Review

Neonatology

Neonatology 2016;110:172–180
DOI: 10.1159/000445708

Received: January 28, 2016
Accepted after revision: March 22, 2016
Published online: May 14, 2016

# Neonatal Jaundice in Low- and Middle-Income Countries: Lessons and Future Directions from the 2015 Don Ostrow Trieste Yellow Retreat

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**Key Words**
Neonatal jaundice · Severe hyperbilirubinemia · Acute bilirubin encephalopathy · Kernicterus · Low- and middle-income countries

**Abstract**
Severe neonatal hyperbilirubinemia, defined as total serum bilirubin (TSB) ≥20 mg/dl, is associated with a higher risk of permanent neurological sequelae and death. Jaundice can and should be promptly diagnosed and treated. Reliable methods for TSB assay are not always readily available, particularly in low- and middle-income countries, making the true incidence of severe neonatal jaundice (NNJ) difficult to estimate. To gather a more comprehensive picture, a symposium addressing NNJ worldwide was organized during the 2015 Don Ostrow Trieste Yellow Retreat. Data collected by several researchers in different regions of the world were presented and differences/similarities discussed. This report points out the need for: (1) a coordinated worldwide effort to define the burden and the causes of severe NNJ and its consequences; (2) aggressive educational programs for families and health personnel to facilitate timely care-seeking, and (3) accurate diagnostics and effective phototherapy.



## Introduction

Over 60% of all newborns develop neonatal jaundice (NNJ), a physiologic condition characterized by yellowish discoloration of the skin and conjunctiva as a consequence of increased levels of serum bilirubin during the first week of life [1–3]. NNJ is usually benign, but in some cases it can progress to severe hyperbilirubinemia, acute bilirubin encephalopathy (ABE) and kernicterus/chronic bilirubin encephalopathy (CBE) [4–8]. ABE and CBE are

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1661–7800/16/1103–0172$39.50/0

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**Fig. 1.** The DOTYR-15 attendees.

largely preventable if severe hyperbilirubinemia is identified early and treated promptly with effective phototherapy or, for hazardous cases, exchange transfusion. Guidelines for managing jaundice have been proposed by the American Association of Pediatrics (AAP), the UK National Institute for Health and Care Excellence (NICE) and others [8–20].

With improvements in prevention and treatment, the number of cases of severe hyperbilirubinemia in high-income countries (HICs) has decreased markedly since the 1990s [21, 22]. As assessed by population-based studies and registries, the incidence of severe hyperbilirubinemia in HICs is currently estimated to be about 31.6/100,000 live births (95% CI 11.8–51.3) [23–27], while the incidences of ABE and CBE have been estimated as being in the range of 1.0–3.7 and 0.4–2.7/100,000 live births, respectively [28–30].

The situation is completely different in low- and middle-income countries (LMICs). No harmonized protocols for hyperbilirubinemia classification and management have been implemented in most LMICs, leading to wide variations in protocols and rendering difficult if not impossible comparisons between different locations. The classification of hyperbilirubinemia in the countries included in this article was usually established at a local level, with the exception of Malaysia and Egypt which adopted the AAP guidelines for NNJ management. Despite these limitations, the prevalence is said to be high in LMICs, where records and documentation of the incidence of NNJ, ABE and CBE are usually poor and variable [1, 20, 31].

A recent Child Health Epidemiology Reference Group (CHERG) modeling study used country-specific and regional estimates of the prevalence of Rhesus (Rh)-positive babies born to Rh-negative mothers, G6PD deficiency, moderate-to-late preterm birth (i.e. 32–36 weeks gestation) and infants with none of these 3 factors, to estimate the risk of neonatal mortality and/or survival with kernicterus worldwide and by geographical region [32]. The

**Table 1.** NNJ in African countries

| Country | Severe NNJ incidence, % | ABE[a] incidence, % | CBE and kernicterus[b] incidence, % of NNJ | NNJ deaths of newborns admitted, % | NNJ deaths with respect to all deaths, % | CFR due to NNJ, % | CFR due to ABE, % | Mortality rate | Reference |
|---|---|---|---|---|---|---|---|---|---|
| Egypt | n/a | 18% of NNJ | n/a | n/a | n/a | 10.5 | 59.1 | n/a | [33] |
| | n/a | 30% of NNJ | 18.1 | n/a | n/a | 6.5 | 22.4 | n/a | [34] |
| Kenya | 34.4 | n/a | n/a | 7.8 | n/a | 22.7 | n/a | n/a | [35] |
| | 9.2 | n/a | n/a | 1.3 | 5.7 | 14.3 | n/a | n/a | [36] |
| Nigeria | 26.9 | 14.9 | n/a | 3.5 | n/a | 13.0 | 23.5 | n/a | |

n/a = Not available.

[a] ABE is a clinical syndrome of lethargy, hypotonia and poor sucking, which may progress to hypertonia (with opisthotonos and retrocollis) with a high-pitched cry and fever, and eventually to seizures and coma.

