,26).



Kramer scale value	TSB $\mu\text{mol/l}$	TSB mg/ml
1	100	5.9
2	150	8.8
3	200	11.8
4	250	14.7
5	> 250	> 14.7

Figure 1 Kramer scale and corresponding TSB levels

Visual assessment with Kramer scale or an adapted version is still widely used worldwide as a first-step screening tool to evaluate the necessity of additional testing in infants with NNJ. It has particular relevance in low-resource settings where other type of equipment is lacking (27).

Multiple studies have been performed in order to evaluate the reliability of visual assessment for NNJ since it is still widely practiced. Results are controversial, even when it is made by experienced health personnel.

Moyer *et al.* studied the correlation among 244 observations made by 2 groups of health workers and bilirubin level in infants with gestational age >36. They found a Pearson coefficient of 0.43

and 0.54 for the 2 groups of observers when comparing visual assessment and TSB, however agreement between observers regarding the presence of jaundice was low. Another finding was that the presence of any visible jaundice beyond the lower chest (between nipples and umbilicus) had the best combination of sensitivity and specificity for a 205  $\mu\text{mol/l}$  (12 mg/dl) bilirubin value, suggesting that infants without jaundice below the nipple line were not likely to have a 205  $\mu\text{mol/l}$  or higher bilirubin value. However 81% of infants with bilirubin values less than 205  $\mu\text{mol/l}$  also presented jaundice below nipple line, concluding that this observation was only useful to exclude high bilirubin level and that visual assessment is neither accurate nor reliable for neonatal jaundice diagnosis (28).

In another study, five neonatologists and 17 nurses made 3532 visual clinical assessments using an own scale called BiliEye developed with the principle of cephalo-caudal progression, in 1129 term and late preterm infants (>35 weeks) before discharge from the hospital on days two to five of life. Level of TSB were measured at the same time. Although a good correlation (0.752) between BiliEye and TSB level was found, it was concluded that visual assessment is not a reliable screening tool to detect significant neonatal hyperbilirubinemia before discharge. Neonates with TSB levels in high-risk zones may be misdiagnosed as low-risk with inadequate follow-up (29).

However, in 2012, Acosta-Torres *et al.* compared Kramer's scale values with TSB in 50 newborns with NNJ of three different ethnic groups in Venezuela (Caucasian, indigenous and Afro-American). They found a correlation index of 0.93 ( $p < 0.005$ ) and no differences among ethnicities, concluding that Kramer's scale is a safe, non-invasive and costless method which is helpful to prevent kernicterus and should be implemented in health facilities lacking bilirubinometers (30).

Some other considerations have been made regarding skin colour. Knudsen and Brodersen concluded that measuring yellow colour in the skin is not a reliable indicator of high bilirubin levels since it depends upon other factors as plasma pH, albumin concentration and basic skin colour besides bilirubin concentration (31).

### **Total Serum Bilirubin**

The most accurate and reliable way to detect NNJ is through TSB quantification obtained by venous, arterial or capillary puncture. TSB levels are relatively easy to measure in the hospital laboratories but obtaining the blood sample may cause discomfort and potential complications for the newborns (32).

Although there are multiple studies of bilirubin levels in healthy newborn populations, it has been difficult to define what is a “normal” bilirubin level. This is attributed to the rapid changes in TSB levels in the first 48 to 72 hours as well as racial, genetic and epidemiological factors, the proportion of breast-fed infants and the laboratory methods used to measure it (33).

For the same reason, there is no a precise definition of pathologic jaundice. According to WHO guidelines, phototherapy must be initiated in newborns without risk factors (which supposes that bilirubin level has the potential to be pathologic) if any jaundice is visible during the first 24 hours, TSB is  $\geq 255 \mu\text{mol/l}$  (15 mg/dl) in the second day of life and TSB  $\geq 306 \mu\text{mol/l}$  (18 mg/dl) in the third day and beyond (34). Jaundice with TSB  $\geq 205 \mu\text{mol/l}$  has also been mentioned as pathologic (28).

Jiménez-Peña *et al.* based on AAP guidelines propose the following pathologic jaundice criteria based on TBS levels and age (26):

- > 120  $\mu\text{mol/l}$  (7 mg/dl) in the first 12 hours of life
- > 171  $\mu\text{mol/l}$  (10 mg/dl) in the first 24 hours of life
- > 222  $\mu\text{mol/l}$  (13 mg/dl) in the first 48 hours of life
- > 290  $\mu\text{mol/l}$  (17 mg/dl) at any time.

There are also charts, graphs and nomograms for the proper evaluation of the newborn. One of the most known and widely used instrument is the one described by Bhutani *et al.* in 1999, which relates the hour-specific bilirubin level to the risk for needing treatment for hyperbilirubinemia and classifies newborns in 4 risk zones: low, low-intermediate, high-intermediate and high. Its predictive ability has been shown in multiple studies and different contexts and has been considered as a useful tool for predicting which infants are likely to develop high serum bilirubin values in order to offer a close follow-up monitoring and repeated bilirubin measurements (1,32,33).

Although TSB measurement is considered the gold standard to determine bilirubin level, there are some studies that report the existence of variability among laboratory results. Vreman *et al.* studied the results of 14 laboratories using automated analytical systems to measure total bilirubin concentration. They found that studied laboratories bilirubin values were generally lower when compared to target values and concluded that precise and accurate bilirubin measurements in clinical laboratories cannot be guaranteed and paediatricians must take into consideration this fact (37). Later, van Imhoff *et al.* studied the variability of measurements of bilirubin and albumin concentrations in the laboratories of 10 neonatal intensive care units in the Netherlands. They

found a large variability between them that potentially can affect treatment of newborns with jaundice. In addition, they demonstrated the lack of standardized devices or methodology for neonatal bilirubin and albumin measurements on the studied laboratories which may lead to the observed variability (38).

Since international hyperbilirubinemia management guidelines are based on TSB, laboratories performing TSB determinations must have frequently quality control procedures. Inaccurate and/or imprecise values can result in misdiagnosis and over or under treatments exposing the infants to unnecessary risks (38).

### ***Transcutaneous bilirubinometry***

Transcutaneous bilirubinometry (TcB) is one of the methods recommended by the American Academy of Pediatrics for the assessment of the risk of hyperbilirubinemia of newborns before discharge (9).

The era of TcB began 40 years ago as a response to the increasing emphasis of non-invasive screening methods in medicine. Nowadays TcB devices are widely used in newborn nurseries, emergency departments, outpatient clinics and offices. TcB advantages include ease of use, non-invasive nature, reduced need of TSB determinations, avoidance of pain and local infection, real-time results, cost-effectiveness compared to TSB and superior performance over visual assessment (23,39).

TcB is based in the principle of analysis of skin remittance (diffuse reflectance) spectra. The bilirubinometer emits light with different wavelengths in the skin which is analysed after being processed in the different cutaneous layers and then returned to the device. The spectra of returned light depends on the concentration of the chromophores in the skin layers. The difference in absorption spectra among them allows the calculation of their concentration through the use of device-specific algorithm and a microcomputer. Through the years, bilirubinometers have become more sophisticated and therefore have improved their performance (23).

Early devices showed variations in different colour skin types. This have been improved with the introduction of microspectrometry which enables greater accuracy in the measurement of the optical density of bilirubin (40).

Regarding the body site used for TcB measurements, multiple studies have been done to determine which one has the best accuracy. The general agreement is that measurements made on the forehead and sternum have the best correlation with TSB, the latter being the most

recommended because is less likely to be exposed to sunlight or ambient light which may have an effect in the results, especially in infants that have been already discharged (21).

Multiple studies regarding TcB utility has been done in the last years being one of the most important research topics in neonatology (41). However, although TcB has shown to be a valid method for assessment of hyperbilirubinemia severity and its used has increased, is still not widespread worldwide. Van Den Esker *et al.* performed in 2016 a telephonic review among 37 hospitals in the Netherlands and found that TcB was used in only 27% of them. Some explanations to low use, can be lack of confidence based on previous studies using old techniques and the assumption that sick neonates need blood sampling anyway for other indications and bilirubin measurement can be just included. Besides, equipment costs can be unaffordable especially for low-income countries or community settings with low resources. However, in such settings TcB may be of great value since laboratory equipment is even more scarce and expensive. The same authors demonstrated that the use of TcB in neonates with hyperbilirubinemia is feasible and safe, with a reduction of the number of blood draws in 38.5% (42).

Another concern about TcB is its accuracy in different skin colours. El-Kabbany *et al.* showed highly statistically significant difference between brown and white skin colour with a better accuracy of TcB forehead measurement in brown colour, but no statistically significant difference between them when measured at sternum (39). In 2018 Varughese *et al.* reported the results of the reliability of TcB in different skin-coloured newborns in India. 448 newborns were classified according to Fitzpatrick skin colour chart, with 74.4% in colour code III, 25.1% code IV and 0.4% code V. They found that mean TcB was uniformly higher than TSB (overestimate) but with high correlation in the different groups ( $r = 0.698-0.932$ ). Regarding skin colour, TcB correlated better in light skin tone than in dark one with  $r = 0.874$  and  $0.856$  respectively (40).

TcB has demonstrated to be reliable in preterm neonates and in infants after discharged. In a systematic review of 21 studies, Nagar *et al.*, concluded that TcB devices reliably estimate bilirubin levels in preterm infants and can be used in clinical practice to reduce blood sampling (43). On the other hand, regarding infants after discharge, it is well known that several factors can affect TcB measurements, like hydration status, age related skin changes (thickness) and exposure of skin to light. In order to evaluate the ability of TcB for prediction of total serum bilirubin levels in newborns after hospital discharge, Ercan and Özgün studied 218 newborns who required TSB measurements during an outpatient follow-up visit. TcB and TSB were determined simultaneously. Predictive indices were identified in different TcB cut-off values for TSB levels of 222, 256 and 291  $\mu\text{mol/l}$ . Forty percent of infants had an age of above 7 days. They found that



for TSB level of at least 256 to 291  $\mu\text{mol/l}$ , a TcB cut-off of 222  $\mu\text{mol/l}$  showed sensitivity of 90.6% and 100% respectively and that 39.4% of TSB measurements could be avoided when TcB cut-off value of 222  $\mu\text{mol/l}$  is used. They concluded that in the outpatient population TcB is a reliable screening method for hyperbilirubinemia which can reduced the number of invasive blood sampling (44).

Nowadays the use of TcB has shown to be a safe, rapid, convenient and non-invasive procedure. However, it must be considered that TcB determination is a screening test and high values should be confirmed by a TSB and that it cannot be used to monitor the progress of phototherapy. The development of special TcB nomograms has helped when a follow-up is needed. It is important to be aware that TcB seems to underestimate bilirubin concentrations of 206-240  $\mu\text{mol/l}$  (12-14 mg/dl), and clinicians should consider this to confirm TSB by laboratory (1,21,23).

Some other considerations that must be taken in account include to avoid testing skin with bruises, birthmarks or covered with hair. As with any other point-of-care test, it is important to frequently assess the competency of the personnel using the device (21).

According to the severity of jaundice, the recommendations are that in infants with mild jaundice, TcB may be all that is needed to assure that TBS levels are safely below those that require treatment. In infants with moderate jaundice, TcB may be useful to determine which patients require a TSB blood test and in infants with severe jaundice, TcB may be a useful tool to fast-track such patients to rapid and aggressive therapy (1).

### ***Additional assessment***

When bilirubin levels are approaching the need for phototherapy, additional studies must be considered according to each particularly situation in order to detect the cause of NNJ or any other complication (1).

#### ***1.1.6 Treatment***

The accepted treatment options for NNJ are phototherapy, high-dose intravenous immunoglobulin (IVIg) and exchange transfusion.

### ***Phototherapy***

Phototherapy is the most widespread therapy. It was serendipitously discovered by Sister Jean Ward in England in the 1950s, when she observed that jaundiced skin became paler after being exposed to light, while non-exposed skin remained yellow (45). It is only effective as bilirubin enters the skin with serum level more than 80  $\mu\text{mol/l}$  and is based in 3 reactions that occur when

bilirubin is exposed to light: photooxidation, configurational isomerization and structural isomerization. Bilirubin photoisomers are excreted in bile and urine. They are water-soluble therefore they are not able to cross the blood-brain barrier, reducing the risk of bilirubin-induced neurotoxicity. The process of photoisomerization starts after 15 minutes of phototherapy. At any given TSB concentration, photoisomers represent 20-25% of the whole amount.

