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Respiratory Distress Syndrome: An analysis of neonatal mortality risk factors within lower- and
middle-income countries using the CHAMPS network

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Respiratory Distress Syndrome: An analysis of neonatal mortality risk factors within lower- and middle-income countries using the CHAMPS network

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Abstract

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Approximately 5.2 million children under the age of five die each year, and <80% of these deaths occur in sub-Saharan Africa and South Asia, indicating the significant burden of child mortality within lower- and middle-income countries (LMIC). Global childhood mortality is driven by neonatal deaths, and prematurity and preterm births are the leading causes of death despite recent advances in obstetric and neonatal care. Respiratory distress syndrome (RDS) is the most common adverse birth outcome and cause of death for neonates, but LMICs lack the health infrastructure and diagnostic resources to accurately determine cause-specific mortality. The Child Health and Mortality Prevention Surveillance (CHAMPS) network was launched to ensure quality data collection on the etiologies of child mortality in LMICs, but little is known about neonatal deaths due to RDS. This study aims to better understand the risk factors for RDS among neonatal deaths to continue reducing childhood mortality in LMICs. Using CHAMPS DeCoDe and verbal autopsy datasets, we conducted Chi-square analyses to investigate the relationship between RDS and site characteristics; Student's t-tests and ANOVA analysis were used to examine differences in mean gestational ages between RDS diagnoses. Univariate and multivariate logistic regression analyses were performed to determine risk factors and predictors of neonatal mortality due to RDS. Among all CHAMPS cases, neonates are more likely to be diagnosed with RDS as a cause of death than non-neonates. Individual CHAMPS sites are also associated with having RDS as a cause of death, suggesting the influence of unique, regional characteristics on survival. Mean gestational ages among age groups and RDS diagnosis were significantly different, indicating the variable as a crucial risk factor. Univariate regression analysis reported a high level of HIV prevalence, multiple gestation, and low gestational age at birth as significant risk factors for RDS among neonatal deaths. Multivariable regression analysis reported low gestational age and dying at another health facility as significant factors. In LMICs, neonates are more susceptible to dying from RDS, and the translation of CHAMPS data can inform local and regional policymakers to advocate for targeted interventions that will further reduce child mortality.

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Introduction

Background

The world has made significant progress in the past three decades regarding child survival, and millions of children have better survival chances than in 1990. The World Health Organization reported that, in 2021, 1 in 26 children died before reaching the age of five compared to 1 in 11 in 1990. This is compounded with efforts and initiatives to reduce child mortality rates in the 2000s compared with the 1990s. According to data provided by UNICEF, the annual rate of reduction in the global under-five mortality rate increased from 1.8% in the 1990s to 4.0% by 2009 and 2.7% by 2021. It is currently estimated that approximately 5.2 million children under the age of five die each year, with 2.4 million of these deaths occurring in the first month of life (neonatal period) (Sharrow et al., 2022). Child mortality disproportionately occurs in the perinatal period and is primarily driven by these neonatal deaths. Therefore, it is essential to address these disparities and reduce global child mortality rates. The global childhood mortality burden and the associated geographic and socioeconomic-based inequities are the core targets of the 2030 U.N. Sustainable Development Goals (SDG) to "end preventable deaths of newborns and children under 5" and to reduce child mortality globally. In addition, based on data from the U.N. Inter-Agency Group for Child Mortality Estimation (UN IGME), approximately 4.3 million of these deaths occur in sub-Saharan Africa and South Asia, accentuating the glaring, significant burden of child mortality within lower- and middle-income countries (LMIC). Sustainable health initiatives, let alone quality data collection, are hampered by a lack of resource allocation, a poor health infrastructure, and restrictive access to diagnostic and prevention tools (Lee, Blencowe & Lawn, 2019). One of the greatest concerns is to provide LMICs the proper tools and training to reduce childhood mortality, especially neonatal deaths, and one of the focused initiatives is to first classify and investigate the causes of death.

Historically, public health officials and medical personnel have relied on sparse data to not only determine the cause of death but to also identify potential maternal and neonatal risk factors for mortality (Cao, Liu & Liu, 2022; Lee et al., 2017). Traditional protocols have underestimated the number of neonatal deaths because of the misclassification as stillbirths. The discrepancies between stillbirth and neonatal death are prevalent among low-resource settings due to the numerous social, political, and religious beliefs held by health facilities and parents (Mabrouk et al., 2022; Lee, Blencowe & Lawn, 2019). Common birth attendant practices in LMICs include avoiding showing a stillborn infant to the mother, the lack of social recognition of a stillbirth, and a family's unwillingness to discuss stillbirths; all these practices contribute to the continuous misclassification of stillbirths and neonatal deaths (Quincer et al., 2022). There is a need for a new or modified approach to collect and interpret child mortality data within existing regional and global frameworks to determine cause-specific mortality and inform future health interventions.

Global childhood mortality is primarily driven by deaths in the neonatal period; in 2021, an estimated 2.4 million of all childhood deaths occur in the newborn period (Ekhaguere et al., 2022). Among these deaths, preterm births (PTB) (born before 37 weeks of pregnancy) have the highest risk of mortality, especially in LMICs. Prematurity is the leading cause of neonatal mortality as well as the leading cause of childhood mortality for children under five (Mabrouk et al., 2022; Vogel et al., 2018). While recent advances in obstetric and neonatal care have reduced mortality and increased chances of survival for preterm infants, most infants in LMICs die from a lack of respiratory support and necessary resources to sustain postnatal care (McElroy et al., 2022). The specific cause of prematurity and preterm birth is still unknown, but it is understood that the etiology is multi-factorial, combining demographic, social, and perinatal factors that contribute to the physical symptoms (Mabrouk et al., 2022). Preterm birth is now thought of as a

"syndrome" of physical manifestations and etiologic factors that has no precise mechanism for all clinical cases (Goldenberg et al., 2008); however, studies have continued to investigate both maternal and neonatal risk factors that can interact and contribute to the increased risk for preterm birth.

Risk Factors for Prematurity and Preterm Birth

Women with multiple gestations (pregnancy with more than one baby at a time) carry a significant risk for preterm birth. There are some possible biological mechanisms for this risk, including uterine contractions due to overdistensions and premature rupture of membranes (PPROM) (Goldenberg et al., 2008; Abaraya, Seid & Ibro, 2018). Approximately 60% of twins are born preterm, and almost all higher multiple gestations will result in preterm delivery. In addition, women whose first birth was preterm are even more likely to a have shorter interval before the second birth (Goldenberg et al., 2008). Another risk factor to consider is maternal HIV status. LMICs are disproportionately affected by the global HIV pandemic, and it is dangerous to ignore the intersection of health complications from HIV infection with delivery and birth outcomes. While there are currently 38.4 million people worldwide living with HIV, the WHO African Region accounts for >70% of the HIV infection burden (Grant & De Cock, 2020). It is understood that both HIV infection and delivery and labor are both inflammatory responses, and previous studies and meta-analyses have shown that HIV-positive women can have up to 3-4 times the risk of preterm birth compared to HIV-negative women (Elenga et al., 2021; Malaba et al., 2017; Ikumi & Matjila, 2022). There have been studies exploring the interaction between antiretroviral therapy (ART) in HIV-positive women and preterm birth, but further research is needed to elucidate this association. Aside from these factors, there are countless other maternal and neonatal characteristics to consider, and current and future research will continue to clarify

important risk factors for the health and wellbeing of all children, especially neonates. These include maternal education status, nutrition status, stress-related factors, and maternal age (Godah et al., 2021) among many others.

Respiratory Distress Syndrome

Prematurity and preterm birth result in a wide host of both short-term and long-term health complications; however, respiratory distress syndrome is one of the most common complications and is a leading cause of global neonatal mortality, especially in LMICs. RDS refers to a condition of inadequate, impaired, or delayed surfactant synthesis and secretion along with immature lung anatomy (Ekhaguere et al., 2022; Hubbard et al., 2018). The primary function of surfactant is to reduce the surface tension of the air-liquid exchange surface in the alveoli, but in cases with RDS, leakage of exudate can result in hypoxemia (low oxygen in the blood) and hyaline membranes (lung damage) (Ekhaguere et al., 2022). Preterm neonates are unable to receive an adequate amount of oxygen and require external respiratory support. Some perinatal risk factors are associated with RDS, including lower gestational age and birth weight, but RDS survival is also dependent on resource availability and access to adequate respiratory care (Bulimba et al., 2022; Kamath et al., 2011). Recent advancements in neonatal critical care in high-income countries have seen a dramatic reduction in neonatal mortality, but RDS remains a leading cause of death for neonates in LMICs, reporting an increased risk of up to 10 times compared to high-income countries (Hubbard et al., 2018; Bulimba et al., 2022). LMICs also face diagnostic challenges to confirm RDS as a cause of death. In high-income countries, diagnostic tools include blood gas analysis, chest radiographs, and pulse oximetry, but these are not readily available in LMICs (Ekhaguere et al., 2022). Low-resource settings often must rely on alternative methods such as scoring systems and eyewitness accounts, which are prone to low

accuracy and underestimation of RDS cases (Hubbard et al., 2018). Many public health and medical professionals have urged to implement transformative RDS therapies, including continuous positive airway pressure (CPAP) and surfactant therapy (SRT). This aligns with the push for novel approaches to determine causes of death, including RDS, among neonatal deaths for more accurate mortality data collection and future health interventions.