[b] CBE and kernicterus consist of the clinical sequelae of ABE characterized by irreversible brain damage associated with athetoid cerebral palsy (with or without seizures), developmental delay, hearing deficit, oculomotor disturbances, dental dysplasia and mental deficiency. Histologically, CBE is characterized by deep-yellow staining of neurons and neuronal necrosis of the basal ganglia and brainstem nuclei.

CHERG study estimated that Rh disease and/or extreme hyperbilirubinemia (EHB; TSB >25 mg/dl) due to other causes, were responsible for a mortality rate of 119/100,000 live births in Eastern Europe/Central Asia, Latin America, sub-Saharan Africa and South Asia, compared with 1/100,000 live births in HICs [32]. In these same 4 geographical regions, the prevalence of kernicterus was estimated at 73/100,000 live births, compared with 10/100,000 live births in HICs [32].

The Don Ostrow Trieste Yellow Retreat (DOTYR-15; fig. 1) is a meeting where basic and clinical aspects of bilirubin are discussed by international experts. In 2015, for the first time, a session was devoted to reports from LMICs from Africa and Asia. This article summarizes what was reported at this meeting on the prevalence of NNJ, ABE and CBE in these countries.

It is important to note that information reported from LMICs is largely drawn from tertiary hospitals that, overwhelmingly, treat infants admitted after the onset of hyperbilirubinemia in the community [1, 20]. The denominator, in the studies described here, is usually the number of infants admitted with NNJ, and thus overestimates the population-based prevalence. If referral hospital(s) were able to capture a whole catchment area where the number of live newborns was known, the incidence of severe jaundice, ABE and CBE might be significantly underestimated. The limited information we report here is therefore reflective of failures in the system of jaundice management, diagnosis and documentation in many LMICs.

## NNJ in Selected African Countries

Recent studies have reported important data on severe hyperbilirubinemia, ABE and CBE in African countries (table 1). An Egyptian study of 247 babies with TB ≥25 mg/dl admitted in 2008 to the Cairo University Children Hospital, a referral children's hospital, reported that 44 (17.7%) presented with moderate or severe ABE and 26 (10.4%) died, leading to a case fatality rate (CFR) of 56.8% (26/44) [33]. A separate study in the same hospital over 15 months in 2009–2010 reported on 193 infants requiring intensive phototherapy or exchange transfusion; 58 (30.0%) had moderate or severe ABE at presentation, with kernicterus diagnosed in 35 (60.3%), and 13 with severe ABE died, giving a CFR of 22.4% among those with ABE [34].

A Kenyan study at a pediatric referral center reported that a total of 306 infants were admitted in the year 2000, with 106 (34.4%) being diagnosed with jaundice; 24 of the jaundiced infants died, giving a CFR of 22.7% [35]. A separate study in a Kenyan district hospital over 19 years (1990–2008) reported that out of 8,756 neonatal admissions, 811 (9.2%) had severe NNJ and 116 of these died, giving a CFR of 14.3% [36].

A recent comprehensive review of 198 studies (1990–2014) based primarily on single-hospital experiences in Nigeria concluded that little progress has been made over the last 50 years [20]. Severe NNJ and kernicterus remain highly prevalent and continue to be associated with a high CFR [20, 37–46].

**Table 2.** NNJ in Asian countries

| Country | Severe NNJ incidence, % | ABE incidence, % | CBE and kernicterus incidence, % | NNJ deaths of newborns admitted, % | NNJ deaths with respect to all deaths | CFR due to NNJ, % | CFR due to ABE, % | Mortality rate | Reference |
|---|---|---|---|---|---|---|---|---|---|
| China | 49.1 | n/a | 0.9 | n/a | n/a | n/a | n/a | n/a | [47] |
| Bangladesh | 15.7 | n/a | 0.5 | 0.6 | n/a | 3.8 | 55.6 (of CBE) | n/a | [48] |
| | 5.9 | n/a | n/a | 0.2 | 1.1 | 3.9 | n/a | n/a | [49] |
| India | 15.3 | n/a | n/a | 1.0 | 4.4% | 6.7 | n/a | n/a | [50] |
| | n/a | n/a | n/a | n/a | n/a | n/a | n/a | 730/100,000 live births | [51] |
| Myanmar | 46.0 | n/a | n/a | n/a | n/a | n/a | n/a | n/a | [52] |
| | n/a | 12.7% NNJ in A<br>21.2% NNJ in B | 2.0% NNJ in A<br>1.5% NNJ in B | n/a | n/a | 7.2 (A)<br>11.2 (B) | 46.9 (A)<br>25.0 (B) | n/a | [53][a] |
| Malaysia | 25–30 | n/a | n/a | n/a | n/a | n/a | n/a | n/a | [54] |
| | 3.8 | n/a | n/a | n/a | n/a | n/a | n/a | n/a | |
| Indonesia | 6.8 | 2.2 | n/a | 1.6 | n/a | 24.2 | 74.9 | n/a | |

n/a = Not available. For the definitions of ABE, CBE and kernicterus, please see footnote to table 1.
[a] The study by Arnolda et al. [53] was conducted in 2 hospitals, denoted as hospital A and hospital B.

