International Development

Prizewinning Dissertation 2025

No.25-TG

Proximate Determinants of Neonatal Sepsis Mortality in Low- and Middle-Income Countries – a quantitative analysis of broader risk pathways

Theresa Grosler

Published: Feb 2026

Department of International Development

London School of Economics and Political Science

Houghton Street

London

WC2A 2AE UK

Tel: +44 (020) 7955 7425/6252

Fax: +44 (020) 7955-6844

Email: d.daley@lse.ac.uk

Abstract

Newborns in LMICs continue to experience the highest sepsis-related mortality worldwide. While most existing research is focused on immediate determinants, this dissertation broadens the scope by introducing an adapted version of Mosley and Chen's child survival framework. Using aggregated panel data from the GBD, WHO, and WB, 10 proximate determinants were analysed to examine associations between broader risk pathways and neonatal sepsis mortality within 128 LMICs between 2007-2021. Two categories, environmental exposure risks and intrapartum and neonatal complications, show significant associations. These results provide valuable evidence for future research and policy, particularly for developing context-sensitive diagnostic tools for low-resource settings.

Acknowledgements

I would like to express my deepest gratitude to Dr Arjan Gjonça for being my mentor throughout this academic year and for guiding the development of this research question from the very inception.

I am also thankful to Masha Burmistrova for her time and invaluable support in addressing the statistical challenges I encountered in this dissertation.

Finally, thank you to my friends and loved ones for always supporting me and my dreams.

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List of Abbreviations

ANC	Antenatal Care
CODEm	Cause of Death Ensemble model
CI	Confidence Interval
DALY	Disability-Adjusted Life Year
DTP3	Diphtheria, Tetanus and Pertussis vaccine (3rd dose)
EOS	Early-Onset Sepsis
FE	Fixed Effects
GBD	Global Burden of Disease
HIC	High-Income Country
HIV	Human Immunodeficiency Virus
ICD-10	International Classification of Diseases, Tenth Revision
ICU	Intensive Care Unit
IHME	Institute for Health Metrics and Evaluation
LIC	Low-Income Country
LMIC	Lower-and Middle-Income Country
LOS	Late-Onset Sepsis
MAR	Missing at Random
MI	Multiple Imputation
MICE	Multivariate Imputation by Chained Equations
MNCH	Maternal, Newborn and Child Health
OECD	Organisation for Economic Co-operation and Development
OL/UR	Obstructed Labour and Uterine Rupture
qSOFA	quick Sequential Organ Failure Assessment
RE	Random Effects
SDI	Socio-Demographic Index
SOFA	Sequential Organ Failure Assessment
STI	Sexually Transmitted Infection
UTI	Urinary Tract Infection
VIF	Variance Inflation Factor
WASH	Water, Sanitation, and Hygiene
WB	World Bank
WHO	World Health Organization

“No research without action,

no action without research”

(1)

1. Introduction

In 2017, an estimated one in five deaths worldwide was related to sepsis. (2) This makes it a leading cause of death worldwide (3) and "a major contributor to the global burden of disease" (4, p. 1). LMICs continue to bear the highest burden in terms of both incidence and mortality, and neonates represent one of the most vulnerable populations. (2) Despite this, most sepsis research to date has neither focused on neonatal populations nor on LMICs. Instead, it has been predominantly concentrated in HICs and directed towards adult sepsis. (5) However, evidence from HICs may not be transferable to LMICs due to contextual and structural differences, (4) and adult-focused research often fails to capture neonatal risk factors and needs. (6) Furthermore, research has historically prioritised symptom-based, immediate determinants, which has resulted in the development of various sepsis scores, designed to help diagnose sepsis, assess severity and predict mortality risk. (7, 8) However, while these scores are undoubtedly important, they primarily focus on sepsis symptoms and therefore often overlook the role of broader determinants of neonatal sepsis, leaving significant gaps in our understanding of how they influence mortality. (9)

This dissertation, therefore, aims to shift the analytical focus and address these gaps by bridging all three shortcomings. It expands beyond the clinical manifestations of neonatal sepsis and examines broader determinants of sepsis mortality, focusing particularly on LMICs, thereby contributing to a more comprehensive understanding of broader risk pathways. In doing so, it not only aims to inform global and national sepsis policies but also potentially guide the contextual adaptation of existing sepsis scores to better suit low-resource settings.

