Infants at risk of significant hyperbilirubinemia in poorly-resourced countries: evidence from a scoping review

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Background: **Neonatal hyperbilirubinemia is frequently associated with disproportionately high rates of bilirubin-induced mortality and long-term morbidities in low- and middle-income countries (LMICs). This scoping review aimed to identify possible etiological/risk factors for clinically significant hyperbilirubinemia in LMICs so as to guide intervention and future research priorities.**

Data sources: **We systematically searched PubMed, Scopus, Excerpt Medica Database, Cumulative Index to Nursing and Allied Health Literature, WHO Library Database, African Index Medicus, African Journals Online, Latin American and Caribbean Health Sciences Literature, and Indian Medical Journals for reports published between January 1990 and August 2014 in LMICs with per capita income of ≤US$ 6000. We included studies on the etiology of neonatal hyperbilirubinemia or hyperbilirubinemia as significant morbidity for relevant maternal, perinatal and neonatal disorders without restriction on study design.**

Results: **A total of 131 studies were identified in 23 LMICs from different regions of the world. The factors most frequently associated with neonatal hyperbilirubinemia (in approximately 10% of all studies) were ABO and Rhesus incompatibilities, diabetes mellitus, glucose-6-phosphate dehydrogenase deficiency, prematurity/low birth weight, infection, birth trauma, and drug-induced labor. The role of exclusive breast-feeding and genetic factors was sparsely explored.**

Conclusions: **Several maternal, perinatal and neonatal factors are associated with neonatal hyperbilirubinemia in LMICs. Improved research efforts and strategies to address these factors are warranted to curtail the disease burden in these countries.**

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Review article

Introduction

Neonatal jaundice is a ubiquitous transitional condition that affects 60%-80% of newborns worldwide,[1,2] often requiring treatment with phototherapy or exchange transfusion in about 10% of the affected infants.[3] Delays in providing timely and effective treatment for infants with or at risk of significant hyperbilirubinemia are widely reported in resource-poor countries, and often expose the affected infants to an elevated risk of acute bilirubin encephalopathy or its chronic form, kernicterus, far beyond rates reported in high-income countries.[4] Bilirubin encephalopathy is associated with at least a mortality of 10% and a long-term morbidity of 70%,[5] particularly in low and middle-income countries (LMICs).[4] Recent global estimates suggest that every year about 1.1 million babies would develop severe hyperbilirubinemia with or without bilirubin encephalopathy worldwide and the vast majority reside in sub-Saharan Africa (SSA) and South Asia (SOA).[6]

After several years of neglect and exclusion from the global child health agenda under the Millennium Development Goals (MDG) initiative, hemolytic disease in newborns and other neonatal jaundice are increasingly acknowledged as important contributors to global neonatal deaths.[7,8] The emerging interest in the early childhood developmental difficulties faced by many survivors of the current maternal and child health interventions in LMICs under the MDG framework has also drawn attention to neonatal jaundice.[9,10] However, the global burden of neonatal hyperbilirubinemia and the underlying factors in LMICs are still poorly characterized

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to guide programmatic policy initiatives.[11,12]

Because of the dearth of well-designed research in LMICs, the traditional approach of gathering evidence through systematic review and meta-analysis often results in the exclusion of several insightful studies that do not satisfy the often stringent inclusion criteria.[13,14] For example, in a recent systematic review of risk factors for significant hyperbilirubinemia in 91 LMICs, only 13 studies from 5 countries out of 131 publications met the strict criteria recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.[14,15] As a result, several potential etiological/risk factors based on checklists published by the American Academy of Pediatrics and other clinical guidelines for the management of neonatal hyperbilirubinemia were omitted primarily because they were reported in case series or descriptive cohort studies.[2,16]

Scoping reviews are widely acknowledged as an effective method of capturing a range of literature to establish available evidence and the overall state of research on the topic of interest.[17,18] Unlike systematic reviews, they allow a broader range of literature to be captured, including all types of study design without emphasis on the assessment of quality as defined within a biomedical research convention.[19] We, therefore, conducted a scoping review 1) to determine more broadly the range of factors associated with neonatal hyperbilirubinemia in LMICs compared with high-income countries, 2) to describe the potential burden associated with these factors, and 3) to identify gaps in the existing literature that should be addressed in future studies.