As part of an ongoing 'Saving Lives at Birth (SLAB)' project, a collaborative study of severe NNJ and ABE prevalence was performed at 9 hospitals in 6 regions of Nigeria in 2014–2015. The prevalence of severe hyperbilirubinemia was high: 26.9% of admissions for jaundice had bilirubin levels >20 mg/dl and 14.9% of hospitalized neonates developed ABE, with a CFR of 13.0% based on infants with NNJ (unpubl. data). A delay in seeking care is common in newborns with severe NNJ [20]. As a consequence, advanced ABE that benefits little from therapy is often present at the time of admission. A high prevalence of G6PD deficiency, combined with exposure to oxidants (e.g. mothballs and menthol creams), is a major cause of hemolytic jaundice, followed by ABO incompatibility and Rh isoimmunization [1, 20].

### NNJ in Selected Asian Countries

The prevalence of serious outcomes associated with NNJ in Asian countries varies widely (table 2). The Chinese Medical Association conducted a survey of all infants discharged from 86 general and maternity hospitals in 2005 and found that 49.1% had NNJ; 0.9% developed bilirubin encephalopathy, with a higher rate in the term neonates (0.9%) than in the preterm neonates (0.5%) [47]. The authors suggest that the higher rate in the term infants could be due to an assumption that jaundice in this group is physiological in origin, leading to a failure to consider pathological risk factors.

Published data on NNJ in Bangladesh is limited. A prospective cohort of neonatal admissions to the Khulna Medical College Hospital over 36 months in 2005–2008 reported that 15.7% of infants presented with NNJ, with 2.8% of these developing kernicterus and 5 of them dying (CFR 55.6%) [48]. In another study, 5.9% of the neonates admitted developed severe jaundice while 0.2% had jaundice-associated deaths (CFR 3.9%) [49]. It is important to note that G6PD deficiency is common in Bangladesh and may be an important contributor to the development of severe jaundice and kernicterus [49].

From India, Dutta et al. [50] reported that severe jaundice represented 15.3% of neonatal admissions, with a CFR of 6.7%, leading to 4.4% of the deaths related to jaundice. An observational study by Bang et al. [51] reported that severe jaundice had a mortality rate of 7.3/1,000 live births in Indian rural villages.

In 2013, statistics from Myanmar government hospitals reported that NNJ was responsible for 46% of hospital admissions country-wide and was a major cause of neonatal morbidity and death [52]. A study of neonates treated with phototherapy in 2 specialized pediatric referral hospitals identified home-births, self-referrals and G6PD screening status as important risk factors for presentation with ABE [53].