2. Background

2.1 What is sepsis?

Sepsis is commonly defined as "the body's extreme response to an infection" (10). Although it is colloquially referred to as 'blood poisoning', this terminology is misleading and not entirely accurate, as sepsis is not considered an infection in itself but rather the reaction to one. (11) While clinical manifestations and symptoms vary depending on the individual and the underlying infection, in its most severe form, sepsis can become a life-threatening condition leading to complete multi-organ failure, including cardiac and renal failure, respiratory distress and breathing problems, and coma. (11) It is important to understand that sepsis is usually triggered by a wide range of pathogens, including bacteria, viruses, parasites and fungi, although bacterial sepsis is most common. (12) Frequently identified sites of primary infection include the lungs (e.g., pneumonia), the urinary tract (e.g., UTIs), the gastrointestinal tract (e.g., appendicitis, peritonitis), the central nervous system (e.g., meningitis), and the skin (e.g., wounds or skin inflammations). (12) Given the rapid progression and high mortality associated with sepsis, early diagnosis and timely initiation of treatment are critical. However, due to the heterogeneity of the condition itself and the variety of causes, clinical diagnosis remains challenging, especially due to the absence of a single definitive diagnostic test. (12) To address this, various sepsis scores have been developed. The most used one is the Sequential Organ Failure Assessment (SOFA) score, with its abbreviated version, the quick SOFA (qSOFA) score. The qSOFA was specifically designed as a simpler and more accessible scoring system, requiring fewer variables and no laboratory values, thereby enabling rapid bedside assessment. (13) It comprises three main clinical criteria. (14)

1. Systolic blood pressure
2. Respiratory rate
3. Altered mental status from baseline

Each parameter is assessed and rated on a scale from 0 to 3. A cumulative qSOFA score≥ 2 is generally considered indicative of poorer outcomes, including prolonged ICU stays and increased mortality. (14, 15) While early diagnosis is extremely important, it must be followed by a prompt administration of antibiotic treatment and other supportive therapies tailored to the severity of the condition. (12) However, even with proper treatment, mortality remains high. Especially in the more severe stages of sepsis, also known as septic shock, mortality rates are usually around 30% (12, 16)

2.2 Neonatal sepsis

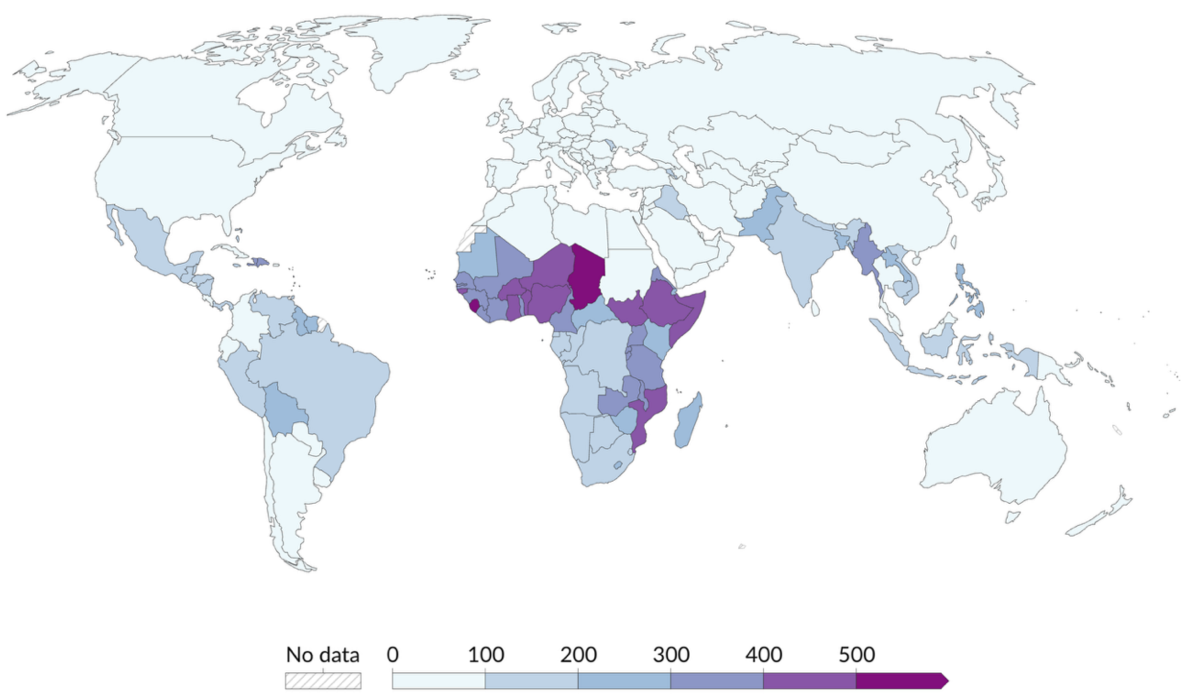
Neonatal sepsis essentially shares the same fundamental pathophysiological mechanisms as sepsis in older children and adults, but it specifically refers to infants ≤ 28 days. (17) Newborns represent a particularly vulnerable population, mostly due to their immature immune system, which puts them at a significantly higher risk of developing severe infections and consequently sepsis, especially when compared to immunocompetent adults. (6, 12) Additionally, Hensler *et al.* (6, p. 8) emphasise that "the differences between neonatal and adult immune response make it impossible to extrapolate findings in adult […] patients to neonates […]", highlighting the importance of viewing neonatal sepsis as a distinct condition, separate not only from adults but also from older paediatric populations. Clinically, neonatal sepsis is commonly categorised into two subtypes: early-onset neonatal sepsis (EOS) and late-onset neonatal sepsis (LOS).