Methods

Study framework

We adopted the methodological framework proposed by Arksey and O'Malley[17] for scoping studies. This framework consists of five stages: defining the research question, identifying the relevant studies, study selection, charting the data and collating, summarising and reporting the results. Our scoping review did not include the optional sixth stage suggesting a consultation exercise to inform and validate findings from the review. The methodological quality of included articles was not evaluated systematically as it was not compulsory under this framework.[17]

Eligible focus countries

The term "LMICs" based on the World Bank classification covers approximately 140 countries with per capita gross national income (GNI) ranging from US$ 150 to US$ 12 745. In view of this wide gap in income distribution and in order to focus on the most disadvantageous LMICs, we selected 91 countries with per capita GNI of ≤US$ 6000 using the Human Development Report 2013 published by United Nations Development Programme.[4,14] By world regions, 42 (46%) countries are from SSA, 18 (20%) from East Asia & Pacific (EAP), 10 (11%) from Latin America & Caribbean (LAC), 8 (9%) from Middle East & North Africa (MEN), 7 (8%) from SOA, and 6 (6%) from Europe & Central Asia.

Defining the research questions

The focus of this study was to address two main questions, namely: 1) "what are the etiological findings among infants diagnosed with significant hyperbilirubinemia with or without bilirubin encephalopathy?" and 2) "what are the specific maternal or infant health conditions that report significant hyperbilirubinemia as a frequent neonatal morbidity?". There are several descriptors for clinically significant hyperbilirubinemia in the literature such as "pathological", "significant", "severe", "extreme", "marked" or "hazardous". The lack of uniform bilirubin thresholds for these various classes of hyperbilirubinemia makes comparability of studies challenging. For this review, hyperbilirubinemia of any unconjugated bilirubin level (typically from total serum bilirubin >12 mg/dL or 205 μmol/L) requiring immediate treatment with phototherapy or exchange transfusion was considered as clinically significant.

Identifying relevant studies

We searched electronic databases including PubMed, Scopus, Excerpt Medica Database (EMBASE) and Cumulative Index to Nursing and Allied Health Literature (CINAHL), WHO Library Database, Latin American and Caribbean Health Sciences Literature, Indian Medical Journals, African Index Medicus and African Journals Online to identify relevant articles published in any of the 91 eligible LMICs between January 1990 and August 2014. The search terms used for major databases such as PubMed, Scopus, EMBASE and CINAHL were "neonatal jaundice" or "neonatal hyperbilirubinemia" and "country name" while the search term for other databases was restricted to "jaundice" or "hyperbilirubinemia" for different countries for improved hit of relevant articles. We reviewed the reference lists of retrieved articles as well as relevant review articles. No limits were used to ensure that the maximum number of relevant reports was identified.

Study selection

We screened all titles and abstracts of retrieved studies from all databases and other sources to identify articles

relevant to our two primary research questions. No restriction was placed on study design at this stage except that all animal or *in vitro* studies were excluded. We included studies of subpopulations of infants with specific risk profile such as diabetic mothers, preterm/low birth weight, sepsis, or hemolytic conditions including glucose-6-phosphate dehydrogenase (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 excluded. Thereafter, duplicates were systematically removed starting with all eligible articles from PubMed through to the last database. Based on the review of the full-texts of eligible studies we decided to exclude all papers in which the number of reported cases or subjects was less than 50, except for rare etiological factors such as diabetes mellitus or genetic conditions. Both authors adopted this selection procedure independently. Discrepancies in the final selection were resolved through consensus after joint reassessment.

