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REVIEW

Neonatal Hyperbilirubinemia in Uganda: Mechanisms, Clinical Consequences, and Health-System Challenges

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Objective: Neonatal hyperbilirubinemia is a prevalent condition characterized by elevated serum bilirubin levels, affecting approximately 50% of term and 80% of preterm infants. While mild cases often resolve without intervention, severe hyperbilirubinemia can lead to life-threatening complications such as bilirubin-induced neurological dysfunction (BIND) and kernicterus, resulting in permanent brain damage, developmental delays, and hearing impairment.

Materials and Methods: A literature review was conducted by searching PubMed, Google Scholar, and UpToDate for English-language articles published between January 2010 and March 2025 on neonatal hyperbilirubinemia. Inclusion criteria were studies on mechanisms, clinical outcomes, and interventions in low- and middle-income countries (LMICs), with a focus on Uganda. Exclusion criteria included case reports, non-English studies, and articles without primary data.

Results: The condition arises from an imbalance between bilirubin production and elimination, influenced by immature liver function, increased red blood cell turnover, enhanced enterohepatic circulation, and genetic predisposition. In low-income countries such as Uganda, additional contributors include delayed postnatal care-seeking, limited availability of phototherapy units, and inadequate early screening programs. The low-income country has inappropriate early screening and poor treatment options, which further exacerbate the burden, contributing to preventable neonatal morbidity and mortality.

Conclusion: Timely screening, improved access to phototherapy and exchange transfusion, and increased awareness among healthcare providers and caregivers are essential for reducing the impact of neonatal hyperbilirubinemia. By integrating biological mechanisms, clinical consequences, and health-system challenges into a single synthesis, this review provides novel, actionable insights for policy-makers and clinicians in Uganda.

Keywords: neonatal hyperbilirubinemia, bilirubin-induced neurological dysfunctions

Introductions

Neonatal hyperbilirubinemia is a significant clinical concern for newborns, characterized by serum bilirubin levels exceeding 85 µmol/L (5 mg/dL).[1] This condition represents a clinical manifestation of elevated total serum bilirubin (TSB), resulting from bilirubin deposition in an infant's skin. Neonatal hyperbilirubinemia is broadly classified into two main types: unconjugated (indirect) hyperbilirubinemia, which is due to elevated levels of bilirubin before liver conjugation, and conjugated (direct) hyperbilirubinemia, which occurs when bilirubin has been conjugated by the liver but cannot be effectively excreted.[1,2] Unconjugated hyperbilirubinemia is diagnosed by assessing bilirubin levels using a transcutaneous measurement device or through blood samples for total serum bilirubin.[1]

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The diagnosis of conjugated hyperbilirubinemia is typically made via laboratory tests, which may include measuring serum aminotransferase levels, evaluating prothrombin time, performing urine cultures, screening for inborn metabolic disorders, and, in some instances, conducting imaging studies.[3] Hyperbilirubinemia, a common condition, affects a significant proportion of newborns, with approximately 50% of term infants and 80% of preterm infants being affected.[4]

The Global Burden of Disease 2016 report estimated that jaundice accounts for approximately 1008 deaths per 100,000 live births, with severe cases primarily occurring in South Asia and Sub-Saharan Africa, where around 1.1 million infants are affected each year.[5] Studies in Ethiopia have reported variable prevalence estimates, though direct comparison is limited by methodological differences. For example, a cross-sectional study at Jimma Medical Center (TSB ≥ 5 mg/dL; serum testing) reported 42.3%,[6] while two separate hospital-based surveys (thresholds ≥ 10 mg/dL) found prevalence rates of 24.6%[7] and 20.5%.[8] In the Democratic Republic of Congo, a cohort study in a semi-rural setting used transcutaneous bilirubin measurement and defined hyperbilirubinemia as ≥ 10 mg/dL, identifying 5.7% of infants within 24–72 hours post-delivery.[9]

In Uganda, a cross-sectional study at Kawempe-Mulago Hospital (TSB thresholds per AAP guidelines) found that 13.6% of neonates aged 24–72 hours required treatment, while 1.3% exceeded the exchange transfusion threshold.[10] Additionally, a retrospective review at Nsambya Hospital analyzed 242 suspected cases of neonatal jaundice, confirming hyperbilirubinemia in 22.7% of cases.[11]

