# The Contribution of Neonatal Jaundice to Global Child Mortality: Findings From the GBD 2016 Study

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Neonatal jaundice (NNJ) is a transitional phenomenon affecting most newborns with largely benign consequences in the first week of life. It typically resolves within 3 to 5 days without significant complications in the absence of comorbid prematurity, sepsis, or hemolytic disorders. In some infants, NNJ may become severe enough to put them at risk for bilirubin-induced mortality or long-term neurodevelopmental impairments necessitating effective evaluation and treatment.[1] However, the contribution of NNJ to the global burden of disease (GBD) remains largely unknown. Perhaps the first attempt to estimate the burden of severe NNJ was reported by Bhutani et al[2] in 2013. Extreme hyperbilirubinemia (total plasma and serum bilirubin >25 mg/dL) was estimated to affect 481 000 late-preterm and term neonates annually, with 114 000 dying and >63 000 surviving with moderate or severe long-term neurologic impairments. However, the data sources were limited, and the disease burden was not compared with other prominent neonatal disorders.

## GBD ESTIMATES OF JAUNDICE-RELATED MORTALITY

The prevailing United Nations' Sustainable Development Goals (SDGs) until 2030 not only target a reduction in child mortality but also recognize disability-related issues among survivors.[3] Consistent with the SDGs, the GBD collaborators led by the Institute for Health Metrics and Evaluation, USA now provide robust and periodically updated comparative estimates of fatal and non-fatal outcomes for major neonatal disorders, including NNJ. As a first step, and in contrast to common practice, "hemolytic disease and other neonatal jaundice" as defined by the *International Classification of Diseases, 10th Revision* codes P55 to P59.9 have been separated from the omnibus category of "other neonatal disorders" under all causes of child death. All deaths are assigned a single underlying cause following the *International Classification of Diseases, 10th Revision* rules. By using advanced analytical techniques on the best available data sources[4,5] and in line with the Guidelines for Accurate and Transparent Health Estimates Reporting,[6] NNJ was estimated to account for ~8 under-5 deaths per 100 000 (95% uncertainty interval [UI]: 7–9) in 2016 globally. It ranked 16th from >100 possible causes of under-5 mortality consistently since 1990.[4,5] Because bilirubin-induced mortality occurs mostly in the first month of life, when almost half of the cases of under-5 mortality happen,[7] it is more insightful to examine the


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mortality pattern within this period. For example, in the early-neonatal period (0–6 days), NNJ accounted for 1309.3 deaths per 100 000 (95% UI: 1116.8–1551.3) and ranked seventh globally (Supplemental Table 1). The burden was highest in countries with sociodemographic index (SDI) values in the low-middle or low quintiles,[4] especially in Sub-Saharan Africa and South Asia, where NNJ was the seventh and eighth leading cause of mortality, respectively. It was the ninth leading cause in Western Europe and 13th in North America within this period. In the late-neonatal period (7–27 days), it accounted for 187.1 deaths per 100 000 (95% UI: 156.7–225.6) and ranked ninth globally. It ranked seventh in South Asia and 12th in Sub-Saharan Africa compared with 15th in Western Europe and 21st in North America.

The mortality rankings among the 10 countries that frequently account for the largest number of neonatal deaths worldwide[7,8] are shown in Fig 1. Half of the countries (Nigeria, the Democratic Republic of the Congo, Ethiopia, Angola, and Kenya) are in Sub-Saharan Africa, 3 (India, Pakistan, and Bangladesh) are in South Asia, and 2 (China and Indonesia) are in East or Southeast Asia. Bilirubin-induced mortality was consistently among the top 15 causes of neonatal mortality in these 10 countries and among the top 20 causes of under-5 mortality in all but Indonesia, Angola, and Kenya. Also, NNJ mortality was uniquely more prominent in the late-neonatal than early-neonatal period in Bangladesh. Evidently, although NNJ may be less prevalent than entities like preterm birth and intrapartum complications (including birth asphyxia, infections, and congenital anomalies), it is nevertheless an important cause of neonatal mortality in high-burden locations. Like any similar endeavor,[7] these estimates are not without limitations, as reported previously,[4,5]