The maximal effect is present in the first 24 to 48 hours and, in the absence of hemolysis, it can be expected that will reduce the TSB level by 25% to 50% during this phase (1,20,46).

Bilirubin absorbs light around 450-460 nm, but longer wavelengths penetrate skin better so lights with output in the blue region of the spectrum (460-490 nm) are the most effective. In practice, white, blue, turquoise, and green wavelengths light is used. Multiple types of phototherapy units have been developed which may use different light sources including blue and white fluorescent tubes, white quartz lamps, fiber optic and light-emitting diode (LED) lights (1).

One key concept in phototherapy is that the stronger the light and the larger the area of skin exposed to light, the more effective it will be (46).

Details about phototherapy procedures are beyond the scope of this research, but there are international, national and local guidelines with algorithms that clinicians may consult when needed (1).

The efficiency of phototherapy can improve by using more than one lamp or with the combination of overhead lamps with a fibre-optic system beneath the newborn. In cases of failure to single phototherapy, multiple lamps applied to a greater body surface area should be used (20).

Although phototherapy is recognized to be a safe procedure is not without side effects. The more common short-term side effects are diarrhoea, temperature instability, increased insensible water loss, erythematous rashes, tanning, bronze baby syndrome and interference with maternal-infant interaction. Potential long-term effects have been mentioned, such as retinal damage, melanocytic nevi and skin cancer, allergic diseases and patent ductus arteriosus (20,47).

Filtered sunlight phototherapy has been mentioned as a novel, practical and inexpensive alternative in LMICs where conventional phototherapy is not available (48).

### ***Intravenous immunoglobulin (IVIG)***

IVIG at high doses has reduced the number of exchange transfusions in the last years, however due to its high costs, is not worldwide available. Nowadays is considered as a second-line

treatment in infants with ABO or Rh isoimmunization in multiple neonatal intensive care units (NICU) (1).

IVIG not only reduces the need for exchange transfusion, but the duration of phototherapy and the length of hospital stay, however recipients are more likely to require RBC transfusions for late anemia. The current recommendation is that IVIG must be reserved for newborns with hemolysis with an increase rate of bilirubin more than  $8.5\mu\text{mol/l/hour}$  despite phototherapy or with ABO incompatibility cases readmitted with a TSB level approaching the exchange transfusions threshold values (20).

### **Exchange transfusion**

Exchange transfusion is indicated when other therapeutic options have failed or are not sufficient to prevent bilirubin neurotoxicity. When an infant is admitted for severe jaundice that appears to require an exchange transfusion, intensive phototherapy is recommend while waiting for cross-matched blood and additional tests needed for the procedure and when blood is available, a re-evaluation of bilirubin levels should be done to decide whether to proceed or not (1,20).

In a recent Norwegian survey of NICU phototherapy practices, it was found that among a 60000-newborn population, the incidence of infants that required exchange transfusions was only 0.01% (1).

Exchange transfusion implies a high risk of morbidity and mortality with overall rates of 5% and 0.3% respectively. The most common side effects are vascular accidents, biochemical and hematological disorders and cardiac complications (20).

### **Other therapies**

Prophylactic treatment with Rh immunoglobulin in Rh-negative women has decreased the incidence and severity of Rh-hemolytic disease and therefore NNJ. Another practice is to interrupt breastfeeding for 24-48 hours and use breast milk substitutes or supplement feeds of breast milk in infants with the so-called breast milk jaundice (1).

## **1.2 eHealth**

In 2001, Eysenbach defined formally for the first time eHealth (e = electronic) as: *“an emerging field in the intersection of medical informatics, public health and business, referring to health services and information delivered or enhanced through the Internet and related technologies. In a broader sense, the term characterizes not only a technical development, but also a state-of-mind, a way of thinking, an attitude, and a commitment for networked, global thinking, to improve*

*health care locally, regionally, and worldwide by using information and communication technology” (49).*

Since 2005, eHealth became a priority for the World Health Organization (WHO). During the fifty eight World Health Assembly, resolution WHA58.28 was adopted mentioning that “*eHealth is the cost-effective and secure use of information and communication technologies (ICT) in support of health and health-related fields, including health-care services, health surveillance, health literature and health education, knowledge and research” (50).*

Through the following years, eHealth has become one of the fastest growing areas of innovation in communication technology and nowadays has impacted every health-related sector.

In order to set context, it took 16 years for the internet to reach its first billion users, but only 6 more years to reach 2 billion, with an increasing rate of one billion new users every 2.7 years. According to one recent report, in 2019 there are 4.39 billion internet users in the world, with an increase of 9% compared to January 2018. This means that one million people come online for the first time each day, more than 11 new users per second. Mobile users have reached 5.11 billion, and there are 3.48 billion social media users. A significant proportion of this growth comes from developing economies, led by India with an annual growth of more than 20% (almost 100 million new users), followed by China with 50 million. African countries also figure in the top list, with the fastest growing internet communities, although many of these started from small bases. Western Sahara reported an increase in internet users of almost 5 times since January 2018 (51) .

With these impressive data, it is not unexpected that the rapid global adoption of technology has permeated the health sector, bringing the opportunity for eHealth to have a different and greater-scale impact than traditional health services and to become an important resource for health services delivery and public health (52).

The report of the third global survey on eHealth made by the Global Observatory for eHealth published in 2016, mentions that 58% of responding Members States have an eHealth strategy and 90% of them have availability to special funding for it. Government support health internet sites that offer information in multiple languages exist in half of countries, 75% of them have institutions that offer pre-service training or continuing education training on ICT for health and 25% offer in-service training on social media for health (52).

The World Health Assembly in 2018 acknowledged the potential of digital technologies to play a major role in improving public health, where delegates agreed on a resolution on digital health.

The resolution urges Member States to prioritize the development and greater use of digital technologies in health as a means of promoting Universal Health Coverage and advancing the Sustainable Development Goals (53) .

eHealth comprises multiple and different elements which are summarized in Figure 2. This chapter will go deeper in mHealth, which is one of the fastest growing technologies with a significant impact on health and is the one within the scope of this research.

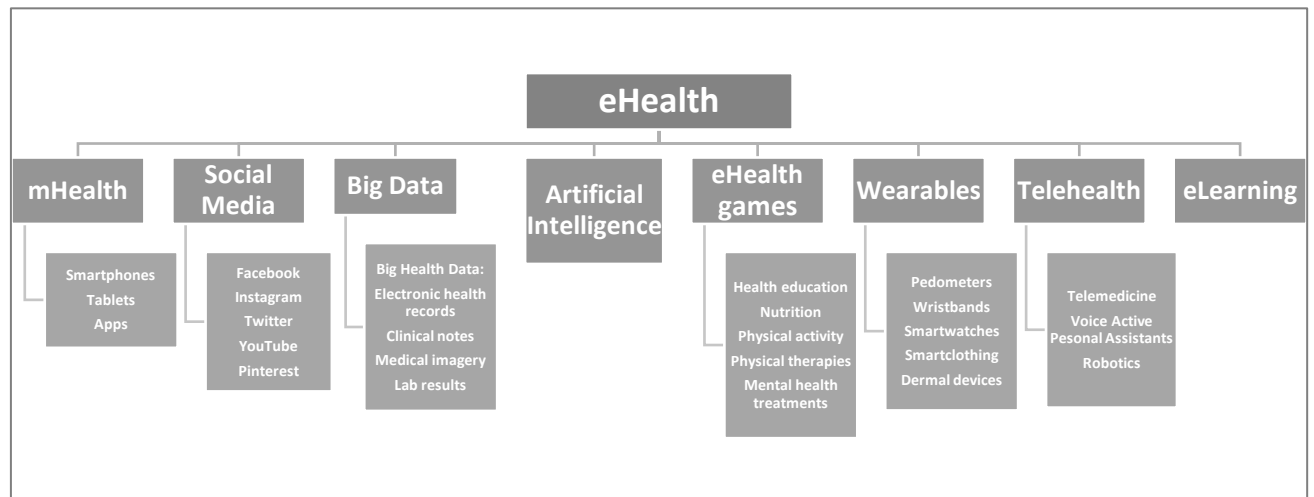


Figure 2 eHealth elements. From Grant AE, Meadows JH. Communication technology update and fundamentals (57).

### 1.2.1 mHealth

WHO refers to mHealth as the use of mobile devices, such as mobile phones, tablets, patient monitoring devices, personal digital assistants and wireless devices, for medical and public health practice (52). mHealth includes from the most basic functions of mobile phones such as voice and short messaging services (SMS) to the most complex such as advanced apps (54).

Mobile wireless technologies, in general are easy to use. They have wide acceptance and broad reach. Another great advantages of mobile devices, particularly mobile phones, is that they are most of time open and available as people tend to carry them everywhere. They are multifunctional tools that can work as photographic and video devices, word processors, electronic organizers and nowadays even as electrocardiograms, thermometers and more (55–57).

Smartphones and tablets combine in a single device computing and communication features. Going back in time, it was just in the beginning of this century in 2002, when the first mobile device, the Blackberry, incorporated these features. Later, in January 2007, Apple launched the first-generation iPhone and subsequently smartphones using Google Android operating system appeared in October 2008. Both systems offered for the first time, touch-screen and advanced

capabilities which increased their popularity. In 2010 Apple introduced the iPad tablet which became another transformative computing tool due to its ease of use, larger screen and portability and the tablet market initiated. In the same year Google Android operating system tablets, such as Samsung Galaxy and others were also launched. In July 2008 Apple “iTunes Appstore” started working, giving Apple devices users the availability to buy and download apps from an online market place, and in 2011 Apple created “Apps for Healthcare Professionals (HCPs)” which was later on divided into subcategories such as reference, medical education, electronic medical records and patient monitoring, nursing, patient education, imaging and personal care. Similarly Google released “Google Play” shop that also includes some HCPs apps (58).

Active mobile broadband subscriptions have increased rapidly, covering 86% of inhabitants in developed countries and 39% in developing ones. There are more than 7 billion mobile phone subscriptions (>120/100 inhabitants) and more than 5 billion mobile phone users worldwide today, 70% of which are in low- or middle-income countries. In many of such countries people have more access to a mobile phone than to electricity, clean water or a bank account, and it is expected that 6.1 billion people or more will use mobile apps in their smartphones by 2020. This higher exponential increase in the developing countries has been driven by more affordable smartphones and mobile data plans which have allowed that two-thirds of the global population nowadays can own a mobile phone of which more than 50% are smartphones. (52,56,57,59)

Considering the aforementioned, the healthcare and business sector have quickly jumped on the opportunity to engage people through mHealth apps. The number of mHealth apps has increased substantially, and it is estimated that of the more than 6.5 million active apps for Apple and Android users, more than 325 000 belong to mHealth apps, nearly the doubled than in 2015, with more than 200 apps added each day (55,57,60). However, such much competition makes difficult to achieve a high number of downloads for an app, and only 4% of mHealth app publishers get more than 1 million downloads annually, and 15% between 50,000 to 250,000 (60).

In the GOe survey from 2016, 83% of WHO Member States reported to have at least one mHealth initiative. Some examples of mHealth applications mentioned were telephone helplines, text message appointment reminders, mobile access to electronic patient information and mobile telehealth. There has been a significant increase in the number of established programs, however only few countries reported evaluations of government-sponsored mHealth programs, therefore the knowledge about their real impact in population health is lacking (52).

Access to mobile apps is easier than to web-based apps. In low-income countries, where infrastructure to support internet or traditional health services is lacking, mobile communications technology infrastructure has been prioritized and is supplying in-person services reducing expenses. (52).

mHealth has been applied and tested in multiple health contexts, such as programs aimed to reduce the burden of diseases linked to poverty including HIV/AIDS, malaria and tuberculosis and in maternal and child health. Timely access to emergency and general health services and information can be improved, as well as help manage patient care, reduce lack of medicines at health clinics and increase clinical diagnosis and treatment adherence (54).