EOS refers to sepsis that manifests in the first 72 hours of life, while LOS occurs up to the 28th day of life. (17, 18) One characteristic that sets neonatal sepsis apart from sepsis in older populations is the combined relevance of neonatal and maternal risk factors. (19) These include direct risk pathways, such as vertical transmission of pathogens during pregnancy or childbirth, as well as indirect maternal and birth-related determinants like intrapartum complications or poor antenatal care. (18) Understanding and acknowledging the critical interplay between maternal and neonatal factors is essential for sepsis prevention, diagnosis and designing appropriate interventions. (20)

2.3 Burden of sepsis in LMICs

Sepsis remains a critical challenge, affecting both HICs and LMICs. With an estimated 48.9 million new cases and 11 million associated deaths reported globally, the impact of sepsis on the global burden of disease is substantial. (2, 4, 21) However, this burden is not evenly distributed. LMICs, particularly those with the lowest SDI, experience both the highest prevalence and mortality rates. (2) Additionally, mortality is even more strongly and inversely associated with SDI than incidence, indicating that the poorest populations worldwide bear a disproportionate share of sepsis-related deaths, as illustrated in *Figure 1*. (2)

Figure 1 *Estimated deaths from neonatal sepsis and other neonatal infections, per 100,000 infants, 2021*



Data source*: IHME, Global Burden of Disease (2024) – with minor processing by Our World in Data (22)*

These disparities become even more pronounced when disaggregated by age. Not only are entire populations in LMICs more affected, but children under the age of five are particularly vulnerable, with a majority of sepsis cases in 2017 occurring within this age group. (2) Among children under five, neonates represent a subgroup with a particularly high risk of infection. This places them among the most vulnerable populations worldwide regarding both sepsis incidence and mortality. (2, 23)

Despite being widely recognised as a "a high-risk disease" and "a major public health problem" (24, p. 1), the burden of neonatal sepsis in LMICs remains understudied (2) Although in 2017 the WHO officially declared sepsis a "global health priority" (25, p. 414) and issued a series of targeted actions and specific recommendations to combat the burden of sepsis, in reality national-level update and implementation have fallen short. (25, 26). A qualitative study from Malawi (26) reported that policymakers, media, and funders alike do not prioritise sepsis, thereby creating as well as contributing to an environment where sepsis is chronically neglected within national health agendas. (27, 28) This low awareness has led to a general lack of standardised definitions of sepsis, particularly paediatric sepsis, resulting in a very heterogeneous use of diagnostic criteria and clinical scoring systems. Additionally, most of these scores have been developed and validated in high-income settings, with little to no consideration of their applicability in LMICs, thereby limiting their practical implementation for routine use in such contexts. (4, 5) This may partly explain why sepsis outcomes in HICs have been improving, but at the same time, "there is little evidence to support a similar trend in LMICs" (4, p. 1). Rudd *et al.* (4) further attribute these disparities in sepsis care to broader differences in population health, pathogen profiles, and systemic barriers. This is supported by survey results revealing that, even in cases where sepsis guidelines exist, their implementation is often not possible due to a "shortage of required hospital facilities, equipment, drugs and disposable materials" (28, p. 10). In LMICs, essential infrastructure to diagnose and manage cases of sepsis, including basic laboratory diagnostics, monitoring devices, and life-saving intensive care support, is often unavailable or severely limited. (29)