Data charting and collation

The data from all the articles that met our inclusion criteria were charted and summarized using a descriptive analytical approach. The extracted data from each study included the data source, country of study, year, author(s), full citation, number of cases and factors reported. We summarized all the identified studies into a master list of etiological or risk factors commonly reported in the literature in high-income countries like USA and UK.[2,16]

Results

Study selection

The initial search yielded 1481 studies across all target databases and 14 from additional sources resulting in a total of 1495 records (Fig. 1). After assessment of titles and abstracts, 313 studies were gathered from all sources, out of which full-texts for 181 studies were required after excluding 132 duplicates. A total of 50 studies were further excluded because they did not satisfy our inclusion criteria for the required minimum sample size resulting in a final selection of 131 studies (Supplementary Table 1).

Characteristics of included studies

The characteristics of the 131 studies included in this review are summarized in Supplementary Table 2. Studies were obtained from 23 (23.1%) out of the 91 eligible LMICs (Fig. 2). These 23 countries have combined annual live births of approximately 53.5 million, accounting for 40% of the global annual live births of roughly 135 million. India recorded the highest number of studies (*n*=51), followed by Nigeria (*n*=21), Egypt (*n*=12), Pakistan (*n*=10), Bangladesh (*n*=7), Nepal (*n*=7), Jordan (*n*=3), two each from Bolivia, Iraq, Sri Lanka and Zimbabwe, and one each from Benin, Congo, Cote d'Ivoire, Cuba, Kenya,

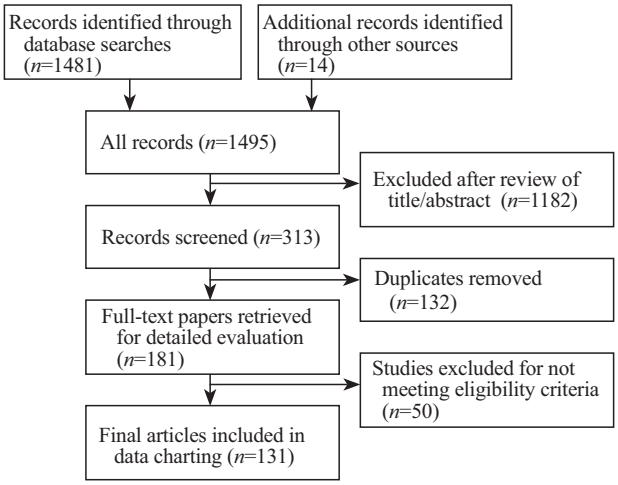

Fig. 1. Flow diagram of the study selection process and results.

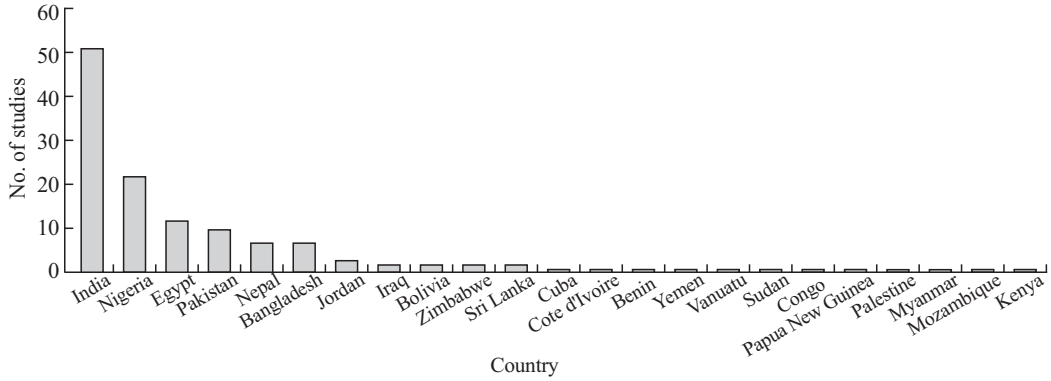

Fig. 2. Distribution of eligible studies across low and middle-income countries.