Nowadays there is almost an app for everything. There are those directed to the general public which provide medical and health information or can help people in self-monitoring body functions and activities, such as devices to measure body weight, energy expended, steps taken, sleep patterns, blood pressure and brain activity. Some others are made to assist patients with different tasks, including to store and access their medical records, treatments, track medical appointments, seek appropriate medical care, belong to patient support networks, share health information with friends and family, monitor and self-managing of chronic diseases such as diabetes or high blood pressure or record their symptoms and manage post-treatment care after acute conditions. And there are those specifically directed to HCPs which have become invaluable tools in their daily practice (61).

Around 90% of physicians believe that mHealth apps can improve patient's health. Surveys have shown that 66% of physicians own a tablet and 54% use it in their practices. HCPs apps include those which can provide detailed anatomical information and visuals, training videos, diagrams and drug prescribing information, but also those to assist in the practice to monitor and measure physical functions and symptoms such as testing glucose, blood pressure, heart, lungs and kidney functions, and using hardware add-on to smartphones so they can be used as medical devices (58,61).

Community health workers have also benefited from mHealth. In the LMICs remote and unattended rural locations, it can help to the diffusion of clinical updates, learning materials and reminders. Mobile devices also provide the opportunity to direct communication with one another and peer support, but also to communicate with community members for health education, promotion, direct patients to services and awareness through SMS, for instance. Another benefit is reporting of data in a more accurate way, reducing time and cost and improving data quality (62).

mHealth offers multiple advantages and if used properly, it has been proved to have a high potential to improve health in different ways, however it is important to mention the negative side of this relatively novel technology.

There are not many studies regarding effectiveness, both cost-wise and clinically, of all health apps. Assessment and research of the different types or specific aspects of apps is needed through clinical trials, which might be difficult given the speed with which this technology advances (63).

For HCPs, the value of an app relies on its ability to provide meaningful, accurate and timely information and guidance in order to achieve the purpose of improving patient outcomes, therefore rigorous evaluation, validation and development of best-practice standards are needed. Besides, some HCPs are still reluctant to use mHealth in clinical practices or are using it without a deep understanding of their risks and benefits (58).

Apps may have limitations and deficiencies, and their development, maintenance, support and updating implies high costs. Not all apps benefit all users and their content is not always adapted to different settings, such as culture, beliefs or customs. Furthermore, many apps are not based on behavioural change guidelines or theories. The ease of installation and popularity of current apps may also bring the risk of download malware, wrong information or of dubious quality and the violation of online privacy (63). Some other potentials harms include conflict of interest and transparency and the impact in doctor-patient relationship (61).

Perhaps one of the most concerning aspects is related to the extent in which eHealth in general, is reinforcing or even more, creating new health inequalities as the result of regional differences, limited access secondary to lack of technological resources, conflicting health system priorities, and the absence of legal frameworks to protect data privacy. In addition, socio-demographic background differences and digital literacy and skills may determine the use of mHealth. Age and education level are associated with mHealth apps, such younger and highly educated people are more likely to use them than older or lesser educated counterparts, which may increase inequalities (55,57).

According to the GOe survey, the most important barriers to implement mHealth programs for low- and middle-income countries are lack of funding and lack of legal regulation. Some suggested strategies include the active evaluation of the process of implementation and programs outcomes by governments, sharing lessons learned by different countries, determine the best areas for governments interventions and regulations and the promotion of indicators of increased access for priority populations to be assessed in all mHealth programs (52).



In its seventy-first world health assembly, WHO recognized the significant role that mHealth plays to achieve universal health coverage, the health-related Sustainable Development Goals and other health objectives and encouraged Member States to set priorities and implement strategies in order to develop, improve and promote greater use of digital technologies including mHealth (64).

### **1.2.2 Smartphones as diagnostic tool devices**

Smartphones have become ubiquitous devices around the world in the recent years. They are equipped with multifunctional components such as visual display, digital camera, LED flash, sensors, fast multicore processor and intuitive user interface. They also have multiple modes of wireless data transfer including cellular data service, Wi-Fi and Bluetooth. These features in addition to the growing need for user-friendly, portable, efficient and affordable diseases diagnosis and prognosis monitoring devices, have led to global attention and recognition in the implementation of smartphones point-of-care diagnostic tools, especially in remote areas lacking professional technicians and laboratory infrastructures. When coupled with special sensing systems or additional attachments such as different type of lenses, filters, diffraction gratings, alternative power or light source and 3D printers for instance, smartphones can be used as a more accessible alternative to standard disease detection and monitoring equipment and as sophisticated biosensing devices through colorimetric, fluorescence, electrochemical and scattering based techniques (65–67).

### **1.2.3 Smartphones as diagnostic tools for detection of NNJ**

As mentioned in the first part of this chapter, the gold standard for NNJ is the quantification of TSB measured in a blood sample. TcBs have shown to be safe, rapid, convenient and non-invasive screening and diagnosis supporting tools, with good correlations with TSB levels and are one of the methods recommended by the AAP for the assessment of the risk of hyperbilirubinemia of newborns before discharge (9,32). However, laboratory facilities are usually not available in poor or remote settings and although TcB can be used as a point-of-care device, its price ranges between US\$3000 to 7000, which is unaffordable for most health care units in the same settings (68). In addition, TcB levels progressively underestimate TSB levels, particularly over 255  $\mu\text{mol/l}$  (15 mg/dl) (69).

New technologies, including mHealth, have become an option for tackling the need of a more affordable and available method to screen newborns for jaundice. One of the first attempts to implement an alternative diagnosis approach was made by a group of researchers from Thailand who designed a non-invasive method for measure bilirubin level in 61 newborns. Images of the chest were obtained using a digital camera and manually inspected and adjusted in Photoshop.

They found a significant ( $p < 0.05$ ) Pearson correlation of 0.86 between serum bilirubin level and bilirubin estimated values obtained from the images (70).

Using also a digital camera to obtain images of the sclera in 110 newborns, Leung *et al.* showed a Pearson correlation of 0.75 between the sclera colour and TSB level, concluding that although such correlation is not high enough to be used to predict the absolute TSB level, their technique may be useful as a screening method to identify newborns with TSB above  $205 \mu\text{mol/l}$  (71).

In 2014, De Greef *et al.* reported the first results of BiliCam, a low-cost smartphone based medical device that uses the embedded camera and a paper colour calibration card. They conducted a study in 100 newborns to correlate BiliCam bilirubin estimates with TSB levels and TcB results. They concluded that BiliCam cannot substitute TSB testing, but it showed statistically equivalent performance as the TcB, so it can be used as an effective screening tool to decide whether TSB testing is needed (67). Later, the same group led by Taylor, reported the results of a sample of 530 newborns with different ethnicities including white, African American, Hispanic and Asian American with an overall high correlation. They concluded that BiliCam provides precise estimates of TSB levels and can be used to effectively screen newborns for jaundice (72).

A study from Turkey reported the results of an advanced image processing technique along with a colour calibration card to analyse smartphone images of 80 newborns. It showed that the obtained bilirubin estimates were consistent with TSB results (73).

In 2016 Rong *et al.* used an automated smartphone image-based bilirubin system named AIB and a colour calibration card for predicting jaundice and compared the results with TcB and TSB in 215 preterm and term neonates. There was no significant difference between AIB and TSB and a good correlation was found but sensitivity and specificity were not high. They concluded that their system can provide results for objective follow-up of progression and regression of jaundice (74).

One year later, another Chinese group assessed the accuracy of the same AIB system using a smartphone app called *BiliScan for Newborn Jaundice* and compared results with TSB and TcB of 296 sets of data from 194 neonates. The accuracy of AIB was not inferior to TcB if TSB value was  $\leq 20 \text{ mg/dl}$ , but it decreased with higher bilirubin values. They concluded that *BiliScan for Newborn Jaundice* is useful for dynamic monitoring moderate jaundice of neonates and early infants at home (75).

Nowadays this app is available on line for free. Its accuracy and reliability have been tested in an Indian population of 35 neonates. Moderate correlation for images obtained from sternum and abdomen was found (76).

In Norway, a group of researchers developed a smartphone app, based on professor Randeberg research on bio-optics (77). Using a novel colour calibration card which reflects differences in newborn skin colour with varying degree of melanin and bilirubin, a clinical trial on 134 Caucasian newborns showed a high correlation with TSB of 0.85 and led to the creation of the company *Picterus* (unpublished results). Table 1 shows a summary of the results of published reports using similar technologies to detect NNJ.

*Table 1 Results of studies using smartphone apps to detect NNJ*

Author	n	Linear correlation	Sensitivity	Specificity	AUC	Observations
Rong, ZH., 2016 (73)	148	0.79	82	60	0.743	
Bo, V., 2018 (74)	194	0.82	----	----	----	TSB $\leq$ 342 $\mu\text{mol/l}$
Swarna, S., 2018 (75)	35	0.66 0.55	----	----	----	Thorax Abdomen
Aydin, M., 2016 (72)	80	0.85	100 83	50 80		TSB $\geq$ 205 $\mu\text{mol/l}$ , system 160 $\mu\text{mol/l}$ TSB $\geq$ 205 $\mu\text{mol/l}$ , system 195 $\mu\text{mol/l}$
De Greef, L., 2014 (66)	100	0.85	----	----	----	
Taylor, JA., 2017 (71)	530	0.91 0.91	100 84.6	76.4 81.3	0.99 0.95	TSB $\geq$ 290 $\mu\text{mol/l}$ , BiliCam 222 $\mu\text{mol/l}$ TSB high risk zone, BiliCam high intermediate + high risk zones Hispanic/Latino
Aune, A. (unpublished results)	134	0.85	95.4 90.9	81 88.6	0.947	TSB $\geq$ 250 $\mu\text{mol/l}$ , app 240 $\mu\text{mol/l}$ TSB $\geq$ 250 $\mu\text{mol/l}$ , app 258 $\mu\text{mol/l}$

Although a huge step has been taken in order to achieve the need of an affordable and available method for neonatal jaundice, there are still gaps to have the ideal one, which may have the same accuracy in all types of skin and can be used in any smartphone.

### 1.3 Mexico demographics, economy and health status overview

Mexico is an upper middle-income country of Latin America and Caribbean region with a 2019 estimated population of 132 million inhabitants, ranking number 10 in the world. Median age is 27.5 years, with sex ratio at birth (male to female) of 1.05. The land area is close to 2 million  $\text{km}^2$ ,

with a population density of 68 per km<sup>2</sup> and 79.9% of people is living in urban areas. According to nominal gross domestic product (GDP) per capita, Mexico ranks in the 74<sup>th</sup> world place and the percentage of working poor at purchasing power parity (PPP) \$3.10 a day is 11.3%. There are still huge inequalities among people from urban and rural areas of the country with 46.2% of its population living in poverty and 9.5% in extreme poverty. Per capita incomes in the northern richest states are between four to six times higher than in the poorest southern ones (78–80).

Informal employment rate is almost 60%, and 22% of youth are neither in formal employment, education or training. These circumstances limit the revenues available to resource public-funded services, such as education, health and social protection (80).

United Nations Development Program 2018 report shows a human development index of 0.774, ranking 74 of 189 countries (81). A summary of last updated data is shown in Table 2.

As in many other countries in the world, morbidity and mortality trends in Mexico have changed in recent years. Although infectious diseases prevail as the main causes of morbidity, noncommunicable diseases (NCDs) now appear as some of the most common, such as obesity, hypertension and diabetes (82).

Heart diseases, diabetes and cancer were the main causes of death among the entire population in 2017 (last data available); however, violence (homicides) and road injuries played a significant role as mortality causes, with a greater impact on the male population (83).

National burden of disease in 2017 shows that the group of diseases with highest disability adjusted life years (DALYs) are lifestyle influenced diseases including diabetes, kidney and cardiovascular diseases and self-harm and violence. Maternal and neonatal disorders rank in place number nine (84).