The Child Health and Mortality Prevention Surveillance

The Child Health and Mortality Prevention Surveillance (CHAMPS) network conducts standardized mortality surveillance following standardized protocols among high child mortality sites in 7 countries in Africa and South Asia (in Bangladesh, Ethiopia, Kenya, Mali, Mozambique, Sierra Leone, and South Africa) (Breiman et al., 2021). The CHAMPS network was established to collect robust, standardized, longitudinal mortality data in a network of sites with the overarching objective of understanding and tracking preventable causes of childhood death in high mortality areas (Salzberg et al., 2019). Some of the work from the CHAMPS network includes detecting stillbirths and deaths in children under 5 years old, obtaining family consent for postmortem studies, collecting minimally invasive tissue sampling (MITS) specimens that undergo pathologic and diagnostic testing, and gathering verbal autopsy (VA) and clinical data to describe events leading to death (Breiman et al., 2021). One of the main goals by CHAMPS is to estimate overall and cause-specific mortality rates (stillbirths and under-5 deaths) in each site and extrapolate the results to other regions with high child mortality beyond the local healthcare settings (Salzberg et al., 2019, Breiman et al., 2021). In many countries with high child mortality, there are weak or non-existent civil registration systems, and death certificates are often not given for stillbirths and children under 5 years of age. In addition, those deaths that occur outside a health facility, especially stillbirths and neonatal deaths, are most likely to be

excluded from official national statistics because they are usually buried quickly after death (Salzberg et al., 2019). While there have been numerous attempts to gather more complete data on childhood mortality, including complete diagnostic autopsies (CDA) and VAs, there is still a crucial need to gather timely and authentic data to drive interventions and accelerate the reduction of childhood death in low-resource settings.

CHAMPS aims to identify and collect data on causes of stillbirths and deaths of children under five years of age by applying advanced laboratory methodologies, diagnosis standards, and a systematic approach to inform public health policy and actions. CHAMPS includes standardized procedures and processes for determining causes of death across the network, and some key features include the use of MITS, the systematic approach to determination of cause of death (DeCoDe), and other quality management processes of data collection (Quincer et al., 2022; Salzberg et al., 2019). All these features will help prioritize the limited resources in LMICs and inform actions to reduce child deaths from debilitating conditions. To capture consistent and updated population data, CHAMPS implements demographic surveillance systems (DSS) to monitor populations and their health over time within the surveillance area. The DSSs provide estimates of population-based mortality rates and health information associated with deaths of children under five years. This includes core data elements, such as age- and sex-specific population size and numbers of deaths, sex-specific number of births, and in- and out-migrations. Each CHAMPS site and their DSS are required to conduct at least biannual rounds of data collection, but some sites have additional rounds to gather more updated information. Also, sites have implemented mortality notification systems to report potentially eligible stillbirths and under-5 deaths. CHAMPS monitors the death notifications to improve the timeliness of them from healthcare facilities and communities and to ensure the data is reflected in national statistics.

The central component to the CHAMPS approach for DeCoDe is the MITS procedure. Compared to a full autopsy, MITS consists of sampling fluids and key organs using biopsy needles along with microbiological and histopathological lab analysis. The procedure is a good alternative to a full autopsy in low-resource settings, especially for death due to infections and malignant tumors, and they are more acceptable to the families of deceased children (Salzberg et al., 2019). While CDAs are the most comprehensive method to determine causes of death, they are rarely performed in LMICs due to lack of resources, personnel, and cultural and religious acceptability (Salzberg et al., 2019). Another method used is the verbal autopsy, which is a WHO-recommended postmortem structured interview with individuals close to the deceased. However, VAs often lack objective diagnostic information and suffer substantial recall bias that leaves gaps in the information provided. VAs also have difficulty in discerning discriminatory information for deaths with congenital abnormalities, deaths in the perinatal period, and stillbirths (Salzberg et al., 2019). While VAs have limited value in decision-making by themselves, they help provide fundamental context to each case. Overall, CHAMPS aims to bridge the gap and provide more precise, detailed, and robust data on causes of child mortality across the globe, especially in locations with high child mortality.

Purpose Statement

This study aims to gain a better understanding as to whether neonates are more likely to be diagnosed with RDS compared to non-neonates within the CHAMPS network. Among those neonatal deaths, we examine various maternal and neonatal risk factors, including gestational age and place of death, to identify predictors of mortality due to RDS that have not been previously explored in CHAMPS. By extrapolating the results, we provide clinical and community suggestions to continue the reduction of childhood mortality among LMICs.

Literature Review

Since 1990, substantial developments and health innovations have reduced the global burden of childhood mortality. The total number of under-five deaths decreased from 12.8 million in 1990 to 5.1 million in 2021. It is currently projected that an estimated 5.2 million children under the age of five die each year, and despite the remarkable progress in child survival over the past two decades, childhood mortality remains high in LMICs (Sharrow et al., 2022). According to the United Nations Inter-Agency Group for Child Mortality Estimation (UN IGME), approximately 4.3 million (83%) of these deaths occur in sub-Saharan Africa and South Asia. Mortality among children 1 to 5 years of age has seen considerable decline, but neonatal deaths remain a significant issue for childhood mortality. Perpetual health disparities highlight the additional challenges these communities face to prevent childhood deaths, and continuing efforts and support systems from all global partners must be implemented. The greatest concern is whether LMICs have the resources and health infrastructure to further prevent childhood deaths. More specifically, initiatives should focus on identifying which factors are associated with childhood mortality. These concerns have given rise to the countless research endeavors to provide a framework for improved outcomes for children on the global stage, especially in LMICs.

Childhood mortality is primarily driven by neonatal deaths (Ekhaguere et al., 2022). Of those deaths occurring in the neonatal period, preterm births (PTB) (born before 37 weeks of pregnancy) have the highest risk of mortality. Prematurity is the leading cause of death for children under the age of five, and in LMICs, most infants die due to a lack of resources, respiratory support, and cost-effective and safe neonatal care for infections or breathing difficulties. Respiratory distress syndrome (RDS), a common complication among premature infants, results from lung immaturity and surfactant deficiency and is a major contributor to

neonatal mortality. The primary purpose of this review is to ascertain the driving risk factors for neonatal mortality among preterm births and any evidence for RDS prevention in LMICs. This holistic literature evaluation highlights the global efforts to address and prevent neonatal deaths in lower-resource settings and lower- and middle-income countries.

What became apparent in this review, however, was that numerous ancillary problems must first be addressed before the issue of evaluating inequities surrounding neonatal survival from RDS can be approached. The first step is to understand the foundation and case definition of prematurity and preterm births. The second problem is to evaluate the epidemiology of prematurity and preterm births and acknowledge the current global burden for childhood mortality. The third step is to determine the predominant risk factors for prematurity and preterm birth, followed by detailing RDS and the current suggestions for interventions and prevention measures among all populations, especially LMICs. The last problem to address is whether adequate respiratory care and equipment are available in LMICs to provide the necessary and life-saving support for preterm infants. Answering these questions is crucial before assessing whether there is evidence that neonatal survival in LMICs is associated with different healthcare settings and their availability of respiratory support. This investigation establishes the structure for this review of the current relevant literature.

While this review is holistic of the current literature on global childhood mortality, the breadth of this investigation is limited. The complex nature of RDS among neonates presents a unique challenge for efficient study designs and community support, so this vulnerable population is often neglected from research initiatives. There must also be a discussion on global prematurity and its associated risk factors that will provide necessary context to the research question. Furthermore, this review does include important research that addresses the inequities that plague preterm births, but there are very few works that focus on LMICs and the unique

challenges they face. Because many LMICs lack quality, high-level research studies with population-representative data, there is tremendous uncertainty for national childhood mortality estimates within these communities. This can prevent the report of important risk factors and result in misleading information about childhood deaths, especially neonatal deaths. This review includes examples of all demographics that discuss childhood mortality, but it can be concluded that further studies are needed to address this issue in LMICs by the global research community.

The Foundation and Case Definition of Preterm Births and Prematurity

The first step in understanding the health inequities among neonatal deaths in LMICs is to uncover the fundamental components of the definition for prematurity and preterm births and examine both the similarities and discrepancies across institutions. The World Health Organization (WHO) remains as one of the leading international voices to reduce health problems and lives lost due to preterm birth. They define preterm births as infants before 37 weeks of pregnancy are completed, and they included sub-categories of preterm birth based on gestational age (GA): extremely preterm (<28 weeks), very preterm (28-32 weeks), and moderate to late preterm (32-37 weeks). To this day, this definition provided by the WHO is the most extensively used and accepted definition of preterm birth (Quinn et al., 2016).

An additional layer to this case definition stems from the cutoff between preterm and term births. Gestational age has been recognized as a useful tool to determine neonatal health outcomes, but the 37-week cutoff is viewed as somewhat arbitrary by some leaders. There have been three broad categorizations of delivery in the past, which include preterm (<37 weeks), term (37-42 weeks), and post-term (>42 weeks). The International Classification of Diseases defines "term" pregnancy as an infant born between 37-42 weeks, yet there is extensive variation in neonatal outcomes within that gestational age range. Quinn et al. (2016) included a 2012

international stakeholder working group and their recommendations for the sub-categorization of term birth to describe the infants' deliveries and health outcomes more accurately. They are early term (37 0/7 weeks through 38 6/7 weeks), full term (39 0/7 weeks through 40 6/7 weeks), late term (41 0/7 weeks through 41 6/7 weeks), and post term (42 0/7 weeks and older). The working group consisted of representatives from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the Society for Maternal-Fetal Medicine (SMFM), the American College of Obstetricians and Gynecologists (the College), and other professional organizations and stakeholders. The addition of these sub-categories is aimed to create uniform labels when describing deliveries and a uniform approach to determine gestational age, further facilitating clinical research, quality health care, and surveillance. The reason that these definitions are included is that early term births (37 and 38 weeks) have shown higher rates of adverse health outcomes compared to term births (39 and 40 weeks) (Chawanpaiboon et al., 2019). There is still uncertainty of the actual cutoff for preterm and term births, but clinicians and researchers are aware of the negative outcomes preterm infants face and will continue to monitor births through these ranges.