Crucially, the challenges extend beyond physical infrastructure. Human resources are equally limited, and many low-resource settings face acute shortages of skilled healthcare workers, as well as training opportunities for healthcare personnel, especially regarding the care of critically ill neonates and children. (30, 31) However, as highlighted previously, timely diagnosis and prompt treatment of sepsis are essential, underscoring the critical need for both physical and human resources.

Ultimately, delivering effective care for neonatal sepsis is extremely challenging, particularly in LMICs, as it demands at least two things: sepsis-specific as well as age-specific equipment, medications, facilities, and educated health personnel. (32) This ultimately creates a dual burden for LMICs, where their already fragile health systems must manage sepsis within the context of an especially vulnerable population with unique needs. (4)

2.4 Research gap

Overall, there are three key research gaps that this dissertation aims to address:

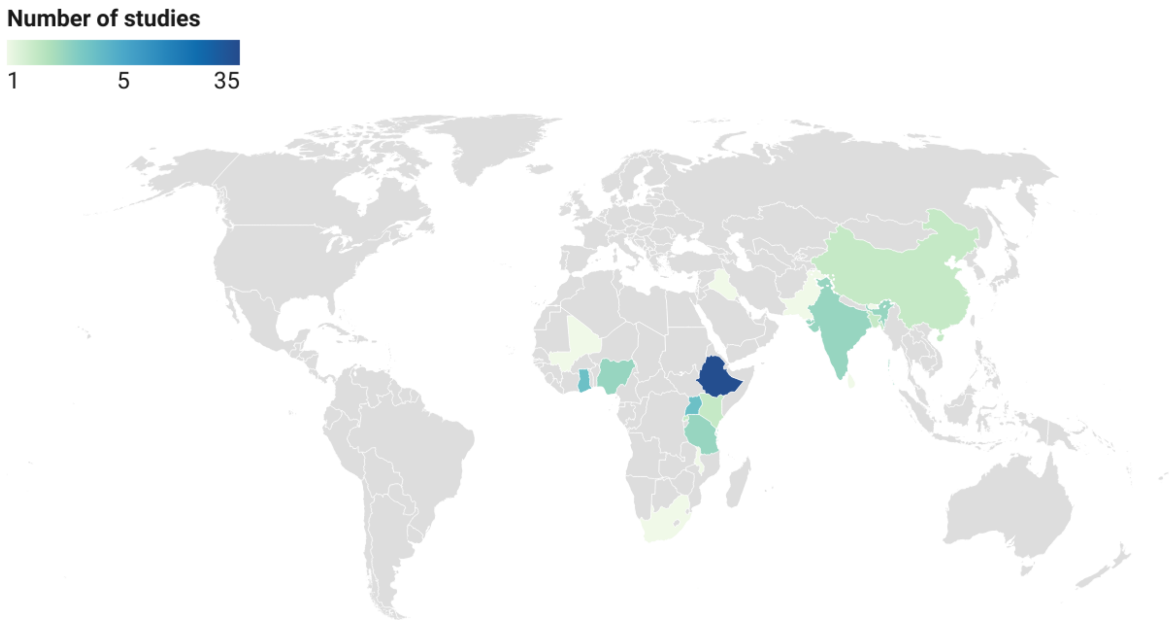
1. Most existing research is disproportionately concentrated in HICs. In 2018, Rudd *et al.* (4) reported that 55% of all registered sepsis trials were conducted in HICs, despite representing a minority of countries globally and despite the fact that the highest incidence and mortality can consistently be observed in LMICs. Additionally, research from HICs is not necessarily transferable to low-income settings. (4, 29) Consequently, there is an urgent need for LMIC-specific or at least LMIC "inclusive research" (4, p. 1) that accounts for contextual and structural differences.