Health services in Mexico face challenges as they are provided through different disconnected sub-systems whose operations are tightly determined by historical and institutional legacies and offer different levels of care. The affiliation to health system is determined by peoples' job. One of the largest providers is the *Instituto Mexicano del Seguro Social* which offers health insurance and health care services such as pensions and other benefits, to salaried (formal) private employees and their families. Other institutions provide similar social security to employees of the federal government, the army, the navy and *Petroleos Mexicanos* (national oil company). People without a formal job or unemployed can enrol with *Seguro Popular* with a different packages and different set of providers. *Seguro Popular* was implemented in 2004 and there are currently around 50 million affiliates, which represents an important step towards universal health

coverage. However, the fragmented health system leads to inequalities in the access and quality of services and there are still 18% of the population without any health insurance. Private sector also plays an important role in the overall health care system and out-of-pocket spending constitutes 45% of health system revenue (80).

Regarding NNJ, it doesn't figure among the main causes of death in Mexico, and specific numbers about its prevalence are lacking (85).

Gallegos *et al.* reported in 2009 the NNJ prevalence of 17% in a NICU in a Mexican hospital. The associated risk factors they found were gestational age < 35 weeks, exclusive breast milk diet and sepsis. The average age for the onset of jaundice in this study was 4.5 ±2.2 days (5).

In 2017 a study was conducted in a Mexico City general hospital to determine the etiology of NNJ over a period of five years. A hundred and twenty-seven patients were admitted to hospital with NNJ. Fourteen different causes of jaundice were found, being the five most frequent physiologic jaundice (24.4%), ABO incompatibility to blood group A (18.9%), to blood group B (13.4%), neonatal sepsis (11.3%) and low weight for gestation (10%) (8).

*Table 2 Mexico economy, development and health data*

Gross national income (GNI) per capita (2011 PPP\$)	16,944	Mortality rate, infant (per 1000 live births)	12.6
Gross domestic product (GDP) per capita (2011 PPP\$)	17,336	Mortality rate, under-five (per 1,000 live births)	14.6
Human development index	0.774	Maternal mortality estimate (per 100,000 live births 2015)	38
Current health expenditure (% of GDP)	5.9	Birth rate (per 1,000 population)	18.3
Fertility rate (number of children per woman)	2.25	Child malnutrition, stunting (moderate or severe)	12.4
Life expectancy at birth (years)	77.3	Internet users, total (% of population)	59.5
Expected years of schooling (years)	14.1	Homicide rate (per 100,000 people)	19.3
Suicide rate, male (per 100,000 people)	8.1	Suicide rate, female (per 100,000 people)	2.1

UNDP. Human Development Reports  
(<http://hdr.undp.org/en/countries/profiles/MEX>)

PPP: Purchasing power parity

### **1.3.1 Irapuato, Guanajuato and Hospital Materno Infantil (Mother and child hospital).**

The present study was conducted in the city of Irapuato which is a municipality belonging to the state of Guanajuato, located in the central zone of Mexico. It is located at 1,730 meters above sea

level and has a territorial extension of approximately 845 km<sup>2</sup> (86). In 2015, Irapuato population was 574,344 inhabitants, and in 2010 the estimated percentage of people living in moderate and extreme poverty was 37% and 6.5% respectively. Around 9% of Guanajuato population is indigenous and 6% is illiterate (87,88).

Regarding the health system, Guanajuato has the most complete network of hospitals providing mother and child health services in the country, through four hospitals located in strategic zones: San Luis de la Paz, Celaya, León and Irapuato (89).

The *Hospital Materno Infantil de Irapuato* (HMII) is the newest one of these hospitals, starting activities in October of 2014. It provides health services coverage to 300,000 women in reproductive age with an area of influence that covers 9 municipalities, attending more than 3 million women and children (90).

HMII has 40 beds for mothers rooming with babies, 20 in neonatal care unit, 7 in NICU, 6 in adult ICU and 6 in adults intermediate care unit. In addition, it has a 24-hours emergency service, laboratory and image diagnosis support department, phototherapy, breast-feeding clinic, outpatients including various specialties for children and women and auditory screening for neonates. Since its opening, an average of 446 births are attended per month (14-15 per day) (records from hospital).

The percentage of cases with diagnosis of NNJ among patients admitted to the emergency room during 2015, 2016 and 2017 was 11, 12.7 and 23.3% respectively. During 2017, along with asphyxia, NNJ was the fourth cause of admission to neonatal care unit, with 59 cases, representing 11.5% of all diagnosis. There was no registers of kernicterus or deaths related with NNJ in the hospital when this study was conducted (internal statistics).

## **2 Purpose and aim**

### **2.1 Rationale of the study**

The highest morbidity and mortality rates related to NNJ complications such as acute bilirubin encephalopathy and kernicterus occur in the poorest regions of the world, particularly in Sub-Saharan Africa and South Asia.

To identify newborns at high risk of developing bilirubin encephalopathy, a blood test for TSB measurement is needed, which requires laboratory equipment and is an invasive, painful and not free of complications method. TcB was developed as an alternative diagnosis method to reduce

the need of blood tests. However, both laboratory facilities and TcB are not available in most health centres in vulnerable places.

In the recent years several mHealth devices have been developed such as smartphones and apps, to fulfil the need of an accurate, affordable and available NNJ screening tool, which have shown different but promising results.

A new smartphone app called *Picterus* was developed at Norwegian University of Science and Technology in Trondheim. It has already been tested at St's Olav Hospital in 134 Caucasian newborns with Fitzpatrick photo type from I to II, and the results showed that it is possible to establish a good correlation (Pearson 0.85) with TSB (Aune, A., unpublished data 2018).

However, this new app has not been tested in non-Caucasian population where the amount of melanin could be a potential influence factor due to its effect on the absorption of light in the skin.

Mexican population includes a broad spectrum of skin types ranging from II to V, but III and IV are the most common. Validating the correlation of TSB with the results obtained using the new app in a different population such as Latin-American, will enrich and complement the previous results and can aid to scale-up this new technology to the most vulnerable populations in the future.

This study will assess the Pearson coefficient correlation of the estimates obtained by the app with the TSB levels and the degree to which the app accurately predicts TSB levels through the calculations of accuracy measures such as sensitivity, specificity and predictive values.

## **2.2 Objectives**

### **2.2.1 Broad Objective**

Validation of a new smartphone app in detecting neonatal jaundice in a population of Mexican newborns.

### **2.2.2 Specific aims**

- a. Determine the correlation between the estimates of bilirubin obtained by the new app and visual inspection using Kramer scale with the TSB level in a population of Mexican newborns.
- b. Assess the accuracy of the new app as a screening tool for NNJ in a population of Mexican newborns.
- c. Determine the correlation between the estimated levels of bilirubin obtained by the new app with total serum bilirubin by risk groups according to Bhutani nomogram.

### **3 Research Question and Hypothesis**

#### **3.1 Research Question**

What is the correlation between the estimated levels of bilirubin obtained using the new app with bilirubin serum levels in a population of Mexican newborns?

#### **3.2 Hypothesis**

H1. There is a high correlation between the estimated levels of bilirubin obtained by the new app with total bilirubin serum levels in a population of Mexican newborns.

H0. There is no a high correlation between the estimated levels of bilirubin obtained by the new app with total bilirubin serum levels in a population of Mexican newborns.

### **4 Methodology**

#### **4.1 Study design**

A descriptive cross-sectional study design was used in this research, since variables were not manipulated and were measured only once in each of the participants. The objective of this study does not imply to determine cause-and-effect relationship between variables, but to establish the correlation between them, and thus this study design was chosen as the optimal way that fits to answer the research question.

#### **4.2 Study setting**

Department of Obstetrics/Neonates ward (mothers rooming with newborns) and outpatients (Breastfeeding clinic) at Hospital Materno Infantil de Irapuato, Guanajuato in Mexico.

#### **4.3 Study period**

A sample size of newborns, sufficient to validate the new app, was calculated (see 4.5). Given the uncertainty of how many parents would accept to participate and knowing the amount of deliveries at Hospital Materno Infantil de Irapuato, > 400 births per month, we planned for a data collection period of 1-2 months. The study was performed in July and August 2018.

#### **4.4 Study participants**

##### **4.4.1 Inclusion criteria**

Healthy newborns with or without signs of jaundice, gestational age >35 weeks, age 0-14 days, weight > 1500 g. Parents acceptance of their children to participate in the study.

To avoid unnecessary vein punctures, only newborns who needed a blood test ordered by the paediatrician for any reason, were included.



#### **4.4.2 Exclusion criteria**

Newborns showing signs or with diagnosis of inborn diseases, transferred to paediatrics ward for any treatment and those who had received phototherapy.

#### **4.5 Sample size**

Sample size calculation was based on standard errors of the 95% limit of agreement, as described by Bland and Altman (91). The standard error of the 95% limit of agreement is approximately  $\sqrt{3 s^2/n}$ , where  $s$  is the standard deviation of the differences between measurements by the two methods and  $n$  is the sample size. Results from the study performed in Trondheim showed a standard deviation ( $s$ ) of the difference between bilirubin estimates from digital images to blood samples of  $35 \mu\text{mol/l}$ . A sample size ( $n$ ) of 150 participants will then give the confidence interval of the limits of agreement of  $9.7 \mu\text{mol/l}$ , a relevant size for clinical use.

#### **4.6 Data Collection**

All data were obtained and collected by the main investigator for this thesis research except the blood samples. A pretested protocol used in Norway was used to register all data obtained (see appendix).

##### **4.6.1 Recruitment of participants**

Recruitment of participants was done in two scenarios. The first one was at the obstetrics/neonate ward during the two daily rounds made by paediatricians at 8 and 13 h. All newborns were evaluated after birth in order to verify if they were able to be discharged. If any risk factor for an inadequate evolution was detected, for example, mother's infection in the last trimester, blood type incompatibility, premature membrane rupture, congenital malformation, etc., complementary studies were usually requested. If a blood test was ordered for any reason and the inclusion criteria were fulfilled, the mother was informed about the purpose of the study and the procedure to obtain the images was explained. In case of acceptance, the informed consent (see appendix) for participation was obtained and signed by her and 2 witness. If the father was localized before the newborn was discharge, informed consent from him was also obtained. TSB test was added to the laboratory request in case that the paediatrician had not ordered it.

The second one was at the "Breastfeeding Clinic". This is a clinic carried out every Tuesday and Friday from 10 to 13 h in the outpatient hospital area. All mothers and newborns are required to attend the clinic during the first 7 days following the discharge. The main purposes of this clinic are to verify adequate weight gain in the newborns, to instruct mothers on the correct technique of breastfeeding, to check any ongoing infection in the umbilical cord and to screen the presence of

jaundice. Usually, around 35 to 50 newborns attend the clinic per day. Two nurses and one paediatrician are in charge of all the activities.

When jaundice was detected by the paediatrician and a TSB test was ordered, the same procedure previously described regarding information about the study and informed consent obtaining was performed by the researcher.

#### **4.6.2 General data collection**

Date and time of birth, birth weight and gestational age (GA) were obtained from the newborns' medical records; visual examination to calculate Kramer scale of the newborn and to determine Fitzpatrick skin type of the mother and father (if he was present) were made by the main investigator (see appendix). Fitzpatrick scale was not determined in newborns since skin colour has variations during the first days of life and is difficult to assess accurately, and it is not validated in this population. All data were stored as de-identified data in the study format design for the study.

#### **4.6.3 TSB blood sample**

All blood samples were obtained by trained laboratory personnel. For newborns at hospital ward, there were three different fixed schedules to obtain the samples: from 10 to 10.30 h, 15 to 15.30 and 18 to 18.30 h depending on the time they were ordered. For newborns at Breastfeeding Clinic, the sample was taken in the laboratory facilities from 13 to 14 h in the same day of the consultation or from 7 to 8 h the next morning. Some blood tests were ordered when the newborn was discharged from the ward. Those were also taken in the later schedule.

Around 1.5 to 2 ml of blood for processing all the ordered tests were obtained from the back of the hand by venous puncture with a 21G x 32 mm needle without the hub (Image 1). The blood used for TSB test was collected in orange media to avoid bilirubin degradation by light.



*Image 1 Obtaining blood sample*

Samples were processed in an Abbot ARCHITECT ci 4100 equipment and once the results were available in the clinical files or in the laboratory electronic platform, TSB levels were registered in the study format.

