REVIEW ARTICLE

The burden and management of neonatal jaundice in Nigeria: A scoping review of the literature

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Abstract

Neonatal jaundice is a leading cause of hospitalization in the first week of life worldwide. If inappropriately managed, it may result in significant bilirubin-induced mortality and disability. We set out to describe the epidemiology of neonatal hyperbilirubinemia as well as the practices and challenges in the care of infants with significant neonatal hyperbilirubinemia (SNH) in Nigeria, as basis for policy intervention and research priorities. We systematically searched PubMed, Scopus, EMBASE, Cumulative Index to Nursing and Allied Health Literature, WHO Library Database, African Index Medicus, African Journals Online, and local journals for studies published between January 1960 and December 2014. We included studies, without restriction on methodological design that provided evidence on the incidence/prevalence, etiological /risk factors and adverse outcomes of hyperbilirubinemia, care-seeking practices, diagnosis and treatment, as well as follow-up evaluation of infants with SNH in Nigeria. A total of 558 studies were identified from all sources out of which 198 (35.5%) were finally selected. SNH accounted for about one in five neonatal admissions and has been associated consistently with substantial case fatality and neuro-developmental sequelae such as cerebral palsy and auditory impairments, especially among out-born babies. Glucose-6-phosphate dehydrogenase (G6PD) deficiency, prematurity/low birth weight, infection, and ABO incompatibility were most frequently, and Rhesus disease rarely, associated with SNH. Late presentation at appropriate health facilities was common and resulted in high rates of acute bilirubin encephalopathy (ABE), kernicterus and avoidable exchange transfusions. Uniform practice guidelines, including developmental assessment and surveillance of infants with SNH, were rare at all levels of healthcare delivery. In summary, since 1960, SHN persists as a major contributor to neonatal mortality and developmental disabilities in Nigeria. The underpinning maternal, perinatal and neonatal factors as well as systems-based constraints are not insurmountable. Systematic and sustained interventions are warranted to curtail the disproportionate and perennial burden of this condition in this population.

Key words: Etiology, bilirubin-encephalopathy, care-seeking behavior, developing country, developmental disabilities, kernicterus, newborn care, risk factors

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Introduction

Hyperbilirubinemia is one of the most common causes of morbidity in newborns worldwide, and the most frequent cause of hospitalization or readmission for special care in the 1st week of life.[1-3] Recent global estimates suggest that every year, roughly 1.1 million babies would develop severe hyperbilirubinemia and the vast majority reside in sub-Saharan Africa and South Asia.[4] Available evidence also shows that severe hyperbilirubinemia, with or without bilirubin encephalopathy, is associated with substantial mortality and long-term morbidities in low- and middle-income countries (LMICs).[5-8] This is corroborated by several studies spanning more than five decades in Nigeria,

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where the burden of severe hyperbilirubinemia is underpinned by widespread glucose-6-phosphate dehydrogenase (G6PD) deficiency,[9-14] and possibly exacerbated by polymorphism of the uridine-diphosphate-glucuronosyl transferase 1A1 gene (UGT1A1),[15] and widespread exclusive breastfeeding in the first few days of life.[16] In one nationwide survey of pediatricians in Nigeria, neonatal jaundice was ranked as a priority neonatal morbidity for global health intervention.[17] However, no comprehensive literature review has been conducted in Nigeria to inform policy initiatives and research priorities for improved newborn care.

Scoping reviews are effective in capturing a range of literature to establish available evidence and the overall state of research on the topic of interest.[18] Unlike systematic reviews, they target all types of study designs without focusing on the assessment of quality as defined within a biomedical research convention.[19] We therefore, conducted a scoping review: (i) To assemble available evidence on the burden of neonatal hyperbilirubinemia, (ii) to identify current practices and challenges for the effective management of infants with clinically significant hyperbilirubinemia, and (iii) to identify gaps in the existing literature that should be addressed in future research efforts.

Methods

Study framework

We adopted the methodological framework proposed by Arksey and O'Malley for scoping studies.[18] The framework consists of five stages: Defining the research question, identifying the relevant studies, study selection, charting the data and collating, summarizing and reporting the results. The optional sixth stage requiring a consultation exercise to validate findings from the review was not considered necessary for our purpose. Furthermore, a systematic evaluation of the methodological quality of included articles was not conducted as such analysis is not mandatory under this framework.[18]

Defining the research questions

The focus of this study was to address two main questions, namely: (i) "What are the epidemiological findings among infants diagnosed with clinically significant hyperbilirubinemia with or without bilirubin encephalopathy?" and (ii) "what are the practices associated with the management of infants with or at risk of significant hyperbilirubinemia in Nigeria?" In addressing the first question, we examined available evidence on the incidence/prevalence, etiological/risk factors, and adverse outcomes of hyperbilirubinemia in Nigeria. The second research question sought evidence on care-seeking practices, diagnosis and treatment, as well as follow-up evaluation for infants with significant hyperbilirubinemia. For the purpose of this review, neonatal hyperbilirubinemia of any unconjugated bilirubin level (typically from total serum bilirubin [TSB] ≥10 mg/dL or 170 μmol/L) requiring immediate treatment with phototherapy or exchange transfusion was considered as clinically significant neonatal hyperbilirubinemia and abbreviated as "SNH".

Identifying relevant studies

Electronic databases including PubMed, Scopus, EMBASE and Cumulative Index to Nursing and Allied Health Literature (CINAHL), WHO Library Database, African Index Medicus and African Journals Online were searched to identify relevant articles published between January 1960 (Nigeria Year of Independence) and December 2014 (55 years). The search terms used for major databases such as PubMed, Scopus, EMBASSE, and CINAHL were "neonatal jaundice" or "neonatal hyperbilirubinemia" and Nigeria while search term for other databases was restricted to "jaundice" or "hyperbilirubinemia" for optimum hit of relevant articles. We applied a snowball method to examine the reference lists of retrieved articles as well as other relevant reports to identify additional studies.

Study selection

Three authors (BOO, FBO and TMS) screened all titles and abstracts of retrieved studies from all the databases and other sources to identify articles relevant to our two primary research questions. We included studies of subpopulations of infants with specific risk profile such as diabetic mothers, preterm/low birth weight, sepsis, or hemolytic conditions including G6PD deficiency, maternal-fetal ABO blood group incompatibility, and rhesus hemolytic disease. Studies exploring the association between neonatal hyperbilirubinemia and adverse neonatal outcomes such as mortality and neurodevelopmental disorders were included. Thereafter, duplicates were systematically removed starting with all eligible articles from PubMed through to the last database. After reviewing full-texts of eligible studies, we excluded papers in which data relevant to our research questions was not provided. Abstracts in conference proceedings without full-texts were excluded. All three authors agreed on this selection procedure. Discrepancies in the final selection were resolved through consensus after joint reassessment.

Data charting and collation

Articles that met our inclusion criteria were listed in the appropriate sub-headings of our two main research questions. Issues related to the main research questions were extracted into a spreadsheet for further descriptive analysis. The selected studies were identified by first author, year of publication and location. Distribution across the six geographical regions in Nigeria: South-West, South-South, South-East, North-West, North-Central, and North-East, was also explored. The most notable findings under each thematic section were agreed among the three authors based on thematic content analysis of the selected references.[20,21]

Results

The initial search yielded 463 studies across databases and 95 from additional sources resulting in a total of 558 records [Figure 1]. After assessment of titles and abstracts, 382 studies were assembled from all sources, out of which full-texts for 223 studies were required after excluding 159 duplicates. A total of 25 studies were further excluded because they did not provide any relevant data for our study objectives resulting in a final selection of 198 studies [Table S1].[w1-w198] The years of publication of the included studies are presented in Figure 2. The earliest studies were published in 1960 and the highest number of studies was recorded in 2011. Of the finally selected studies, 37.4% (n = 74) were retrieved from PubMed and 48.0% (n = 95) from sources outside the major databases [Figure 3]. By geographical spread, 51% (n = 101) were conducted in Southwest, 19.2% (n = 38) in South-South, 12.1% (n = 24) in South-East, 8.1% (n = 16) in North-West, 7.6% (n = 15) in North-Central, 1.0% (n = 2) in North-East, and 1% (n = 2) were multi-center. The studies addressing each of the sub-themes of interest are presented in Table 1.[w1-w198] The key findings from the eligible studies are summarized as follows:

Incidence/prevalence of neonatal hyperbilirubinemia

All but one of the studies that provided data on the incidence of SNH was hospital-based. In the only community-based study in inner-city Lagos, 351 (6.7%) of 5262 infants enrolled were reported to be jaundiced based on parental history. From this group, 291 (82.9%) were treated with phototherapy while 98 (27.9%) had exchange transfusion.[w134] Crude incidence of severe hyperbilirubinemia was at least 5.5% (95% confidence interval: 4.9–6.2%).

The incidence of SNH is likely to be grossly under-reported in hospital cohorts without adequate postdischarge surveillance till the 8th day after birth. Only two studies appeared to have met this requirement.[w30, w43] The first study was conducted in 1971 in Ibadan (South-West) over a period of 12 months.[w43] In a cohort of 6502 live births from two hospitals, a total of 1052 (17%) babies were reported with jaundice.[w43] Out of 741 jaundiced infants in one of the two hospitals, 240 (32.4%) had TSB ≥10 mg/dL (170 μmol/L). From this group, 131 (54.6%) had TSB >15 mg/dL (255 μmol/L) and 53 (2.3%) required exchange transfusion. In the second and more recent study in 2011, 140 (21.7%) of the 644 term and near-term (35–36 weeks) infants recruited consecutively over a 6-month period in Ile-Ife (South-West) were found to have SNH (TSB ≥12 mg/dL or 204 μmol/L) and 134 (95.7%) received phototherapy.[w30] No infants developed SNH that required exchange transfusion.

Three studies provided data on the incidence SNH from birth cohorts but without adequate information on surveillance in the 1st week of life. For example, in one study from Enugu (South-East), jaundice (TSB ≥10 mg/dL or 170 μmol/L) was reported in 206 (10%) of 2,140 live births.[w29] Of this group, 80 babies (39%) had TSB >15 mg/dL (255 μmol/L), and 25 (12.1%) required exchange transfusion. Similarly, a study from Zaria (North-West), showed that 30 (2%) of a cohort of 1,478 live births in Zaria developed jaundice (TSB ≥10 mg/dL or 170 μmol/L).[w195] Another study from Port Harcourt, (South-South) reported that