Birth weight was initially used as a proxy for measuring infant maturity. However, gestational age is a better predictive measure of neonatal and childhood mortality than low birth weight (LBW; below 2500 grams). Prematurity is difficult to accurately determine based on birthweight alone. Over 95% of LBW infants are born in LMICs, which have the most difficulty in reporting accurate estimates of gestational age (Pusdekar et al., 2020). Using LBW is an imperfect strategy to determine preterm birth because term babies can also be LBW due to other growth factors and complications. The U.S. Institute of Medicine Committee on Understanding Premature Birth and Assuring Health Outcomes calls attention to avoid using birth weight as a proxy for prematurity because it may miss many preterm infants in its definition. Many preterm

infants may also be large for their gestational age but have normal birth weight. Researchers are now calling for updated estimates for infants both preterm and LBW as they have the highest risk for neonatal mortality, but there is still limited information and data reporting from LMICs.

It is crucial to develop a more concrete case definition for preterm birth because accurate estimates can enact more precise prevention strategies in a timely manner and raise awareness for preterm birth as a global public health complication (Quinn et al., 2016; Chawanpaiboon et al., 2019). Because preterm birth is an important adverse birth outcome to address, a case definition can help mobilize research projects and resources for global maternal and child health initiatives.

The Epidemiology of Preterm Births and Prematurity

Understanding the global burden and estimates of preterm birth can provide useful information for epidemiologic surveillance, health policies, resource management, and awareness campaigns. The first attempt to provide global, regional, and subregional estimates of the incidence of preterm birth was published by Beck et al. (2010) for the year 2005. The investigators extracted data from a previous WHO systematic review of both published and unpublished data on maternal mortality and morbidity from 1997 to 2002. They also supplemented the collection with data from 2002 to 2007 with an updated systematic search for national-level data on preterm births using several databases. The statistical analysis included several multiple regression models based on country groupings. Most of the studies were cross-sectional analyses of retrospective case records or prospective surveys, and estimates were either derived from preterm rates, using deliveries as denominators, or from model selection. Beck et al. (2010) estimated that, among 92 countries, approximately 12.9 million births were definable as preterm, which represents 9.6% of births in 2005. The study also emphasized that the burden

of preterm birth is disproportionately focused in Africa and Asia, where ~85% of preterm births occurred (10.9 million births). The high numbers and overall burden among developing countries are associated with the greater number of births compared to developed countries. However, there are limitations with this study as the data must be used with caution. The biggest challenge was the data collection and the representativeness and completeness of the study reports in each country. The countries with the highest burden often had limited number of studies and sites, and the studies that were performed were based on facility-wide data instead of population-based data. Using only facility-wide data based on non-population-representative information may lead to underestimation of the true preterm birth incidence. Beck et al. (2010) concluded the study by reporting only subregional, regional, and global summaries for preterm birth estimates as a foundation for the epidemiology of a significant global, perinatal health issue.

The study performed by Blencowe et al. (2012) followed the study done by Beck et al. (2010) by reporting global-, regional-, and national-level estimates for the year 2010. The researchers added to the existing literature gaps by addressing the lack of national systematic estimates of preterm birth rates and the lack of a multi-country time trend analysis. Blencowe et al. (2012) implemented a similar methodological approach with a systematic review of major sources and databases, including national registries, Reproductive Health Surveys, and published papers. The analysis to produce preterm birth estimates contained country-level loess regression and model selection using a forward stepwise approach for two areas: Millennium Development Goals regions "Developed region", "Latin America", and "the Caribbean" with 65 countries, and all the other world regions with 106 countries. Variables were retained in each model if there was evidence of predictive value after accounting for other variables. Blencowe et al. (2012) reported a global average preterm birth rate of 11.1% with 14.9 million preterm births in 2010 among 99 countries. There is a wide variety of preterm birth rates between countries, but the rates were

highest for low-income countries with an average rate of 11.8%. At the national level, preterm birth rates ranged from 5% to 18%. The regions with the highest preterm birth rates were Southeastern Asia, South Asian, and sub-Saharan Africa, where more than 60% of all preterm births are estimated to have occurred (with 9.1 million preterm births; 12.8% of livebirths). The study also reported that most preterm births (84%; 12.5 million births) occurred after 32 weeks of gestation. Most newborns would survive without neonatal intensive care, but there is a large survival gap between high-income countries and LMICs. As with the study by Beck et al., (2010) this study had similar limitations of data availability and estimation, especially in LMICs. 85 of the 184 countries included had no data available and could indicate non-population-representative data. In LMICs, births are not often recorded, and estimation values could be inaccurate for future research. Nonetheless, Blencowe et al. (2012) contributed to the literature by providing the first national estimates of preterm birth rates in 2010.

The current global estimates of preterm births were provided by the study results from Chawanpaiboon et al. (2019) and summarized by the World Health Organization. The investigators performed a systematic review in databases of vital statistics and national civil registration to determine preterm birth estimates in 2014. The analysis consisted of multiple linear mixed regression models with variable selection. Overall, the study reported that the estimated global preterm birth rate for 2014 was 10.6%, representing 14.84 million preterm births. Similar to the trends reported in the previous studies, Asian and sub-Saharan African countries accounted for 81.1% of preterm births (12.03 million births) globally in 2014. The study limitations also included the possibility of disproportionate availability from high-income countries compared to LMICs. The variable quality can lead to misclassification and incompleteness, and the use of non-population-representative data create greater uncertainty for estimates in LMICs. Overall, Chawanpaiboon et al. (2019) published the most current estimates

for global preterm births, and the WHO establishes a similar estimate, stating that 15 million

infants are born preterm every year.

Risk Factors for Preterm Births and Prematurity

There are many reasons why preterm births occur. Most preterm births occur

spontaneously, but there are a wide variety of potential risk factors that can lead to early labor.

Essentially, additional research is required to determine the causes and mechanisms of preterm

birth, and current studies attempt to uncover associations between risk factors and preterm births

among all communities. PTB is now considered to be a "syndrome" of causes and physical

symptoms, but it remains challenging to establish a precise mechanism for all cases of preterm

births (Goldenberg et al., 2008; Mabrouk et al., 2022). Current research initiatives are now

exploring these risk factors, especially the interaction of multiple factors, to explain preterm birth

and illuminate a possible pathway. The identification of risk factors is crucial for the initiation of

risk-specific treatments and prevention strategies (Goldenberg et al., 2008). This section of the

literature review will include analyses of selected publications of PTB risk factors that are

relevant to the study population of this paper.

Multiple Gestations

It is highly understood that multiple gestations (pregnancy with more than one baby at a

time) carry a substantial risk for preterm birth. Goldenberg et al. (2008) provides an overview of

the general burden of multiple gestations on preterm birth. Even though only 2-3% of global

births result from multiple gestations, it accounts for 15-20% of all preterm births.

Approximately 60% of twins are born preterm, and this is caused by several mechanisms

(Goldenberg et al., 2008). A scoping review of preterm births by Mabrouk et al. (2022) further

elucidates this obstetric factor as an essential predictor to consider for preterm birth prevention.

Mabrouk et al. (2022) conducted a systematic review of the overall burden of preterm birth in Sub-Saharan Africa (SSA), where most neonatal deaths occur among LMICs. The investigators identified nine separate studies that consistently reported multiple gestation as a risk factor for PTB. For example, the study by Abaraya, Seid & Ibro (2018) was conducted at Jimma University Medical Center in southwest Ethiopia and consisted of an unmatched case-control study with bivariate and multivariate logistic regression models to determine possible risk factors for PTB. The results of the study showed that women who had multiple pregnancies had nearly three times the risk of PTB, with an adjusted OR of 2.7 (95% CI: 1.7-4.5), compared to those with a singleton pregnancy. The researchers also postulated possible mechanisms for PTB, including uterine contractions due to overdistensions, pre-eclampsia, and preterm premature rupture of membranes (PPROM). Another study published by Aregawi et al. (2019) reported similar findings among preterm births in Axum and Adwa Town public hospitals in northern Ethiopia. Using a cross-sectional study design and face-to-face questionnaires, the analysis also consisted of bivariable and multivariable logistic regression models. The results of this study reported that mothers with multiple pregnancy outcomes were nearly six times more likely to have PTB, with an adjusted OR of 5.59 (95% CI: 2.17-14.40), compared to mothers with a singleton pregnancy. Both studies support the conclusions and calls for action by Mabrouk et al. (2022) to increase monitoring for future pregnancies and to develop intervention programs and promote optimal neonatal care, especially for women with multiple pregnancies.

Maternal HIV status

The global HIV pandemic disproportionately affects people in LMICs, especially in sub-Saharan Africa. HIV infection is well established in the general population, and in southern Africa, the adult HIV prevalence can reach up to 30% (Grant & De Cock, 2020). There are currently 38.4 million people worldwide living with HIV, and yet, the WHO African Region is

the most affected region with >70% of the HIV infection burden globally. The African Region

also accounts for almost two-thirds of the worldwide total of new HIV infections. There have

been numerous studies to explore the association of maternal HIV infection and preterm birth

because both delivery/labor and HIV infection are inflammatory responses. Ikumi & Matjila

(2022) summarized two separate meta-analyses that examined the association of maternal HIV

status and PTB. The first meta-analysis consisted of 52 cohort studies (from Africa, U.S.,

Europe, and Asia), and the investigators reported that maternal HIV infection was significantly

associated with PTB with a pooled odds ratio of 1.56 (95% CI: 1.49-1.63) (Xiao et al., 2015).

The second meta-analysis included 14 prospective and 8 retrospective cohort studies (countries

in sub-Saharan Africa, Asia, Europe, and the Americas), and the authors reported an association

between maternal HIV infection and an increased risk of PTB in both the prospective studies

(RR = 1.50, 95% CI: 1.24-1.82) and the retrospective studies (RR = 1.82, 95% CI: 1.41-2.34)

(Wedi et al., 2016). The analysis by Ikumi & Matjila (2022) continues to describe the biological

mechanisms of maternal HIV and preterm birth using resident placental immune cells, but this is

not relevant to this literature review and research question. There is a foundation established that

explores maternal HIV infection and PTB, but further research is needed to clarify the

association among LMICs.