2. Tomlinson *et al.* (33, p. 2) argue that global health research often focuses on "single diseases or issues […] at a single point in a child's life". In the context of neonatal sepsis, this "siloed approach" (33, p. 2) tends to reduce research and interventions to immediate determinants, neglecting broader influences. In fact, most studies typically centre their attention on the symptoms that patients present with in the hospital, thus only capturing a limited window into a patient's life. (34, 35) Although some scholars have highlighted the importance of broader determinants in the pathogenesis of sepsis and sepsis-related mortality, empirical research is scarce but urgently needed. (36, 37)

3. Initial findings from this dissertation's scoping review revealed huge disparities in the geographical distribution of sepsis research across LMICs. Of the 130 LMICs currently classified by the WB, only a small fraction even had registered studies addressing broader determinants of neonatal sepsis. The extreme scarcity of LMIC-specific research is therefore further exacerbated by a highly uneven distribution of existing research. (*Figure 2*)

The overarching motivation for this dissertation is therefore twofold. First, it seeks to move beyond the dominant focus on symptom-based immediate determinants by adopting a wider lens on neonatal sepsis mortality to examine broader influences. Secondly, it aims to maximise inclusivity and avoid the common limitation of an overly narrow geographic focus by utilising aggregated panel data from as many LMICs as possible.

Figure 2 *Number and geographical distribution of studies on broader determinants of neonatal sepsis in LMICs*



Source: *Scoping review, author's own compilation - created with Datawrapper (38)*

2.5 Research questions

This dissertation consists of two research questions:

1. Which broader determinants are significantly associated with neonatal sepsis mortality in LMICs?

2. How might these associations inform our understanding of broader risk pathways and guide the contextual adaptation of paediatric sepsis scores in low-income settings?

While the first question represents the primary focus of the analysis, the second question is more exploratory. It aims to connect the identified associations with existing gaps in sepsis research and clinical care, thereby providing a foundation for future studies and the development of context-sensitive sepsis tools for use in low-resource settings.

2.6 Positionality

I also wish to critically reflect on my positionality as a researcher. I was born and raised, and I am currently studying in a high-income country. This context inevitably shapes my perspective, my access to resources, as well as my ability to interpret the results of my analysis. However, as Yegros-Yegros *et al.* (39, p. 1) remind us, "[…] global health needs are unmet by research efforts […]", mostly because much of global health research is being produced in HICs by researchers from HICs, whereas researchers from LMICs remain under-represented. (39-41)

While it is impossible for this dissertation to avoid these inequities completely, I aim to remain critically aware of them throughout the research process.

3. Methodology

3.1 Conceptual framework

To challenge the narrow focus and contribute towards the relatively limited body of literature that examines child survival and mortality through a wider lens, this dissertation aims to "reach […] beyond the sphere of the individual child" (33, p. 3) and adapt a broader conceptual framework.

While the WHO's Social Determinants of Health framework is widely recognised and applied within global health research, it primarily emphasises - as the name already suggests – the social determinants in which individuals are "born, grow, live, work and age", as well as their "access to power, money and resources" (42). While these factors remain undeniably relevant, a key conceptual challenge arises for this dissertation: neonates (≤ 28 days) have only had minimal direct exposure to these broader determinants; they have not yet 'lived, worked, or aged' (42). However, this does not mean that broader determinants are irrelevant in the neonatal period. Instead, neonatal health requires a special life-course approach, one that also acknowledges the close interdependence with maternal health and recognises how neonatal outcomes are often shaped during pregnancy and birth. (43) This allows for a more comprehensive understanding of how broader determinants influence a child's biological vulnerability and health outcomes.