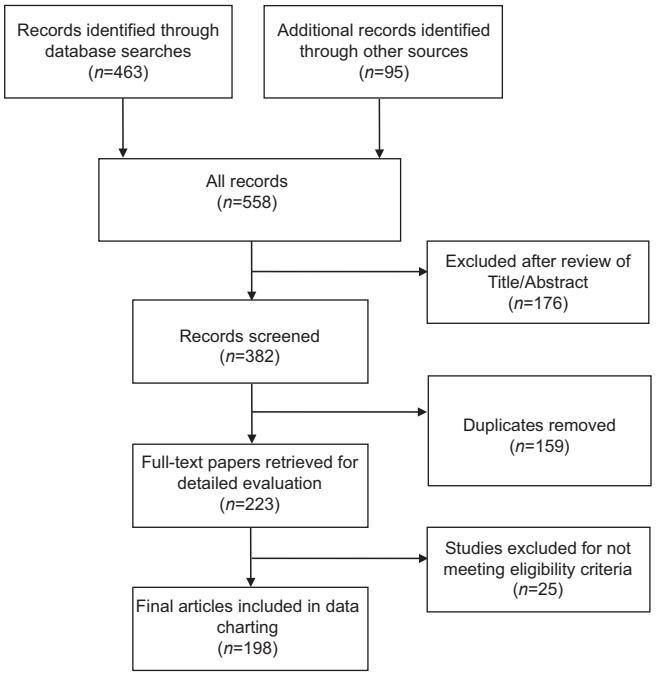

Figure 1: Flow diagram of the study selection process and results

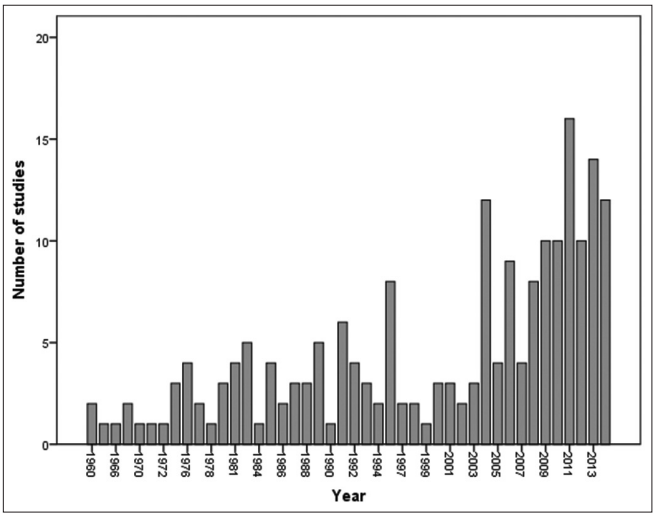

Figure 2: Year of publication of eligible studies on neonatal jaundice in Nigeria

Web Table S1: List of eligible studies (w1-w198)

Serial number	Source	Year	Studies (listed by first author alphabetically)
1	OTH	1983	Abdulrahman MB. Why our children die. A study of mortality pattern in an emergency paediatric unit in Kaduna, Nigeria. Niger Med Pract 1983;5:57-62
2	PUB	1998	Abulu EO, Uriah N, Aigbefo HS, Oboh PA, Agbonlahor DE. Preliminary investigation on aflatoxin in cord blood of jaundiced neonates. West Afr J Med 1998;17:184-7
3	AJOL	2010	Adebami OJ, Joel-Medewase VI, Oyedji OA, Oyedeji GA. A review of Neonatal Admissions in Osogbo, Southwestern Nigeria. Niger Hosp Pract 2010;5:36-41
4	OTH	2011A	Adebami OJ, Onigbinde OM, Joel-Medewase V, Oyedeji AG, Afolabi AA. Neurological disorders among children in Osogbo, Southwestern Nigeria. J Pediatr Neurol 2011;9:341-5.[A]
5	SCOP	2011B	Adebami OJ. Factors associated with the incidence of acute bilirubin encephalopathy in Nigerian population. J Pediatr Neurol 2011;9:347-53. [B]
6	CIN	1989	Adedoyin CO. Impediments to child survival. West Afr Coll Nurs J 1989;2:10-7
7	OTH	2010	Adeolu AA, Arowolo OA, Alatise OI, Osasan SA, Bisiriyu LA, Omoniyi EO, *et al*. Pattern of death in a Nigerian teaching hospital; 3-decade analysis. Afr Health Sci 2010;10:266-72
8	PUB	1997	Adeyemo AA, Gbadegesin RA, Omotade OO. Major congenital malformations among neonatal referrals to a Nigerian university hospital. East Afr Med J 1997;74:699-701
9	OTH	1980	Adeyokunnu AA, Taiwo 0, Antia AU. Childhood Mortality among 22,255 Consecutive Admissions in the University College Hospital, lbadan. Niger J Paediatr 1980;7:7-15
10	OTH	2013	Afolabi BM, Clement CO, Inem VA. Review of Neonatal Morbidity and Mortality in an Intensive Care Unit of a Paediatric Health Facility in Lagos, Nigeria. J Trop Dis 2013;1:115
11	PUB	1995A	Ahmed H, Hendrickse RG, Maxwell SM, Yakubu AM. Neonatal jaundice with reference to aflatoxins: An aetiological study in Zaria, northern Nigeria. Ann Trop Paediatr 1995;15:11-20. [A]
12	OTH	1995B	Ahmed H, Hendrickse RG, Yakubu AM, Maxwell SM. Glucose-6- Phosphate Dehydrogenase (G-6-PD) Status, Aflatoxins and Neonatal Jaundice. Niger J Paediatr 1995;22:3-10. [B]
13	PUB	1995C	Ahmed H, Yukubu AM, Hendrickse RG. Neonatal jaundice in Zaria, Nigeria – A second prospective study. West Afr J Med 1995;14:15-23. [C]
14	OTH	1997	Ahmed H. Neonatal Jaundice in Nigeria: An overview of four decades of medical research. Niger J Med 1997;6:97-105
15	SCO	1992	Airede AI. Relation of peak total serum bilirubin concentrations to neurodevelopmental outcome at 2 years of age in premature African neonates. Ann Trop Paediatr 1992;12:249-54
16	OTH	2000	Aisien AO, Lawson JO, Okolo A. Two years prospective study of perinatal mortality in Jos, Nigeria. Int J Gynaecol Obstet 2000;71:171-3
17	OTH	1983	Akarakiri TAF, Laditan AAO. Effects of Exchange Blood Transfusion on Serum Electrolytes, Calcium, and Phosphorus among Neonates with Jaundice. Niger J Paediatr 1983;10:89-92
18	PUB	1995	Akinyinka OO, Omigbodun AO, Akanmu TI, Osanyintuyi VO, Sodeinde O. Hyponatraemia, birthweight and neonatal jaundice. Afr J Med Med Sci 1995;24:55-7
19	OTH	2014	Alex-Hart BA, Dotimi DA, Opara PI. Mothers' recognition of newborn danger signs and health seeking behaviour. Niger J Paediatr 2014;41:199-203
20	PUB	1991	Anate M. Instrumental (operative) vaginal deliveries: Vacuum extraction compared with forceps delivery at Ilorin University Teaching Hospital, Nigeria. West Afr J Med 1991;10:127-36
21	PUB	1971	Animashaun A. Aetiology of cerebral palsy in African children. Afr J Med Sci 1971;2:165-71
22	OTH	1992	Antia Obong OE. Paediatric emergences in Calabar. Niger Med Pract 1992;23:51-5
23	SCO	2013	Aronu AE, Ibekwe RC, Ojinnaka NC. Epilepsy in Nigerian children with cerebral palsy in Enugu. J Pediatr Neurol 2013;11:23-27
24	OTH	1980	Asindi AA, Ekanem AD. Neonatal deaths in Calabar, Nigeria. East Afr Med J 1980;65:333-41
25	OTH	1991	Asindi AA, lbia EO, Udo JJ. Mortality pattern among Nigerian children in the 1980s. J Trop Med Hyg 1991;94:152-5
26	OTH	1986	Asindi AA. The pattern of neurological disabilities in children seen at the University of Calabar Teaching Hospital. Niger J Paediatr 1986;13:127-32
27	PUB	2011	Ayede AI, Akingbola TS. Pattern, indications and review of complications of neonatal blood transfusion in Ibadan, southwest Nigeria. Ann Ib Postgrad Med 2011;9:30-6
28	OTH	2005	Ayoola OO, Orimadegun AE, Akinsola AK, Osinusi K. A five-year review of childhood mortality at the University College Hospital, Ibadan. West Afr J Med 2005;24:175-9
29	PUB	1985	Azubuike J. Neonatal Jaundice in Eastern Nigeria. J Trop Pediatr 1985;31:82-5
30	PUB	2014	Badejoko BO, Owa JA, Oseni SB, Badejoko O, Fatusi AO, Adejuyigbe EA. Early Neonatal Bilirubin, Hematocrit, and Glucose-6-Phosphate Dehydrogenase Status. Pediatrics 2014;134:e1082-8
31	PUB	1990	Bamgboye EA, Familusi JB. Mortality pattern at a children's emergency ward, University College Hospital, Ibadan, Nigeria. Afr J Med Med Sci 1990;19:127-32
32	PUB	2009	Belonwu RO, Gwarzo GD, Adeleke SI. Cerebral palsy in Kano, Nigeria--a review. Niger J Med 2009;18:186-9