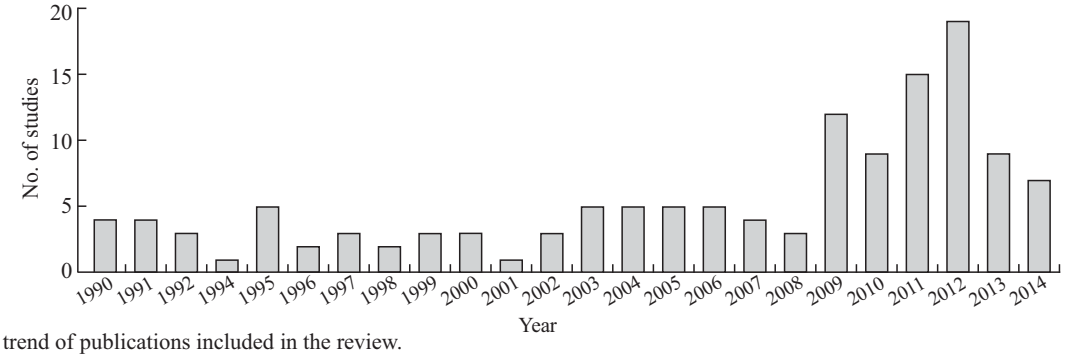

Fig. 3. Yearly trend of publications included in the review.

Mozambique, Myanmar, Palestine, Papua New Guinea, Sudan, Vanuatu and Yemen. The first six countries accounted for 82.3% of all studies. By world regions, 77 (58.8%) of all studies were from SOA, 29 (22.1%) from SSA, 19 (14.5%) from MEN, 3 (2.3%) from EAP and 3 (2.3%) from LAC. The number of eligible studies peaked in 2012 with 19 records and dropped sharply to 9 records in 2013, less than the levels in 2009 and 2011 (Fig. 3). The maternal, prenatal and neonatal factors associated with significant hyperbilirubinemia in LMICs are summarized in Supplementary Table 3. The definition and diagnostic criteria for hyperbilirubinemia and the related factors were unclear in many studies making any quantitative synthesis of effect size impracticable.

Maternal factors associated with hyperbilirubinemia

Similar to the available evidence in high-income countries, complications during pregnancy such as ABO incompatibility, Rhesus disease and diabetes mellitus were widely associated with neonatal hyperbilirubinemia in LMICs. ABO incompatibility was reported in 47 studies from 9 countries, especially India and Nigeria. Rhesus incompatibility was reported in 33 studies from 7 countries. The use of oxytocin induction and augmentation during labor was most commonly reported from SOA, accounting for 10 out of the 12 studies. Few studies (n=3) investigated the impact of exclusive breastfeeding while only two studies explored the association between ethnicity and the risk of significant hyperbilirubinemia. Mode of delivery, rarely reported in high-income countries, was identified in four studies from India and Nigeria. Similarly, primiparity and teenage pregnancy were associated with hyperbilirubinemia in few studies (n=4).

Perinatal factors associated with hyperbilirubinemia

Infection was widely associated with neonatal hyperbilirubinemia in 41 studies from 14 countries followed by birth trauma, including cephalhematoma. Most of the studies were from SOA (n=22), SSA (n=10) and MEN (n=8), with India (n=10) and Nigeria (n=8) recording the highest number of studies. Male gender and birth asphyxia were reported in six studies.