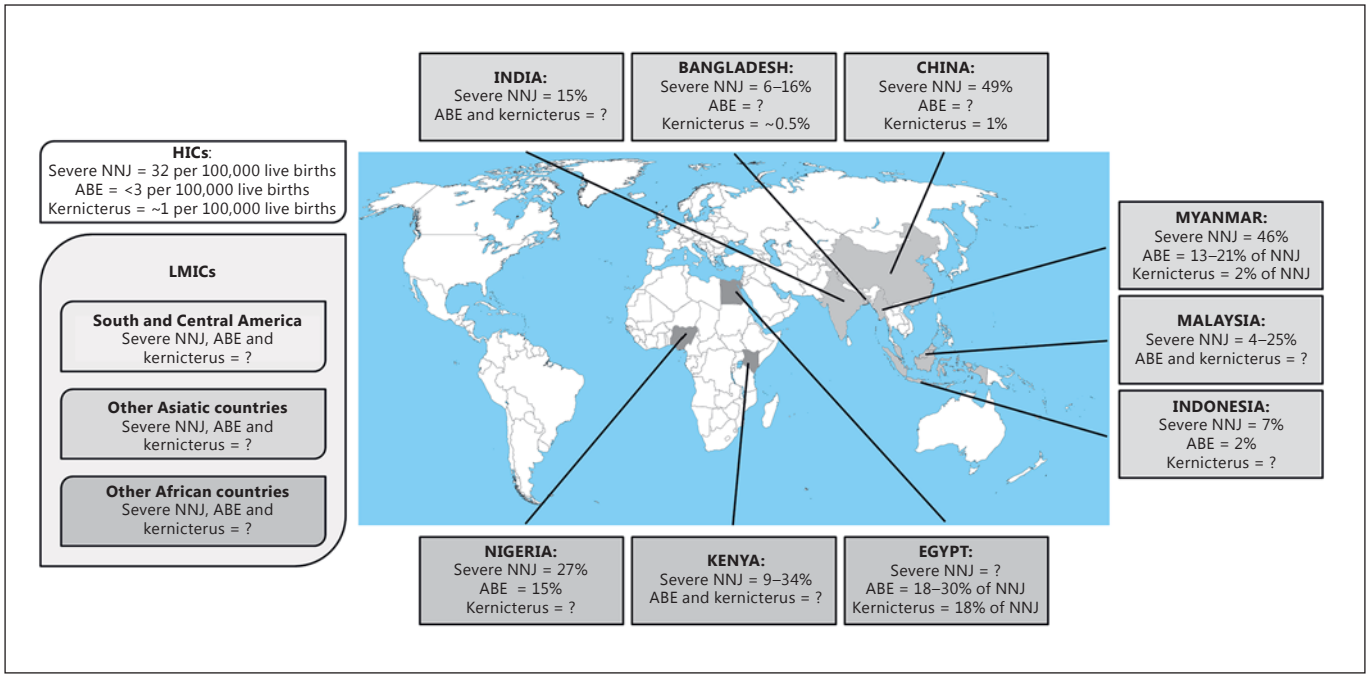


**Fig. 2.** Incidence of severe NNJ in LMICs. The data reported correspond to hospital statistics. No national records were found in the literature.

In 1999, a preliminary report of the National Perinatal Health Conference stated that about 25–30% of babies admitted to selected hospitals in Malaysia were severely jaundiced with serum bilirubin of >20 mg/dl [54]. The incidence of severe jaundice reported from 4 Malaysian major centers in 2012 varied widely. In 3 of these centers, severe jaundice (bilirubin levels >20 mg/dl) represented 1.7–3.5% of NICU admissions, while data reported by Selayang Hospital at DOTYR-15 showed that severe jaundice was present in 15.8% of its NICU admissions. Data on ABE and kernicterus have not been routinely or systematically collected, so their incidence in Malaysia is unknown.

A recent study analyzing NNJ in Indonesia with SLAB funding assessed the prevalence of severe jaundice (TSB >20 mg/dl) and ABE at 8 hospitals in 3 regions of Indonesia [unpubl. data]. The prevalence of severe jaundice and ABE in babies admitted during the study was 6.8 and 2.2%, respectively, leading to a CFR caused by NNJ of 24.2 and 74.9%, respectively, for ABE. However, most of the deaths from ABE were associated with neonatal sepsis. The data showed different patterns of severe hyperbilirubinemia and ABE. Of note is the observation that the majority of ABE cases were in hospitals located in remote regions, where fewer resources for NNJ management are available.

## Future Data Needs and Directions

The data reported above (graphically represented in fig. 2) are not based on a systematic review of the literature; rather, they reflect a convenience sample of data familiar to the DOTYR-15 attendees (for the list of authors who participated in the collection of the data, see the Appendix). Nevertheless, it is clear that there is a need for a data collection strategy that can inform the development of a worldwide approach for the early diagnosis and appropriate management of NNJ, in order to prevent the tragedy of bilirubin-induced neurological damage. Such a strategy could combine internationally developed frameworks for data collection that are adopted and adapted to local conditions and capacities. The process of local adaptation could commence with national scoping studies like that undertaken in Nigeria [20] that identify and review relevant data already published in peer-reviewed and grey data. This information can then be used as a basis for identifying the research priorities and routine collecting of information that are needed to inform national policy and practice.

### The Present and the Future in Preventing Serious NNJ

The CHERG modeling study estimated that 78% of cases of EHB are attributable to Rh disease, 6% to G6PD, 2% to moderate/late preterm birth and 15% to other causes; 80% of the affected neonates are in countries with a neonatal mortality rate ≥15/1,000 live births with the distribution of risks similar to that found worldwide [9].

Although the incidence of severe hyperbilirubinemia due to Rh disease in sub-Saharan Africa appears to be less than that due to G6PD deficiency [20], it can be prevented by anti-D prophylaxis [55]. The CHERG model estimates that there is no EHB attributable to Rh disease in HICs thanks to effective prevention and treatment, but at the same time notes that the high cost of immunoprophylaxis needs to be addressed in LMICs [9]. The importance of Rh disease varies widely with the prevalence of Rh-negative maternal status, but the issue of affordable prophylaxis is clearly a priority for many LMICs. The lack of routine maternal and neonatal blood testing in many LMICs is also a barrier, and also impacts the management of ABO incompatibility as a risk factor for serious NNJ [7, 32, 53, 56–59].

A WHO Working Group recommended in 1989 that, in all regions with a prevalence of G6PD deficiency of 3–5% or more in males, there should be universal screening accompanied with an education campaign for parents and health workers [60, 61]. A recent review noted the lack of empirical evidence of the efficacy of such programs in reducing the risk of severe hyperbilirubinemia, but nevertheless echoed this recommendation on the basis of the available evidence and understanding [1, 9, 10, 31, 53, 56, 62–66]. While screening of cord-blood for G6PD deficiency is of relatively low cost, the experience of the DOTYR-15 participants is that there would need to be a substantial investment in infrastructure to support universal screening programs.