 A matched case-control study was conducted by Elenga et al. (2021) within the

pregnancy outcome registry of Cayenne Hospital in French Guinea. In French Guinea, HIV

prevalence exceeds 1% among pregnant women, and this study aims to provide more concrete

evidence as previous studies have only provided conflicting results between maternal HIV

infection and preterm birth. The study included only single deliveries, and the registry data

contained multiple variables that were used in the bivariate analysis and multivariate logistic

regression model. Overall, the results of the study showed that HIV-positive women were more

likely to experience preterm birth (adjusted OR = 3.1, 95% CI: 1.7-5.7) (Elenga et al., 2021).

However, the study lacks the focus of exploring the association among LMICs. Even though it is

important to investigate the association on a global scale, more focus should be placed on LMICs

to inform target-specific prevention methods where the burden is higher. Another study

conducted by Malaba et al. (2017) focused efforts on the exposure of ARTs in HIV-infected

women and preterm birth. This prospective cohort study was conducted among consecutive HIV-

infected and HIV-uninfected women seeking antenatal care at a large, community-based public

primary care facility in Cape Town, South Africa. While this analysis draws on data from a larger

multi-component study, the authors implemented a similar analytic procedure with bivariate and

multivariate logistic regression analysis. The study results provided an analogous association

with the study by Elenga et al. (2021). HIV-infected women had a higher incidence of preterm

birth compared to HIV-negative women (OR = 1.94, 95% CI: 1.34-2.82). After adjusting for

several demographic variables, HIV infection was still associated with an increased odds of

preterm birth (aOR = 2.03, 95% CI: 1.33-3.10) (Malaba et al., 2017). This study supports the

conclusions by Elenga et al. (2021), but there are still several limitations to both studies. As

stated before, many births are still not documented at home facilities and local clinics. Therefore,

the associations could be biased since it contains population-representative data within a larger,

public-sector hospital. Nevertheless, these studies have emphasized the importance of

considering maternal HIV status as a crucial risk factor for preterm birth on a global scale.

Respiratory Distress Syndrome

Complications from preterm birth and prematurity include a wide host of short-term and

long-term medical problems, including immature lung development, apnea, brain hemorrhages,

and hypothermia. However, RDS remains as one of the most common complications that preterm

neonates suffer from, accounting for a significant influence in child morbidity and mortality in LMICs (Bulimba et al., 2022). An article by Ekhaguere et al. (2022) summarizes the biological etiology, diagnostic challenges, and care pathways for infants suffering from RDS. One of the key highlights from this review article is the emphasis of impaired or delayed surfactant synthesis and secretion in the immature lung as predominant drivers for RDS. The primary function of surfactant is "to reduce the surface tension of the air-liquid interface in the alveoli," and with deficient levels, it can result in hypoxemia, leakage of exudate, and formation of hyaline membranes in the lungs. Another highlight from the article is the inverse association between RDS and gestational age. Ekhaguere et al. (2022) documents that RDS occurs in 98% of preterm infants between 22 and 24 weeks gestational age, but RDS is found in only 25% of infants with a birth weight between 1,251 to 1,500 grams. In LMICs, it is often challenging to definitively diagnose and screen infants for RDS as the traditional instruments of chest radiographs, pulse oximetry, and blood gas analysis are resource-intensive and not commonly available compared to high-income countries. LMICs must rely on objective criteria for assessing work of breathing, like scoring systems that are simple, non-invasive, and inexpensive, but there is a greater possibility for human error and low inter-rater reliability. The authors stress the importance of addressing RDS as a driver for neonatal mortality in LMICs. The article concludes with calls for implementing transformative RDS therapies (e.g., CPAP, surfactant therapy (SRT)) in LMICs since they are the standard of care in high-income settings. Further thoughtful research designs are required to investigate the impact of these RDS-specific interventions in LMICs. This article by Ekhaguere et al. (2022) is the cornerstone for the conversation about RDS and preterm births for this review.

A prospective study by Bulimba et al. (2022) provides a more comprehensive dive into early outcomes (death or survival) of preterm neonates with RDS in LMICs and attempts to

identify potential risk factors associated with both mortality and survival. The study was conducted between October 2019 and January 2020 at Muhimbili National Hospital in Tanzania. A total of 246 preterm neonates with RDS were followed up for 7 days, and the researchers generated a Kaplan-Meier survival curve to collect time-to-death along with a Cox regression analysis to ascertain factors associated with the outcome. For the procedure, the New Ballard score was used to determine gestational age, and two groups of neonates were formed from a cutoff age (<32 weeks and >32 weeks). The study results showed that, by day 7 of age, 77 participants (31.3%) had died, and the majority of those alive (109/169 participants, 64.5%) continued respiratory support. From the regression analysis, several factors were independently associated with mortality, including a birth weight of <1500 grams (adjusted HR = 2.11; 95% CI: 1.16-3.85), lack of antenatal steroids (aHR = 2.18; 95% CI: 1.11-18.9), and oxygen saturation <90% at 6 hours post admission (aHR = 4.45; 95% CI: 1.68-11.7). Bulimba et al. (2022) reported findings to suggest that high mortality among preterm neonates admitted with RDS mainly occurred within the first week of life. Based on this study population, preterm neonates with very low birth weight, mothers with no antenatal steroids, and whose oxygen saturation was less than 90% at 6 hours of admission were at higher risk of mortality. This study contributes to the growing research body of prevention techniques for preterm infants with RDS in LMICs. The findings by Bulimba et al. (2022) aligns with the conclusions by Ekhaguere et al. (2022) in that continued research into RDS-prevention strategies within LMICs is a priority to reduce poor birth outcomes.

An additional study performed by Hubbard et al. (2018) further elucidates the complications that infants with RDS face in LMICs. This retrospective study is similar in design to Bulimba et al. (2022), but it describes practice and treatment patterns for RDS along with identifying risk factors and mortality rates. The study site was an academic, semi-private referral

center in Dhaka, Bangladesh, and it is important to note that the management of respiratory support machines (e.g., CPAP, mechanical ventilators) is left completely to physicians as respiratory therapists are not on staff. Surfactant is also available, but the cost prevents many families to rely on its benefits. To diagnose infants with RDS, physicians relied on clinical features (respiratory distress within 4 hours of birth, apnea, etc.) and imaging findings from chest x-rays. Multivariable logistic regression analysis was used to determine any risk factors associated with death before discharge. The results found that of the total number of 107 neonates with RDS in the study, 38 neonatal deaths were reported for a mortality rate of 36.5%. 79 patients required non-invasive ventilation (i.e., CPAP), but 34 (43.0%) of those eventually required invasive ventilation. Overall, of 59 total patients that required invasive ventilation, the mortality rate was 62.7% (37 patients). In identifying risk factors, Hubbard et al. (2018) had similar results with Bulimba et al. (2022) in reporting birth weight <1500 grams as an associated factor for negative health outcomes. This study provides a few highlights in the research of RDS among neonates in LMICs. First, providers in LMICs adopt a protocol of care escalation, reserving invasive treatments for the most critically ill patients. This is different than mindsets in high-income settings like the United States, where intubation and mechanical ventilation are provided for neonates early in the disease process. Hubbard et al. (2018) reported an alarmingly high mortality rate of invasively ventilated patients, so there should be a shift in using non-invasive techniques like CPAP or nasal cannulas. Second, the use of surfactant therapy requires additional research to determine its effectiveness. The cost of surfactant promotes a continuous barrier for preterm infants to access its life-saving benefits. Overall, Hubbard et al. (2018) published a study that is well-aligned with both the conclusions from Bulimba et al. (2022) and Ekhaguere et al. (2022).

As an additional voice for RDS and potential treatment options, Kamath et al. (2011) performed a historical analysis and literature review of past interventions, their efficacy, and the trends in RDS in LMICs over the past 60 years. They determined that two technologies and therapies for RDS demonstrated the greatest decline in RDS-specific mortality: widespread use of oxygen and CPAP. If both interventions were implemented alongside a supportive health infrastructure and general newborn care, LMICs can further their goal to reduce neonatal mortality to all-time lows.

Current Respiratory Therapy and Support

The availability of current respiratory therapy and support differs significantly between LMICs and high-income countries. Well-resourced and high-income countries have access to several neonatal respiratory care tools, especially non-invasive support methods such as nasal cannula oxygen, CPAP, and heated humidified high flow oxygen (HHHF) (Lategan et al., 2022). On the other hand, LMICs have a more challenging issue in receiving adequate access to respiratory care interventions; oftentimes, LMICs rely on basic oxygen support, a small percentage of CPAP availability, and a lack of trained respiratory staff (Lategan et al., 2022; Thukral et al., 2016). This literature review will focus on a select number of respiratory care methods for preterm infants in LMICs: CPAP and bubble-CPAP.

Continuous Positive Airway Pressure

The implementation of CPAP for preterm neonates in LMICs has been the subject of rigorous research studies in recent years. Questions about its feasibility, cost, and sustainability are the key drivers for observational and experimental studies. Thukral et al. (2016) conducted a systematic review across several databases to evaluate the feasibility, efficacy, safety, and cost-effectiveness of CPAP therapy in LMICs. Overall, the researchers did not find any randomized

trials from LMICs that investigated CPAP therapy, but several observational studies offered unique insights and evidence for CPAP as a safe and effective mode of therapy for preterm neonates with RDS. A pooled analysis of four observational studies reported a 66% reduction in mortality from CPAP therapy among preterm neonates (OR = 0.34, 95% CI: 0.14-0.82). However, there were eight studies from LMICs that reported a high failure rate (varied between 20-40%) of neonates who failed CPAP therapy and required mechanical ventilation. Across nine studies, the incidence of air leaks from CPAP masks varied from 0% to 7.2%, and one study reported a significant reduction in surfactant use and the costs associated with SRT with CPAP implementation. Thukral et al. (2016) published a well-organized systematic review that investigates the current evidence for CPAP utilization for preterm neonates in LMICs. The study concludes that the current available evidence supports the use of CPAP as a safe and effective therapy method for preterm neonates with RDS in LMICs. CPAP reduces mortality and the need for advanced mechanical ventilation. However, because of the lack of experimental studies and low-quality evidence in LMICs, additional research is needed to elucidate the feasibility and efficacy of CPAP therapy for the protection of all preterm infants.