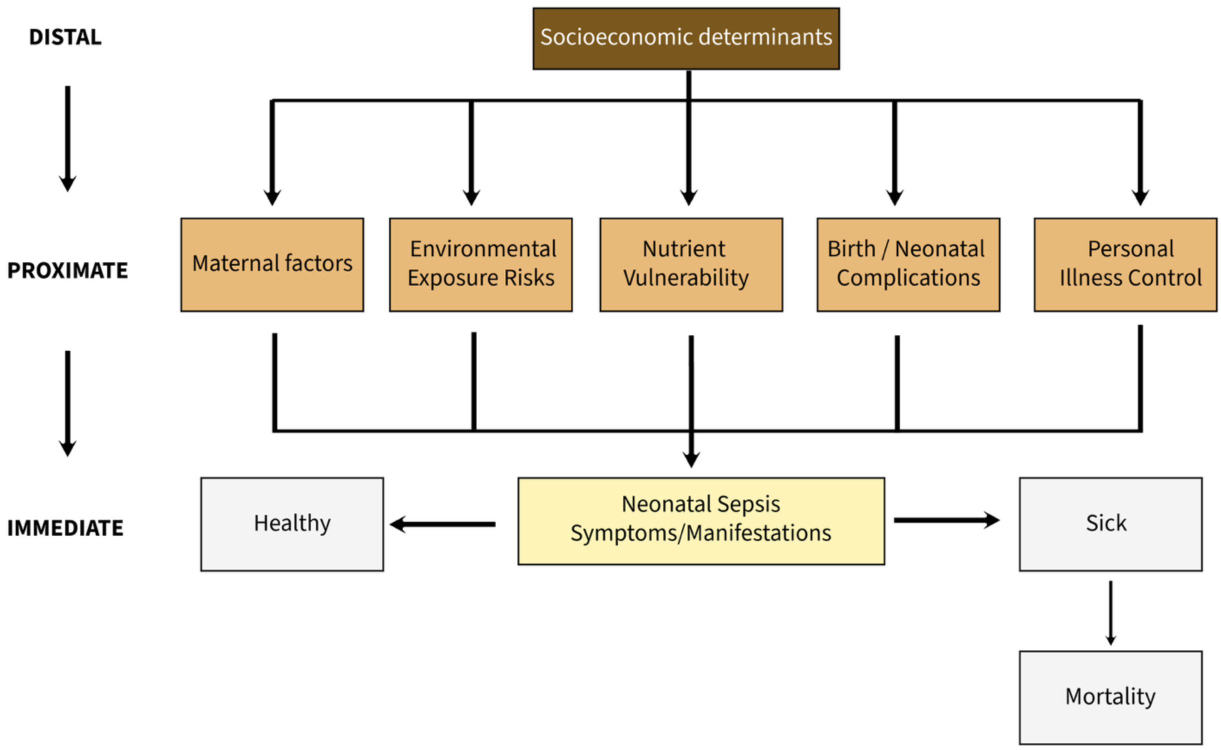
In 1984, Mosley and Chen developed such a framework, originally to examine child mortality in developing countries. (44) Their model distinguishes five categories of proximate determinants, which influence mortality and morbidity, and three socioeconomic ones, which operate indirectly through the proximate level. (44) To better capture the specific complexities of neonatal sepsis as a condition, this dissertation introduces an adapted version of the original framework, integrating a third 'immediate determinant' layer. (*Figure 3*)

The three levels are as follows:

- **Immediate determinants** represent sepsis symptoms and clinical manifestations which directly affect sepsis mortality and are typically captured in sepsis scoring systems.

- **Proximate determinants** include broader non-symptom-based influences that shape neonatal vulnerability to sepsis. Unlike immediate determinants, they are not causal in a clinical sense, but they can influence incidence and mortality.
- **Socioeconomic or Distal determinants** refer to the even broader structural factors that mainly exert their influence through the proximate determinants. This layer includes variables on the individual, household, and community level. (44)

Figure 3 *Conceptual Framework: Determinants of Neonatal Sepsis Mortality*



***Note**: adapted from Mosley and Chen's model "Operation of the five groups of proximate determinants on the health dynamics of a population" (45) - modified by the author*

Using this structure, the author hopes to demonstrate that while immediate clinical factors are undoubtedly important in understanding sepsis-related mortality, and social determinants remain essential to situate neonatal health within a wider context, there is a critical and underexplored space in between. This dissertation, therefore, focuses specifically on the underlying proximate group of determinants – a set of factors that must be better understood to clarify the causal pathways through which socioeconomic determinants manifest clinically.

3.2 Research Design

This dissertation employs a multi-step methodological approach, combining a scoping literature review with a quantitative analysis. Considering the limited existing evidence on broader determinants and risk pathways of neonatal sepsis mortality in LMICs, the preliminary scoping review was a necessary first step to inform the selection of suitable proxy variables for the subsequent quantitative analysis.