Where routine maternal and neonatal blood testing and universal screening for G6PD deficiency are currently unavailable, a number of low-cost interventions remain immediately feasible. Extremely important are: the education of parents and health care workers on the risks of bilirubin-induced neurological damage, the avoidance of exposure to triggers of hemolysis and the appropriate follow-up of newborns after delivery [67–70]. Public awareness and parental training for the identification of the signs of NNJ [68–75], together with proper training for health care providers [10, 75–77], can contribute significantly to reducing the high prevalence of severe hyperbilirubinemia and ABE in low-resource settings.

Furthermore, the lack of affordable tools for the real-time objective measurement and monitoring of bilirubin levels continues to be a challenge [1, 31]. Health facilities often face long delays for TSB results and in primary health care settings or remote areas, testing is usually unavailable. The Bilistick System (Bilimetrix S.R.L., Trieste, Italy) is a low-cost, point-of-care bilirubin assay able to provide early NNJ diagnosis by determining TSB concentration from a tiny drop of blood, and is currently in advanced testing [78]. If successful, it could fulfil the need for rapid results and predischarge screening in already-equipped facilities and for decentralized testing and referral to support visual assessments.

The lack of effective phototherapy units, especially those capable of providing intensive irradiance (>30 μW/cm$^2$), contributes to the incidence of severe NNJ [1, 45, 79–81]. A recent report described a canopy for providing filtered-sunlight phototherapy, which was found to be effective in reducing TSB in infants with mild-to-moderate hyperbilirubinemia [70]. In addition, we have seen rapid growth in the availability of robust LED phototherapy, both single- and double-sided, designed specifically for use in low-resource settings.

### Conclusions and Perspectives

It is clear that severe NNJ remains a life-threating condition in many areas of the world, though the true dimension of the problem is largely unknown. Severe NNJ has different etiologies, dependent on variable genetic backgrounds and geographical location, even within regions of the same country. The identification of needs and a concerted effort to improve management at different levels of the health system can significantly reduce ABE and improve opportunities for thousands of newborns around the world.

The prime importance of educational programs for families and health care personnel to achieve early identification of the signs of NNJ and seek prompt treatment should be highlighted. Moreover, we stress the need for introducing newborn screening methods for G6PD deficiency in LMICs, increasing the number of regular check-ups of ABO-incompatible and Rh-negative pregnant women and the application of specific Rh disease protection as important public health perspectives.

We recommend the introduction of inexpensive and simple-to-use devices, for measuring bilirubin and effectively treating NNJ, as essential tools required in LMICs.

Last, but not least, is the need of support from national health systems and international agencies to recognize NNJ as a priority and to invest resources to address this tragic, and largely preventable, condition.

## Appendix

*List of Authors Who Participated in the Collection of the Data*

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## Acknowledgements

This study and the 2015 session of the Don Ostrow Trieste Yellow Retreat were made possible by an in-house grant from the Fondazione Italiana Fegato (FIF). We are grateful to Lucia Napoli and Sabrina Corsucci of the FIF for the support in organizing the event and to the AREA Science Park for providing logistic help.

The studies on NNJ performed in Nigeria and Indonesia were possible due to the generous support of the Saving Lives at Birth partners: the US Agency for International Development (USAID), the government of Norway, the Bill & Melinda Gates Foundation, Grand Challenges Canada and the UK government (FOG award No. AID-OAA-F-13-00072).

We would like to thank Bolajoko Olusanya, PhD Centre for Healthy Start Initiative, Lagos, Nigeria, and Tina M. Slusher and Tara Zamora, University of Minnesota and Hennepin County Medical Center, Minn., USA, for their help in collecting the supporting data for the global data presented. Dr. Marcelina Heidy Limanto at the Dr. Cipto Mangunkusumo Hospital, Jakarta, is acknowledged for her very efficient assistance during the Indonesian data collection.

## References

1 Olusanya BO, Ogunlesi TA, Slusher TM: Why is kernicterus still a major cause of death and disability in low-income and middle-income countries? Arch Dis Child 2014;99:1117–1121.
2 Burke BL, Robbins JM, Bird TM, Hobbs CA, Nesmith C, Tilford JM: Trends in hospitalizations for neonatal jaundice and kernicterus in the United States, 1988–2005. Pediatrics 2009;123:524–532.
3 Young Infants Clinical Signs Study Group: Clinical signs that predict severe illness in children under age 2 months: a multicentre study. Lancet Lond Engl 2008;371:135–142.
4 Hansen TWR: Mechanisms of bilirubin toxicity: clinical implications. Clin Perinatol 2002; 29:765–778, viii.
5 Newman TB, Maisels MJ: Evaluation and treatment of jaundice in the term newborn: a kinder, gentler approach. Pediatrics 1992;89: 809–818.
6 Volpe JJ: Neurology of the Newborn. Amsterdam, Elsevier Health Sciences, 2008.
7 Maisels MJ: Managing the jaundiced newborn: a persistent challenge. CMAJ 2015;187: 335–343.
8 Barrington KJ, Sankaran K; Canadian Paediatric Society Fetus and Newborn Committee: Guidelines for detection, management and prevention of hyperbilirubinemia in term and late preterm newborn infants (35 or more weeks' gestation) – summary. Paediatr Child Health 2007;12:401–407.
9 World Health Organization: WHO recommendations on postnatal care of the mother and newborn 2014 (cited December 23, 2015). http://www.who.int/iris/handle/10665/97603.
10 World Health Organization: Pocket Book of Hospital Care for Children: guidelines for the management of common childhood illnesses. Geneva, World Health Organization, 2013.
11 NICE/National Institute for Health and Care Excellence: Neonatal jaundice 2010. https://www.nice.org.uk/guidance/cg98/evidence/full-guideline-245411821.
12 NICE/National Institute for Health and Care Excellence: Updated neonatal jaundice pathway 2014 (cited December 23, 2015). http://pathways.nice.org.uk/pathways/neonatal-jaundice.