Another study by B et al. (2017) conducted an observational clinical study at the Kempegowda Institute of Medical Sciences in Bangalore, Karnataka, India where it aimed to assess whether the implementation of CPAP results in improved health outcomes in preterm neonates. The study decided to focus on preterm babies with gestational age ≤ 36 who were diagnosed with RDS. Out of a total of 77 preterm neonates on CPAP, the incidence of CPAP failure was 22.1% (95% CI: 14.27-32.54%). The researchers also reported a mortality rate of 6.5% (95% CI: 2.81-14.32%). The overall conclusion of this study supports the early introduction of CPAP to manage RDS in premature neonates as it significantly reduces the need for mechanical ventilation and surfactant therapy. This study is also supported by conclusions

from other related publications where they showed an improved outcome in neonates treated with CPAP; CPAP is also considered as a primary mode of respiratory support in resource-poor settings from these studies (Koyamaibole et al., 2006; Pieper et al., 2003).

Bubble-CPAP

Recent considerations for bubble-CPAP (bCPAP) have warranted a closer look into its feasibility and sustainability as a respiratory treatment option for preterm neonates with RDS. Bubble-CPAP differs from regular CPAP in that instead of delivering a constant pressure of heated humidified gas to the infant, the gas flow generates bubbles under the water that causes oscillations. Bubble-CPAP can be a cheaper and more accessible alternative in LMICs, especially in more lower-resource settings. Mwatha et al. (2020) conducted a randomized control trial in a tertiary hospital in Northern Tanzania to determine the effectiveness of bCPAP compared to oxygen therapy. Out of a total of 824 infants admitted to the NICU during the study period, 187 infants were born preterm, and 48 participants (3 were eventually excluded) were enrolled and randomized to either study arm. The study results showed that preterm infants treated with bCPAP had higher survival (17/22; 77.3% survival) compared to the oxygen therapy group (11/23; 47.8% survival). Infants with bCPAP also had a lower risk of death (HR = 0.48; 95% CI: 0.16-1.43), but it was not a statistically significant outcome. Mwatha et al. (2020) were among the first groups of researchers to conduct a randomized trial in the region exploring the effectiveness of bCPAP, or any non-invasive respiratory care method, for preterm infants with RDS. There were several limitations to the study that require additional research support. The participants did not have a definitive diagnosis of RDS, so it introduced the possibility for infants to be in the study with other respiratory conditions or infections. The study also had a small study sample, so a larger sample could provide higher-powered evidence for the association between bCPAP and neonatal health outcomes. However, this study presented groundbreaking

research into the possible implementation and widespread distribution of bCPAP and other non-invasive respiratory options for LMICs.

Koyamaibole et al. (2005) conducted a retrospective, observational analysis of prospectively collected data from two time periods: 18 months before and after the introduction of bubble-CPAP. The study site was at the Colonial War Memorial Hospital in Fiji, and it is the only hospital that provides NICU services for the island. The goal of this review was to determine if bubble-CPAP was effective and feasible to reduce neonatal mortality due to respiratory distress. Based on the results, the authors found that the introduction of bubble-CPAP was associated with a 50% reduction in the need for mechanical ventilation (10.2% to 5.1%), but there was no significant change or difference in mortality. The authors also found that, with 1-2 months of on-site training, nurses could safely apply bubble-CPAP, increasing the amount of staff available for respiratory care. However, this study had several limitations that call for caution of the results and interpretation. This was not a randomized trial, and other factors potentially confounded the mortality rates. Also, both populations (before and after bubble-CPAP) were variable, and severity of illness was not considered. However, this study was significant in providing strong evidence for bubble-CPAP as a potential method for respiratory support.

Another study by Kawaza et al. (2014) investigated the use of bubble-CPAP on preterm infants with RDS in a neonatal ward in Malawi. The high cost of bubble-CPAP is not widely used in LMICs, so this study aimed to provide additional support for the implementation of bubble-CPAP to improve neonatal survival. Kawaza et al. (2014) conducted a non-randomized convenience sample study, and 87 neonates were recruited with 62 participants treated with bCPAP therapy and 25 participants treated with oxygen therapy. The study results showed that the survival rate for neonates with bCPAP was 71.0% (44/62) compared to a rate of 44.0%

(11/25) for the control group. Of the neonates with RDS receiving bCPAP, 64.6% (31/48) of

neonates survived to hospital discharge compared to 23.5% (4/17) of the control group. The

findings reported by Kawaza et al. (2014) seem to align with the conclusions by Koyamaibole et

al. (2005) and strengthen the argument by Mwatha et al. (2020) to use bubble-CPAP more in

LMICs.

Conclusion

The conversation around global childhood mortality involves a breadth of challenges and

research, especially among preterm infants with respiratory distress syndrome. The current

literature details the significant progress made by LMICs to advance respiratory care and overall

health outcomes, but additional research is needed to further elucidate prevention techniques

against mortality from RDS. Understanding the foundation of prematurity and preterm birth,

alongside their risk factors, is crucial to begin working towards equitable access to all available

resources for LMICs. The global community must collaborate and provide innovative solutions

that will protect and strengthen the health of all infants, regardless of their background.

Methods

Study Population

The CHAMPS network, promoted by the Bill & Melinda Gates Foundation, consists of

seven sites in sub-Saharan Africa and South Asia, each with a geographically defined catchment

area. The sites include Baliakandi and Faridpur, Bangladesh; Bamako, Mali; Kersa and Harar,

Ethiopia; Makeni, Sierra Leone, Manhiça, Mozambique; Siaya and Kisumu, Kenya; and Soweto

and Thembelihle, South Africa. All these sites represent geographically and culturally distinct

regions with high rates of child mortality and limited available data on disease burden and cause

of death; they also have strong engagement and partnerships with local and national public health

leaders. We analyzed CHAMPS cause of death (CoD) data from all seven sites to characterize

the distribution of conditions (i.e., RDS) that are listed as causes of death for neonates (both

early and late neonates). Site selection and characteristics have been previously described and

published by Breiman et al. (2021) and Salzberg et al. (2019). Overall, the sites were selected

based on a variety of factors, including history of conducting (or capacity to conduct)

surveillance, demonstrated mortality of >50 deaths per 1,000 live births in children less than 5

years old at the time of site selection (2015), a willingness of the local lead investigator to use a

common, multisite protocol and to share data globally in real time, and an emphasis to maintain

ecologic and geographic diversity. Another key consideration in site selection was the possibility

for a strong relationship between the site and the local ministry of health and/or national public

health institute to ensure that the collected data contributed to local public health action and

policy.

Procedures

When a child death or stillbirth occurs in a CHAMPS catchment area, either in a facility or in the community, CHAMPS staff are notified by family members or healthcare workers. In cases of perinatal mortality, if the mother of the stillbirth or neonatal death is a usual resident of the catchment area, the case is eligible for enrollment in CHAMPS. Additional general eligibility includes the age of the deceased child <60 months or stillbirths, and the time of death is after initiation of CHAMPS mortality surveillance at the site. A team of trained staff confirms the eligibility for CHAMPS and approaches the parents or guardians of the neonate or stillbirth for consent for the MITS procedure, clinical record abstraction, and verbal autopsy. If written and informed consent is obtained, the case is reported to CHAMPS within 24-36 hours (or within 72 hours if refrigeration is used), and the body is available for the procedure, the case is eligible for MITS. Non-MITS eligible cases are also enrolled in CHAMPS after written and informed consent. The Informed Consent Forms are adapted for each site, and they provide several options for families to participate: the full MITS procedure, data collection and re-contacting after MITS, only data collection (non-MITS), or withdrawal to participate. During enrollment, the CHAMPS team members collect basic information, including if the death was a stillbirth. While non-MITS cases will not have tissue sampling performed, both MITS and non-MITS cases will have their clinical record data abstracted from maternal health records and neonatal health records; the verbal autopsy is also performed. Collectively, these data are reviewed by local experts through each site's determining cause of death (DeCoDe) panels, following WHO guidelines for death certification. The expert panel considers all available data to classify the case as a stillbirth, neonatal death, infant death, or child death (Quincer et al., 2022; Salzberg et al., 2019; Breiman et al., 2021).

Surveillance Measures

For the 12 to 18 months before initiating any CHAMPS activities or surveillance, each site established a social-behavioral sciences (SBS) team to examine local social, cultural, and religious norms and to engage with communities to explain the goals of the CHAMPS program and to earn their support. The SBS teams conducted focus groups, assisted with rumor identification and mitigation, connected with families, and engaged with the community through a variety of activities.

As stated before, most sites conduct surveillance using a health and demographic surveillance system (HDSS), which estimates the size and structure of a population by recording all births, deaths, and in- and out-migration patterns in the area (Salzberg et al., 2019). The team conducts an initial census followed by continued updates 1 to 4 times per year. This information includes key population indicators and characteristics, including fertility, mortality, and migration rates, and it also provides the total death count to determine the level and biases of ascertainment of deaths. In addition, there is wide variation across HDSS systems. Several sites began surveillance with limited-to-no HDSS infrastructure, but these systems are still being developed within the CHAMPS surveillance model. For sites with an existing HDSS, their surveillance systems are regularly reviewed and strengthened to provide reliable denominators for rate calculations.

