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# Respiratory distress in term neonates in low-resource settings

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A B S T R A C T

Most neonatal deaths worldwide occur in low- and middle-income countries (LMICs). Respiratory distress is an important cause of neonatal morbidity and mortality. The epidemiology of respiratory distress among term neonates who constitute the vast majority of births is under reported. The scarcely available data from LMICs suggest an incidence of 1.2% to 7.2% among term live births and greater morbidity compared to that in high-income countries. Pneumonia and meconium aspiration syndrome are the predominant causes among outborn neonates, but next only to transient tachypnea among inborn neonates. Community management of neonatal sepsis/pneumonia using simplified antibiotic regimens when referral is not feasible, implementation of non-invasive ventilation, and innovative low-cost technologies to deliver respiratory therapy are important advances that have taken place in these settings. There is an urgent need to generate data on respiratory morbidities among term neonates so that the limited resources in these settings can be allocated judiciously.



## 1. Introduction

Low- and middle-income countries (LMICs) are home to 95% of the 2.9 million neonates who die annually worldwide [1]. The three major causes of neonatal death, namely prematurity, perinatal asphyxia, and sepsis may present with respiratory signs. Respiratory distress (RD) is reported to occur in 4–7% of neonates of all gestational ages [2,3] and is an important cause of morbidity and mortality [4]. Whereas the most frequent cause of RD in a preterm neonate is respiratory distress syndrome (RDS), the causes are more varied in the term neonate and include transient tachypnea of the newborn (TTN), meconium aspiration syndrome (MAS), sepsis/pneumonia, pulmonary hypoplasia, and persistent pulmonary hypertension of the newborn (PPHN) [5–7].

The epidemiology of respiratory morbidities in term neonates is less well characterized compared to preterm neonates. Increasing rate of elective cesarean section, higher risk of certain disorders such as MAS, asphyxia, and a greater predisposition to PPHN increase the morbidities in the term neonate. In LMIC settings, pregnant women are poor, malnourished, and do not seek prenatal care. High-risk conditions in pregnancy remain undetected, a significant proportion of deliveries happen outside hospital settings, and neonatal care is poor. In this article, we review the literature on the epidemiology of respiratory distress (RD) in LMIC settings with specific reference to term neonates. We then attempt to understand why the epidemiology and outcomes are different in LMIC settings, followed by some of the improvements in neonatal respiratory care that have taken place in these settings.

## 2. Methods

We searched Medline (1966 to February 2017) via PubMed and Cochrane CENTRAL (Cochrane Library, Issue 2, June 2017) using broad search terms: (Infant OR Newborn) AND (respiratory OR pneumonia OR meconium OR ventilation OR respiratory failure OR assisted ventilation OR respiratory distress syndrome OR transient tachypnea). Searches were limited to human studies published in the English language. In addition, we reviewed the reference list of retrieved studies to identify additional citations. The search terms for LMIC countries were adapted from the list of World Health Organization (WHO) classification of countries based on the World Bank Atlas method. Studies that included neonates of all gestational ages wherein data pertaining to term neonates could not be extracted were excluded.

## 3. Results

A total of 2834 citations were retrieved from databases and four

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more citations from other sources. After excluding duplicates, the title and abstract of citations were screened to identify 44 relevant articles (full text retrieved from 42 articles). Five studies on epidemiology of RD [3,8–11] and nine on MAS [12–20] were chosen for inclusion in this narrative review and 28 articles (13 on epidemiology of RD and 15 on outcomes of mechanically ventilated neonates) were excluded, as information pertaining to term births could not be determined from the data provided.

## 4. Epidemiology of respiratory morbidity in term neonates from LMIC settings

Five small single-center reports from LMIC settings [3,8–11] that describe the incidence and/or etiology of term RD are summarized below.

### 4.1. Incidence

A study (1993–94) from JIPMER, a tertiary care teaching hospital in South India, reported the incidence of RD to be 6.7% among neonates of all gestational ages and the incidence among term and post-term neonates to be 4.2% and 20.7% respectively [3]. Razak et al. from India studied the incidence of respiratory morbidity exclusively among term neonates delivered by elective cesarean section [10]. In this category, while the overall incidence was 4%, it was higher (23%) among neonates delivered at 37 weeks gestation compared to 4% among ≥38 weeks gestation. Nada et al. [11] from Egypt in a randomized trial of dexamethasone for term elective cesarean section reported an incidence of 1.6% in neonates exposed to antenatal dexamethasone compared to 3.9% in the control group. The incidence of RDS among term neonates was 0.6% and 1.6% in the dexamethasone and control groups, respectively.