The burden and outcomes of neonatal hyperbilirubinemia differ markedly between resource settings. In high-income countries, advances in early detection and intervention have reduced the incidence of kernicterus to approximately 1 case per 100,000 live births.[12] In contrast, neonates in low-income regions particularly in Sub-Saharan Africa and South Asia experience disproportionately higher rates, with estimates ranging from 25 to 38 cases per 100,000 live births.[13] Moreover, a systematic review and meta-analysis reported that the incidence of severe neonatal jaundice in Sub-Saharan Africa and Southeast Asia exceeds 600 per 10,000 live births, compared with only 3–4 per 10,000 in Europe and the Americas, reflecting a substantially higher risk of acute bilirubin encephalopathy and the need for exchange transfusion in low-resource regions.[14]

To date, no published work has combined the biological mechanisms, clinical consequences, and health-system challenges of neonatal hyperbilirubinemia in Uganda into a single comprehensive synthesis. Existing Ugandan studies focus largely on prevalence or treatment outcomes, often at single facilities, without integrating mechanistic insights or national policy considerations. This review seeks to address that gap, ensuring the contribution is novel, evidence-based, and relevant to both clinical and policy audiences. Unlike previous studies that focused only on prevalence or treatment outcomes at single facilities, this is the first review to integrate biological mechanisms, clinical consequences, and Uganda-specific health-system challenges into a unified synthesis, producing novel, actionable insights for both clinical practice and policy development.

Materials and Methods

A narrative review was performed by searching PubMed, Google Scholar, and UpToDate for English-language articles (2010–2025) on neonatal hyperbilirubinemia mechanisms, outcomes, and interventions in low-resource settings. Priority was given to studies from Sub-Saharan Africa.

Inclusion Criteria

1. Peer-reviewed articles, guidelines, or official reports.

2. Studies conducted in Uganda or low- and middle-income countries (LMICs) with relevance to Uganda.

3. Articles addressing at least one of the following: pathophysiological mechanisms, clinical outcomes, screening and treatment strategies, or health-system/policy challenges.

4. Publications in English.

A. Case reports with insufficient methodological detail.

B. Studies not involving neonates.

C. Articles without relevance to mechanisms, impacts, or health-system responses

Quality Appraisal

To ensure the reliability and credibility of the evidence included in this narrative review, each selected study was appraised for methodological quality. The evaluation criteria included clarity of study objectives, appropriateness of the study design, adequacy of sample size, validity and reliability of measurement tools, and transparency in reporting results. Priority was given to studies published in peer-reviewed journals, with clear descriptions of methodology and ethical considerations. Although formal scoring systems, such as the Newcastle Ottawa Scale or the Cochrane Risk of Bias Tool, were not applied due to the narrative nature of this review, a consistent and critical appraisal.

Mechanisms of Neonatal Hyperbilirubinemia

Neonatal hyperbilirubinemia arises from an imbalance between bilirubin production and elimination, influenced by various physiological and pathological factors. Bilirubin, a byproduct of heme catabolism, is primarily processed in the liver before being excreted. While these mechanisms are universal, their impact in Uganda is magnified by systemic healthcare limitations, including delayed diagnosis, inadequate access to phototherapy, and limited laboratory capacity, which collectively increase the risk of severe disease and its complications.[10,15] As illustrated in Figure 1, neonatal hyperbilirubinemia results from increased bilirubin production, reduced hepatic conjugation, and impaired excretion processes further compounded by systemic health-system limitations in low-resource settings.

Excessive Bilirubin Production

One primary mechanism is the excessive production of bilirubin due to higher red blood cell (RBC) turnover in neonates[16,19], Fetal erythrocytes have a lifespan of approximately 70–90 days, compared with 120 days in adults, resulting in a proportionally greater bilirubin load.[20]

The rapid breakdown of RBCs increases the quantity of unconjugated bilirubin circulating in the bloodstream, thereby heightening the risk of hyperbilirubinemia.[3]

Several pathological conditions may exacerbate bilirubin production:

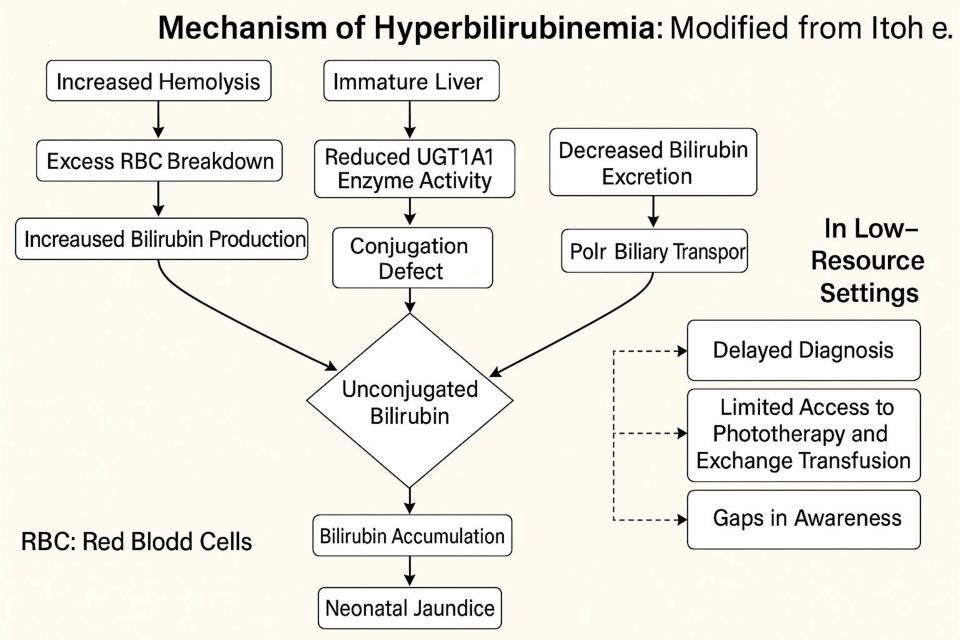

Figure 1 Mechanism of hyperbilirubinemia; created by the author using information from[1,16,18], his figure illustrates the primary mechanisms contributing to neonatal hyperbilirubinemia. The first is increased hemolysis, leading to excessive RBC breakdown and overproduction of unconjugated bilirubin. The second is reduced bilirubin conjugation due to decreased UGT1A1 enzyme activity, often related to liver immaturity or genetic variants. The third is decreased bilirubin excretion, which may result from poor biliary transport. In low-resource settings, these mechanisms are compounded by delayed diagnosis, limited access to phototherapy and exchange transfusion, and gaps in awareness. Understanding these factors is important for identifying potential interventions such as enhancing bilirubin conjugation or reducing enterohepatic circulation to lower bilirubin levels and prevent kernicterus or other bilirubin-induced neurologic dysfunctions.[16]

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- Hemolytic diseases such as ABO and Rh incompatibility, which accelerate RBC destruction.[18,21]
- Cephalohematomas and other birth-related injuries, which increase hemoglobin breakdown.[22]
- Infections such as sepsis and TORCH, which can trigger immune-mediated hemolysis.[23]

In Uganda, the clinical consequences of these conditions are exacerbated by limited pre-discharge bilirubin screening, slow laboratory turnaround times, and shortages of diagnostic reagents for blood group determination and Coombs testing. In rural health facilities, assessment is often reliant on visual inspection, which is inherently insensitive and leads to delayed recognition of severe cases.

Hepatic Immaturity

The liver plays a central role in bilirubin metabolism, primarily through the processes of conjugation and excretion. However, in neonates, the liver enzyme uridine diphosphate-glucuronosyltransferase (UGT1A1), which is responsible for bilirubin conjugation, is underdeveloped at birth. This enzymatic immaturity results in reduced bilirubin conjugation, causing excessive accumulation of unconjugated bilirubin in the bloodstream jaundice,[2] Preterm infants are particularly at risk due to a Lower UGT1A1 activity compared to term neonates, Delayed maturation of hepatocyte function and Reduced albumin levels, impairing bilirubin binding and transport.[24]

Enterohepatic Circulation

Another major contributor to neonatal hyperbilirubinemia is enhanced enterohepatic circulation. In neonates, intestinal β-glucuronidase activity is elevated, leading to the deconjugation of bilirubin that has already been processed. This unconjugated bilirubin is reabsorbed into the bloodstream instead of excreted in stool[25], Factors that increase enterohepatic circulation include: Delayed meconium passage (standard in preterm infants), Exclusive breastfeeding without adequate milk intake (breastfeeding jaundice) and Gastrointestinal disorders that slow bilirubin elimination.[15]