To identify deaths occurring outside of health facilities (e.g., at home, other clinics), CHAMPS sites use a variety of community notification channels to enhance HDSS rounds. Community reports may have a cell phone and/or airtime to allow them to notify study staff of potentially eligible deaths via short messaging service (text messaging) or phone calls. If possible, reporters ensure that this information is integrated into the site's existing vital registration system. This can be done by referring all deaths in the community to a health center

to acquire a death certificate prior to CHAMPS enrollment. CHAMPS actively monitors timeliness, completeness, and representativeness of death notifications from facilities and the community through standardized metrics and data dashboards to improve the representation of data over time.

Ethics and IRB Approval

All individual sites have received approval from appropriate ethics review committees to conduct CHAMPS mortality surveillance. The CHAMPS Program Office (PO), based at Emory University in Atlanta, Georgia, has received approval from the Emory University Institutional Review Board (IRB). In addition, since the initiation of CHAMPS, a team of ethicists from the Emory Center for Ethics conducts ongoing review of program practices and policies. Parents or guardians of stillborn fetuses or deceased children provided written informed consent before any collection of data, specimens, or information on the mothers. All CHAMPS cases were anonymized prior to review.

MITS Procedure

After enrollment by the CHAMPS team, the deceased body is transported to a designated MITS procedure room within a local facility, and a series of tissue (e.g., brain, both lungs, liver, bone marrow, heart) and non-tissue specimens (e.g., blood, cerebrospinal fluid (CSF), stool via rectal swabs, and respiratory secretions via nasopharyngeal/oropharyngeal swabs) are collected. For deaths in the community depending on the site, consent is obtained to transport the body to a pre-determined private location either in a health facility, specially equipped vehicle, or mobile site based on discussions with site leadership. For stillbirths and neonatal deaths, specimens from the placenta, membranes, and umbilical cord are also collected if they are available. A family

member or designee may attend the procedure if they choose to do so and if deemed culturally appropriate. Once the procedure is completed, the body is transported back to a nearby location that the family has requested for burial.

Maternal and Child Clinical Data Abstraction

CHAMPS staff will attempt to abstract all available clinical information pertaining to the deceased child as well as relevant maternal health information for a subset of deaths. Each site may vary on the completeness of the data. The clinical records can be obtained from all levels of health facilities, antenatal care clinics, or family members directly. Some information abstracted from child health records include recent hospital encounters leading to death, physical examination results, immunization records, child HIV and TB information, and growth charts. Some information abstracted from maternal health records include antenatal clinic history, placenta and cord descriptions, laboratory testing and results, medications and transfusions, and information on previous pregnancies and pregnancy outcomes.

Verbal Autopsy

Every enrolled CHAMPS case requires consent to conduct a verbal autopsy interview with a parent, other family members, or caregivers close to the child. The VA is ideally conducted 2 to 4 weeks after the death, and the standardized interview is intended to detail the symptoms and signs related to the most common causes of death. Trained interviewers administer the WHO 2016 VA questionnaire, which is adapted to capture CHAMPS and HDSS identifiers. CHAMPS also has a software application to receive and validate VA versions in the field. After the VA is conducted, a probable cause of death will be determined by physician review. Tissue sampling will be conducted if cases were eligible for MITS. Together, the VA

interview responses and tissue sampling results will be provided to the DeCoDe panel to determine the ultimate cause of death.

The WHO 2016 VA questionnaires have been designed to collect information on the history of the final episode of illness as well as the symptoms and signs preceding death. There are three available questionnaire categories; however, CHAMPS only uses two: deaths of children aged under 4 weeks (for perinatal and neonatal deaths) and deaths of children aged 4 weeks to 11 years (for post-neonatal and child deaths). The layout and question flow of the questionnaires follow the same structure and are organized to be used by both medically and non-medically trained interviewers with various levels of literacy. The general structure of all three questionnaires includes specific content, including information about the field site, household, and/or residency in the area, socio-demographic information about the deceased, history of injuries/accidents, health services used by the deceased during illness, and the symptom duration checklist. The end of the interview also includes an open narrative for the respondent to summarize the illness or causes leading to the death.

DeCoDe Process

The DeCoDe panel consists of at least one of each of the following: clinician (e.g., pediatricians, neonatologists, obstetricians), pathologist, epidemiologist, and microbiologist. The panelists will receive all available data on each CHAMPS case, including linked maternal data, child clinical data, individual demographic data, VA results, microbiology, molecular testing, clinical diagnostics (e.g., HIV, TB, malaria), photographs from the MITS procedure, and histopathology findings. Everything is compiled into a packet, and the panelists will assign underlying, antemortem, and immediate (and other contributing) causes of death. A unique version identifier and date/time stamp are created when a packet is created that will allow new

information to be added or if a new panel reviews and provides another set of cause of death results.

The CHAMPS Diagnosis Standards (DS) provide essential guidance to the standardized assignment of causes of death for each CHAMPS case across all sites and DeCoDe panels for which the MITS procedure was performed. **Table 1** highlights the summary definitions of respiratory distress syndrome according to CHAMPS. Those who were diagnosed with respiratory distress syndrome were denoted with the code "P22.0" in the DeCoDe dataset.

Statistical Analysis

We studied the DeCoDe and verbal autopsy datasets, which report all childhood deaths within the CHAMPS network who consented. We computed summary statistics (e.g., N and proportions) overall and by CHAMPS site for maternal and neonatal characteristics as well as site characteristics pertaining to preterm births and respiratory distress syndrome. Continuous variables were summarized using means and standard deviation (SD) while categorical variables were summarized using frequency and proportions. Distribution of site characteristics and population demographics associated with RDS were studied and compared using the Chi-square test of independence. The Student's t-test was used for comparing the means of gestational age (weeks) at birth with normal distribution. A one-way analysis of variance (ANOVA) was used for comparing the means of gestational age across the different age groups. Univariate logistic regression analysis was performed to explore whether demographic and clinical covariates were related to death caused by RDS for all eligible participants. Multiple logistic regression analysis was used to calculate adjusted odds ratios (aOR) for death due to RDS and their corresponding 95% confidence intervals for neonates within the CHAMPS network. Results were considered

significant at the 5% level (p-value < 0.05). We conducted all analyses with SAS (version 9.4;

SAS Institute Inc., Cary, NC).

Results

Among 3,605 stillbirths, deaths within the first 24 hours, neonatal, infant, and child

deaths enrolled in the CHAMPS, a cause of death (CoD) was determined in 3,604 cases; only

one case was considered undetermined after review of all data from the panel. Of the 3,604

CHAMPS cases with a determined CoD, a total of 1,720 cases (47.72%) were considered after

excluding all stillbirths and deaths within the first 24 hours (1,884 cases). Of the 1,720 CHAMPS

cases, 561 were classified as early neonatal deaths (32.62%), 263 were late neonatal deaths

(15.29%), 477 were infant deaths (27.73%), and 419 were child deaths (24.36%). 824 total

neonates (both early and late neonates) were included in the primary analysis. Among all

neonatal, infant, and child deaths, the DeCoDe process identified a total of 277 (16.10%)

diagnoses of RDS with 262 cases (94.58%) among neonates (**Table 2**). **Table 3** describes the

case-type classifications of neonatal deaths as reported at enrollment and the demographic and

baseline characteristics of the CHAMPS neonates. Sex was listed as male in 459 cases (55.70%)

and as female in 365 cases (44.30%). The distribution of cases among the individual CHAMPS

sites were also included.

Of the 3,605 total enrolled CHAMPS cases, verbal autopsy (VA) results were provided

for 3,331 cases. The data from the same 824 cases of neonatal deaths were considered for

analysis. **Table 3** describes the neonatal and maternal characteristics that were extracted for

analysis. The place of death was reported as in the home for 41 cases (5.92%), at the hospital for

635 cases (91.63%), as on route to a health facility for 6 cases (0.87%), and at another type of

health facility for 11 cases (1.59%). There were 131 missing verbal autopsy results for place of

death that were excluded from the analysis. The status of HIV prevalence within the region was

also documented as very high for 140 cases (18.94%), high for 553 cases (74.83%), low for 40

cases (5.41%), and very low for 6 cases (0.81%). There were 85 missing cases for HIV

prevalence that were excluded from the analysis. Data was also collected for whether the neonate

was part of a multiple gestation; there were 93 births (13.46%) that were part of a multiple

gestation and 598 cases (86.54%) that were not. There were 133 missing results for multiple

gestation that were excluded from the analysis. The neonatal and maternal characteristics were

also stratified by RDS diagnosis, and the values were included in **Table 3**.

Among the 824 neonates, 591 reported their gestational age (weeks) at the time of

enrollment. The overall mean gestational age for all neonates was 32.84 weeks (SD: 5.17). The

mean gestational age was also reported and stratified by neonatal age group and RDS diagnosis.

The overall mean gestational age for early neonates was 33.09 weeks (SD: 5.34); for late

neonates, it was 32.33 weeks (SD: 4.68). Stratified by RDS diagnosis, the overall mean

gestational age was 28.97 weeks (SD: 3.46) for neonates with RDS and 35.10 weeks (SD: 4.64)

for neonates without RDS. For early neonates, the mean gestational age was 29.07 weeks (SD:

3.79) for neonates with RDS and 35.55 weeks (SD: 4.70) for neonates without RDS. For late

neonates, the mean gestational age was 28.76 weeks (SD: 2.60) for those with RDS and 34.23

weeks (SD: 4.43) for those without RDS (**Table 3**).

Gestational Age at Birth

The gestational ages at birth for all neonates ranged from 24 to 45 weeks. In comparing

the mean gestational ages at birth for all neonates (both early and late neonates combined) (N =

591, M = 32.84 weeks, SD = 5.17) and non-neonates (infant and child deaths) (N = 228, M =

35.93 weeks, SD = 4.55), there is a significant difference in the mean values with neonates

having a lower gestational age at birth at the 5% significance level ($t(817)$ = -7.92, p = <.0001).