The first four methodological steps were informed by Cotache-Condor *et al.* (46), who investigated determinants of delays in paediatric cancer care. Their structured approach and methodology, grounded in recommendations by the OECD (47), were considered highly applicable to address both the data limitations and the methodological ambiguity surrounding neonatal sepsis mortality on a global level. Available literature is often fragmented, highly clinical or biomedical in focus, and lacks a coherent structure for incorporating broader determinants.

These steps also form the structure for the following methodology section, which is as follows: (46, 47)

1. *Theoretical Framework* – Scoping literature review

2. *Data Selection* – Mapping determinants identified in the literature to proxy indicators

3. *Imputation of Missing data* - Multiple imputation by chained equations (MICE) to address incomplete country-year observations

4. *Regression Analysis* – Multiple regression analysis using aggregated panel data

3.3 Step 1: Theoretical Framework

The first step involved conducting a scoping literature review using the electronic databases PubMed and Scopus. This approach was chosen over a systematic review, as the objective was to broadly map and capture the full spectrum of potential risk factors and determinants influencing neonatal sepsis mortality, rather than applying narrow and exclusionary criteria. The search string was built around four main terms: "*neonates", "LMICs", "sepsis"*, and *"determinant"*, which were combined using the Boolean operator AND.[1] Search results were filtered by language (English and German) and the years 2005-2025. Studies were excluded if they did not explicitly mention neonatal sepsis, as existing research suggests that determinants are often age-specific and differ significantly by age group. (48, 49). Studies were further excluded if they examined only immediate determinants. Following abstract and full text screening, a total of 61 studies met the inclusion criteria and were retained for analysis.[2] Each

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[1] See *Appendix 1* for full search string
[2] See *Appendix 2 for PRISMA flow-chart*

study was systematically catalogued into an Excel spreadsheet, and all identified determinants were subsequently grouped using the modified Mosely and Chen framework. They were either categorised as *proximate* determinants – falling under one of the five domains: maternal factors, nutrient vulnerability (neonatal and maternal), environmental exposure risks, intrapartum and neonatal complications, and personal illness control (including care during and after pregnancy and childbirth) - or as *distal* determinants, which indirectly influence neonatal mortality through proximate pathways. (44) In total, the scoping review identified 56 proximate and 15 distal determinants of neonatal sepsis mortality in LMICs.

3.4 Step 2: Selection of Proxy Variables

The next step involved the identification of suitable proxy variables corresponding to the previously identified proximate determinants. The GBD Results Tool, led by the Institute of Health Metrics and Evaluation (IHME), (50) was selected as the primary database, as it provides an extensive and, most importantly, standardised collection of global health estimates covering a wide range of causes of death, risk factors and diseases across multiple years and countries. (51) The online tool is currently offering estimates across 204 countries and territories, 372 diseases and injuries and 88 risk factors, spanning the years 1990 to 2021. (50, 51) The GBD's custom-developed modelling tool – the cause of death ensemble model (CODEm) – synthesises data from a wide range of sources (including e.g. vital registration, surveys, and surveillance systems) to estimate cause-specific mortality on a global scale. The CODEm, along with its exact calculation methods, have been extensively described in previous literature. (52, 53) For determinants not represented by the GBD dataset - such as some health system or macro-economic variables – the WHO Global Health Observatory (54) and WB Open Data platform (55) were systematically searched for relevant indicators.

In cases where no suitable proxy indicator could be identified across these sources, the determinant was labelled a *"no match"*. In alignment with the approach proposed by Cotache-Conder *et al*. (46), all other proxy variables were also evaluated and matched according to their conceptual closeness to the original determinant identified in the literature review. *'Exact matches'* were proxy variables that fully captured the scope and definition of the original determinant, *'close matches'* demonstrated a certain degree of conceptual proximity but with minor limitations and '*fair-matches'* were proxy indicators that captured only general aspects of the original determinant.[3] As Sir David Cox reminds us, the "translation [from subject-matter

[3] See *Appendix 3* for a full list of proxy variables and matches

problem to statistical model] must be reasonably faithful" (56, p. 197). Following his advice, only those proxy variables classified as exact or close matches were retained, leading to a careful selection of relevant indicators for the quantitative model.