### 4.2. Etiology

In the study from JIPMER, the most prevalent etiologies among term neonates were TTN (50.3%), MAS (16.4%), pneumonia (9.9%), RDS (0.5%), and other (22%), which included congenital heart disease, congenital diaphragmatic hernia, pulmonary hypoplasia and anemia [3]. In the study by Thomas et al. (67 term neonates with RD), pneumonia (37%) was the most prevalent etiology followed by TTN (32%), MAS (16.4%), pneumothorax (2.9%), and others [8]. In another study (100 term neonates with RD) the distribution was TTN 59%, early-onset sepsis 20%, MAS 17%, and congenital malformations 4%.

### 4.3. Outcome

There is a paucity of published data on outcomes of term neonates with RD. In the JIPMER study, the overall case fatality rate (CFR) for RD (all gestational ages) was 19%, highest for RDS (57.1%), followed by MAS (21.8%) and infection (15.6%). Term neonates who developed RDS after elective cesarean section were reported to have high morbidity: 70% required continuous positive airways pressure (CPAP) and 19% required both surfactant and mechanical ventilation [10].

### 4.4. Unpublished data

In view of the paucity of published literature, we have reproduced some unpublished data on term neonates from the National Neonatal Perinatal Database (NNPD) of India (years 2002–03) and recent data from two tertiary care neonatal units in India (Table 1). The NNPD is a network of 18 institutions in India that collect data on neonatal morbidity and mortality using standard definitions [21]. In the years 2002–03 for which data were available, 18 centers provided data on 151,436 inborn deliveries and 17 provided data on 11,026 outborn admissions. The All India Institute of Medical Sciences, the Nodal Center for data collection, retrieved data pertaining to term neonates for this review.

According to the NNPD data the incidence of RD among inborn term neonates was 4.4% and the etiologies were TTN (46.7%), followed by MAS (29%), RDS (3.7%), pneumonia (2.1%), and pneumothorax (3.4%). Nineteen percent of neonates with RD required mechanical ventilation and the overall CFR was 25%. Among term outborn neonates admitted to various network neonatal intensive care units (NICUs), 31% had RD and the two most prevalent etiologies were pneumonia and MAS. Two-thirds of neonates with RD required mechanical ventilation and the overall CFR was 38.5%. Table 2 shows the clinical profile of respiratory distress among inborn and outborn neonates. The difference in distribution of etiology resulted from a referral bias, as sicker neonates and those requiring respiratory support are more likely to be referred to a higher center than those with self-resolving conditions such as TTN.

For some recent reports we have provided data (Table 1) from the All India Institute of Medical Sciences, an apex tertiary care teaching (public sector) hospital in India, which caters to a predominantly inborn high-risk population of neonates (~2600 live births per annum) with a few extramural admissions, and Fernandez Hospital, a private tertiary care hospital in South India (data provided for inborn neonates only).

In summary:

- We could not identify any published population-based data from LMIC settings on the incidence of RD/failure among term neonates.
- Hospital-based reports suggest that among term inborn neonates, the incidence of RD varies from 1.2% to 7.2%. Transient tachypnea is the most prevalent etiology (~50%–75% of all cases). However, pneumonia and meconium aspiration are also important etiologies in 15–30% and 25–44% respectively. The overall CFR varies from 8% to 25% (depending on center and distribution of cases) and 15–19% of cases seem to require invasive ventilatory support.
- Among term outborn neonates admitted to various NICUs, 30–43% have a diagnosis of respiratory distress. Infections and meconium aspiration syndrome are more frequent and the rates of respiratory failure and mortality are higher in this group.

By comparison, population-based studies from higher-resource countries report an overall incidence of respiratory distress among term neonates to be 1.2% in Italy [22] and 1.1% among Irish neonates with birthweight >2500 g [23]. In the Italian cohort, the incidences of RDS, TTN, and MAS were 0.11%, 0.7%, and 0.11%, respectively, and the overall mortality was 4%. In the Irish study, the most frequent etiologies were TTN (68%), RDS (16.4%), and MAS (8.5%). A population-based study from France that included 65,000 term live-born neonates reported the incidence of severe respiratory distress requiring mechanical ventilation to be 0.19 per 1000 live term births [24]. Term neonates with severe respiratory disorders had a mortality rate of 3.9% compared to those without severe RD (0.04%). Clark et al. [4] reported that among term and late preterm neonates with hypoxic respiratory failure, 5% died, 11% developed chronic lung disease, and 9% developed neurological complications. Thus despite the limitations of data and inability to make direct comparisons between high-income countries (HICs) and LMICs, it appears that term neonates in LMICs have a higher burden of RD/failure and higher CFR. Long-term morbidities and neurodevelopmental outcomes of neonates in LMICs are not

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