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Serial number	Source	Year	Studies (listed by first author alphabetically)
33	PUB	1976	Bienzle U, Effiong C, Luzzatto L. Erythrocyte glucose-6-phosphate dehydrogenase deficiency (G6PD type A-). Acta Paediatr Scand 1976;65:701-3
34	PUB	1976	Bienzle U, Effiong CE, Aimaku VE, Luzzatto L. Erythrocyte enzymes in neonatal jaundice. Acta Haematol 1976;55:10-20
35	PUB	1963	Capps FP, Gilles HM, Jolly H, Worlledge SM. Glucose-6-Phosphate Dehydrogenase Deficiency and Neonatal Jaundice in Nigeria: Their relation to the use of Prophylactic Vitamin K. Lancet 1963;2:379-83
36	SCO	2011	Chime HE, Egenede JA, Arute JE. Prevalence of Neonatal Jaundice on Central Hospital, Warri, Delta State, Nigeria. Int J Health Res 2011;4:123-6
37	PUB	2013	Cline BK, Vreman HJ, Faber K, Lou H, Donaldson KM, Amuabunosi E, *et al*. Phototherapy device effectiveness in Nigeria: Irradiance assessment and potential for improvement. J Trop Pediatr 2013;59:321-5
38	SCO	1977	Coulter JB, Akpabio MA, Jikeme SON, Kay T. Neonatal jaundice in Northern Nigeria. Niger J Paediatr 1977;5:12-5
39	OTH	1970	Dada TO. Epilepsy in Lagos, Nigeria. Afr J Med Sci 1970;1:161-84
40	PUB	1984	Dawodu AH, Owa JA, Familusi JB. A prospective study of the role of bacterial infection and G6PD deficiency in severe neonatal jaundice in Nigeria. Trop Geogr Med 1984;36:127-32
41	OTH	1992	Duggam MB, Ogalo W. Cerebral palsy in Nigeria–a report from Zaria. Ann Trop Pediatr 1992;2:7-11
42	AJOL	2004	Duru LA. Features of Neonatal Jaundice at Irrua Specialist Hospital, Irrua, in Edo State, Nigeria. J Medical Lab Sci 2004;13:36-40
43	PUB	1975	Effiong CE, Aimaku VE, Bienzle U, Oyedeji GA, Ikpe DE. Neonatal jaundice in Ibadan. Incidence and etiologic factors in babies born in hospital. J Natl Med Assoc 1975;67:208-13
44	OTH	1976A	Effiong CE, Laditan AA. Neonatal Jaundice in Ibadan: A study of cases seen in the Out-Patients Clinic. Niger J Paediatr 1976;3:1-8. [A]
45	SCO	1976B	Effiong CE. Neonatal morbidity and mortality in Ibadan: A review of cases seen in the out-patient clinic. J Trop Pediatr Environ Child Health 1976;22:265-7. [B]
46	PUB	2013	Egube BA, Ofili AN, Isara AR, Onakewhor JU. Neonatal jaundice and its management: Knowledge, attitude, and practice among expectant mothers attending antenatal clinic at University of Benin Teaching Hospital, Benin City, Nigeria. Niger J Clin Pract 2013;16:188-94
47	OTH	2007	Ejike CA, Chukwuka CA, Chukwuka. A five year retrospective study on neonatal jaundice at the Abia State University Teaching Hospital (ABSUTH), Aba Nigeria. Abia State University Medical Students' Association Journal, ABSUMSAJ 2007;4:13-15
48	OTH	2008	Ekanem AD, Anah MU, Udo JJ. The prevalence of congenital malaria among neonates with suspected sepsis in Calabar, Nigeria. Trop Doct. 2008;38:73-6
49	OTH	1994	Ekanem EE, Young MU. Knowledge of the Causes and Management of Neonatal Jaundice by Primary Health Care Staff. Niger J Paediatr 1994;21:37-42
50	OTH	2013	Eke GK, Opara PI. Discharge against medical advice amongst patients admitted into the Paediatric wards of the University of Port Harcourt Teaching Hospital. Niger J Paediatr 2013;40:40-4
51	OTH	2005	Ekure EN, Ezeaka VC, lroha O, Egri-Okwaji MTC. Neonatal Mortality of Inborns in the Neonatal Unit of a Tertiary Centre in Lagos, Nigeria. Nig Otr J Hosp Med 2005;15:55-8
52	PUB	2014	Ekwochi U, Ndu IK, Nwokoye IC, Ezenwosu OU, Amadi OF, Osuorah D. Pattern of morbidity and mortality of newborns admitted into the sick and special care baby unit of Enugu State University Teaching Hospital, Enugu State. Niger J Clin Pract 2014;17:346-51
53	PUB	2014	Ekwochi U, Osuorah DC, Ndu IK, Ezenwosu OU, Amadi OF, Nwokoye IC, *et al*. Out-of-pocket cost of managing sick newborns in Enugu, Southeast Nigeria. Clinicoecon Outcomes Res 2014;6:29-35
54	AJOL	2008	Eneh AU, Oruamabo RS. Neonatal jaundice in a Special Care Baby Unit (SCBU) in Port Harcourt, Nigeria: A prospective study. Port Harcourt Med J 2008;2:110-7
55	PUB	2009	Eneh AU, Ugwu RO. Perception of neonatal jaundice among women attending children outpatient and immunization clinics of the UPTH Port Harcourt. Niger J Clin Pract 2009;12:187-91
56	OTH	2014	Enyuma CO, Meremikwu MM, Udo JJ, Anah MU, Asindi AA. Malaria parasite positivity among febrile neonates. Niger J Paediatr 2014;41:321-325
57	PUB	2014	Ezeaka CV, Ugwu RO, Mukhtar-Yola M, Ekure EN, Olusanya BO. Pattern and predictors of maternal care-seeking practices for severe neonatal jaundice in Nigeria: A multi-centre survey. BMC Health Serv Res 2014;14:192
58	PUB	2004	Ezeaka VC, Ekure EN, Iroha EO, Egri-Okwaji MT. Outcome of low birth weight neonates in a tertiary health care centre in Lagos, Nigeria. Afr J Med Med Sci 2004;33:299-303
59	OTH	2003	Ezeaka VC, Ogunbase OA, Awogbemi OT, Grange AO. Why Our Children Die: A Review of Paediatric Mortality in a Tertiary Centre in Lagos, Nigeria. Nig Qtr J Hosp Med 2003;13:17-21
60	OTH	2004	Ezechukwu CC, Ugochukwu EF, Egbuonu I, Chukwuka JO. Risk factors for neonatal mortality in a regional tertiary hospital in Nigeria. Niger J Clin Pract 2004;7:50-2
61	OTH	2014	Fadairo J, Aladenika S, Osaiyuwu C, Olaniyan M, Aghatise K. Evaluation of Some Etiological Factors of Haemolytic Disease of the New Born in Ile-Ife. Open J Clin Diagn 2014;4:5-11
62	OTH	1987	Fagbule D, Joiner KT. Pattern of Childhood Mortality at the University of Ilorin Teaching Hospital. Niger J Paediatr 1987;14:1-5

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Serial number	Source	Year	Studies (listed by first author alphabetically)
63	AJOL	2011	Fajolu IB, Egri-Okwaji MTC. Childhood mortality in children emergency centre of the Lagos University Teaching hospital. Niger J Paediatr 2011;38:131-135
64	OTH	2000	Falusi AG, Ademowo OG, Latunji CA, Okeke AC, Olatunji PO, Onyekwere TO, *et al*. Distribution of ABO and RH genes in Nigeria. Afr J Med Med Sci 2000;29:23-6
65	OTH	1981	Familusi JB, Dawodu AH, Owa JA. Some epidemiological aspects of neonatal hyperbilirubinaemia in Nigeria. In: Fukuyama Y, Arima M, Maokawa K, *et al*., eds. Child neurology. International Congress Series 579, Proceedings of IYDP. Amsterdam: Excerpta Medica 1981:272-80
66	PUB	1985	Familusi JB, Dawodu AH. A survey of neonatal jaundice in association with household drugs and chemicals in Nigeria. Ann Trop Paediatr 1985;5:219-22. [Published earlier as: Familusi JB, Dawodu AH. Neonatal jaundice in association with household drugs and chemicals: A survey of 450 Nigerian families. Niger Med J 1983;13:45-9]
67	AJOL	2001	Fawole AO, Sotiloye OS, Hunyinbo KI, Durodola A, Omisakin SI, Bale AO, *et al*. A review of rhesus iso–immunization in a Nigerian obstetric population. Trop J Obstet Gynaecol 2001;18:69-72
68	OTH	2007	Fetuga B, Ogunlesi T, Adekanbi F, Olanrewaju D, Olowu A. Comparative analyses of childhood deaths in Sagamu, Nigeria: Implications for the fourth MDG. South Afr J Child Health 2007;1:106-11
69	OTH	2011	Frank-Briggs AI, Alikor EAD. Sociocultural issues and causes of cerebral palsy in Port Harcourt, Nigeria. Niger J Paediatr 2011;38:115-9
70	OTH	2013	Gbadamosi IT, Obogo SF. Chemical Constituents and In Vitro Antimicrobial Activities of Five Botanicals Used Traditionally for the Treatment of Neonatal Jaundice in Ibadan, Nigeria. Nat Sci 2013;11:130-5
71	OTH	2008	George IO, Akani NA, Oruamabo RS. Glucose-6-phosphate Dehydrogenase Deficiency and Severity of Neonatal Jaundice: A Prospective Study from Port Harcourt. Niger J Paediatr. 2008; 35:31-37. [Duplicated in: George IO, Akani NA. Evaluation of Glucose-6-Phosphate Dehydrogenase Deficiency in Icteric Newborns in Nigeria. Am J Trop Med Public Health 2011;1:73-8]
72	OTH	1960	Gilles HM, Arthur LJS. Erythrocyte Enzyme Deficiency in Unexplained Neonatal Jaundice. W Afr Med J. 1960;9:266. [Letter]
73	OTH	1999	Ibe BC. Neonatal Jaundice. In: Azubuike JC, Nkangineme KE, editors. Paediatrics and child health in a tropical region. Owerri: African Educational services; 1999. pp. 204-11
74	OTH	2009	Ibekwe CR, Muoneke VU, Nnebe-Agumadu UH, Amadife MU. Factors influencing discharge against medical advice among paediatric patients in Abakaliki, Southeastern Nigeria. J Trop Pediatr 2009;55:39-41
75	OTH	2011	Ibekwe PC, Ugboma HU, Onyire N, Muoneke U. Perinatal mortality in Southern Nigeria; less than a decade to the Millennium Development Goals. Ann Med Health Sci Res 2011;1:215-22
76	PUB	2012	Ibekwe RC, Ibekwe MU, Muoneke VU. Outcome of exchange blood transfusions done for neonatal jaundice in Abakaliki, South Eastern Nigeria. J Clin Neonatol 2012;1:34-7
77	OTH	2002	Ibeziako SN, lbekwe RC. Pattern and Outcome of Admissions in the Children's Emergency Room of the University of Nigeria Teaching Hospital, Enugu. Niger J Paediatr 2002;29:103-7
78	OTH	1995	Ibhanesebhor SE. Clinical characteristics of neonatal malaria. J Trop Pediatr 1995;41:330-3
79	OTH	1993	Ibrahim I, Udomah MG, Abduwahab I. Infant Mortality at Usmanu Danfodiyo University Teaching Hospital, Sokoto. Niger J Paediatr 1993;20:17-20
80	AJOL	2010	Idu M, Erhabor JO, Efijuemue HM. Documentation on Medicinal Plants Sold in Markets in Abeokuta, Nigeria. Trop J Pharm Res 2010;9:110-8
81	OTH	1966	Ifekwunigwe AE, Luzzatto L. Kernicterus in G-6-PD. Deficiency. Lancet 1966;1:667
82	PUB	2010	Iliyasu A, Abubakar IS, Gajida AU. Magnitude and leading causes of in-hospital mortality at Aminu Kano Teaching Hospital, Kano, Northern Nigeria: A 4-year prospective analysis. Niger J Med 2010;19:400-6
83	OTH	1989	Iloeje SO. The pattern of childhood epilepsy with mental retardation in Nigeria. J Trop Pediatr 1989;35:163-8
84	AJOL	2012	Israel-Aina YT, Omoigberale AI. Risk factors for neonatal jaundice in babies presenting at the University of Benin Teaching Hospital, Benin City. Niger J Paediatr 2012;39:159-63
85	PUB	1989	Izuora GI, Iloeje SO. A review of neurological disorders seen at the Paediatric Neurology Clinic of the University of Nigeria Teaching Hospital, Enugu. Ann Trop Paediatr 1989;9:185-90
86	PUB	1981	Izuora GI, Okoro AB. Some clinical aspects of cerebral palsy among Nigerian Igbo children. Cent Afr J Med 1981;27:155-9
87	PUB	1985	Izuora GI. Aetiology of mental retardation in Nigerian children around Enugu. Cent Afr J Med 1985;31:13-6
88	OTH	1975	Kaine W, Okolie J. A review of the causes of hospitalisation as a guide to the pattern of disease in Eastern Nigeria. Niger J Med 1975;7:205-9
89	PUB	2008	Kaplan M, Slusher T, Renbaum P, Essiet DF, Pam S, Levy-Lahad E, *et al*.(TA)n UDP-glucuronosyltransferase 1A1 promoter polymorphism in Nigerian neonates. Pediatr Res 2008;63:109-11
90	PUB	2005	Kotila TR, Odukogbe AA, Okunlola MA, Olayemi O, Obisesan KA. The pregnant Rhesus negative Nigerian woman. Niger Postgrad Med J 2005;12:305-7
91	OTH	2014	Kuti BP, Ogundele T, Adeniyi AT, Kuti DK. Kernicterus in Two Generations: A Need for More Aggressive Preventive Measures. Iran J Neonatol 2014;5:33-36 [Case Report]
92	SCO	2003	Kuti O, Owa JA. Gestational age-specific neonatal mortality among preterm singleton births in a Nigerian tertiary institution. Int J Gynaecol Obstet 2003;80:319-20