#### **4.6.4 Obtaining the images**

Images were obtained within 60 minutes before or after the blood sample was taken, using the camera of a single smartphone Samsung Galaxy S7 provided by the project with the study app downloaded. The following procedure was followed. A calibration card to adjust different light conditions and apply colour corrections was placed on the naked chest of the newborn, with its central hole over the sternum (Image 2). Using the app, once the smartphone was aligned with the calibration card, 6 images, 3 with and 3 without flash, were automatically obtained by the camera, and a consecutive identification number was given by the app, which was written in the participant data collection format. It was planned to upload images automatically to the app server, but for unknown reasons it could not be done and since the memory of the smartphone did not have enough capacity to store all the images, they were stored in a USB memory stick and in an external hard drive for later colour analysis.



*Image 2 Calibration card*

#### **4.6.5 Data analysis**

Data were organized in an Excel sheet and analysed with SPSS version 25. For demographic and clinical characteristics, descriptive statistic was used, and results are shown in tables and figures. Correlation between TSB levels and the app estimates values, TSB and Kramer scale and the app and Kramer scale was determined by Pearson coefficient. Linear regression analysis was performed for TSB and the app. Agreement between TSB and the app was assessed using Bland Altman method. Receiver Operating Characteristic (ROC) and area under the curve (AUC) analysis were performed to determine sensitivity and specificity of different cut-off values of the

app estimates to predict TSB levels of 171, 222, 255 and 290  $\mu\text{mol/l}$  which correspond to the limits among Bhutani nomogram risk zone groups. Positive predictive values (PPV) and negative predictive values (NPV) were calculated using standard crosstabs. TSB levels and the app estimates were plotted in Bhutani nomogram (see appendix) to classify the participants in risk zone groups and correlation and accuracy measures of the results were estimated.

#### **4.7 Ethics**

Mexican health care providers from HMII were always present while the researcher was giving information to the participants' mothers about the study, in order to assist in case of any issue related to it, since an alien doctor to hospital and from a foreign university may be a power imbalance.

Written informed consent was obtained from newborns' mother (and father if available) prior to participation and signed by two witnesses and all data were anonymized.

The study was granted ethical approval from both, The Regional Committee for Medical and Health Research Ethics (REC) in Norway (2018/1001) as well as from The Regional Ethics and Research Committee in Hospital Materno Infantil of León, Guanajuato (Ext-06-2018) (see appendixes).

For all studies with a goal of increasing identification of disease, it is important that treatment is available, and that identified cases do not result untreated. In our study, the treatment consists of phototherapy, which is available at Hospital Materno Infantil of Irapuato.

### **5 Results**

Images and TSB levels were obtained from 174 newborns. Inclusion criteria were not fulfilled in 5 participants (gestational age <35 weeks) and 3 images were obtained out-of-time (more than 60 minutes after the blood sample was done). 166 newborns were included for the analysis of which 117 were recruited in the hospital ward and 49 in the Breastfeeding clinic.

The means  $\pm$  standard deviation (SD) and range of the continuous variables studied are summarized in Table 3.

According to GA, 17 (10.3%) were preterm (35-36 weeks), and 149 (89.7%) were term neonates ( $\geq 37$  weeks).

Fitzpatrick scale was obtained from 165 mothers and 51 fathers; 94% and 100% ranged between type III and IV respectively (Table 4).

Different degrees of jaundice were detected by Kramer scale in 88 participants. Complete estimates are shown in Table 5.

*Table 3 Birth weight, gestational age, age in hours, TSB levels and the app estimates. N=166*

Variable	Mean ± SD	Range
<b>Birth weight in grams</b>	3088 ± 468	1910 – 4400
<b>Gestational age in weeks</b>	38,4 ± 1.4	35 - 41
<b>Age in hours</b>	74,7 ± 89.5	3 - 341
<b>Bilirubin μmol/l</b>	143 ± 89	46 - 470
<b>App μmol/l</b>	144 ± 78	46 - 357

*Table 4 Fitzpatrick Scale in Parents*

Fitzpatrick scale	Mother	Father
<b>II</b>	1	0
<b>III</b>	43	17
<b>IV</b>	113	34
<b>V</b>	8	0
<b>Missing</b>	1	115
<b>Total</b>	166	166

*Table 5 Kramer scale*

Kramer scale	Frequency	%
<b>0</b>	78	47
<b>1</b>	34	20.5
<b>2</b>	34	20.5
<b>3</b>	17	10
<b>4</b>	3	2
<b>5</b>	0	0
<b>Total</b>	166	100

The proportion of children classified by groups according to Bhutani nomogram with TSB and the app values is shown in Table 6. Most of the newborns were classified in the low and low-intermediate risk zone groups, 71% using TSB and 63.8% using the app.

Table 6 Risk group zone according to Bhutani nomogram

Risk group zone	TSB		App	
	Frequency	%	Frequency	%
Low	57	34.3	62	37.3
Low-intermediate	61	36.7	44	26.5
High-intermediate	34	20.5	34	20.5
High	14	8.5	26	15.7

The Pearson correlation coefficient between TSB levels and the app bilirubin estimates (Figure 3) was 0.87 (95% confidence interval [CI] 0.83-0.90,  $p < 0.01$ ).

In Bland Altman analysis, the mean difference between the app and TSB was 0.618  $\mu\text{mol/l}$  and 95% limits of agreement were -84 to 85.2  $\mu\text{mol/l}$ , with a range from -201.8 to 105.2  $\mu\text{mol/l}$ . (Figure 4). The app tends to overestimate TSB levels below 150  $\mu\text{mol/l}$ , but underestimates above that figure. For preterm newborns, the correlation was 0.9 (95% CI 0.73-0.95) and for term newborns was 0.86 (95% CI 0.82-0.89).

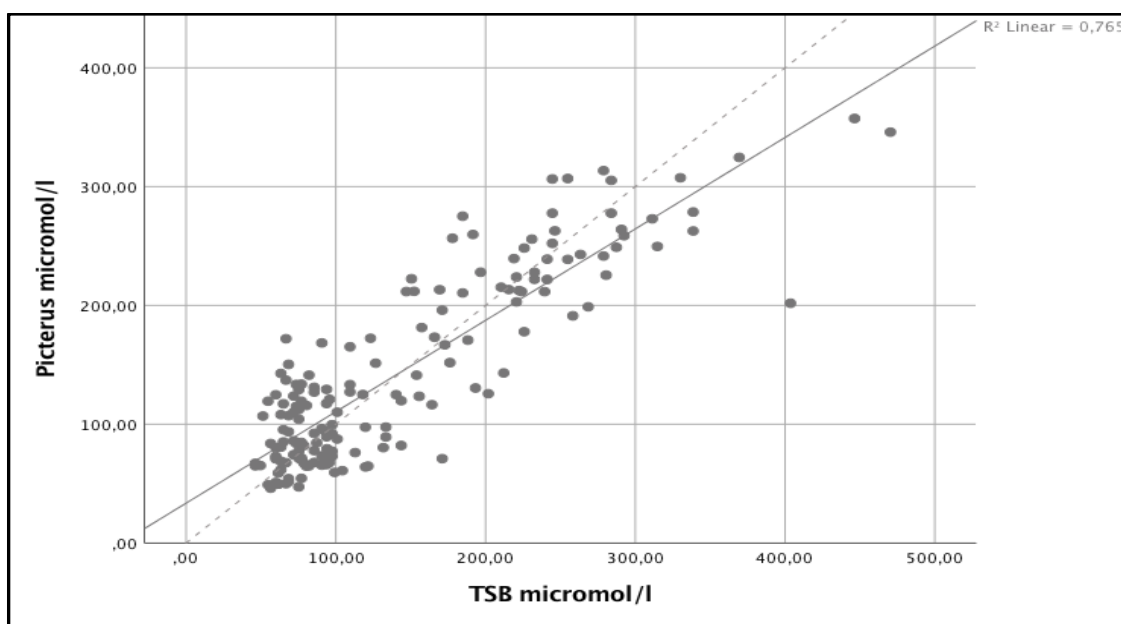


Figure 3 Linear regression between TSB and the app

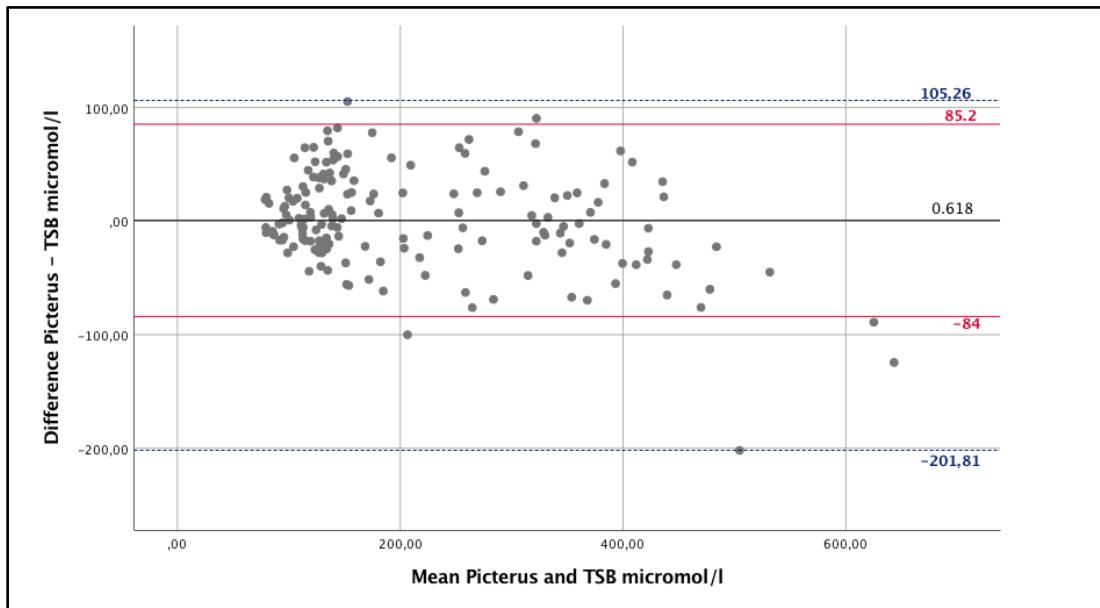


Figure 4 The Bland-Altman analysis comparing the app estimates and TSB values. The black solid line shows the mean difference, the red lines show the 95% upper and lower limits of the agreement and the blue dotted lines the highest and lowest values.

ROC analysis (Figure 5) was performed to determine measures of accuracy for several cut-off values of the app to predict TSB levels of 171, 222, 256 and 291  $\mu\text{mol/l}$ . (Table 7) These values were determined according to the Bhutani nomogram risk group limits.