13 NICE/National Institute for Health and Care Excellence: Updated postnatal care 2014 (cited December 23, 2015). https://www.nice.org.uk/guidance/cg37.
14 Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics 2004;114:297–316.
15 Screening of infants for hyperbilirubinemia to prevent chronic bilirubin encephalopathy: US Preventive Services Task Force recommendation statement. Pediatrics 2009;124:1172–1177.
16 Bhutani VK; American Academy of Pediatrics Committee on Fetus and Newborn: Phototherapy to prevent severe neonatal hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics 2011; 128:e1046–e1052.
17 Whyte R: Safe discharge of the late preterm infant. Paediatr Child Health 2010;15:655–666.
18 NANN Board of Directors: Prevention of acute bilirubin encephalopathy and kernicterus in newborns. Position Statement #3049. Adv Neonatal Care 2011;11(suppl):S3–S9.
19 Queensland Health Statewide Maternity and Neonatal Clinical Guidelines Program: Neonatal jaundice clinical guideline supplement 2012 (cited December 23, 2015). https://www.health.qld.gov.au/qcg/documents/s_jaundice.pdf.
20 Olusanya BO, Osibanjo FB, Mabogunje CA, Slusher TM, Olowe SA: The burden and management of neonatal jaundice in Nigeria: a scoping review of the literature. Niger J Clin Pract 2016;19:1–17.
21 Bhutani VK: Editorial: building evidence to manage newborn jaundice worldwide. Indian J Pediatr 2012;79:253–255.
22 Bhutani VK, Vilms RJ, Hamerman-Johnson L: Universal bilirubin screening for severe neonatal hyperbilirubinemia. J Perinatol 2010;30(suppl):S6–S15.
23 Ebbesen F, Andersson C, Verder H, Grytter C, Pedersen-Bjergaard L, Petersen JR, et al: Extreme hyperbilirubinaemia in term and near-term infants in Denmark. Acta Paediatr 2005;94:59–64.
24 Manning D, Todd P, Maxwell M, Jane Platt M: Prospective surveillance study of severe hyperbilirubinaemia in the newborn in the UK and Ireland. Arch Dis Child Fetal Neonatal Ed 2007;92:F342–F346.
25 Sgro M, Campbell D, Shah V: Incidence and causes of severe neonatal hyperbilirubinemia in Canada. CMAJ 2006;175:587–590.
26 Zoubir S, Mieth RA, Berrut S, Roth-Kleiner M; Swiss Paediatric Surveillance Unit: Incidence of severe hyperbilirubinaemia in Switzerland: a nationwide population-based prospective study. Arch Dis Child Fetal Neonatal Ed 2011;96:F310–F311.
27 Bjerre JV, Petersen JR, Ebbesen F: Surveillance of extreme hyperbilirubinaemia in Denmark. A method to identify the newborn infants. Acta Paediatr 2008;97:1030–1034.
28 McGillivray A, Evans N: Severe neonatal jaundice: is it a rare event in Australia? J Paediatr Child Health 2012;48:801–807.
29 Gotink MJ, Benders MJ, Lavrijsen SW, Rodrigues Pereira R, Hulzebos CV, Dijk PH: Severe neonatal hyperbilirubinemia in the Netherlands. Neonatology 2013;104:137–142.
30 Bhutani VK, Johnson L: Kernicterus in the 21st century: frequently asked questions. J Perinatol 2009;29(suppl 1):S20–S24.
31 Olusanya BO, Imam ZO, Emokpae AA, Iskander IF: Revisiting the criteria for exchange transfusion for severe neonatal hyperbilirubinemia in resource-limited settings. Neonatology 2016;109:97–104.
32 Bhutani VK, Zipursky A, Blencowe H, Khanna R, Sgro M, Ebbesen F, et al: Neonatal hyperbilirubinemia and Rhesus disease of the newborn: incidence and impairment estimates for 2010 at regional and global levels. Pediatr Res 2013;74(suppl 1):86–100.
33 Gamaleldin R, Iskander I, Seoud I, Aboraya H, Aravkin A, Sampson PD, et al: Risk factors for neurotoxicity in newborns with severe neonatal hyperbilirubinemia. Pediatrics 2011; 128:e925–e931.
34 Iskander I, Gamaleldin R, El Houchi S, El Shenawy A, Seoud I, El Gharbawi N, et al: Serum bilirubin and bilirubin/albumin ratio as predictors of bilirubin encephalopathy. Pediatrics 2014;134:e1330–e1339.
35 Simiyu DE: Morbidity and mortality of neonates admitted in general paediatric wards at Kenyatta National Hospital. East Afr Med J 2003;80:611–616.