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Serial number	Source	Year	Studies (listed by first author alphabetically)
93	OTH	1975	Laditan, AA0, Effiong CE, Antia AU. Morbidity and Mortality from Exchange Blood Transfusion in Neonatal Jaundice. Niger J Paediatr 1975;2:42-46
94	OTH	2006	Lagunju IA, Adedokun BO, Fatunde OJ. Risk factors for epilepsy in children with cerebral palsy. Afr J Neurol Sci 2006;25:29-37
95	PUB	2010	Lesi FE, Mukhtar MY, Iroha EU, Egri-Okwaji MT. Clinical presentation of congenital malaria at the Lagos University Teaching Hospital. Niger J Clin Pract. 2010;13:134-8
96	OTH	2000	Lesi FEA, Temiye EO, Epelle TGS. The changing pattern of childhood mortality in the children's emergency room of the Lagos University Teaching Hospital after 20 years. Niger Med J 2000;38:38-41
97	OTH	1978	Lesi FEA. Infant mortality, diet and disease in Nigeria. Niger Med J 1978;8:114-8
98	OTH	1968	Luzzatto L, Allan NO. Relationship between the genes of glucose-6-phosphate dehydrogenase and for haemoglobin in a Nigerian population. Nature 1968;219:1041-42
99	OTH	1977	Mee J, Scott D. Phototherapy for neonatal jaundice in rural Africa. Trop Doct 1977;7:33-4
100	PUB	2007	Mukhtar-Yola M, Iliyasu Z. A review of neonatal morbidity and mortality in Aminu Kano Teaching Hospital, Northern Nigeria. Trop Doct 2007;37:130-2
101	OTH	1994	Njokanma OF, Sule-Odu AO, Akesode FA. Perinatal mortality at the Ogun State University Teaching Hospital, Sagamu, Nigeria. J Trop Pediatr 1994;40:78-81
102	OTH	1991	Nottidge VA, Okogbo ME. Cerebral palsy in Ibadan, Nigeria. Dev Med Child Neurol 1991;33:241-5
103	OTH	2006	Nte AR, Yarhere I, Fiebai P. Paediatric Mortality: A Review of Causes among Admissions at the University of Port Harcourt Teaching Hospital (January 2003 -December 2005). Niger J Paediatr 2006;33:90-8
104	PUB	2012	Obasa TO, Adesiyun OO, Mokuolu OA, Ojuawo AI. Comparative analysis of glucose-6-phosphate dehydrogenase levels in pre-term and term babies delivered at University of Ilorin Teaching Hospital. Pediatr Rep 2012;4:e7:21-4
105	OTH	2011	Obasa TO, Mokuolu OA, Ojuawo A. Glucose 6 phosphate dehydrogenase levels in babies delivered at the University of Ilorin teaching hospital. Niger J Paediatr 2011;38:165-9
106	OTH	2004	Obi SN, Onyire BN. Pattern of neonatal admission and outcome at a Nigerian Tertiary Health Institution. Orient J Med 2004;16:31-37.
107	PUB	1991	Odugbemi T, Egri-Kwaji MT. Screening of children for enteric bacterial pathogens in the outborn neonatal ward in Lagos, Nigeria. Eur J Epidemiol 1991;7:427-30
108	CIN	2006A	Ogunfowora OB, Adefuye PO, Fetuga MB. What do expectant mothers know about neonatal jaundice? Int Elect J Health Educ 2006;9:134-40. [A]
109	PUB	2006B	Ogunfowora OB, Daniel OJ. Neonatal jaundice and its management: Knowledge, attitude and practice of community health workers in Nigeria. BMC Public Health 2006;6:19. [B]
110	OTH	2008	Ogunlesi T, Ogundeyi M, Adekanmbi F, Fatuga B, Ogunfowora O, Olowu A. Socio-clinical issues in cerebral palsy in Sagamu, Nigeria. South Afr J Child Health 2008;3:50-8
111	OTH	2009	Ogunlesi TA Ogunfowora OB, Ogundeyi MM, Ayeni AV. Jaundice among Hospitalized Newborn Infants in Sagamu: Observations on Aetiology and Clinical Course. Niger J Paediatr 2009:72-9
112	PUB	2007	Ogunlesi TA, Dedeke IO, Adekanmbi AF, Fetuga MB, Ogunfowora OB. The incidence and outcome of bilirubin encephalopathy in Nigeria: A bi-centre study. Niger J Med 2007;16:354-9
113	OTH	2006	Ogunlesi TA, Ogunfowora OB, Adekanmbi AF, Fetuga MB, Runsewe-Abiodun TI, Ogundeyi MM. Neonatal Mortality at Olabisi Onabanjo University Teaching Hospital, Sagamu. Niger J Paediatr 2006;33:40-6
114	PUB	2011A	Ogunlesi TA, Ogunfowora OB. Pattern and determinants of blood transfusion in a Nigerian neonatal unit. Niger J Clin Pract 2011;14:354-8. [A]
115	OTH	2011B	Ogunlesi TA, Ogunfowora OB. Predictors of Acute Bilirubin Encephalopathy Among Nigerian Term Babies with Moderate-to-severe Hyperbilirubinaemia. J Trop Pediatr 2011;57:80-6. [B]
116	PUB	2012	Ogunlesi TA, Ogunlesi FB. Family socio-demographic factors and maternal obstetric factors influencing appropriate health-care seeking behaviours for newborn jaundice in Sagamu, Nigeria. Matern Child Health J 2012;16:677-84
117	PUB	2013	Ogunrin OA, Adeyekun A, Adudu P. Etiologies of epilepsy and health-seeking itinerary of patients with epilepsy in a resource poor setting: Analysis of 342 Nigerian Africans. Seizure 2013;22:572-6
118	PUB	2006	Ojukwu JU, Abonyi LE, Ugwu J, Orji IK. Neonatal septicemia in high risk babies in South-Eastern Nigeria. J Perinat Med 2006;34:166-72
119	OTH	2004	Ojukwu JU, Ogbu CN. Analysis and outcome of admissions in the special care baby unit of the Ebonyi State University Teaching Hospital, Abakaliki. J Coll Med 2004:9:2:93-6
120	AJOL	2004	Ojukwu JU. Ezeonu CT, Ogbu CN. Severe Malaria in Neonates Masquerading as Septicaemia. Niger J Paediatr 2004;31:48-55
121	PUB	2009	Okechukwu A, Achonwa A. Morbidity and mortality patterns of admissions into the special care baby unit of University of Abuja Teaching Hospital. Niger J Clin Pract 2009;12:389-94
122	OTH	2011	Okechukwu AA. Discharge against medical advice in children at the University of Abuja Teaching Hospital, Gwagwalada, Nigeria. Afr J Med Med Sci 2011;2:949-54

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Serial number	Source	Year	Studies (listed by first author alphabetically)
123	OTH	2012	Okeke TC, Ocheni S, Nwagha UI, Ibegbulam OG. The prevalence of Rhesus negativity among pregnant women in Enugu, Southeast Nigeria. Niger J Clin Pract 2012;15:400-2
124	OTH	2013	Okike CO, Onyire BN, Ezeonu CT, Agumadu HU, Adeniran KA, Manyike PC. Cerebral palsy among children seen in the neurology clinic of Federal Medical Centre (FMC), Asaba. J Community Health 2013;38:257-60
125	PUB	2013	Okoli CA, Okolo SN, Collins JC. Plasmodium falciparum infection among neonates in the North Central region of Nigeria. J Infect Dev Ctries 2013;7:365-71
126	PUB	1988	Okolo AA, Omene JA, Scott-Emuakpor AB. Physiologic jaundice in the Nigerian neonate. Biol Neonate 1988;53:132-7
127	OTH	1985	Okolo AA, Omene JA. Trends in neonatal mortality in Benin City, Nigeria. Int J Gynaecol Obstet 1985;23:191-5
128	PUB	2004	Okoromah CN, Egri-Qkwaji MT. Profile and control measures for paediatric discharges against medical advice. Niger Postgrad Med J 2004;11:21-5
129	AJOL	2013	Okperi BO: Neonatal jaundice and birth asphyxia as major causes of cerebral palsy in Nigeria: Are doctors' wrong beliefs and practices part of the problem? Int J Med Biomed Res 2013;2:226-30
130	OTH	2004	Oladokun RE, Orimadegun AE, OlowuJA. A Ten-Year Review of Neonatal Deaths in the Special Care Baby Unit at the University College Hospital, Ibadan. Niger J Paediatr. 2004;31:119-25
131	OTH	1983	Olowe SA, Ransome-Kuti O, Ahmed I. Missed jaundice in black infants. Br Med J (Clin Res Ed). 1983;286(6380):1819
132	PUB	1981	Olowe SA, Ransome-Kuti O. Exchange transfusion using G-6-PG deficient or Hgb-AS blood in icteric neonates. J Natl Med Assoc 1981;73:811-9
133	PUB	1980	Olowe SA, Ransome-Kuti O. The risk of jaundice in glucose-6-phosphate dehydrogenase deficient babies exposed to menthol. Acta Paediatr Scand 1980;69:341-5
134	PUB	2009A	Olusanya BO, Akande AA, Emokpae A, Olowe SA. Infants with severe neonatal jaundice in Lagos, Nigeria: Incidence, correlates and hearing screening outcomes. Trop Med Int Health 2009;14:301-10. [A]
135	PUB	2012A	Olusanya BO, Ezeaka CV, Ajayi-Obe EK, Mukhtar-Yola M, Ofovwe GE. Paediatricians' perspectives on global health priorities for newborn care in a developing country: A national survey from Nigeria. BMC Int Health Hum Rights 2012;12:9. [A]
136	PUB	2014	Olusanya BO, Imam ZO, Mabogunje CA, Emokpae AA, Slusher TM. Maternal satisfaction with a novel filtered-sunlight phototherapy for newborn jaundice in Southwest Nigeria. BMC Pediatr 2014;14:180
137	CIN	2011	Olusanya BO, Inem VA, Abosede OA. Infants Delivered in Maternity Homes Run by Traditional Birth Attendants in Urban Nigeria: A Community-Based Study. Health Care for Women Int 2011;32:474-91
138	PUB	2006	Olusanya BO, Okolo AA. Adverse perinatal conditions in hearing-impaired children in a developing country. Paediatr Perinat Epidemiol 2006;20:366-71
139	PUB	2012B	Olusanya BO, Solanke OA. Maternal and neonatal profile of late-preterm survivors in a poorly resourced country. J Matern Fetal Neonatal Med 2012;25:346-52. [B]
140	PUB	2009B	Olusanya BO, Somefun AO. Sensorineural hearing loss in infants with neonatal jaundice in a developing country: A community-based study. Ann Trop Paediatr 2009;29:119-28. [B]
141	PUB	2010A	Olusanya BO. Perinatal profile of very low birth weight infants under a universal newborn hearing screening programme in a developing country: A case-control study. Dev Neurorehabil 2010;13:156-63. [A]
142	CIN	2010B	Olusanya BO, Roberts AA, Olufunlayo TF, Inem VA. Preference for private hospital-based maternity services in inner-city Lagos, Nigeria: An observational study. Health Policy 2010;96:210-6. [B]
143	OTH	2014	Omekwe DE, George MD, Kennis BT, Fakuma BN, Evidence CC, Destiny EF, Seimiekumo FE, Owoeye GIO. Survey and Management Outcome of Neonatal Jaundice from a Developing Tertiary Health Centre, South Nigeria. J Dental Med Sci 2014;13:35-9
144	PUB	1993	Omigbodun AO, Akindele JA, Osotimehin BO, Fatinikun T, Fajimi JL, Adeleye JA. Effect of saline and glucose infusions of oxytocin on neonatal bilirubin levels. Int J Gynaecol Obstet 1993;40:235-9
145	OTH	2010	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;13:321-5
146	OTH	1999	Omotade OO, Adeyemo AA, Kayode CM, Falade SL, Ikpeme S. Gene frequencies of ABO and Rh (D) blood group alleles in a healthy infant population in Ibadan, Nigeria. West Afr J Med 1999;18:294-7
147	AJOL	2006	Onwere S, Okoro O, Nwoko N, Okoro B. Causes of neonatal jaundice in neonates admitted into the newborn unit of the Abia State University Teaching Hospital between 2000 and 2004. Abia State University Medical Students' Association Journal (ABSUMSAJ) 2006;3:18-9
148	PUB	2011	Onwuanaku CA, Okolo SN, Ige KO, Okpe SE, Toma BO. The effects of birth weight and gender on neonatal mortality in North Central Nigeria. BMC Res Notes 2011;4:562
149	AJOL	2004	Onwuhafua PI, Adze J. Pregnancy in Rhesus Negative Women in Kaduna, Northern Nigeria. Trop J Obstet Gynaecol, 2004;21:21-23
150	OTH	2011	Onyearugha CN, Onyire BN, Ugboma HAA. Neonatal jaundice: Prevalence and associated factors as seen in Federal Medical Centre Abakaliki, Southeast Nigeria. J Clin Med Res 2011;3:40-45
151	OTH	2011	Onyiriuka AN. Pediatric discharge against medical advice: Experience from a Nigerian secondary healthcare institution. Med J Islamic Rep Iran 2011;25:194-199