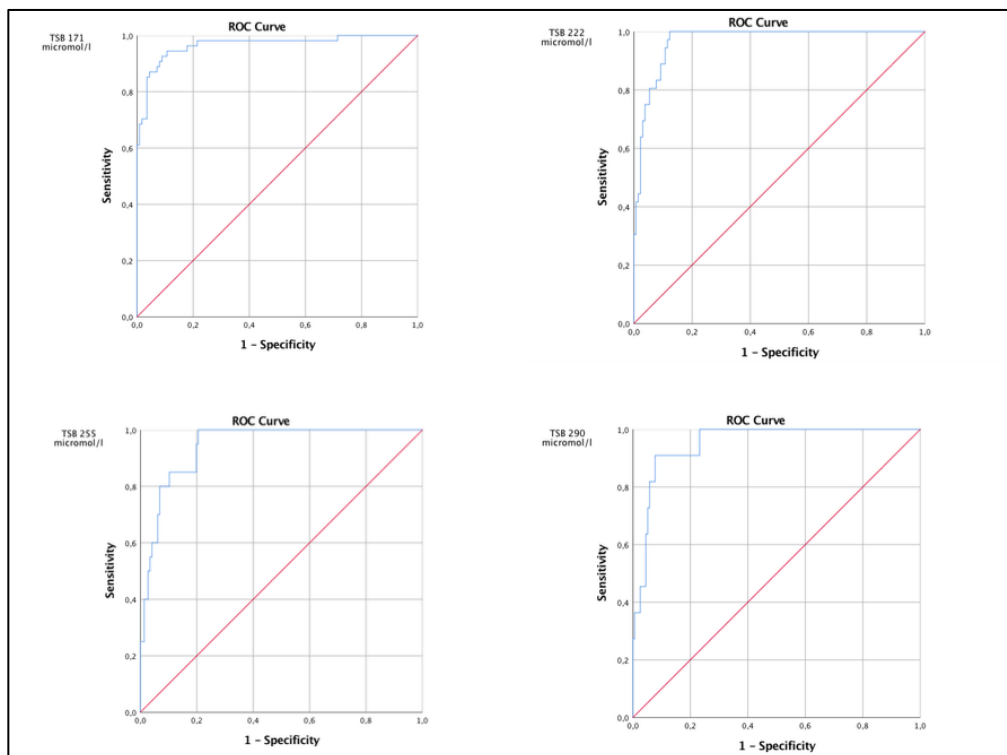


Figure 5 ROC curves for the app estimates and TSB values of at least 171, 222, 255 and 290  $\mu\text{mol/l}$  (AUC: 0.966, 0.968, 0.943, 0.951 respectively,  $p < 0.001$ )

Table 7 Accuracy measures of different cut-off values of the app for TSB levels of 171, 222, 256 and 291  $\mu\text{mol/l}$

TSB $\mu\text{mol/l}$	App	Sensitivity %	Specificity %	PPV %	NPV%
<b>171</b> Positive cases = 54	125	98.1	78.6	67.9	98.8
	142	94.4	88.4	79.7	97
	165	90.7	92	83	95.3
	171	87	92.9	85.4	93.7
<b>222</b> Positive cases = 36	175	100	87.7	69.2	100
	197	94.4	89.2	70.8	98.3
	212	80.6	92.3	73	95.2
	222	75	94.6	79.4	93.1
<b>255</b> Positive cases = 20	186	100	79.5	40	100
	200	90	80.1	38.2	98.3
	224	85	89.7	53.1	97.7
	255	60	94.5	60	94.5
<b>290</b> Positive cases = 11	200	100	76.8	23.4	100
	249	90.9	92.3	45.4	99.3
	261	72.7	94.8	50	98
	290	36.4	97.4	50	95.5

Correlation between TSB and Kramer scale was 0.81 (95% CI 0.76-0.86,  $p < 0.01$ ) and between the app and Kramer scale 0.77 (95% CI 0.70-0.82,  $p < 0.01$ ). Accuracy measures of Kramer scale to detect different values of TSB are shown in Table 8. These values were determined according to the given values for each Kramer scale group.

Table 8 Kramer scale accuracy measures for TSB levels of 80, 100, 150, 200 and 250  $\mu\text{mol/l}$

TSB $\mu\text{mol/l}$	Sensitivity %	Specificity%	PPV %	NPV %
<b>80</b> Positive cases = 112	72.3	87	92	60.2
<b>100</b> Positive cases = 80	66.2	98.8	98	75.8
<b>150</b> Positive cases = 61	32.7	100	100	71.9
<b>200</b> Positive cases = 43	6.9	100	100	75
<b>250</b> Positive cases = 20	0	100	100	88



Sensitivity, specificity, PPV and NPV to detect TSB high risk cases were determined using the app high-intermediate and high-risk categories together, showing values of 78.5, 67.7, 18.3 and 67.7 respectively

## 6 Discussion

### 6.1 General Discussion

Our results showed a high correlation of 0.87 (95% CI 0.83-0.90,  $p < 0.01$ ) between TSB and the app, therefore our null hypothesis can be rejected. The use of smartphones as devices to detect NNJ is a relatively new topic, with the first reports published in 2014 (67). This novel technology has the potential to be a useful, affordable and reliable option as a screening tool to identify NNJ. In a previous report from United States (72), different races and ethnicities were studied, including Hispanic/Latino newborns, however, to our knowledge, this is the first study of its kind carried out in a Mexican population.

Our findings of birth weight and skin colour according to Fitzpatrick scale agree with previous data from general population in Mexico. For term newborns, the most common reported birthweight range is 2500-3500g and most frequent skin types in Mexican population are III and IV (92,93). We did not use Fitzpatrick scale to determine skin type in the newborns because it has not been validated in this life stage, however since most parents belong to type III and IV, we may assume that newborns skin may have a similar skin colour. Varughese *et al.*, in a study about reliability of TcB, classified newborns skin colour according to Fitzpatrick scale using a colour chart printed on a transparent sheet that was placed in the abdomen to compare with newborn skin and determine the colour in an easier way (40). A similar technique would have been useful in our study to determine newborns type of skin instead of parents and may be considered to be used in future studies.

Jaundice was clinically detected by Kramer scale in 53% of our sample. The global prevalence of jaundice varies among different reports, but in general has been reported to be 60 to 70% in term and 80% in preterm newborns, however most reports do not mention how jaundice diagnosis was made, if by visual assessment or any other diagnostic method. The use of Kramer scale as screening method for NNJ has been widely debated, since results of different studies show great variations. For example, Moyer *et al.*, found low to moderate correlation between visual assessment and TSB levels in 2 groups of observers (0.43 and 0.54) and Riskin *et al.*, 0.75. Both studies concluded that visual assessment is neither accurate nor reliable for detect NNJ and that the decision to perform TSB test should be based on additional factors, since newborns with high

levels of TSB may be clinically misdiagnosed as having low levels (28,29). On the other hand, studies from Mexico and Venezuela found high correlations between Kramer scale and TSB levels (0.82 and 0.93 respectively), concluding that Kramer scale is a reliable method to detect NNJ and should be implemented in units lacking TcB (26,30). Kramer scale and TSB levels correlation in this study was 0.81, which can be considered as a high correlation, however the sensitivity to detect any degree of jaundice was 72%. Thirty one of 112 positives cases (TSB  $\geq$  80  $\mu\text{mol/l}$ ) were not identified as jaundiced by Kramer scale. Specificity was higher (87%), therefore in this study Kramer scale was useful to detect newborns without jaundice, but not as a screening tool for NNJ.

Similar technologies using images obtained with smartphones and software-based analysis to detect NNJ have been studied by a few groups of researchers.

Rong *et al.*, in China, used an automated image-based bilirubin (AIB) technique, currently called BiliScan, which included a colour calibration card to obtain images. In 2016, they published the results of a study in 148 newborns. The correlation with TSB was 0.79, with 82% sensitivity, 60% specificity and the ROC AUC of 0.743 (74). Using the same technology, Bo *et al.*, published the results of 194 newborns in 2018, reporting a correlation between AIB and TSB of 0.82 when TSB  $\leq$  342  $\mu\text{mol/l}$  (20 mg/dl), but with lower accuracy at higher TSB levels (75). Similarly, a group from India carried out a study in a 35 newborns sample. Results showed a low to moderate correlation of 0.60 between TSB and the app when it was used in the chest and of 0.55 in the abdomen (76). BiliScan app is currently available for free, for both Android and IOS smartphones. When downloading the app, the user receives an image of the calibration card which can be printed in a regular colour ink jet or laser printer (KONICA, RICOH, EPXON, HP, Xerox and Canon are recommended) and photographic or art paper must be used respectively. This fact can explain in part the low to moderate performance of the app since the role of a good quality calibration card is relevant to the image analysis by the software.

In 2016, Aydin *et al.*, published the results of a study carried out in Turkey. They developed an image analysis system based on machine learning regression in a group of 40 healthy and 40 jaundiced newborns. Using a colour calibration card placed on the abdomen, they obtained images of the whole body. Correlation of 0.85 was calculated for the jaundiced group. Using a system estimate cut off value of 160  $\mu\text{mol/l}$  ROC curve analysis showed a 100% sensitivity and 50% specificity for predict TSB levels of 205  $\mu\text{mol/l}$ . They reported a process time of the system of approximately 1.95 s (73).

The most similar work to ours and with the biggest sample, is the one from Taylor and De Greef group at Seattle, US, which developed BiliCam. In 2014 they published the results of a 100 newborns sample. To evaluate the performance of BiliCam to identified newborns at risk of jaundice and compare it to TcB, they classified the participants according to the Bhutani nomogram. A correlation of 0.85 between BiliCam and TSB and 0.92 between TcB and TSB was reported. They concluded that their app had statistically equivalent performance to TcB to detect high risk cases and could be used as screening tool for NNJ instead of TcB with the advantage of higher accessibility (67). In 2018 their results from a greater sample of 530 newborns with different races and ethnicities (white, African American, Asian American, Hispanic/Latino) were published. To assess the utility of BiliCam and TcB as screening tools to identify newborns with significant jaundice they used 2 decision rules, considering as positives cases newborns with TSB  $\geq 290 \mu\text{mol/l}$  (17 mg/dl) and classified in the high-risk zone of Bhutani nomogram. For both decision rules the cut off values for BiliCam and TcB were TSB  $\geq 222 \mu\text{mol/l}$  (13 mg/dl) and Bhutani's high-intermediate and high-risk zones. The overall correlation between BiliCam and TSB was 0.91 (95% CI 0.90-0.93). Latino Hispanic ethnicity correlation was 0.91 as well, but with wider 95% CI (0.88-0.94), with the lowest correlation being in the Asian American (0.88). The sensitivity and specificity for the outcome of TSB  $\geq 290 \mu\text{mol/l}$  (17 mg/dl) were 100 and 76.4, and for the outcome high-risk zone were 84.6 and 81.3 respectively. Similar values were found for TcB performance (72).

Although the correlation found in this study between TSB levels and the app estimates was high 0.87 (95% CI 0.83-0.90,  $p < 0.01$ ), there is a trend of the app to underestimate TSB at higher values (Figure 4), which has also been reported with the use of TcB. One of the explanations to this fact is that TSB is an intravascular measurement of bilirubin concentration while TcB measures extravascular bilirubin, therefore it is expected to have different values (44). The same may be applied to results obtained from digital images of jaundiced skin. The Bland Altman analysis shows 95% limits of agreements values to be of around  $\pm 80 \mu\text{mol/l}$ . Considering that in Bhutani nomogram the differences between risk group limits are not higher than  $40 \mu\text{mol/l}$ , our limits of agreement are wider and may led to have misclassification of newborns. In this setting, the app cannot be considered as a diagnosis method that can substitute the measurement of TSB, however it can be useful as a screening tool.

The purpose of any NNJ screening method is to avoid missing detection of newborns with high levels of bilirubin that may lead to complications. This means that it needs to have a high sensitivity. It is preferable to have false positives, which may imply unnecessary confirmatory

blood testing than false negatives that would be misdiagnosed and neglected. Using ROC analysis we found app cut off values with high sensitivity to predict high TSB levels (Table 4). Our results in accuracy measures are similar to the reported by Taylor *et al.*, (72) however our sample size is smaller. The app did not show a high ability to predict high risk zone newborns according to Bhutani nomogram. An explanation may be to the low number of newborns in this group.

The correlation between TSB levels and the app estimates and its performance as screening tool found in this study is consistent with the study by Aune *et al.*, (unpublished data) in Caucasian newborns, therefore it can be assumed that the app has similar ability to detect jaundice in Fitzpatrick skin types range from I to IV. However, the app accuracy will need to be evaluated in populations with different skin type, such as V and VI of Fitzpatrick scale as well as in other ethnicities, such as Asiatic and African newborns.

## **6.2 Limitations and strengths**

### **6.2.1 Limitations**

This study has some limitations. Most of the participants were recruited in the first 24 hours of life when bilirubin levels are usually normal. With a broader range of ages and bilirubin levels we could have assessed the app performance in a bigger spectrum of newborns and results could be different. In addition, in order to avoid unnecessary punctures, only newborns who needed a blood test for any reason were included, which may lead to bias in the sample selection. Another limitation is related to Kramer scale. The researcher (the Master student) had no previous experience with it and although Kramer scale chart was used as a guide, this fact could contribute to some bias (misclassification). Besides, other conditions could influence the observer decision making, such as variation of lighting in the different settings and the time of the day in which the newborns were assessed, as well as newborn age, since skin colour may change during the first days of life (94). Therefore, Kramer scale results in this study should be valued with some caution.

Regarding to Fitzpatrick scale, it was missing in several fathers due to their absence during the moment of data collection. Although it is known that Mexican colour skin generally ranges from III to V, the results could be enriched having these missing variables.

Finally, it was planned to do simultaneous measurements of bilirubin with TcB to compare with the app estimates values, however unexpected issues related to TcB delivering happened which didn't allow to have the device on time for the study period. Having this comparison could have given more strength to the results.