Genetic Factors

Genetic factors play a critical role in bilirubin metabolism. Polymorphisms in the UGT1A1 gene can impair bilirubin conjugation, leading to prolonged neonatal jaundice. Specific genetic conditions associated with hyperbilirubinemia include Gilbert syndrome - Characterized by mild, chronic unconjugated hyperbilirubinemia due to reduced UGT1A1 activity[26], Crigler-Najjar syndrome -A severe inherited disorder leading to dangerously high bilirubin levels, often requiring lifelong phototherapy or liver transplantation and Neonates of African and Asian descent show higher prevalence of genetic UGT1A1 variations, making them more susceptible to severe hyperbilirubinemia.[5]

Understanding these mechanisms is crucial for the early identification and management of hyperbilirubinemia. In Uganda, where diagnostic resources are often limited, a clear grasp of these mechanisms among healthcare providers is critical for prioritizing high-risk infants and initiating timely interventions. Timely screening, proper phototherapy, and preventive interventions can significantly reduce bilirubin-related complications such as kernicterus and bilirubin-induced neurological dysfunction.

The Impact of Hyperbilirubinemia on Neonatal Health

Neonatal hyperbilirubinemia is a common yet potentially severe condition caused by an excess of unconjugated bilirubin in the bloodstream. While physiological jaundice is typically benign and resolves without intervention, severe hyperbilirubinemia can lead to life-threatening complications.[15]

Acute Bilirubin Encephalopathy and Kernicterus

Excess bilirubin can cross the immature blood-brain barrier, leading to bilirubin-induced neurotoxicity. Acute Bilirubin Encephalopathy (ABE) presents with Lethargy, Poor feeding, Abnormal muscle tone (hypotonia/hypertonia), High-pitched crying and irritability (Pranty, Shumka; Adjaye 2022), If left untreated, ABE progresses to kernicterus,

a permanent and irreversible neurological condition characterized by Athetoid cerebral palsy, Sensorineural hearing loss and Cognitive impairments and learning disabilities.[25]

The economic burden of treating kernicterus and providing lifelong care for affected children can be substantial for families and healthcare systems,[21] In Uganda and similar low-income settings, these costs can be catastrophic, often pushing households into long-term financial hardship,[27] This economic strain underscores the importance of prioritizing preventive measures over reactive, high-cost interventions. Data from Sub-Saharan Africa indicate that infants who survive severe hyperbilirubinemia frequently face schooling difficulties and social stigma, further perpetuating cycles of disadvantage.[18]

Feeding and Growth Issues

Severe jaundice can cause Poor feeding due to lethargy, leading to weight loss and Dehydration, worsening hyperbilirubinemia through reduced bilirubin excretion,[28] Delayed treatment exacerbates neonatal morbidity, making early breastfeeding support and hydration critical in managing the condition.[29]

Neurodevelopmental Delays

Studies suggest that neonates with prolonged or severe hyperbilirubinemia are at increased risk of a range of neurodevelopmental impairments. These include cognitive deficits such as lower IQ scores and memory problems, motor delays marked by poor coordination and muscle stiffness, and speech and language difficulties,[26] such impairments can have lasting consequences on educational attainment, employment opportunities, and overall quality of life, particularly in low-resource settings where early detection and intervention services are limited. A prospective cohort study using the Denver Developmental Screening Test II (DAS-II) found a statistically significant correlation between the severity of neonatal hyperbilirubinemia and developmental delay at six months ($P < 0.001$),[30] Higher bilirubin levels were associated with delays in fine motor, language, and social domains, demonstrating that even moderate cases can disrupt early developmental milestone.[30]

These findings are consistent with a review of bilirubin-induced neurologic dysfunction (BIND), which highlighted that even without kernicterus, milder but sustained elevations of bilirubin can lead to cognitive impairment, motor coordination difficulties, and behavioral problems together, these studies underscore that bilirubin-related injury can occur across a spectrum of severity and may result in permanent, life-altering outcomes if not promptly identified and managed.[31,32] However, there is currently no published Ugandan research directly examining the long-term neurodevelopmental outcomes of neonates with severe hyperbilirubinemia, representing a critical gap in understanding the local burden and guiding prevention strategies.