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Serial number	Source	Year	Studies (listed by first author alphabetically)
152	PUB	2010	Opara PI, Jaja T, Onubogu UC. Morbidity and mortality amongst infants of diabetic mothers admitted into a special care baby unit in Port Harcourt, Nigeria. Ital J Pediatr 2010;36:77
153	OTH	2008	Orimadegun AE, Akinbanmi FO, Tongo OO, Okereke JO. Comparison of Neonates Born Outside and Inside of Hospital in a Children Emergency Unit, South West Nigeria. Paediatr Emerg Care 2008;24:354-8
154	OTH	1987	Oruamabo RS. Analysis of paediatric medical cases admitted to the University of Port Harcourt Teaching Hospital (UPTH) Nigeria. East Afr Med J 1987;64:520-6.
155	PUB	2011	Owa JA, Adebami OJ, Fadero FF, Slusher TM. Irradiance readings of phototherapy equipment: Nigeria. Indian J Pediatr 2011;78:996-8
156	OTH	1987	Owa JA, Dawodu AH, Familusi JB. Kernicterus in Nigerian Infants. West Afr J Med 1987;6:11-20
157	OTH	1991A	Owa JA, Dawodu AH. Influence of glucose-6-phosphate dehydrogenase status on bilirubin and hematocrit in healthy Nigerian neonates. Niger Med Pract 1991;22:47-49. [A]
158	PUB	1988	Owa JA, Dawodu AH. Neonatal Jaundice Among Nigerian Preterm Infants. East Afr Med J 1988;65:552-6. [Duplicated in: Owa JA, Dawodu AH. Neonatal jaundice among Nigerian preterm infants. West Afr J Med 1990;9:252-7]
159	PUB	1991B	Owa JA, Durosinmi MA, Alabi AO. Determinants of severity of neonatal hyperbilirubinaemia in ABO incompatibility in Nigeria. Trop Doct 1991;21:19-22. [B]
160	OTH	1995	Owa JA, Esimai VC, Olowu WA and Jegede OA. Correlation between readings on Icterometer, Jaundicemeter and Serum Bilirubin Concentrations in Newborn Infants. Niger J Paediatr 1995; 22:24-30
161	PUB	1993	Owa JA, Izedonmwen OE, Ogundaini AO, Ogungbamila FO. Quantitative analysis of 1-naphthol in urine of neonates exposed to mothballs: The value in infants with unexplained anaemia. Afr J Med Med Sci 1993;22:71-6
162	PUB	2009	Owa JA, Ogunlesi TA. Why are we still doing so many exchange blood transfusions. World J Pediatr 2009;5:51-5
163	PUB	1998	Owa JA, Osinaike AI. Neonatal morbidity and mortality in Nigeria. Indian J Pediatr 1998;65:441-9
164	OTH	1989A	Owa JA, Taiwo O, Adebiyi JAO, Dogunduro SA. Neonatal jaundice at Wesley Guild Hospital, Ilesa and Ife State Hospital, Ile-Ife. Niger J Paediatr 1989;16:23-30. [A]
165	PUB	1989B	Owa JA. Relationship between exposure to icterogenic agents, glucose-6-phosphate dehydrogenase deficiency and neonatal jaundice in Nigeria. Acta Paediatr Scand. 1989;78:848-52. [B]
166	OTH	1988	Owa JA. Relationship between values of serum bilirubin as determined by two methods: Implications for the management of neonatal jaundice. E Afr Med J 1988;65:92-8
167	PUB	1983	Oyebola DD. Care of the neonate and management of neonatal jaundice as practised by Yoruba traditional healers of Nigeria. J Trop Pediatr 1983;29:18-22
168	SCO	1983	Oyedeji GA, Olamijulo SK, Joiner KT. Experience at Wesley: 1391 consecutive admissions into the Neonatal Unit (Hurford Ward). J Trop Paediatr 1983;29:205-12
169	PUB	2004	Pam S, Bode-Thomas F, Joseph DE, Akor F, Ejeliogu E. Which babies get blood in Jos, Nigeria? Pediatr Hematol Oncol 2004;21:669-76
170	OTH	1992	Patel A, Owa JA, Harvey D. Use of Aluminium Foil in Phototherapy. Niger J Paediatr 1992;19:93-5
171	OTH	2012	Peters GO, Ojo JD. Cerebral palsy in Maiduguri, Nigeria: A case for meningitis prevention. J Trop Pediatr 2012;58:524-5
172	OTH	2009	Peters GO, Adetola A. Aetiology of cerebral palsy as seen at the physiotherapy department of a Nigerian children's hospital: A 3-year review. Afr J Med Sci 2009;2:57-60
173	OTH	1986	Ransome-Kuti O. Child health in Nigeria: Past, present, and future. Arch Dis Child 1986;61:198-204
174	OTH	1972	Ransome-Kuti O. The problems of paediatric emergencies. Niger Med J 1972;2:62-70
175	OTH	1987	Sathiakumar N, Yakubu AM. Cerebral palsy in Zaria, Northern Nigeria--is it preventable? J Trop Pediatr 1987;33:263-5
176	OTH	2008	Shehu UA, Hassan-Hanga F, Ibrahim M. Morbidity and mortality pattern among 3869 consecutive admissions at Aminu Kano Teaching Hospital, Kano. Niger J Paediatr 2008;35:67-74
177	PUB	2004	Slusher TM, Angyo IA, Bode-Thomas F, Akor F, Pam SD, Adetunji AA, McLaren DW, *et al*. Trancutaneous bilirubin measurements and serum total bilirubin levels in indigenous African infants. Pediatrics 2004;113:1636-41
178	PUB	2013	Slusher TM, Olusanya BO, Vreman HJ, Wong RJ, Brearley AM, Vaucher YE, *et al*. Treatment of neonatal jaundice with filtered sunlight in Nigerian neonates: Study protocol of a non-inferiority, randomized controlled trial. Trials 2013;14:446
179	OTH	1995	Slusher TM, Vreman HJ, McLaren DW, Lewison LJ, Brown AK, Stevenson DK. Glucose-6-phosphate dehydrogenase deficiency and carboxyhemoglobin concentrations associated with bilirubin-related morbidity and death in Nigerian infants. J Pediatr 1995;126:102-8
180	PUB	2014	Slusher TM, Vreman HJ, Olusanya BO, Wong RJ, Brearley AM, Vaucher YE, *et al*. Novel treatment of neonatal jaundice: safety and efficacy of filtered sunlight in African neonates. Pediatrics 2014;133:e1568-74
181	PUB	1995	Sodeinde O, Chan MC, Maxwell SM, Familusi JB, Hendrickse RG. Neonatal jaundice, aflatoxins, and naphthols: Report of a study in Ibadan, Nigeria. Ann Trop Paediatr 1995;15:107-13
182	OTH	1960	Sofoluwe GO, Gans B. Neonatal Jaundice in Lagos. W Afr Med J 1960;9:145-152
183	OTH	2006	Somefun OA, Lesi FE, Danfulani MA, Olusanya BO. Communication disorders in Nigerian children. Int J Pediatr Otorhinolaryngol 2006;70:697-702

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Serial number	Source	Year	Studies (listed by first author alphabetically)
184	AJOL	2009	Sotimehin SA, Runsewe-Abiodun TI, Fetuga MB, Adedeji AA, Njokanma OF. Clinical Profiles of Newborns with Malaria Parasitaemia in Sagamu. Niger Hosp Pract 2009;3:90-97
185	SCO	2012	Suleiman BM, Mokuolu OA, Adesiyun OO, Adeniyi. A. Pattern of perinatal mortality in babies delivered at the University of Ilorin Teaching Hospital, Ilorin, Nigeria. West Afr J Med 2012;31:102-8
186	OTH	2013	Toma BO, Ige OO, Abok II, Onwuanaku C, Abah RO, Donli A. Pattern of neonatal admissions and outcome in a tertiary institution in North Central Nigeria. J Med Trop 2013;15:121-5
187	PUB	2008	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;11:285-9
188	AJOL	2001	Udoma EJ, Udo JJ, Etuk SJ, Duke ES. Morbidity and Mortality among Infants with Normal Birthweight in a New Born Baby Unit. Niger J Paediatr 2001;28:13-17
189	AJOL	2002	Ugochukwu EF, Ezechukwu CC, Agbata CC, Ezumba I. Preterm Admissions in a Special Baby Care Unit: The Nnewi Experience. Niger J Paediatr. 2002;29:75-79
190	AJOL	2005	Ugochukwu EF, Ezechukwu CC, Ukwuije UT, Okonkwo CC, Olisaeke FI. Malaria in the neonate: How common is it? Trop J Med Res 2005;9:8-11
191	OTH	2010	Ugwu GIM. Prematurity in Central Hospital and GN Children's Clinic in Warri Niger Delta. Niger Med J 2010;51:10-3
192	OTH	2012	Ugwu GMI. Pattern of morbidity and mortality in the newborn special care unit in a tertiary institution in the Niger Delta region of Nigeria: A two-year prospective study. Global Adv Res J Med Sci 2012;1:133-8
193	PUB	2003	Uko EK, Agwunobi SN, Udoh JJ. Glucose-6-phosphate dehydrogenase (G-6-PD) levels in jaundiced neonates in Calabar. Niger J Med 2003;12:98-102
194	OTH	2013	Vreman HJ, Slusher TM, Wong RJ, Schulz S, Olusanya BO, Stevenson DK. Evaluation of window-tinting films for sunlight phototherapy. J Trop Pediatr 2013;59:496-501
195	SCO	1981	Werblinska B, Stankiewicz H, Oduloju MO, Atuchukwu CM, Fleming AF. Neonatal Jaundice in Zaria, Northern Nigeria. Niger J Paediatr 1981;8:3-10
196	OTH	2014	West BA, Tabansi PN. Prevalence of neonatal septicaemia in the University of Port Harcourt Teaching Hospital, Nigeria. Niger J Paediatr 2014;41:33-7
197	PUB	2013	Williams O, Gbadero D, Edowhorhu G, Brearley A, Slusher T, Lund TC. Glucose-6-phosphate dehydrogenase deficiency in Nigerian children. PLoS One 2013;8:e68800
198	OTH	1968	Worlledge S, Luzzatto L, Ogiemudia SE, Luzzatto P, Edington GM. Rhesus Immunization in Nigeria. Vox Sang 1968;14:202-10

PUB=PubMed; SCO=Scopus; AJOL=African Journals Online; CIN=CINAHL; OTH=Other sources (e.g., reference lists of selected studies)

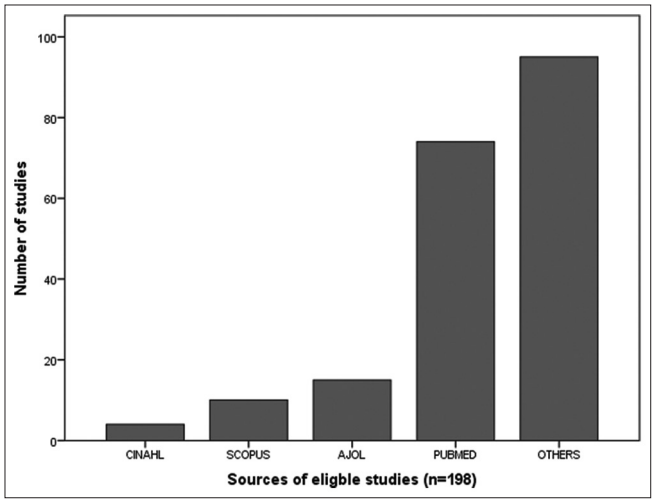

Figure 3: Sources of studies included for review

18 (1.6%) of the 1120 live births born within a 6-month period had jaundice (TSB ≥10 mg/dL or 170 μmol/L).[w54]

Overall, barring methodological limitations, these studies suggest that SNH is highly prevalent in Nigeria when compared to the rates per 100,000 live births reported in developed countries which ranges from 7.1 to 45 for SNH and 0.4 to 2.7 for kernicterus.[22,23] SNH was also less commonly reported and also less severe in babies born and observed in hospitals in the 1st week of life than in those delivered at home, as well as in those discharged from hospital within 48 h of birth.[w44, w65] Investigation of the underlying causes and risk factors of SNH in this population is therefore warranted.