### **6.2.2 Strengths**

The researcher is a medical doctor native from Mexico, which facilitated all the administrative procedures related to carry out this study and there was not a language barrier with participants and hospital personnel. Besides, she is a dermatologist who is used to classify colour skin according to Fitzpatrick scale.

The Hospital Materno-Infantil is public and opened to whole population which allowed to have a wide range of participants belonging to different social and economic groups.

Kramer scale was performed only by the researcher, which reduced interobserver variations in the assessment.

The blood tests were performed in the same laboratory using the same equipment, so the results are expected to be homogenous.

The images were obtained in two settings which could have had different light conditions, both artificial and natural, so the results can be valid in such different environments. In addition, images were obtained by the same person (the researcher) who had received a previous training. This could avoid variations in the image obtaining technique. However, this is an easy-to-use app, and it is expected that any person following the functioning instructions can be able to use it in a correct way.

Finally, all images were obtained within 60 minutes of the blood test, so it is expected that the app estimates levels correspond more accurately to the TSB levels obtained.

## **7 Future implications**

The performance of the new app needs to be tested in broader range of skin types, including darker colours. If ongoing and future studies in different types of skin show that the app have similar results to the previously found, it will have several implications.

Since the app only requires internet connection and the calibration card, it has the potential to be a point-of-care diagnosis tool with availability in any health care unit having internet access, regardless its geographical location or type (public/private, low/high income setting). Being a friendly-to-use app, it can be easily used by any health care personnel in charge of newborns care. Having a more accurate and reliable screening method than visual assessment can help to avoid diagnosis delays that can result in severe consequences. Besides, unnecessary blood test can also

be avoided, which may result in both, reducing probable complications related to the procedure but also reducing health care centres costs.

In underprivileged settings with high morbidity and mortality related to NNJ and where usually accurate diagnosis methods to its screening are lacking, this new technology has the potential to transform NNJ detection and follow-up, with the resulting timely diagnosis and treatment.

Phototherapy equipment may not be available in such settings, but newborns with high risk of complications can be transferred to better equipped units or alternative options can be provided, such as filtered sunlight phototherapy. These facts can contribute to decrease the global burden of complications, long term consequences and deaths which nowadays should be 100% preventable.

Future challenges imply the possibility of using the app without internet connection, accurate functioning in any smartphone with a proper resolution camera and an easy and safe delivery of the calibration card to the users.

## **8 Conclusion**

The study results suggest that the new smartphone app can provide accurate estimates of TSB levels in populations of newborns with different skin colours. It cannot substitute blood test to measure TSB levels, but it can potentially substitute and/or support visual assessment to screen and closely follow-up newborns with risk to develop higher levels of bilirubin and to determine which ones require a blood test.

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## Appendixes

### Data collection form

Case Report Form							
ID	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>						
Birth weight (g)	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>						
Gestational age (weeks + days)	<input type="text"/> <input type="text"/> + <input type="text"/>						
Date of birth (MM/DD/YYYY)	<input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>						
Time of birth (hh:mm)	<input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/>						
Fitzpatrick scale	I	II	III	IV	V	VI	Unknown
Mother	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Father	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Kramer's scale	0	1	2	3	4	5	
	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	
Transcutaneous bilirubin	<input type="text"/> <input type="text"/> <input type="text"/> $\mu\text{mol/l}$						
Bilirubin in blood sample	<input type="text"/> <input type="text"/> <input type="text"/> $\mu\text{mol/l}$						
Time for blood sample (hh:mm)	<input type="text"/> <input type="text"/> : <input type="text"/> <input type="text"/>						
Comments							

## Guideline

**ID :** Unique ID number for each newborn. ID appears on smartphone application after finishing image sampling.

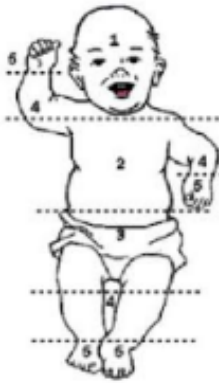
**Birth weight:** Enter **birth** weight in gram. (*Not current weight*)

**Gestational Age:** Enter gestational age. If unknown leave blank.

**Date and time of birth:** Enter date and time of birth to closest hour.

**Fitzpatrick scale:** Tag appropriate box.  
If not known, tag *unknown*.

**Kramer's scale:** Visual determination of jaundice. Has to be performed before other analysis are made. Grade degree of jaundice after following scale:



Clinical Extent	Grade
None	0
Limited to the head and neck	1
Involves the (chest and upper abdomen) and/or back	2
Involves the abdomen below the umbilicus to the knees	3
Involves the legs below the knees and/or upper and lower arms	4
Involves hands and/or feet	5

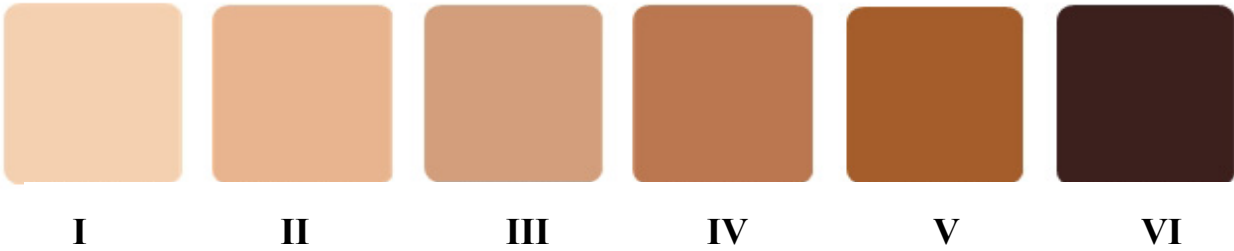
**Transcutaneous bilirubin:** Enter result of measurement from transcutaneous bilirubinometry

**Bilirubin in blood sample:** Enter result of measurement of bilirubin in blood sample

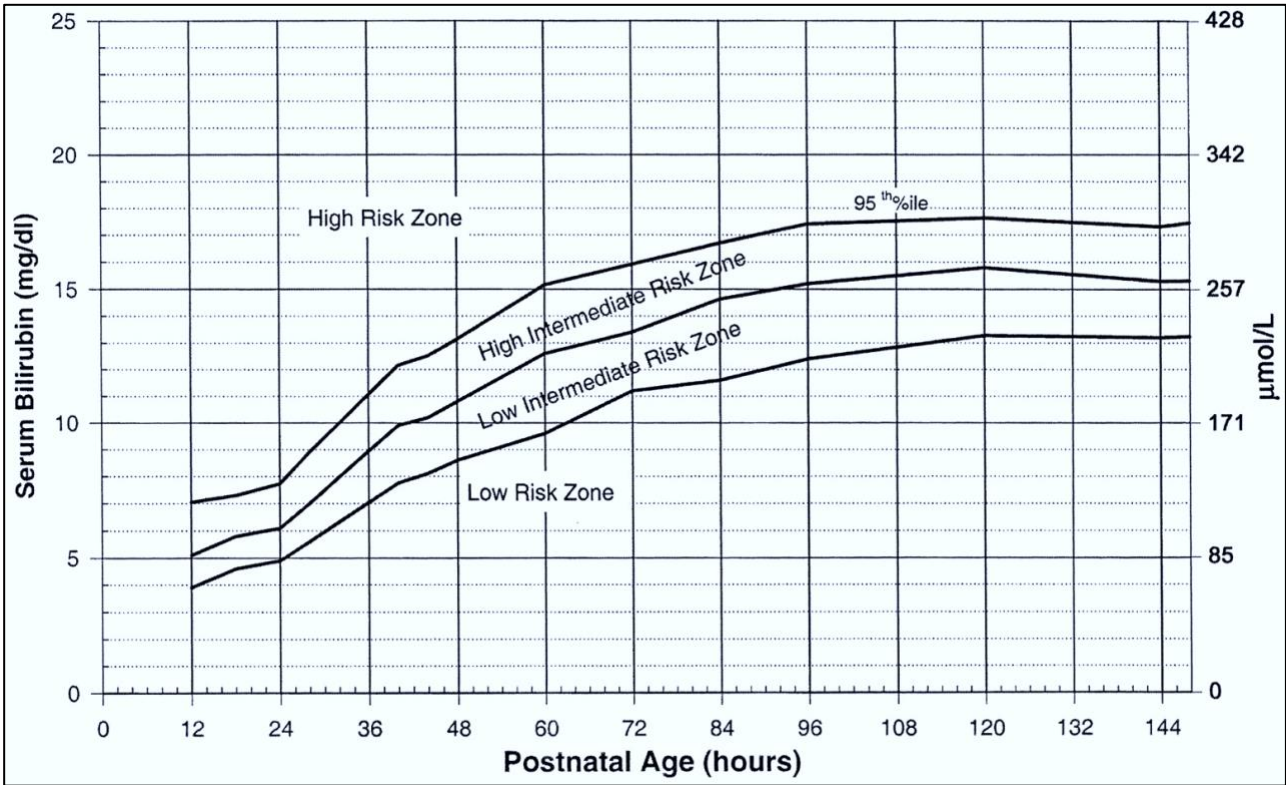
**Time for blood sample:** Enter time for blood sample. Should be within 60 minutes from obtaining images.



**Fitzpatrick Scale**



**Bhutani nomogram**



## ***Inform consent format Spanish version***

### CONSENTIMIENTO INFORMADO

#### **Dispositivo móvil como herramienta diagnóstica en la valoración de ictericia neonatal en una población mexicana**

Esta es una solicitud para ustedes (madre, padre o ambos) para permitir que su hijo participe en un proyecto de investigación en el cual un nuevo método para detectar ictericia neonatal será evaluado. Hemos desarrollado una aplicación para el teléfono celular (App) mediante la cual, a través de una fotografía digital se puede medir el grado de ictericia.

#### ANTECEDENTES

La ictericia es una condición en donde los niveles de una sustancia llamada bilirrubina se elevan y la piel se torna amarilla. La ictericia es muy frecuente en los recién nacidos y generalmente desaparece sola y no tiene consecuencias graves. Sin embargo, en algunos casos puede ser severa y si no se detecta a tiempo puede tener consecuencias severas con daño cerebral.

La forma convencional de medir los niveles de bilirrubina es mediante una muestra de sangre. Como la piel de los bebés se torna amarilla, se han desarrollado algunos instrumentos que miden el color de la piel (bilirrubinómetros). En muchas partes del mundo hay carencia de estudios de laboratorio y los instrumentos mencionados son muy costosos y no todos los centros de salud tienen acceso a ellos. Es por eso que existe la necesidad de contar con instrumentos de bajo costo, accesibles para la mayoría y que sean fáciles de utilizar para detectar esta condición en los recién nacidos.

El uso de teléfonos celulares se ha incrementado en todo el mundo, incluso en lugares con pocos recursos. Nosotros hemos desarrollado una App que utiliza la cámara del teléfono celular para obtener una fotografía que sirva para el diagnóstico de la ictericia. Esperamos que esta App pueda ser una forma barata y confiable con la cual se puedan salvar muchas vidas y disminuir el número de niños con discapacidades.

#### METODOS

Para poder estar seguros que esta App es confiable, necesitamos probarla en muchos recién nacidos con y sin diferentes grados de ictericia. Nos gustaría por lo tanto, tomar una fotografía de su bebé con un teléfono celular y analizar el color de la piel. El resultado de este análisis será comparado con el resultado de la muestra de sangre.

Si su bebé presenta cualquier grado de ictericia, se requiere hacer la prueba de sangre y utilizaríamos ese resultado para nuestro estudio. Si su bebé no presenta ictericia se obtendrá una muestra de 1.5 ml de sangre del dorso de la mano por personal calificado del servicio de pediatría para determinar el nivel de bilirrubina. En este último caso (que su bebé no tenga

ictericia), ustedes podrán estar presentes en el momento de la toma de la muestra si así lo desean.

Se tomará una fotografía de la piel de su bebé a nivel del pecho estando acostado boca arriba en la mesa de exploración. Si la cara del bebé es visible se eliminará esa fotografía.

#### ALMACENAMIENTO DE DATOS

La fotografía de su bebé será almacenada junto con los resultados de las pruebas de sangre y la medición del bilirrubinómetro. Además obtendremos otros datos de su bebé como edad gestacional (semanas de embarazo al nacimiento), edad del bebé el día de la fotografía, peso al nacer y tipo de piel tanto del bebé como de la madre.