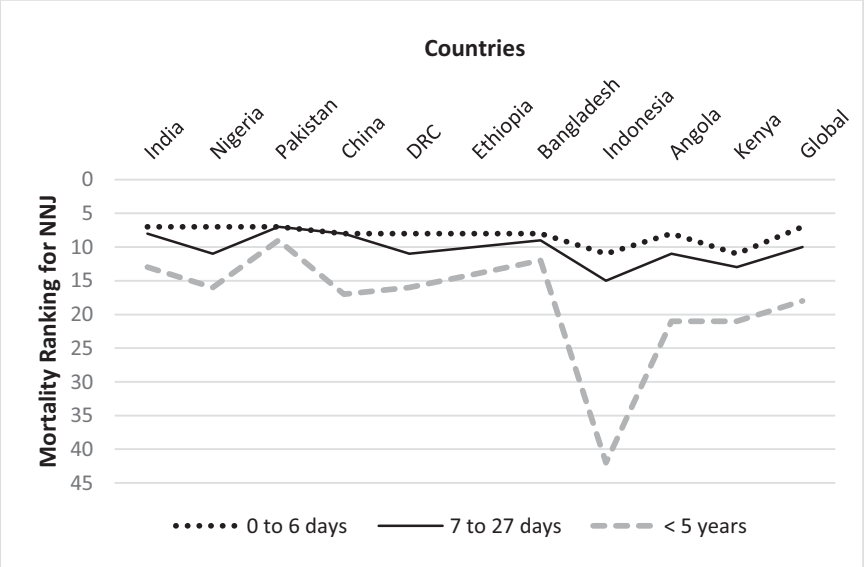


**FIGURE 1**
Mortality ranking of hemolytic disease and other NNJ in 2016 globally and in the 10 countries with the largest neonatal mortality. DRC, Democratic Republic of the Congo.

but represent perhaps the best available evidence for policy makers.

## MAIN DRIVERS OF BILIRUBIN-INDUCED MORTALITY

The risk of severe NNJ is highest between ~3 and 6 postnatal days when the plasma or serum bilirubin level reaches its peak in most infants. Timely detection, monitoring, and treatment within this window is effective in preventing most bilirubin-induced mortality. For example, in many developed countries, infants are routinely screened during their birth hospitalization and monitored for the risk of subsequent severe hyperbilirubinemia postdischarge. This system facilitates a timely referral for jaundiced infants. However, the care pathway for jaundiced infants in resource-limited countries is compromised in many ways.[1] Firstly, a significant proportion of births occur outside hospitals,[8] thus disproportionately saddling mothers with the responsibility of recognizing severe NNJ in their newborns. The health-seeking behavior for neonatal illness is often characterized by sequential treatment, first with home-based therapies before presenting in hospitals. Secondly, access to health facilities with appropriate resources to treat NNJ is also commonly hampered by financial, logistical, and cultural factors. Thirdly, and perhaps most troubling, are occasions when infants presented in good time at health facilities, but the health workers were constrained in delivering effective treatment because of a lack of facilities for rapid, routine bilirubin determination or suboptimal irradiance (<8–10 $\mu W/cm^2/nm$) from poorly maintained phototherapy devices.[1] These 3 levels of delay for effective intervention underpin the significantly higher rates of avoidable and potentially harmful exchange transfusion as well as bilirubin-induced mortality in developing countries.[1]

## REDUCING THE BURDEN OF NNJ IN HIGH-BURDEN COUNTRIES

Unlike most neonatal disorders, much of NNJ cannot be prevented. The goal of any intervention is to prevent its progression to potentially fatal acute bilirubin encephalopathy

and kernicterus. Even in hospitals with the best facilities, bilirubin encephalopathy and the associated adverse consequences are irreversible beyond certain levels of severity. Timely access to effective phototherapy is key to curbing excessive rates of exchange transfusion and bilirubin-induced mortality in high-burden countries. Therefore, late presentation in hospitals must be averted, as a priority. For example, mothers should be empowered to recognize the onset of severe NNJ and seek professional care promptly. This should include effective prenatal and public education on the potential dangers of exposure to oxidative agents and delayed or inappropriate treatment and the provision of simple-to-use tools for detecting severe NNJ at home before the onset of acute bilirubin encephalopathy. Routine screening for glucose 6-phosphodehydrogenase deficiency, strict antiseptic adherence to avoid neonatal infections, and control of rhesus (Rh) isoimmunization with Rh-immunoglobulin prophylaxis for Rh-negative mothers should reduce the incidence of hemolytic jaundice.[1,9] A global effort to make point-of-care bilirubin measuring devices and phototherapy units affordable for hospital and home use is needed. In tropical, rural communities with limited access to electricity, heliotherapy (using filtered sunlight) may be the only available treatment, weather permitting, to prevent fatal outcomes.[10]

## CONCLUSIONS

The GBD 2016 report on the health of children younger than 5 years suggests that NNJ prevention is important in the first week of life in Sub-Saharan Africa and South Asia, especially in the majority of the countries with the highest global burden of neonatal mortality. Although NNJ cannot be completely prevented in newborns, opportunities exist for timely interventions to arrest its progression to the more debilitating stage of kernicterus and curtail the associated mortality as well as the long-term neurologic impairments faced by survivors. The SDG agenda provides a unique opportunity for concerted global health engagement to effectively address the perennial burden of avoidable bilirubin-induced mortality and disability, particularly in resource-limited countries.


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## ABBREVIATIONS

GBD: global burden of disease
NNJ: neonatal jaundice
Rh: rhesus
SDG: Sustainable Development Goal
SDI: Sociodemographic index
UI: uncertainty interval

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