Etiological and risk factors for significant neonatal hyperbilirubinemia

A summary of etiological or risk factors associated with SNH is presented in Table 2. The leading causes of SNH from studies that conducted appropriate clinical and laboratory investigations among infants detected with TSB ≥10 mg/dL (170 μmol/L) were G6PD deficiency, ABO incompatibility, sepsis and prematurity/low birth weight, singly or in combination. A quantitative synthesis of the reported rates was hampered by inadequate treatment of cases with multiple etiologies across studies. G6PD deficiency was the leading cause of SNH in the vast majority of the studies. Infection, especially umbilical sepsis resulting from traditional practices regarding cutting and subsequent management of the newborn cord with unsterile materials as well as delivery in the unhygienic environment was common among babies delivered outside

Table 1: Studies on the burden and management of neonatal hyperbilirubinemia in Nigeria (1960-2014)

Theme	Number of studies	References: First author, year of publication (study location)
Epidemiology		
Incidence/prevalence/ hospitalization	28	Ransome-Kuti 1972 (Lagos), Effiong 1975 (Ibadan), Kaine 1975 (Enugu), Effiong 1976A (Ibadan), Effiong 1976B (Ibadan), Coulter 1977 (Ibadan), Werblinka 1981 (Zaria), Oyedeji 1983 (Ilesha), Azubuike 1985 (Enugu), Oruamabo 1987 (Port Harcourt), Antia-Obong 1992 (Calabar), Ahmed 1995C (Zaria), Adeyemo 1997 (Ibadan), Ibe 1999 (Book Chapter), Ibeziako 2002 (Enugu), Chime 2011 (Warri), Duru 2004 (Irrua), Ojukwu 2004A (Abakaliki), Onwere 2006 (Aba), Eneh 2008 (Port Harcourt), Orimadegun 2008 (Ibadan), Udo 2008 (Calabar), Olusanya 2009A (Lagos), Onyearugha 2011 (Abakaliki), Israel-Aina 2012 (Benin City), Toma 2013 (Jos), Badejoko 2014 (Ile-Ife), Omekwe 2014 (Yenagoa)
Etiological factors	53	Gilles 1960 (Lagos), Sofoluwe 1960 (Lagos), Capps 1963 (Ibadan), Ifekwunigwe 1966 (Ibadan), Luzzatto 1968 (Ibadan), Worlledge 1968 (Ibadan), Effiong 1975 (Ibadan), Bienzle 1976A (Ibadan), Bienzle 1976B (Ibadan), Effiong 1976A (Ibadan), Coulter 1977 (Ibadan), Werblinka 1981 (Zaria), Akarakiri 1983 (Ibadan), Dawodu 1984 (Ibadan), Azubuike 1985 (Enugu), Owa 1987 (Ibadan), Owa 1988 (Ibadan), Owa 1989A (Ilesha), Odugbemi 1991 (Lagos), Owa 1991A (Ile-Ife), Owa 1991B (Ilesa), Ahmed 1995A (Zaria), Ahmed 1995B (Zaria), Ahmed 1995C (Zaria), Slusher 1995 (Eku), Sodeinde 1995 (Ibadan), Ahmed 1997 (Zaria), Ibe 1999 (Book Chapter), Omotade 1999 (Ibadan), Fawole 2001 (Abeokuta), Uko 2003 (Calabar), Ezeaka 2004 (Lagos), Onwuhafua 2004 (Kaduna), Kotila 2005 (Ibadan), Ojukwu 2006 (Abakaliki), Onwere 2006 (Aba), Ejike 2007 (Aba), Ogunlesi 2007 (Sagamu), George 2008 (Port Harcourt), Ogunlesi 2009 (Sagamu), Opara 2010 (Port Harcourt), Adebami 2011B (Osogbo), Chime 2011 (Warri), Obasa 2011 (Ilorin), Onwuanaku 2011 (Jos), Ibekwe 2012 (Abakaliki), Israel-Aina 2012 (Benin City), Obasa 2012 (Ilorin), Okeke 2012 (Enugu), Williams 2013 (Eku), Badejoko 2014 (Ile-Ife), Fadairo 2014 (Ile-Ife), West 2014 (Port Harcourt)
Risk factors	17	Olowe 1980 (Lagos), Familusi 1981 (Ibadan), Familusi 1985 (Ibadan), Owa 1989B (Ilesha), Anate 1991 (Ilorin), Owa 1993 (Ile-Ife), Sodeinde 1995 (Ibadan), Kaplan 2008 (Eku), Olusanya 2009A (Lagos), Olusanya 2010A (Lagos), Olusanya 2010B (Lagos), Adebami 2011B (Osogbo), Ogunlesi 2011B (Sagamu), Olusanya 2011 (Lagos), Olusanya 2012B (Lagos), Omigbodun 1993 (Ibadan), Kuti 2014 (Ile-Ife)
Mortality	64	Ransome-Kuti 1972 (Lagos), Kaine 1975 (Enugu), Laditan 1975 (Ibadan), Effiong 1976B (Ibadan), Lesi 1978 (Lagos), Adeyokunnu 1980 (Ibadan), Asindi 1988 (Calabar), Werblinka 1981 (Zaria), Abdulrahman 1983 (Kaduna), Akarakiri 1983 (Ibadan), Oyedeji 1983 (Ilesha), Okolo 1985 (Benin City), Ransome-Kuti 1986 (Lagos), Fagbule 1987 (Ilorin), Oruamabo 1987 (Port Harcourt), Adedoyin 1989 (Lagos), Owa 1989A (Ilesha), Bamgboye 1990 (Ibadan), Asindi 1991 (Calabar), Antia-Obong 1992 (Calabar), Ibrahim 1993 (Sokoto), Njokanma 1994 (Sagamu), Ahmed 1995C (Zaria), Slusher 1995 (Eku), Ahmed 1997 (Zaria), Owa 1998 (Ilesha), Aisen 2000 (Jos), Lesi 2000 (Lagos), Udoma 2001 (Calabar), Ibeziako 2002 (Enugu), Ugochukwu 2002 (Nnewi), Ezeaka 2003 (Lagos), Kuti 2003 (Ile-Ife), Ezechukwu 2004 (Enugu), Obi 2004 (Abakaliki), Oladokun 2004 (Ibadan), Ayoola 2005 (Ibadan), Ekure 2005 (Lagos), Nte 2006 (Port Harcourt), Ogunlesi 2006 (Sagamu), Ejike 2007 (Aba), Fetuga 2007 (Sagamu), Mukhtar-Yola 2007 (Kano), Ogunlesi 2007 (Sagamu), Eneh 2008 (Port Harcourt), Shehu 2008 (Kano), Udo 2008 (Calabar), Okechukwu 2009 (Abuja), Owa 2009 (Ile-Ife), Adebami 2010 (Osogbo), Adeolu 2010 (Ile-Ife), Iliyasu 2010 (Kano), Omeigberale 2010 (Benin City), Ugwu 2010 (Warri), Ayede 2011 (Ilorin), Fajolu 2011 (Lagos), Ibekwe 2011 (Abakaliki), Ibekwe 2012 (Abakaliki), Israel-Aina 2012 (Benin City), Suleiman 2012 (Ilorin), Ugwu 2012 (Oghara-Delta), Afolabi 2013 (Lagos), Toma 2013 (Jos), Omekwe 2014 (Yenagoa)
Neurodevelopmental disorders	26	Dada 1970 (Lagos), Animashaun 1971 (Lagos), Izuora 1981 (Enugu), Izuora 1985 (Enugu), Asindi 1986 (Calabar), Sathiakumar 1987 (Zaria), Iloeje 1989 (Enugu), Izuora 1989 (Enugu), Nottidge 1991 (Ibadan), Airede 1992 (Jos), Duggam 1992 (Zaria), Lagunju 2006 (Ibadan), Olusanya 2006 (Lagos), Somefun 2006 (Lagos), Ejike 2007 (Aba), Ogunlesi 2008 (Sagamu), Belonwu 2009 (Kano), Olusanya 2009B (Lagos), Peters 2009 (Maiduguri), Adebami 2011A (Osogbo), Frank-Briggs 2011 (Port Harcourt), Peters 2012 (Maiduguri), Aronu 2013 (Enugu), Ogunrin 2013 (Benin City), Okike 2013 (Asaba), Okperi 2013 (Effurum)
Care of jaundiced infants		
Care-seeking practices	13	Olowe 1983 (Lagos), Ekanem 1994 (Calabar), Ogunfowora 2006A (Sagamu), Ogunfowora 2006B (Sagamu), Eneh 2009 (Port Harcourt), Ogunlesi 2012 (Sagamu), Olusanya 2012 (National), Egube 2013 (Benin City), Okperi 2013 (Effurum), Alex-Hart 2014 (Port Harcourt), Ekwochi 2014 (Enugu), Ezeaka 2014 (Multicentre), Olusanya 2014 (Lagos)
Diagnosis and treatment	23	Effiong 1975 (Ibadan), Effiong 1976A (Ibadan), Mee 1977 (Africa), Olowe 1981 (Lagos), Oyebola 1983 (Ibadan), Okolo 1988 (Benin City), Owa 1988 (Ibadan), Patel 1992 (Ile-Ife), Owa 1995 (Ilesha), Pam 2004 (Jos), Slusher 2004 (Eku & Jos), Owa 2009 (Ile-Ife), Ibekwe 2012 (Abakaliki), Idu 2010 (Abeokuta), Ogunlesi 2011A (Sagamu), Owa 2011 (Ile-Ife), Cline 2013 (Multicentre), Gbadamosi 2013 (Ibadan), Okperi 2013 (Effurum), Slusher 2013 (Eku), Slusher 2013 (Lagos), Vreman 2013 (Lagos), Slusher 2014 (Lagos)
Follow-up evaluation	1	Ejike 2007 (Aba)
Other issues		
Congenital malaria and NNJ	8	Ibhanesebhor 1995 (Benin City), Ojukwu 2004 (Abakaliki), Ugochukwu 2005 (Nnewi), Ekanem 2008 (Calabar), Sotimehin 2009 (Sagamu), Lesi 2010 (Lagos), Okoli 2013 (Jos), Enyuma 2014 (Calabar)
Aflatoxins	4	(Ahmed 1995A [Zaria], Ahmed 1995B [Zaria]), Sodeinde 1995 (Ibadan), Abulu 1998 (Ekpoma)
Hyponatremia	2	Omigbodun 1993 (Ibadan), Akinyinka 1995 (Ibadan)
Discharge against medical advice	6	Okoromah 2004 (Lagos), Ejike 2007 (Aba), Ibekwe 2009 (Abakaliki), Okechukwu 2011 (Abuja), Onyiriuka 2011 (Benin City), Eke 2013 (Port Harcourt)