However, there is not a significant difference in mean gestational ages between early neonates (N

= 395, M = 33.09, SD = 5.34) and late neonates (N = 196, M = 32.33, SD = 4.68) at the 5%

significance level (t(589) = 1.68, p = 0.0938). Lastly, in a one-way ANOVA, there was a significant difference in mean gestational ages at birth among the CHAMPS age groups at the 5% significance level for the four groups (F(3, 815) = 24.23, p = <.0001).

Stratifying for RDS diagnosis, there is a significant difference in mean gestational ages between neonates with and without RDS at the 5% significance level (t(589) = 16.92, p=<.0001). Among early neonates, there is also a significant difference in mean gestational ages between neonates with and without RDS at the 5% significant level (t(393) = 14.30, p=<.0001). Among late neonates, there is a significant difference in mean gestational ages as well (t(194) = 9.34, p=<.0001) (**Table 4**).

Respiratory Distress Syndrome

Neonates (both early and late neonates) were significantly associated with being diagnosed with RDS as a cause of death (Pearson χ^2 = 288.26, df = 1, p = <.0001) and had a relative risk of 1.44 (95% CI: 1.37 – 1.51) compared to non-neonates (infant and child deaths). The risk of developing RDS as a cause of death among neonates is 1.44 times the risk of developing RDS as a cause of death among non-neonates; in other words, neonates have a 44% increased risk of having RDS as a cause of death compared to non-neonates. On the other hand, looking at just both levels of neonates, there is no significant association developing RDS as a cause of death between early neonates (1 to 6 days) and late neonates (7 to 27 days) (Pearson χ^2 = 1.497, df = 1, p = 0.221). In addition, there was no difference in risk of developing RDS as an early neonate compared to being a late neonate (RR = 1.06; 95% CI: 0.97 – 1.17). Lastly, among neonatal deaths, there is a significant association with individual CHAMPS sites and having RDS as a cause of death (Pearson χ^2 = 105.18, df = 6, p = <.0001).

Risk Factors for RDS among Neonates

Risk factors associated with RDS among neonatal deaths included HIV prevalence level within the country or region (i.e., very high, high, low, very low), place of death (i.e., hospital, on route to health facility, home, other health facility), multiple gestations (yes vs. no), the number of maternal previous births, and the gestational age at birth. Univariate logistic regression analysis indicated that three risk factors were related to RDS as a cause of death for neonates: a high level of HIV prevalence within the country as compared to a low level (OR = 2.67; 95% CI: 1.16 – 6.15; p = <.0001), the birth as part of a multiple gestation (OR = 2.20; 95% CI: 1.41 – 3.44; p = .0005), and a low gestational age at birth (OR = 0.74; 95% CI: 0.70 – 0.77, p = <.0001). The number of maternal previous births was not significantly associated with RDS among neonatal deaths in the univariate analysis (OR = 1.10; 95% CI: 0.99 – 1.23; p = 0.0682). The place of death at another health facility compared to a hospital was also not significantly associated with RDS among neonatal deaths (OR = 0.77; 95% CI: 0.20 – 2.93; p = 0.701), and it indicates that neonatal deaths occur less often in other health facilities compared to hospital settings. However, the variable only had quasi-complete separation of data points, and there were many missing values that could have influenced the analysis. In a multivariate logistic regression analysis, two of the risk factors were independent predictors of having RDS among neonates: low gestational age at birth and dying at another health facility. Three of the risk factors, high HIV prevalence, part of a multiple gestation, and a high number of previous births, were not significant at the 5% significance level and, therefore, are not independent predictors (**Table 5**).

Discussion

CHAMPS is an ambitious, longitudinal mortality surveillance project that aims to determine the causes of child mortality across seven sites in sub-Saharan Africa and South Asia. These sites reflect regions with high child mortality and a limited capacity to regularly provide specific CoD information. The CHAMPS team and sites work closely with local government and public health officials to ensure timely data collection for targeted interventions, policy changes, and continuous advocacy. This analysis adds to the existing push for global interventions to target the common causes of neonatal deaths, especially RDS, to achieve the Sustainable Development Goals by 2030 on reducing global child mortality. The analysis shows that neonates had a higher risk (44% more likely) of developing RDS as a cause of death compared to non-neonates. Between early neonates and late neonates, there was no significant difference in the likelihood of developing RDS, suggesting that the small difference in age at the time of death does not impact the chance of having RDS as a health complication. Additionally, it is important to mention the significant relationship between the individual CHAMPS sites and the diagnoses of RDS as a CoD. It could suggest the impact of unique regional features on the risk for RDS; however, this may be due to complications when recruiting and enrolling infants and children with sites. Not all CHAMPS sites were established at the same time, so these differences may be more of a reflection on enrollment. These data could also suggest possible gaps in the implementation of basic resuscitation measures at delivery per WHO recommendations and in the available respiratory care across all health facilities, specifically at each site. While this analysis cannot assess the potential errors within the sites, the finding does suggest a future vulnerability assessment to determine what specific factors are playing a role for respiratory care at each site. This can help ensure a quality collection of data for CHAMPS to accurately inform local policy makers about targeted preventions and strategies for reducing child mortality.

The provision of culturally appropriate and respectful health interventions within the community is not possible without a thorough understanding of the social, cultural, and economic factors contributing to individual and community perceptions of child mortality, especially the neonatal and maternal risk factors for RDS. Gestational age at birth has traditionally been used as a predictor for prematurity and preterm birth, with a lower gestational age at a higher risk for adverse birth outcomes and long-term complications (Chawanpaiboon et al., 2018). The analysis illustrates a difference in the mean gestational age at birth between all neonatal deaths and non-neonatal deaths, suggesting a lower gestational age as a possible risk factor for neonatal deaths among CHAMPS sites, more broadly across LMICs. There is not a significant difference in mean gestational age between early and late neonates, suggesting the consideration for all neonatal deaths for future research and targeted interventions. There is, however, a distinction that the gestational age is different among all four age groups (early neonate, late neonate, infant, child). Early neonatal deaths have the lowest mean gestational age at birth and child deaths have the highest, which further emphasizes low gestational age as a very risky health factor. However, because CHAMPS only reports on childhood deaths, the ability to compare risk to the general population (i.e., children who do not die) is not easy. There would need to be a control group, which CHAMPS does not have, but the information presented can still be used to inform prevention strategies. Targeted interventions can be tailored to suit specific vulnerable populations since each age group might be predisposed to certain health outcomes: neonates for birth outcomes and RDS, and infants and children for infections and other chronic conditions. There can be a more efficient protocol for the care process among each age group. The root of this discrepant finding is beyond the scope of the analysis, but it could stem from the health facilities themselves, the availability of respiratory care, and other life-saving techniques

that are present at each site. Further push for perinatal and postnatal care could be a possible prevention strategy for neonatal deaths.

In addition, when stratifying for RDS diagnosis among all neonates, early neonates, and late neonates, there are significant differences in mean gestational ages among each comparison. Neonates with RDS have a significantly lower gestational age at birth compared to neonates without RDS, further emphasizing the consideration of gestational age as an essential risk factor for adverse birth outcomes, including RDS. Neonates born more prematurely could be more susceptible to develop RDS, and this finding can help inform the local health teams and larger healthcare systems to strategize care efforts for neonates with lower gestational age at birth and mitigate further adverse health outcomes. This can mean that when an infant is born at a certain gestational age, there can already be an established clinical protocol to initiate their care process and to avoid any treatment delays, based upon their birth outcome. Healthcare personnel and local public health officials in LMICs can immediately triage infants born more prematurely to provide respiratory support (i.e., CPAP or oxygen) and promptly report the preterm birth for national statistics and epidemiology.

Neonatal and maternal risk factors for RDS cover a wide variety of characteristics, and they could also vary by CHAMPS site. However, in review of all sites, the analysis is able to identify a handful of potential risk factors for RDS among all neonates. Previous literature has expressed a wealth of support for low gestational age as a precursor for premature and preterm birth, leading to adverse birth outcomes (Chawanpaiboon et al., 2018; Pusdekar et al., 2020). The findings suggest that gestational age continues to be a significant risk factor for developing RDS among neonatal deaths. In high-income countries, health facilities and clinics have access to traditional instruments for screening, diagnosing, and treating neonates with RDS; in LMICs, it is often difficult promote and sustain neonatal health outcomes due to the lack of resources (e.g.,

respiratory care) and trained personnel (Mabrouk et al., 2022). There is currently a large survival gap for neonates between high-income countries and LMICs, and gestational age is only a small factor in the larger conversation to promote the health and wellbeing of all neonates in LMICs (Pusdekar et al., 2020). There are other risk factors that were identified from the analysis, including multiple gestations and HIV prevalence status within the site. While the verbal autopsy data contained many missing values about maternal HIV status, the CHAMPS site's HIV prevalence provided another alternative to determine if it impacts the risk for RDS. Both HIV infection and delivery and labor are both inflammatory responses, and previous studies have reported an association and increased risk for preterm birth with maternal HIV infection (Elenga et al., 2021; Ikumi & Matjila, 2022). When adjusting for other risk factors, high HIV prevalence is not a significant predictor for RDS among neonates in this analysis, but further research and more complete data is needed to elucidate the relationship with HIV status, other risk factors, and RDS. Multiple gestations is another risk factor for RDS, more so for preterm birth and prematurity. Research across LMICs, especially in sub-Saharan Africa, have shown that women who had multiple pregnancies had nearly three times the risk of preterm birth, enhancing the probability for other adverse neonatal health outcomes in the future (Mabrouk et al., 2022; Abaraya, Seid & Ibro, 2018). While multiple gestation status is also not a significant predictor for RDS among neonates in this analysis, it stands to reason that public health officials and targeted prevention strategies should focus their efforts on women with multiple gestations as a vulnerable population. The number of previous births has the potential to influence subsequent preterm births and RDS as neonatal health outcomes, but this analysis suggests that the number of previous births is a neutral factor for preterm birth and RDS. However, further research is needed to explore this relationship. The place of death is the primary variable of interest, and when considered with other risk factors, the odds of dying in another health facility for neonates

with RDS were eight times the odds of dying in a hospital setting. While the CHAMPS data does not have enough valuable data points to provide a more robust analysis for associations with places of death, the findings suggest a bigger conversation about the availability of life-saving treatments and respiratory support for those treated outside of hospital settings. Local clinics might not have CPAP machines or other ventilators for preterm infants, and there could be a scarcity of trained medical personnel (i.e., respiratory therapists or physicians) in non-hospital settings to diagnosis and treat infants with RDS. Even though neonates might not develop RDS, it does not rule out other respiratory complications. A total of 58 neonates (8.4%) were treated outside of hospital settings and could have been saved if they were treated with surfactant therapy (SRT) and respiratory equipment at hospitals. There is also an important point to build more capacity to treat RDS in hospitals as infants are already reaching those facilities. Neonatal deaths due to RDS are still happening in hospital settings, so there should be a regulatory review on how to improve respiratory therapy and support for hospitals.