36 Mwaniki MK, Gatakaa HW, Mturi FN, Chesaro CR, Chuma JM, Peshu NM, et al: An increase in the burden of neonatal admissions to a rural district hospital in Kenya over 19 years. BMC Public Health 2010;10:591.
37 Ugwu RO, Eneh AU, Oruamabo RS: Blood transfusion therapy in neonates admitted into the Special Care Baby Unit (SCBU) of University of Port Harcourt Teaching Hospital, Port Harcourt. Niger J Med 2006;15:401–405.
38 Ojukwu JU, Abonyi LE, Ugwu J, Orji IK: Neonatal septicemia in high risk babies in South-Eastern Nigeria. J Perinat Med 2006;34:166–172.
39 Owa JA, Osinaike AI: Neonatal morbidity and mortality in Nigeria. Indian J Pediatr 1998;65: 441–449.
40 Okechukwu AA, Achonwa A: Morbidity and mortality patterns of admissions into the Special Care Baby Unit of University of Abuja Teaching Hospital, Gwagwalada, Nigeria. Niger J Clin Pract 2009;12:389–394.
41 Udo JJ, Anah MU, Ochigbo SO, Etuk IS, Ekanem AD: Neonatal morbidity and mortality in Calabar, Nigeria: a hospital-based study. Niger J Clin Pract 2008;11:285–289.
42 Etuk SJ, Etuk IS, Ekott MI, Udoma EJ: Perinatal outcome in pregnancies booked for antenatal care but delivered outside health facilities in Calabar, Nigeria. Acta Trop 2000;75: 29–33.
43 Omoigberale AI, Sadoh WE, Nwaneri DU: A 4-year review of neonatal outcome at the University of Benin Teaching Hospital, Benin City. Niger J Clin Pract 2010;13:321–325.
44 Ezeaka VC, Iroha EO: Physical health status of pupils in a school for the mentally disabled in Lagos. Niger Postgrad Med J 2003;10:238–242.
45 Owa JA, Adebami OJ, Fadero FF, Slusher TM: Irradiance readings of phototherapy equipment: Nigeria. Indian J Pediatr 2011;78:996–998.
46 Eneh AU, Ugwu RO: Perception of neonatal jaundice among women attending children out-patient and immunization clinics of the UPTH Port Harcourt. Niger J Clin Pract 2009; 12:187–191.
47 Wei K-L, Yang Y-J, Yao Y-J, Du L-Z, Wang Q-H, Wang R-H, et al: Epidemiologic survey on hospitalized neonates in China. Transl Pediatr 2012;1:15–22.
48 Rasul CH, Hasan MA, Yasmin F: Outcome of neonatal hyperbilirubinemia in a tertiary care hospital in Bangladesh. Malays J Med Sci 2010;17:40–44.
49 Islam MN, Siddika M, Hossain MA, Bhuiyan MK, Ali MA: Morbidity pattern and mortality of neonates admitted in a tertiary level teaching hospital in Bangladesh. Mymensingh Med J 2010;19:159–162.
50 Dutta D, Bhattacharya MK, Bhattacharya SK, Chaudhuri A, Lahiri M, Mitra U, et al: Influence of admission weight on neonatal mortality amongst hospitalised neonates in Calcutta. J Indian Med Assoc 1992;90:308–309.
51 Bang AT, Bang RA, Baitule S, Deshmukh M, Reddy MH: Burden of morbidities and the unmet need for health care in rural neonates – a prospective observational study in Gadchiroli, India. Indian Pediatr 2001;38: 952–965.
52 Myanmar Department of Health: Annual hospital statistics 2010–2011, 2013 (cited December 23, 2015). http://www.moh.gov.mm/file/Annual%20Hospital%20Statistics%20Report%202010–2011.pdf.
53 Arnolda G, Nwe HM, Trevisanuto D, Thin AA, Thein AA, Defechereux T, et al: Risk factors for acute bilirubin encephalopathy on admission to two Myanmar national paediatric hospitals. Matern Health Neonatol Perinatol 2015. DOI: 10.1186/s40748-015-0024-3.
54 Selvaraju S: Preliminary report: a survey on severe neonatal jaundice cases admitted to selected hospitals in Malaysia. Proc Natl Perinat Health Conf, 1999, pp 70–79.
55 Crowther C, Middleton P: Anti-D administration after childbirth for preventing Rhesus alloimmunisation. Cochrane Database Syst Rev 2000;CD000021.
56 Malla T, Singh S, Poudyal P, Sathian B, Bk G, Malla KK: A prospective study on exchange transfusion in neonatal unconjugated hyperbilirubinemia – in a tertiary care hospital, Nepal. Kathmandu Univ Med J 2015;13:102–108.