NNJ=Neonatal jaundice, Source: references w1-w198 (web Table S1)

Table 2: Summary of reported etiological/risk factors for SNH in Nigeria*

Category	Factors	Identified studies† (web reference number)
Maternal/family	Rhesus disease	w5, w17, w30, w36, w37, w44, w111, w112, w147, w163, w180
	ABO incompatibility	w5, w11, w13, w17, w30, w34, w36, w37, w39, w41, w44, w45, w84, w111, w112, w147, w155, w163, w180, w195
	Exclusive breastfeeding	Not reported
	Race or Ethnicity	Reported but not confirmed
	Oxytocin during labor	w13
	Religion	w134
	Occupation	w134
	Maternal age	w5
	Social class	w5, w115
	Primiparity	
	Herbal drug in pregnancy	w13, w134
	Mode of delivery	w21
	Place of delivery	w5, w115, w134, w137, w142
	Family history of jaundice	Not reported
	Sibling treated for jaundice	Not reported
Perinatal	Infections	w5, w11, w17, w30, w34, w36, w37, w39, w41, w44, w45, w84, w111, w112, w147, w155, w163, w180, w195
	Birth trauma	w13, w111, w180, w195
	Male gender	w134
	Birth asphyxia	w84
	Multiple gestation	w134
	Severe anemia	w115
	Acidosis	w115
Neonatal	G6PD deficiency	w5, w11, w17, w30, w31,w34, w37, w39, w41, w44, w45, w111, w112, w155, w163, w180, w195
	Preterm birth	w34, w36, w39, w84, w111, w112, w137, w147, w195
	Low birth weight	w5, w11, w13, w17, w30, w37, w41, w44, w45, w141, w155, w163, w180
	Underweight/weight loss	w5, w134
	UGT1A1 gene polymorphisms	w89
	Icterogenic agents	w67, w133
	TcB/TSB level	Not reported
	Free bilirubin	Not reported
	Hypothermia	Not reported
	Serum aflatoxin	w2, w180

*Inclusive of acute bilirubin encephalopathy and kernicterus; †Cohort, cross-sectional or case-control studies only. Studies with duplicated primary data were excluded. TcB=Transcutaneous bilirubin; TSB=Total plasma/serum bilirubin; G6PD=Glucose-6-phosphate dehydrogenase

hospitals.[w13, w29, w54, w84, w164, w167, w182, w195] Such infection often triggered hemolysis in both G6PD deficient and normal infants.

Rhesus disease was not confirmed in several studies as a major cause of SNH in this population especially among outpatients.[w12, w13, w29, w33, w38, w44, w54, w84, w156, w182, w195] This was also noted in the few studies that reported isolated cases, especially among inborn patients.[w5, w29, w36, w43, w111, w112, w147, w164, w181] The proportion of idiopathic SNH ranged from 7.8% to 54.5%.[w11, w12, w36, w47, w111, w156]

Several studies, predominantly from the South-West, demonstrated exposure to icterogenic agents or oxidant stressors such as insecticides, menthol-based, naphthalene-camphor products, sulfonamides or sulfa-containing drugs and herbal concoctions as important contributors to the incidence, and severity of SNH especially in G6PD-deficient babies.[w30, w40, w66, w71, w84, w133, w150, w156, w159, w165, w181] One study established the prevalence of UGT1A1, confirming that unconjugated bilirubin levels in infants with G6PD deficiency in combination with $(TA)_n$ promoter polymorphism may rise exponentially from hemolysis triggered by exposure to oxidant stressors such as sepsis and menthol-based products.[w89] While one study from Ibadan (South-West) found aflatoxins to be an important contributor to the severity of SNH,[w181] other reports from Zaria (North-West), did not find any such association.[w11, w12]

Few case-control studies have explored risk factors for SNH, with explicit adjustment for confounding variables. For example, in one recent systematic review and meta-analysis,[24] only four studies were adjudged to provide

reliable data on possible maternal and neonatal risk factors for SNH in Nigeria.[w5, w115, w134, w181] Factors reported in two or more studies were social class, delivery outside hospital and underweight/excessive weight loss. Factors reported in single studies included religion, occupation, herbal drug use in pregnancy, serum aflatoxin, gender (male), severe anemia, and acidosis. One study from Zaria (North-West) however, found no association between maternal use of herbal medication during pregnancy and SNH.[w13] Factors reported in other descriptive studies without adjustment for confounders, included oxytocin in labor,[w13, w144] birth trauma including cephalhematoma,[w13, w111, w150, w181] and birth asphyxia.[w84] Two studies suggested that hyponatremia contributed significantly to SNH associated with oxytocin use in labor.[w18, w144] These findings are comparable to those reported from other developing countries.[24,25]

In general, some studies have suggested some plausible but unverified link between SNH and congenital malaria, Nigeria being a prominent malaria endemic country [Table 1]. For example, jaundice, irritability, and poor feeding were reported in one birth cohort in Lagos as the most common symptoms associated with congenital malaria; and that jaundice was significantly associated with malaria parasitemia between day 7 ($P = 0.04$) and day 14 ($P = 0.002$).[w95] A few studies also reported SNH as one of the neonatal conditions accounting for self-discharge by mothers of sick infants against medical advice. Although breastfed babies are more likely than bottle-fed babies, to develop jaundice within the 1st week of life, the impact of the ubiquitous exclusive breastfeeding in Nigeria was not documented in any study. In some culture, jaundice is believed to be transferred from the mother to the fetus or caused by shortage of blood in the newborn, fever, mosquito bites, blood spilling into the eyes of the baby at birth, bad water in the baby's body, the mother eating bananas during pregnancy or germs in mother's breast milk.[w46, w55, w109, w167, w173]

Table 2 provides an overview of putative factors that have not been (sufficiently) investigated based on findings from other LMICs.[24,25]

Adverse neonatal and long-term outcomes

Several studies showed that SNH was one of the most common causes of readmissions.[w45, w53, w54, w100, w174] The proportion of total neonatal admissions into children emergency departments or Special Care Baby Units varied from 9.4% in one study from Kano (North-West),[w100] to 64% in Lagos (South-South).[w174] Studies that failed to disaggregate neonatal admissions from overall pediatric admissions were likely to under-report the contribution of SNH to neonatal morbidity in the 1st week of life as demonstrated in some older reports from Benin City.[26,27] Acute bilirubin encephalopathy (ABE) or kernicterus was more commonly reported among outborn infants presenting late for emergency treatment.[w5, w111, w112, w156, w162]

As shown in Table 1, several studies as far back as 1972 have reported bilirubin-induced mortality among infants with SNH. These reports demonstrated significant rates of mortality among infants with SNH or a substantial contribution of SNH-related deaths to overall neonatal mortality.[w9, w31, w45, w68, w82, w84, w96, w113, w163, w185] One study that examined the trend in child mortality over a 20 year period in the Children's Emergency Unit of a Teaching Hospital in Lagos reported a significant rise in the contribution of SNH to mortality from 4.0% in 1972,[w174] to 13.1% in 1990.[w96]

While routine developmental evaluation of survivors of SNH including ABE/kernicterus was rarely reported, several studies have implicated SNH as a major contributor to the incidence of cerebral palsy and hearing impairment in infants and young children [Table 1]. Prior to the introduction of newborn hearing screening in Nigeria, available evidence on the association between SNH and hearing impairment relied on parental reports or medical records predominantly in school-aged children.[28,29] Recent studies among infants enrolled for newborn hearing screening based on otoacoustic emissions and auditory brainstem response audiometry have shown significant risks of hearing impairments including auditory neuropathy spectrum disorders in infants with SNH even after phototherapy and/or exchange transfusion.[w134, w140,30] Other less frequently reported adverse long-term outcomes include epilepsy (with or without cerebral palsy),[w24, w83, w117] speech and language disorders,[w182] and mental retardation.[w87]

A national survey among pediatricians in Nigeria to elicit their perspectives on priorities for newborn care showed that neonatal jaundice ranked next to preterm birth/low birth weight and birth asphyxia for disability; and above tetanus by all measures except mortality [Figure 4].[w135] In effect, the exclusion of SNH in the global health campaign for newborn care under the millennium development goals (MDG) project was inappropriate for Nigeria.

Care-seeking practices for jaundiced infants

The vast majority of babies in Nigeria are delivered outside

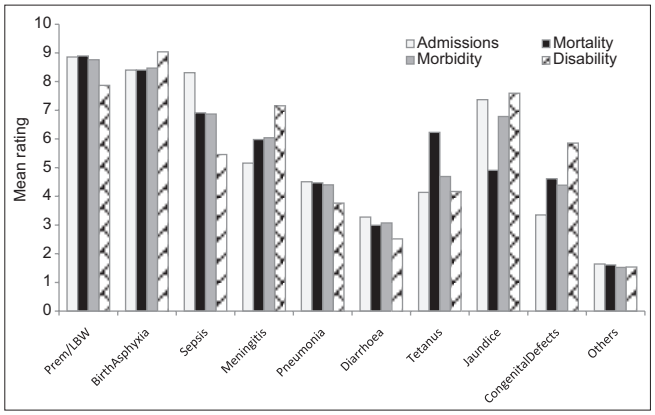

Figure 4: Priority rating of common neonatal conditions by pediatricians in Nigeria [source: Reference w135]

hospitals. Based on data from the Nigeria Demographic and Health Survey 2008, 35% of births in Nigeria are delivered in a health facility (20% in public hospitals and 15% in private facilities).[31] Of the 65% delivered outside hospitals, 62% occur at home. South-East has the highest proportion of institutional deliveries (74%), followed by South-West (70%), while North-West has the lowest proportion (8%). Among those delivered in hospitals and with uneventful delivery, hospital stay rarely exceeded 48 h of birth. In one birth cohort of 741 preterm and term babies delivered in a Teaching Hospital in Ibadan, onset of jaundice was reported on the 1st day in 12.8% of the infants, between the 2nd and 4th day in 72.4%, and between the 5th and the 8th day in 14.8%.[w43] In another cohort of 208 preterm babies admitted in the same hospital, jaundice was noticed by the 2nd day of life in 78 (37.5%), on the 3rd day in 74 (35.6%) and on the 4th day in 34 (16.3%). Thus, by the 4th day of life, jaundice had manifested in 186 (89.4%) of the preterm infants.[w158] Thus, the onset of SNH in the vast majority of both inborn and outborn babies occurred outside hospital. It was often difficult to ascertain the time of onset in out-born babies. However, such infants typically presented between the 3rd and 9th day of life.[w5, w29]

A number of studies have reported that many mothers are able to distinguish jaundice by yellowish discoloration of the skin and sclera of the newborn, but have a poor knowledge of the underlying causes and potential consequences.[w46, w55, w57, w108, w116, w134] Late presentation in hospitals was therefore a major contributor to the high incidence of avoidable exchange transfusions and adverse outcomes among infants with SNH in Nigeria [Table 1]. The delay in seeking timely and appropriate care was underpinned by several factors including late or failed recognition of the onset of severe jaundice and poor perception of its severity.[w5, w55, w109, w116, w129, w162,5] Before seeking medical attention, mothers commonly resorted to self-medication with antibiotics, vitamins or traditional therapies such as herbal preparations and exposure to direct "early morning" sunlight.[w109, w116, w129] Inappropriate advice from health workers was also not uncommon. For example, it was reported in one study that over 25% of community health workers at primary care centers were likely to prescribe antibiotics, natural (direct sunlight) phototherapy or herbal therapies.[w109] On occasions when mothers chose to seek care outside their homes, they could be constrained by difficulties with accessibility to health facilities and/or finances or identifying an "appropriate" hospital that routinely admits and provides essential care for sick babies.[w53] Some mothers therefore presented first to the nearest primary health centers or private clinics most of which were poorly-equipped to provide special care for sick neonates.[5]