Neonatal factors associated with hyperbilirubinemia

Prematurity and/or low birth weight was the most frequently reported newborn factor associated with hyperbilirubinemia in 42 studies drawn from 11 countries. This was followed by G6PD deficiency reported in 35 studies from 9 countries, especially India and Nigeria. Pyruvate kinase deficiency, another enzymatic defect, was reported in three studies while bilirubin glucuronosyl transferase polymorphism was reported in four studies from India and Egypt. Low intake of breast-milk, dehydration or excessive weight loss (>10%) was reported in 10 studies from seven countries including Bolivia and Myanmar. Polycythemia and erythrocyte structural defects were reported in eight and seven studies respectively. Other neonatal factors reported in very few studies were breast-milk jaundice, galactosemia and hypoglycemia.

Other related factors

Eight studies, principally from India, Egypt and Sri Lanka, identified previously treated jaundice in a sibling as a possible risk factor. High pre-discharge transcutaneous bilirubin and/or total serum/plasma bilirubin was reported exclusively from eight studies conducted in India, whereas use of hemolytic agents such as naphathelene/menthol-based products was reported in five studies exclusively from Nigeria. Being born outside hospital was reported in nine studies drawn predominantly from Nigeria, and two studies mentioned aflatoxins. Hypothermia was reported in four studies exclusively from SOA, and one study from India identified folate deficiency as a risk factor for neonatal jaundice.

Discussion

There are four overarching findings from this review. 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 identified in a prior comparable systematic review and meta-analysis in which 10 factors were documented in 13 studies from 5 countries.[14] Second, most of the factors commonly associated with neonatal hyperbilirubinemia in high-income countries were also reported in LMICs.[2,16] Third, the factors that were most commonly reported (in at least 30 studies) are also leading causes of neonatal hyperbilirubinemia in high-income countries.[2,16] Fourth, a few factors such as mode of delivery and use of hemolytic substances contextually relevant to LMICs but rarely reported in high-income countries were identified. Although available studies for this review were drawn from 23 of the 91 eligible countries, there is no evidence to suggest that these maternal, perinatal and neonatal factors will not be important for the rest of the region because of similarities in the prevailing health and socio-economic conditions.

Blood group incompatibilities, infections, prematurity and G6PD deficiency were the most frequently reported factors in LMICs. The associated burden is perhaps best characterized by the global pattern and prevalence of these factors in LMICs compared with high-income countries. For example, in a recent review by Bhutani et al,[6] 373 300 babies were estimated to be affected by Rhesus hemolytic disease in 2010 worldwide, with a global prevalence of 276/100 000. However, the regional data showed a Rhesus disease prevalence of 386/100 000 for SSA and 385/100 000 for SOA, which were in sharp contrast to an estimated prevalence of 2.5/100 000 in high-income countries. This pattern is likely to be replicated for ABO hemolytic disease, which is more prevalent than Rhesus incompatibility from available etiological studies especially in SOA and SSA.

The greatest number of studies associating neonatal infection such as sepsis with hyperbilirubinemia was from SOA and SSA. Recent global data on severe neonatal bacterial infection has shown that SOA and SSA have the highest prevalence of neonatal sepsis worldwide with approximately 900 and 590 cases per 1000 live births, respectively.[20] The combined evidence would suggest that neonatal infection is a significant contributor to the burden of neonatal hyperbilirubinemia in LMICs. This is corroborated by one comprehensive systematic review that attributed 13.9% of all cases of hyperbilirubinemia or kernicterus in Africa and between 9.7% and 31.2% in Asia to infection, compared with 1.9% in Europe and North America.[2] However, the prevention of sepsis-related hyperbilirubinemia may be different from that of hyperbilirubinemia due to other causes in LMICs.

Preterm and low birth weight infants are more likely to have substantially elevated risk of severe hyperbilirubinemia and bilirubin encephalopathy than full-term infants.[21] Of the estimated 14.9 million preterm births worldwide in 2010, 5.0 (33%) million were delivered in SOA and 3.9 million (26%) in SSA in contrast to 1 million (7%) in high-income countries.[22] In fact, India, Nigeria, Pakistan, Bangladesh and Democratic Republic of Congo are among the top ten countries that account for 60% of preterm births worldwide. These data indicate that why preterm births are significant contributors to the burden of hyperbilirubinemia, even after the high rates of perinatal mortality are adjusted in the affected countries.