Economic and Healthcare Burden

The cost of treating kernicterus and its lifelong complications places a significant burden on families and healthcare systems. High costs of hospitalizations, phototherapy, and exchange transfusions, Specialized care needs for children with permanent disabilities (, hearing aids, physiotherapy), and increased dependency on caregivers, impacting family income and well-being.[5]

As shown in Table 1, neonatal hyperbilirubinemia can cause a range of short- and long-term complications, adapted from peer-reviewed pediatric neurology and neonatology literature. Short-term effects describe clinical signs observed during the neonatal period, whereas long-term effects denote deficits that persist beyond infancy.[16,25,26,28,33,34]

Preventive Measures and Interventions in Uganda's Healthcare System

Despite Uganda's progress in neonatal care, challenges such as limited access to screening tools, shortages of phototherapy units, and delayed healthcare-seeking behavior continue to impact hyperbilirubinemia management.[15] There is currently no nationwide guideline specifically for the prevention and early detection of neonatal hyperbilirubinemia, and phototherapy coverage remains highly uneven across districts.

In most health centers, serum bilirubin testing is not available, and in regional referral hospitals (RRHs), results often take a long time because biochemical machines are few and sometimes overbooked. This delay in obtaining results can

Table 1 Short- and Long-Term Complications of Hyperbilirubinemia

Complication	Definition	Short-Term Effects	Long-Term Effects	References
Acute Bilirubin Encephalopathy (ABE)	Early, potentially reversible stage of bilirubin-induced neurologic dysfunction	Lethargy, poor feeding, abnormal muscle tone	Progression to kernicterus, permanent brain damage	[26,28,33,34]
Kernicterus	Chronic and permanent bilirubin-induced neurologic damage	–	Athetoid cerebral palsy, hearing loss, cognitive impairment	[26,28,33,34]
Neurodevelopmental Delays	Delays in acquisition of motor, cognitive, or language skills	Irritability, poor reflexes	Speech, motor, and cognitive deficits	[16,25,34]
Feeding and Growth Issues	Inability to feed effectively and gain weight appropriately	Weak sucking reflex, dehydration	Malnutrition, failure to thrive	[16,25,34]

Notes: As shown in Table 1, neonatal hyperbilirubinemia can cause a range of short- and long-term complications, from acute neurological syndromes to permanent developmental disabilities. Definitions are adapted from peer-reviewed pediatric neurology and neonatology literature. Short-term effects describe clinical signs observed during the neonatal period, whereas long-term effects denote deficits that persist beyond infancy.[16,25,26,28,33,34]
Abbreviation: ABE, acute bilirubin encephalopathy.

lead to progressive hyperbilirubinemia before treatment is initiated. Furthermore, TcB screening is not yet adapted in the majority of health facilities across Uganda, and there is no routine bilirubin screening before discharge from maternity wards. These gaps contribute to missed or delayed diagnoses.

In Uganda, national new-born screening policies for hyperbilirubinemia remain in pilot stages, with limited rollout in public hospitals since 2019.[35] Although no local cost-effectiveness analyses have been published, evidence from Nigeria suggests that early phototherapy screening programs can be highly cost-saving over the lifetime of a child (Emokpae et al 2016; Slusher et al 2015). Similar modelling in other low-income African countries shows that incorporating bilirubin screening into existing maternal and child health programs could reduce long-term disability adjusted life years (DALYs) at a fraction of the treatment cost for kernicterus.

Strengthening referral pathways, ensuring functional phototherapy devices at all levels of care, and integrating jaundice screening into the national essential new-born care package are key steps. Collaboration with community health workers can also improve early caregiver recognition of jaundice.

Key Strategies to Reduce Hyperbilirubinemia-Related Complications in Uganda and Other Resource-Limited Settings Include

- Implementation of universal bilirubin screening programs in maternity wards.
- Introduction of TcB meters in both health Centre and general and regional referral hospitals, in both urban and rural areas, to allow rapid, non-invasive screening.
- Educating healthcare providers and mothers/caregivers on early clinical signs.
- Expanding adequate and intensive phototherapy availability in Health Centre IV facilities, all general hospitals, and regional referral hospitals.
- Improving exchange transfusion facilities for severe cases.
- Promoting timely initiation of breastfeeding to reduce enterohepatic bilirubin circulation.

Training midwives and community health workers to identify high-risk newborns, educating mothers on jaundice warning signs (eg, yellowing of skin and eyes, poor feeding), and strengthening policies for affordable neonatal care (eg, subsidized phototherapy).