57 Louis D, More K, Oberoi S, Shah PS: Intravenous immunoglobulin in isoimmune haemolytic disease of newborn: an updated systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed 2014;99:F325–F331.
58 Izetbegovic S: Occurrence of ABO and RhD incompatibility with Rh negative mothers. Mater Sociomed 2013;25:255–258.
59 Bhutani VK, Wong RJ: Bilirubin neurotoxicity in preterm infants: risk and prevention. J Clin Neonatol 2013;2:61–69.
60 Glucose-6-phosphate dehydrogenase deficiency. WHO Working Group. Bull World Health Organ 1989;67:601–611.
61 Olusanya BO, Neumann KJ, Saunders JE: The global burden of disabling hearing impairment: a call to action. Bull World Health Organ 2014;92:367–373.
62 Thaddeus S, Maine D: Too far to walk: maternal mortality in context. Soc Sci Med 1994;38:1091–1110.
63 Johnson LH, Bhutani VK, Brown AK: System-based approach to management of neonatal jaundice and prevention of kernicterus. J Pediatr 2002;140:396–403.
64 Kumar K, Sohaila A, Tikmani SS, Khan IA, Zafar A: Screening for G6PD deficiency among neonates with neonatal jaundice admitted to tertiary care center: a need in disguise. J Coll Physicians Surg Pak 2015;25:625–626.
65 M Abo El Fotoh WM, Rizk MS: Prevalence of glucose -6-phosphate dehydrogenase deficiency in jaundiced Egyptian neonates. J Matern Fetal Neonatal Med 2016;3:1–4.
66 Goyal M, Garg A, Goyal MB, Kumar S, Ramji S, Kapoor S: Newborn screening for G6PD deficiency: A 2-year data from North India. Indian J Public Health 2015;59:145–148.
67 Boo NY, Gan CY, Gian YW, Lim KSL, Lim MW, Krishna-Kumar H: Malaysian mothers' knowledge and practices on care of neonatal jaundice. Med J Malaysia 2011;66:239–243.
68 Ng SY, Chong SY: What do mothers know about neonatal jaundice? Knowledge, attitude and practice of mothers in Malaysia. Med J Malaysia 2014;69:252–256.
69 Ogunlesi TA, Abdul AR: Maternal knowledge and care-seeking behaviors for newborn jaundice in Sagamu, southwest Nigeria. Niger J Clin Pract 2015;18:33–40.
70 Slusher TM, Olusanya BO, Vreman HJ, Brearley AM, Vaucher YE, Lund TC, et al: A randomized trial of phototherapy with filtered sunlight in African neonates. N Engl J Med 2015;373:1115–1124.
71 Poon WB, Ho WLC, Yeo CL: Survey on parenting practices among Chinese in Singapore. Singapore Med J 2007;48:1006–1011.
72 Ogunfowora OB, Adefuye PO, Fetuga MB: What do expectant mothers know about neonatal jaundice? Int Electron J Health Educ 2006;9:134–140.
73 Khalesi N, Rakhshani F: Knowledge, attitude and behaviour of mothers on neonatal jaundice. J Pak Med Assoc 2008;58:671–674.
74 Amirshaghaghi A, Ghabili K, Shoja MM, Kooshavar H: Neonatal jaundice: knowledge and practice of Iranian mothers with icteric newborns. Pak J Biol Sci 2008;11:942–945.
75 Kuzniewicz MW, Escobar GJ, Wi S, Liljestrand P, McCulloch C, Newman TB: Risk factors for severe hyperbilirubinemia among infants with borderline bilirubin levels: a nested case-control study. J Pediatr 2008;153:234–240.
76 Rylance S, Yan J, Molyneux E: Can transcutaneous bilirubinometry safely guide phototherapy treatment of neonatal jaundice in Malawi? Paediatr Int Child Health 2014;34:101–107.
77 National Neonatology Forum of India: Management of neonatal hyperbilirubinemia (cited January 3, 2016). http://www.nnfi.org.
78 Coda Zabetta CD, Iskander IF, Greco C, Bellarosa C, Demarini S, Tiribelli C, et al: Bilistick: a low-cost point-of-care system to measure total plasma bilirubin. Neonatology 2013;103:177–181.
79 Thairu L, Wirth M, Lunze K: Innovative newborn health technology for resource-limited environments. Trop Med Int Health 2013;18:117–128.
80 Arnolda G, Thein AA, Trevisanuto D, Aung N, Nwe HM, Thin AA, et al: Evaluation of a simple intervention to reduce exchange transfusion rates among inborn and outborn neonates in Myanmar, comparing pre- and post-intervention rates. BMC Pediatr 2015;15:216.
81 Ngerncham S, Jirapaet K, Suvonachai R, Chaweerat R, Wongsiridej P, Kolatat T: Effectiveness of conventional phototherapy versus Super light-emitting diodes phototherapy in neonatal hyperbilirubinemia. J Med Assoc Thai 2012;95:884–889.