The data on the global prevalence of G6PD deficiency have shown that LMICs countries especially in the malaria-endemic regions have the highest burden of this disorder.[23-25] For example, this X-linked hereditary genetic defect is estimated to affect over 400 million people globally with the highest rates (up to about 34%) reported in SSA.[24] Of the 36 LMICs with the national prevalence of G6PD deficiency of at least 10%, 25 (70%) are in SSA.[25] Benin, with an annual birth rate of 356 000, has the highest national prevalence of 23%, but Nigeria with an annual birth rate of 6.5 million has an estimated prevalence of 16.5%. Hyperbilirubinemia may be exacerbated further in ethnic populations where $(TA)_n$ promoter polymorphism of the urine-diphosphate-glucuronosyl transferase 1A1 gene is prevalent.[26]

The less frequently reported factors such as maternal diabetes, oxytocin induction, and birth trauma should not by any means be regarded as less important in LMICs. For example, maternal and perinatal mortality secondary to obstetric complications during pregnancy are well documented.[27,28] The evidence demonstrated by the available studies in this review clearly suggests that not all the survivors will be sequelae-free. The impact of the ubiquitous exclusive breastfeeding in LMICs is also under-reported. Breastfed babies are more likely, than bottle-fed babies, to develop jaundice within the first week of life, but the mechanism underpinning this association is still not well understood. Factors such as primiparity, teenage pregnancy, birth asphyxia, use of menthol-based hemolytic substances and non-institutionalized birth rarely reported in high-income countries deserve further investigation to establish their potential impact on the risk of significant neonatal hyperbilirubinemia. The potential contribution of genetic polymorphism and mutations also warrants further investigation.

Our liberal literature search strategy provided a broader insight into the impact of the various maternal and neonatal factors on the incidence of neonatal hyperbilirubinemia in LMICs. However, less than ten studies were identified every year for

nearly two decades between 1990 and 2008. No consistent improvement in relevant research output has been observed since 2009, which perhaps has contributed to the lack of global health attention to the burden of neonatal hyperbilirubinemia in LMICs during the current MDG era till 2015. Evidently, more good quality research is urgently needed especially in countries where the projected burden of hyperbilirubinemia is likely to be substantial.

Like many scoping reviews, this study has a number of limitations. First, no quality assessment of the included studies and the diagnostic criteria for the reported risk factors was undertaken to determine publication bias across the studies. Second, despite the liberal inclusion criteria, studies were only identified for less than 25% of the eligible countries. Third, we broadened the definition of clinically significant neonatal hyperbilirubinemia to include all severity types: mild, moderate, severe, extreme hyperbilirubinemia as well as acute and chronic bilirubin encephalopathy, whereas associated factors may differ for various levels of severity. Notwithstanding, the key findings from this review are consistent with evidence from more advanced nations and highlight areas for further research in LMICs.

Conclusions

This scoping review has shown that many of the causes or risk factors for neonatal hyperbilirubinemia in high-income countries are present in varying degrees in LMICs. The four leading causes of hyperbilirubinemia in high-income countries: prematurity, blood group incompatibilities, G6PD deficiency and infections also emerged as the most frequently reported factors associated with hyperbilirubinemia in the most developmentally disadvantaged LMICs. This is against the backdrop of the potential impact of exclusive breast feeding which is almost universal but sparsely reported in the countries included in this review. The burden of neonatal hyperbilirubinemia is likely to be disproportionately higher in LMICs because of the high prevalence of these factors. While improved research is necessary to address the methodological weaknesses observed in most of the available studies, nonetheless, the findings in this review provide compelling evidence of the need for appropriate interventions to curtail the burden of neonatal hyperbilirubinemia in LMICs.

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