Se asignará un número de identificación de estudio al bebé el cual será guardado en forma separada de la información que lo identifique, por lo cual no será posible por ningún motivo, identificar a su bebé en la serie de datos. Toda la información se almacenará en computadoras con estrictas medidas de seguridad.

#### PARTICIPACIÓN VOLUNTARIA

La participación en este estudio es totalmente voluntaria y aún cuando ustedes hayan firmado este consentimiento informado pueden retirarse del estudio en cualquier momento si así lo desean, lo cual deben informar al investigador a cargo del mismo, Dra. Gabriela Jiménez Díaz. Si no desean participar o se retiran del estudio, esto no tendrá ninguna repercusión en el tratamiento y cuidado de su bebé.

#### RESPONSABILIDAD

El investigador principal de este estudio es la Dra. Elisabeth Darj, profesora de Salud Global, médico gineco-obstetra en la Universidad de Ciencia y Tecnología de Noruega. Cualquier pregunta puede ponerse en contacto con ella en el correo electrónico [elisabeth.darj@ntnu.no](mailto:elisabeth.darj@ntnu.no).

Los datos y las imágenes serán recolectados por la Dra. Gabriela Jiménez Díaz, médico dermatólogo, estudiante de maestría en Salud Global en la misma universidad.

#### QUÉ PASARÁ CON EL ANÁLISIS Y LA INFORMACIÓN?

La información que se obtenga será utilizada únicamente para lo anteriormente descrito. Nosotros deseamos publicar los resultados de este estudio en una revista científica, pero no será posible identificar a su bebé en esa publicación.

CONSENTIMIENTO PARA PARTICIPAR

Autorizo que mi hijo(a) participe en este proyecto de investigación

Lugar, fecha: \_\_\_\_\_

\_\_\_\_\_

Madre (Nombre completo, firma, teléfono y/o correo electrónico)

\_\_\_\_\_

Padre (Nombre completo, firma, teléfono y/o correo electrónico)

\_\_\_\_\_

Testigo (Nombre completo, firma, teléfono y/o correo electrónico)

\_\_\_\_\_

Testigo (Nombre completo, firma, teléfono y/o correo electrónico)

Confirmando que se dio toda la información sobre el estudio

\_\_\_\_\_

Fecha, nombre y firma del investigador

## ***Inform consent English version***

### **Evaluation of a smartphone based diagnostic tool to assess neonatal jaundice in a Mexican population.**

This is a request to you as parents, to let your child participate in a research project, where a new method for detecting neonatal jaundice is being evaluated. We have developed a smartphone application (app), where we use the camera in the smartphone to assess the degree of jaundice.

#### **Background**

Jaundice is a condition where the levels of a compound called bilirubin is elevated and baby skin turns yellow. Jaundice is common among newborns and in most cases is self-limiting and harmless. However, when it is severe and unrecognized it can be fatal or cause serious brain injury.

Traditionally, the measurement of bilirubin is done by blood samples. As the skin of a newborn with jaundice turns yellow, optical devices that measure jaundice through assessment of skin color has been developed. In many parts of the world, access to blood sample analysis is scarce. In addition, the optical devices available today are expensive and not affordable for many hospitals. This results in the need for low-cost, reliable and easy-to-use screening tools that can identify newborns with this condition.

The distribution of smartphones is increasing in all parts of the world, including areas with limited resources. We have developed a smartphone-based screening tool for jaundice, where we use the camera in the phone. We hope that this can be a cheap and reliable tool that could have the potential to save tens of thousands of lives and reduce the number of children with disabilities.

#### **Methods**

To make sure that the mobile app is reliable, we need to test it on newborns with various degrees of jaundice and without it. We would like to take a picture of your child with a smartphone and analyze the skin color in the picture. This analysis will be compared with the result from a blood test.

If your child has jaundice the standard procedure is to draw a blood sample. We will then use that result in our study. If your child does not have jaundice, we will obtain some extra blood (1.5 ml) from the back of the hand, when blood for the newborn metabolic screen is drawn. We will take a picture of the skin of the chest while your baby is lying on the back on the examination table. If the face of your child is visible in the picture, this will be anonymized. We will also use a standard medical device called bilirubinometer for measuring jaundice through the skin of your newborn.

#### **Storing of data**

The picture of your newborn's skin will be stored together with the results of the blood test and the standard skin test for jaundice. In addition, we will collect and store information about your child including age, birthweight, and due date. As different levels of skin pigmentation could influence the result of our analysis, we also want to include the skin type of child and mother.

Your child will be given an identification number in the study, and this will be stored separately from the information that identifies your child. Thus, it will not be possible to identify your child in the data set. All information will be stored on secure computers.

**Participating is voluntary**

Participation in this study is voluntary. If you wish not to participate, your decision will have no consequences for the further treatment and care for your child.

**Responsibility**

The principal investigator of this study is Elisabeth Darj, Professor of Global Health, PhD,MD (obstetrics and gynecology) at Norwegian University of Science and Technology in Trondheim. If you have questions, or would like to withdraw your child from this study, you can contact Elisabeth Darj by email: [elisabeth.darj@ntnu.no](mailto:elisabeth.darj@ntnu.no)

The data and images will be collected by Gabriela Jimenez Diaz, master student of Global Health

**What happens with the analysis and information?**

The information that is collected will only be used as stated above. We want to publish the results of this study in scientific journals. It will not be possible to identify your child in this published document.

**Consent for participation**

I allow my child to participate in this research project.

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(Place and date)

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Mother's name, signature, telephone number and/or e-mail

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Father's name, signature, telephone number and/or e-mail

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Witness name, signature, telephone number and/or e-mail

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Witness name, signature, telephone number and/or e-mail

I confirm that information about the study has been given

Researcher name, signature and date:

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## Ethical approval from Norway



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<b>Region:</b> REK sør-øst	<b>Saksbehandler:</b> Silje U. Lauvrak	<b>Telefon:</b> 22845520	<b>Vår dato:</b> 25.06.2018	<b>Vår referanse:</b> 2018/1001 REK sør-øst D
			<b>Deres dato:</b> 07.05.2018	<b>Deres referanse:</b>

Vår referanse må oppgis ved alle henvendelser

Elisabeth Darj  
Norges teknisk-naturvitenskapelige universitet

### **2018/1001 Evaluering av et smarttelefonbasert diagnostisk verktøy for å vurdere neonatal gulsott i en meksikansk befolkning.**

**Forskningsansvarlig:** Norges teknisk-naturvitenskapelige universitet  
**Prosjektleder:** Elisabeth Darj

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst D) i møtet 13.06.2018. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10.

#### **Prosjektleders prosjektbeskrivelse**

*We will evaluate a smartphone-based App to diagnose neonatal jaundice. This App was developed at NTNU and has been tested previously in a Norwegian population in Trondheim with good results. Our aim is to test the App in another population with different skin type in order to determine if the results are similar to the previous ones. We will conduct a descriptive cross-sectional study in a Mexican hospital in a population of 150 newborns. Demographic data (birth weight, age on examination and gestational age) will be collected. We will obtain 4 digital images of the newborns for colorimetric analysis. Results will be compared with a clinical scale (Kramer) and with bilirubin levels which will be determined by blood samples and transcutaneous bilirubinometer. This App may be an affordable tool for detecting neonatal jaundice fast and easily in health care centers with low economic resources and therefore decrease the risk of severe or fatal hyperbilirubinemia complications in newborns.*

#### **Vurdering**

The Committee has no objections to implementation of the Research Project. The newborns will not have any risk of misdiagnosis since all standard procedures for detecting jaundice will be carried out.

The Committee presupposes that the project is approved by the local Health Research Ethics Committee in Mexico.

The Committee does, however, have some comments to the letter of information:

- For newborns with jaundice the standard procedure is to draw a blood sample for measuring bilirubin levels, and the result will be used in this study. For newborns without jaundice, there will be drawn some extra blood when blood for the newborn screen is drawn. The letter of information must clearly indicate how much extra blood will be drawn from these newborns.
- The Health Research Act of 2008, paragraph 17, requires that all the legal guardians of the participating child must sign the consent form. Because of this, the letter of information must make space for the signatures of all the legal guardians of the participating child.
- Please submit the revised letter of information to REK.

---

**Besøksadresse:**  
Gullhaugveien 1-3, 0484 Oslo

**Telefon:** 22845511  
**E-post:** post@helseforskning.etikkom.no  
**Web:** http://helseforskning.etikkom.no/

All post og e-post som inngår i saksbehandlingen, bes adressert til REK sør-øst og ikke til enkelte personer

Kindly address all mail and e-mails to the Regional Ethics Committee, REK sør-øst, not to individual staff

**Vedtak**

The project is approved on the condition that it is conducted as described in the Application Form, and the Research Protocol, and on the condition that the letter of information will be updated in accordance with the above-mentioned comments.

The approval is valid until 30.06.2019. For documentation and follow-up purposes, the data will need to be kept until 30.06.2024. The data must be stored as de-identified data, i.e. a file with key identifiable information stored separately from the file containing other data. The data must, be either deleted or anonymised within 6 months after this date.

The Committee's decision was unanimous.

**Appeals process**

The decision of the Committee may be appealed to the National Committee for Research Ethics in Norway. The appeal must be submitted to the Regional Committee for Research Ethics, Section B, South East Norway. The deadline for appeal is three weeks from the date on which you receive this letter.

Med vennlig hilsen

Finn Wisløff  
Professor em. dr. med.  
Leder

Silje U. Lauvrak  
Rådgiver

**Kopi til:** elisabeth.darj@ntnu.no  
Norges teknisk-naturvitenskapelige universitet ved øverste administrative ledelse:  
postmottak@adm.ntnu.no



**Ethical approval from Mexico**



**HOSPITAL DE ESPECIALIDADES MATERNO INFANTIL DE LEON  
COMITÉ DE ETICA EN INVESTIGACION  
REGISTRO CONBIOETICA-11-CEI-002-20160627**

Fecha: 06 de junio del 2018.  
OFICIO: CEI 03 – A /2018.  
Asunto: Dictamen de  
Protocolo: Ext-06-2018.

NOMBRE DEL INVESTIGADOR (S): Dra. Gabriela Jiménez Díaz.

Folio: Ext-06-2018

Dictamen **APROBADO**: CONBIOETICA HEMIL--11-CEI-Ext-06-2018-002-20160627

**"DISPOSITIVO MÓVIL COMO HERRAMIENTAS DIAGNÓSTICA EN LA VALORACIÓN DE  
ICTERICIA NEONATAL EN UNA POBLACIÓN MEXICANA"**

Me permito informarle que su protocolo de investigación con el Folio: Ext-06-2018 ha sido revisado por el Comité de Ética en Investigación, y en base al artículo 16 del Capítulo 1 del título segundo de la Ley General de Salud se emite el dictamen de APROBADO.

Se le solicita de la manera más atenta que a la conclusión del mismo nos retroalimente con los resultados y de las presentaciones en físico o escritas que pudieran generarse en relación al presente protocolo.

Se le recuerda que el presente dictamen, tiene vigencia de 1 año. En caso de no terminarse o de no entregar resultados deberá registrarse nuevamente o se solicitará estado por parte de nuestro comité. A partir de ahora, se podrá realizar el registro de su proyecto en la siguiente plataforma de la Secretaría de Salud del estado de Guanajuato:

<http://salud3.guanajuato.gob.mx/proyectos>

Sin otro particular por el momento, aprovecho para reiterarle las seguridades de mi más distinguida consideración.

Atentamente

"GUANAJUATO ORGULLO Y COMPROMISO DE TODOS"

DRA. MA. SALUD ALEJANDRA VALADEZ ORTEGA

PRESIDENTE CEI HEMIL

C.c.p. LEO. Marta Patricia Aguilar Secretaria del CEI, Minutario.  
**Hospital de Especialidades Materno Infantil de León**  
Avenida de la Juventud No. 116, Col. Jol-Gua-Ber, León, Gto. C.P. 37410 Tels. (477) 777 08 94, (477) 777 83 58  
[salud.guanajuato.gob.mx](http://salud.guanajuato.gob.mx)