International models, such as the "Bilirubin Screening Before Discharge" program using transcutaneous bilirubinometer, demonstrate that universal screening can significantly reduce the incidence of severe cases. Adapting this

approach to Uganda could be both feasible and cost-effective, particularly if integrated into existing maternal and child health programs.

Summary of Key Limitations

1. Language and Source Restriction: Only English-language, peer-reviewed publications were included, which may omit relevant data from other sources.
2. Heterogeneity of Studies: Variation in study design, bilirubin thresholds, and measurement methods limits comparability.
3. Cross-Country Differences: Differences in health systems and diagnostic practices across study locations restrict direct comparison of prevalence figures.
4. Potential Publication Bias: Studies with significant or positive findings are more likely to be published than those reporting null results, which may overestimate the true burden or effects observed.

Discussion

This review highlights persistent gaps in Uganda's neonatal hyperbilirubinemia prevention and management, despite notable improvements in neonatal care. The absence of a nationwide guideline for early detection and prevention, limited access to bilirubin testing, and uneven phototherapy coverage remain critical barriers to reducing severe cases. These findings align with international evidence showing that early, standardized screening and timely interventions are essential to preventing acute bilirubin encephalopathy and kernicterus.

Systematic reviews demonstrate that universal bilirubin screening using either transcutaneous bilirubin (TcB) meters or serum bilirubin (TSB) testing before hospital discharge significantly reduces the incidence of severe hyperbilirubinemia and subsequent readmissions.[36] The evidence from these reviews provides an interpretative basis for recommending such strategies in Uganda, as Implementing this strategy in Ugandan maternity wards could close the current diagnostic gap, especially in facilities without routine screening.

International and national pediatrics guidelines consistently emphasize objective bilirubin measurement rather than relying solely on visual assessment.[37] Adapting these guidelines to Uganda's newborn care package would require both policy alignment and capacity-building to ensure consistency of practice across different health system levels.

The Canadian Pediatric Society's 2025 position statement reports a more than threefold decline in severe hyperbilirubinemia cases following nationwide adoption of universal screening protocols.[38] This outcome underscores the potential impact of a coordinated national approach, which could be contextually adapted in Uganda through phased implementation within existing maternal and child health programs. The Recent evidence recommends measuring bilirubin levels between 24 and 48 hours after birth or earlier if the infant is discharged sooner using either transcutaneous bilirubin (TcB) or total serum bilirubin (TSB) assessment.[39] This timing ensures early identification of at-risk infants and allows prompt initiation of phototherapy or other interventions before bilirubin levels reach neurotoxic thresholds.

Addressing equipment shortages, decentralizing phototherapy services to Health Centre IV facilities, and training healthcare providers in early recognition remain urgent priorities. Strengthening community health worker engagement to educate caregivers on jaundice warning signs could further improve early presentation. A coordinated financing plan, including government budget allocation alongside donor support, will be necessary to sustain these interventions in the long term. Investment in affordable screening technologies, combined with national policy support, would ensure sustainable improvements in neonatal outcomes. This review was narrative in nature, which may limit generalizability.

Limitations of this review include its narrative design, which may limit generalizability, and the exclusion of non-English literature, which could omit regionally relevant data. Further operational research is needed to evaluate cost-effectiveness, logistical feasibility, and health outcomes of universal bilirubin screening in Uganda. Additionally, studies on long-term neurodevelopmental outcomes following early intervention could strengthen the evidence base for policy adoption.

Conclusion

Neonatal hyperbilirubinemia is a common and preventable condition that remains a contributor to neonatal morbidity and mortality in Uganda. Its burden is sustained by physiological risk factors and compounded by health system gaps, including delayed diagnosis, limited phototherapy access, and absence of universal screening.

To address these challenges, a coordinated strategy is required:

1. National policy development for universal pre-discharge bilirubin screening, using both transcutaneous and serum methods where possible.
2. Infrastructure improvement to ensure equitable distribution and regular maintenance of phototherapy units and exchange transfusion facilities across all health system levels.
3. Capacity building through continuous training of healthcare providers in early detection and management of neonatal jaundice.
4. Community education to improve caregiver recognition of jaundice and timely care-seeking.
5. Surveillance and research to generate community-level data and assess the impact of implemented interventions.

Implementing these actions within Uganda's essential newborn care framework will help prevent severe complications, improve neonatal survival, and promote healthier developmental outcomes.

Disclosure

The authors report no conflicts of interest in this work.

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