Diagnosis and treatment

Practice guidelines for the prevention, diagnosis and management of infants with SNH do not exist in Nigeria. The guidelines for hyperbilirubinemia in developed countries such as the NICE in UK,[2] or the American Academy of Pediatrics,[32] were rarely cited because their adoption and implementation was constrained by several systems-based and biological factors.[33] Modern tools for real-time objective measurement or monitoring of bilirubin levels (transcutaneous bilirubin [TcB] and plasma/serum bilirubin [TSB]) have been reported in several studies.[w30, w177] The noninvasive TcB measurement has also been demonstrated as a reliable proxy for the more invasive and diagnostic TSB.[w172] However, these tools were not routinely available in most hospitals including tertiary institutions. As a result, it was common practice for hospital personnel to make a clinical judgment based on visual assessment of the cephalocaudal progression or ominous signs of ABE/kernicterus particularly among outborn infants. Similarly, laboratory investigations such blood typing for baby and mother, direct Coombs' test, blood culture, G6PD assay, and full blood count to establish the risk status of infants were not readily available in most hospitals. In some hospitals, facilities for laboratory investigations were located far away from neonatal units, thus, forestalling quick turn-around in obtaining results for prompt clinical decisions.

Phototherapy and exchange transfusion were the mainstay treatments for hospital patients. Case definition for SNH and treatment thresholds for phototherapy and exchange transfusion varied across studies. The minimum TSB threshold for clinically significant jaundice across studies was 10–12 mg/dL for term infants. In general, phototherapy was commenced at approximately TSB ≥12 mg/dL (204 μmol/L) in otherwise healthy normal weight (≥2500 g) babies.[w43, w44, w76, w162, w164] Exchange transfusion was indicated at TSB ≥20 mg/dL (340 μmol/L) in apparently healthy term infants and sometimes at TSB <20 mg/dL (340 μmol/L) in very ill term infants with or without features of kernicterus. Exchange transfusion was indicated in preterm at TSB> 10 mg/dL per kilogram body weight.

Effective first-line treatment with conventional blue-light phototherapy requires light emission spectrum within the bilirubin absorption spectrum of 400–520 nm (peak 450 ± 20 nm); irradiance level ≥30 μW/cm^2/nm, exposed to ~80% of an infant's body surface area, and optimized duration of exposure.[34] However, in one survey, the vast majority (94%) of 63 phototherapy devices tested in twelve referral level hospitals delivered irradiances of ≤10 μW/cm^2/nm and none were ≥30 μW/cm^2/nm.[w155] This finding was corroborated in another report in which 76 "functional" phototherapy devices across 16 hospitals were evaluated.[w37] The functionality of the devices was frequently compromised by erratic power supply and breakdowns due to poor device maintenance. High rates of exchange transfusion were therefore common due to sub-therapeutic phototherapy and lack of intensive phototherapy especially

in combination with late presentation of outborn babies with SNH.[w27, w76, w93, w114, w164, w170]

Because of the widespread constraints with conventional phototherapy, a novel, low-cost canopy has been developed in Lagos as a potential alternative for treating infants with SNH in Nigeria and other tropical countries.[w178, w180] It is a noteworthy advancement to the initial "sunshine phototherapy cot" piloted almost three decades ago by a foremost neonatologist in Nigeria.[35] The canopy is covered with special window-tinting films that filter out virtually all ultraviolet (UV)-A, UV-B, and UV-C light, as well as significant levels of infrared radiation (heat) in natural sunlight. The need for this device was further prompted by the common practice of mothers and caregivers to expose their jaundiced babies to direct sunlight, with or without the support of health workers.[w46, w49, w55, w129] The canopy allows mothers to sit comfortably while holding or feeding their babies during treatment. Preliminary data from a randomized clinical trial has established that this phototherapy device is no less efficacious than conventional blue-light phototherapy.[36] Mothers have also expressed satisfaction with the device as an alternative to conventional phototherapy.[w136] However, its use is still experimental and limited to daytime care and periods with favorable climatic conditions.

Other traditional therapies typically for mild-to-moderate SNH included medicinal plants, herbal concoctions, black soap, and water extract of unripe pawpaw.[w70, w80, w116, w167] Traditional treatment for severe SNH (TSB ≥20 mg/dL or 340 μmol/L) including ABE or kernicterus was not documented in any study.

Postdischarge developmental surveillance

Although long-term adverse outcomes such as cerebral palsy, hearing impairments, epilepsy, and intellectual difficulties have been reported in studies [Table 1], developmental screening and evaluation of survivors of ABE or kernicterus was rarely considered as a component of the clinical management for SNH. In the only study identified in this review with evidence of postdischarge surveillance, 4 (5%) of the 79 infants treated for SNH over a 5-year period were followed up.[w47] Two were diagnosed with motor retardation and the remaining two had poor neck control between 6 and 12 months. Hearing evaluation was not reported.

Discussion

To our best knowledge, this is the first comprehensive review of the burden of SNH in Nigeria or any other LMIC in sub-Saharan Africa. There are six overarching observations to be noted. First, as expected and barring weaknesses in study design and quality of available records, the scoping methodology resulted in a substantially greater number of studies and a wider range of factors than would have been identified in a traditional systematic review.

Second, no remarkable progress has been observed on the epidemiological profile of SNH since the earliest reports 55 years ago.[w35, w81, w96, w98, w174, w182,37-39] SNH is highly prevalent in Nigeria and continues to be associated with substantial case fatality and long-term morbidity.[4,40] The dearth of population-based epidemiological studies often preferred for global health programming cannot be justifiably construed as an evidence of lack of disease burden in this population. For example, one unpublished nationwide survey conducted in 2012 by Nigerian Society of Neonatal Medicine (NISONM) estimated that SNH accounted for 1 out every 5 neonatal admissions. NISONM data also suggests that SNH accounts for at least 5% of all neonatal mortality in Nigeria.

Third, the most frequently reported etiological factors for SNH are still G6PD deficiency, ABO incompatibility, prematurity, and infection. Despite the significant national G6PD deficiency allele frequency of at least 15.0% and its important contribution to the incidence of SNH in this population in particular,[w197,14] routine screening for G6PD deficiency as recommended by WHO,[41] is rare in birthing hospitals.

Fourth, contrary to a recent report on the worldwide prevalence of rhesus disease and its contribution to the global burden of SNH based primarily on mathematical modeling,[4] this review has established that this factor is not a significant contributor to the burden of SNH in Nigeria. This observation is consistent with earlier reports that suggested that the predicted frequency of hemolytic disease of newborn due to rhesus immunization is about 1–800 as only 5% of Nigerian women are estimated to be rhesus negative.[w198] It is also postulated that rhesus-negative Nigerians have a low iso-immunization potential, probably due to some genetic predisposition.[w97, w198]

Fifth, the current weaknesses in the care-seeking pathways and clinical framework for the management of infants with or at risk of SNH are not insurmountable to significantly curtail the burden of this condition.[14,33]

Finally, the burden of SNH has not been sufficiently documented in some regions which may lead to under-representation of the nationwide burden and challenges of SNH.

The substantial burden of SNH in regions with adequate data can be attributed to three phases of delay in the care of jaundiced infants: The decision to seek appropriate care, reaching an appropriate health facility, and receiving

adequate/appropriate care. Strategies to address these delays have been well documented in a recent review.[5] At the very core is the need for a bold public health initiative to educate women of childbearing age routinely on the early signs of the onset of SNH and dangers of late presentation to appropriate health facilities. All birthing hospitals should be equipped to provide effective and timely phototherapy for jaundiced infants. Infants who have been treated for SNH should also be placed under developmental surveillance routinely at least in the first year of life to facilitate early detection of disabilities. As has been demonstrated in developed countries, the burden of SNH and the current excessive rates of exchange transfusion can be substantially curtailed by timely and effective phototherapy even among high-risk infants. The development of a novel, low-cost filtered-sunlight phototherapy device offers the prospect of expanding the coverage of this treatment beyond traditional hospital settings.

The exclusion of SNH in the global agenda for newborn care within the MDG framework in the last 15 years has contributed in no small measure to the lack of globally-backed national programs for this condition. While conditions such as prematurity, birth asphyxia, and infection remain prominent contributors to neonatal mortality in LMICs, they should not distract from the substantial and perennial burden of SNH in many LMICs including Nigeria. This is corroborated by the views of pediatricians in a nationwide survey on the preferred component of essential newborn care in Nigeria.[w135] It is therefore gratifying to observe increasing global interest in addressing the burden of SNH in LMICs. For example, for the 1st time ever, "hemolytic disease in fetus and newborn, and other neonatal jaundice" has been recognized by the WHO's Child Health Epidemiology Reference Group and the Global Burden of Disease Collaborators as a distinct entity under the leading causes of neonatal mortality and long-term morbidity.[4,40] The lack of a robust and practical framework for the effective management of infants with or at risk of SNH at all levels of health care delivery in LMICs has been addressed by a team of international experts from all world regions in a landmark paper.[33] The tasks and resources required to ensure optimal care of infants with SNH have been outlined comprehensively in the document. This framework can be easily adapted to suit the local practice needs in different settings in Nigeria, especially at the primary care level which is the first level of medical intervention for the vast majority of infants with SNH.[42]

Finally, the number of publications on SNH peaked in 2011. Furthermore, most (82.3%) of the identified studies in this review were conducted in Southern regions. Evidently, there is need to reverse the downward trend since 2011 and build greater research capacity for SNH in the rest of the country to more accurately determine possible differences in the epidemiological and clinical practice profile across the country. It is also important that studies are published in journals indexed by key databases to improve accessibility for potential users.

Typical of scoping reviews, this study has a number of limitations that are worth noting. First, no quality assessment of the included studies was undertaken to determine publication bias or the validity of the diagnostic criteria for the reported etiological factors. Second, despite the liberal inclusion criteria, it was still possible to have excluded other relevant studies not available from the selected databases. Third, no distinction was made in the severity of SNH including acute and chronic bilirubin encephalopathy whereas associated factors may differ for various levels of severity. Notwithstanding, the key findings from this review clearly underscore the scope of the burden of SNH in a poorly-resourced African setting and the urgent need for appropriate intervention. While jaundice cannot be prevented in newborns, its progression to bilirubin-induced neurologic dysfunction and the potential adverse outcomes can be prevented. They also highlight areas for focused education for mothers and care-givers to address erroneous beliefs and customs on SNH as well as capacity-building for further research and advocacy to facilitate improved care for infants with or at risk of SNH in this population and comparable LMICs.

Conclusion

This scoping review has highlighted the epidemiological profile of SNH and the current challenges for the effective care of the affected infants in Nigeria. No significant progress appeared to have been recorded for more than half a century in all regions of the country, especially during the 15-year MDG era ending 2015. The emerging global interest and recognition for hemolytic disease and neonatal jaundice as an important contributor to neonatal mortality and long-term morbidity especially in LMICs presents a unique opportunity to address the disease burden in Nigeria through appropriate maternal and child health initiatives.

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