Analyzing this data set for potential risk factors for neonatal deaths, not just from RDS, is a crucial step to implementing preventative programs to reduce child mortality in LMICs. These findings can help evaluate the status of CHAMPS missions and goals and optimize future guidance to achieve the SDG 2030 goals, given our current state of understanding the risk factors for RDS among neonatal deaths. By identifying vulnerable populations, like both early and late neonates, health facilities and public health officials can prioritize their efforts to provide the best postnatal care (i.e., respiratory support, neonatal nutrition), and policy makers can advocate for increased attention and support for the most neglected communities. Some initiatives can include additional allocation of funding and respiratory care, especially CPAP machines and SRT, and focused training programs for all medical personnel to increase competency for respiratory support for all health facilities (Thukral et al., 2016; Lategan et al., 2022). Currently, there is a

severe lack of resources and life-saving interventions in LMICs for the health of children under five years. In these CHAMPS sites, women in rural areas face additional challenges in transportation to and from health facilities, hindering their access to necessary postnatal care. With the preliminary identification of possible risk factors for RDS among neonates, the CHAMPS team and local and regional health professionals can direct their initiatives to those at a higher risk: infants with a lower gestational age, mothers who are HIV positive, and mothers with multiple previous births and multiple gestations. The intersectionality of social determinants and risk factors must be addressed as preterm birth and RDS are not caused by one single variable. There is also evidence to suggest that the place of death is a factor for neonatal deaths from RDS, as the initial investigation revealed a difference in neonatal death across health facilities with potentially differing levels of respiratory support. As a result, further research into the individual health facilities within the CHAMPS sites is warranted.

This analysis, and future subsequent investigations, will continue to address the inequities that plague LMICs regarding child mortality. One of the strengths of this study is the fact that it is a CHAMPS-wide population-based assessment of the burden of RDS among neonates. The analysis is among the first to explore RDS across CHAMPS sites and to determine any potential risk factors, indicating that further research of association of these risk factors may help refine public health messaging and strategies. The current findings add to the existing literature by reinforcing the urgency for necessary public health actions for maternal and child health in LMICs. With the inter- and intra-professional collaboration among the CHAMPS team and local and regional staff, the ongoing data collection will provide refined context for how the public health team can advance their efforts. The exploration and identification of RDS risk factors in neonates advance the CHAMPS mission that much closer to achieving the SDG 2030 goals of reducing child mortality. Regardless, this analysis lays the foundation for holistically considering

the sites, the communities, and the social determinants of health to promote the health of not just neonates but the entire under-five population.

The study does have a few limitations. The CHAMPS dataset, including the DeCoDe and verbal autopsy results, represents a specific moment in time of the growing health data collection of child mortality surveillance within the network of sites. There are many cases delivered in health facilities that were missing essential data around RDS and associated risk factors, presenting a challenge to analyze those factors and conclude how public health messaging can be organized. With the primary research question investigating deliveries and subsequent survival across facilities, those births in communities and in homes might have even less data to report, suggesting the possibility of systematic bias in cases with more complete data. This is also reflected in the number of verbal autopsy results available compared to DeCoDe results. There were 273 cases where VA results were not included, suggesting a gap and significant influence within the analytical findings. This is the same for other demographic characteristics and variables, including gestational age at birth, place of death, and RDS diagnoses. Lastly, CHAMPS is attempting to collect social determinants of health data, so the DeCoDe panels currently do not consider social and health system-associated contributors (e.g., poverty, availability of safe water and hygiene) when determining cause of death. Risk factors could be overlooked, and the true cause of death can be underestimated without the availability of accurate data.

In conclusion, the findings of the study provide unique insights on how public health actions and site-specific clinical management teams can support the health of children under five, especially neonates, through prevention and treatment methods for RDS. As data continues to be collected from the CHAMPS network, the understanding of risk factors for RDS, prematurity, and preterm birth will only become clearer as to how targeted interventions can be implemented

for more vulnerable populations in LMICs. Emerging child mortality data, especially neonatal

mortality, from LMICs and other high mortality areas need to be regularly monitored and

transformed into public health actions.

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Tables

Table 1. DeCoDe Definitions of Respiratory Distress Syndrome

Definition of Respiratory Distress Syndrome (RDS)	
Level 1	**EITHER** Strong histological evidence of RDS (i.e., hyaline membranes) in lung tissue **OR** Moderate histological evidence of RDS in lung tissue AND Medical documentation of **TWO** or more of the following clinical/radiographic criteria: • Chest x-ray positive for characteristic "ground glass" appearance • Respiratory rate >70/minute • Central cyanosis (dusky, bluish lips or mucus membranes) • Severe retractions/lower chest wall indrawing • Grunting • Nasal flaring
Level 2	One of the following: • Medical documentation of birth at <37 weeks **AND TWO** or more of the above clinical radiographic criteria PLUS inadequate postmortem lung biopsy • Moderate histologic evidence of RDS without availability of supporting clinical signs and symptoms necessary for level 1 diagnosis
Level 3	Verbal autopsy report of birth more than one month early and **TWO** or more signs of respiratory distress: difficulty breathing, breathing fast, breathlessness, lower chest wall/ribs being pulled in, or grunting breath sounds PLUS inadequate postmortem lung biopsy.

Table 2. Respiratory Distress Syndrome Diagnosis

Variable	Total (N = 1720)	Total # of RDS Diagnoses (n = 277)	% of positive RDS diagnosis
Age Group			
Early Neonate	561	186	33.16%
Late Neonate	263	76	28.90%
Infant	477	15	3.14%
Child	419	0	0.00%

Table 3. Demographic and Baseline Characteristics of Neonates (N=824)

Variable	N (%)	RDS	No RDS
Sex			
Male	459 (55.70%)	145	314
Female	365 (44.30%)	117	248
CHAMPS sites			
Bangladesh	103 (12.50%)	15	88
Ethiopia	52 (6.31%)	11	41
Kenya	77 (9.34%)	12	65
Mali	47 (5.70%)	8	39
Mozambique	150 (18.20%)	41	109
Sierra Leone	78 (9.47%)	10	68
South Africa	317 (38.47%)	165	152
Place of Death (N=693)			
Home	41 (5.92%)	0	41
Hospital	635 (91.63%)	208	427
On route to health facility	6 (0.87%)	0	6
Other health facility	11 (1.59%)	3	8
Missing	131		
HIV Prevalence in Country (N=739)			
Very high	140 (18.94%)	23	117
High	553 (74.83%)	200	353
Low	40 (5.41%)	7	33
Very low	6 (0.81%)	1	5
Missing	85		
Maternal Multiple Gestations (N=691)			
Yes	93 (13.46%)	43	50
No	598 (86.54%)	168	430
Missing	133		
GA at Birth (weeks)	**Mean (SD)**	**Mean (SD, N)**	**Mean (SD, N)**
Overall (N=591)	32.84 (5.17)	28.97 (3.46, 218)	35.10 (4.64, 373)
Early Neonates (N=395)	33.09 (5.34)	29.07 (3.79, 150)	35.55 (4.70, 245)
Late Neonates (N=196)	32.33 (4.68)	28.76 (2.60, 68)	34.23 (4.43, 128)

Table 4. Comparison of Gestational Age at Birth (Weeks) for Neonatal Deaths due to RDS and Other Causes

	RDS (N=262)	No RDS (N=562)	t-value	Degrees of freedom (df)	p-value
All neonates (mean, SD, N)	28.97 (3.46, 218)	35.10 (4.64, 373)	16.92	589	<.0001
Early Neonates (mean, SD, N)	29.07 (3.79, 150)	35.55 (4.70, 245)	14.30	393	<.0001
Late Neonates (mean, SD, N)	28.76 (2.60, 68)	34.23 (4.43, 128)	9.34	194	<.0001

Table 5. Risk factors Independently Associated with Neonatal RDS

	RDS	No RDS	Adjusted OR	95% Confidence Interval (CI)	p-value
HIV prevalence					
Very high	23	117	1.30	0.34 – 5.02	0.700
High	200	353	2.60	0.75 – 8.77	0.135
Very low	1	5	N/A	N/A	0.994
Low (reference)	7	33	1.00		
Multiple gestations					
Yes	43	50	1.46	0.75 – 2.82	0.263
No (reference)	168	430	1.00		
Place of Death					
Other health facility	3	8	8.06	1.02 – 63.62	0.0478*
Home	0	41	N/A	N/A	0.9745
On route to health facility	0	6	N/A	N/A	0.9929
Hospital (reference)	208	427	1.00		
Gestational age at birth			0.74	0.70 – 0.79	<.0001*
Number of previous births			1.06	0.90 – 1.25	0.483

* Indicates significance at the 5% significance level