Data was then collected across 131 LMICs, as classified by the World Bank's income classification (57) as of June 2025.[4] The 15-year study period from 2007-2021 was specified as it aligns with the most recent GBD study in 2021. (53) Furthermore, it became evident during the research and data selection process that earlier years were missing a significant amount of data, and consequently, the analysis was limited to the period from 2007 onwards.

Dependent Variable – Neonatal sepsis mortality

Neonatal sepsis mortality rates were retrieved from the GBD Results tool, and data were extracted for the Level 4 cause *neonatal sepsis and other neonatal infections,* a subcategory under the broader parent grouping neonatal disorders. (50, 58) This category includes the ICD-10 codes P36-P36.9 *(Bacterial sepsis of newborn)* and P38 *(Omphalitis of newborn with or without mild haemorrhage)* and P39-P39.9 *(Other infections specific to the perinatal period)*. (59, 60) Although the data extends beyond just focusing on neonatal sepsis as the sole cause of death, it was considered the most appropriate option for this analysis. This is consistent with Li *et al.*'s approach (61), who similarly relied on the composite category as a proxy for neonatal sepsis mortality due to ongoing limitations in the availability of global sepsis data, which have been highlighted by several previous studies. (2, 3, 61) Neonatal sepsis mortality rates were collected as deaths per 100,000 population, and results were filtered to include neonates (<28days) of both sexes.

Independent variables

Independent variables were sourced from both the GBD study and supplementary global health datasets, using the same selection and filtering process. (50, 54, 57) Neonatal morbidity indicators were reported as prevalence rates per 100,000 population (neonates aged <28 days). Maternal morbidity indicators were reported as prevalence rates per 100,000 population (women of reproductive age 15-49 years), unless a maternal-specific subgroup was available. Most environmental and health service indicators were expressed as percentages of the relevant

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[4] Due to changes in income classification for FY26 (effective July 1, 2025 – June 2026) Costa Rica has been newly classified as a high-income country, while Ethiopia was unclassified. However, since the primary period of data selection for this dissertation was prior to the implementation of the FY26 update, both countries are included as LMICs

population. Health workforce density variables were measured as the number of workers per 10,000 population. Disease burden was reported as DALYs per 100,000 population.

3.5 Data analysis

All relevant variables were merged into a single dataset in Stata 18.0, using country-year as the unique identifier. The panel ultimately included data from 130 LMICs over 15 years, yielding a total of 1950 observations.[5]

Data missingness

STATA's *misstable summarize* command was used to initially assess the extent of missingness across all variables. 11 out of 23 variables exhibited varying degrees of missing data.[6] While listwise or case deletion is commonly applied to handle missingness, it would have resulted in the exclusions of valuable country-year information which may introduce bias (62) Given that this dissertation aims to include all or at least as many LMICs as possible rather than restricting the analysis to a smaller subset of countries, alternative strategies to handle missing data were prioritised before considering any form of deletion. One such strategy is the use of multiple imputation. (62) Recent recommendations by Junaid *et al.* (63) demonstrated that, particularly for longitudinal health data with missing values of up to 50%, MI remains effective. This threshold was therefore adopted for the present analysis, and variables with higher levels of missingness were excluded. Four variables – prevalence of maternal anaemia, access to basic drinking water, density of nurses and midwives, and DTP3 immunisation coverage – were retained despite having incomplete data, as their missingness ranged from 0.7% to 20% at the variable level. To avoid implausible extrapolation across time for countries with little or no valid data points, country-level patterns of missingness were examined to determine if the distribution of missing values was driven by a few countries missing many years or by many countries missing a few years. Using the aforementioned threshold, countries that were missing data for more than 50% of the study period for a given variable (≥ 8 out of 15 years) were excluded from the imputation model and subsequent analysis. (63) This led to the exclusion of two countries, Côte d'Ivoire and Nicaragua. For the remaining dataset, a series of logistic regressions was performed to further assess the pattern of missing data and its suitability for MI. For each variable with missing data, a binary 'missingness indicator' was created to examine associations with other independent variables. (64) In all cases, the likelihood of

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[5] See *Appendix 4* for a full list of included and excluded LMICs

[6] See *Appendix 3*

missingness was found to be significantly associated with a range of other observed factors supporting the assumption of Missing at Random (MAR), and the suitability of MI to address the missingness. (64-67)

Imputation Model

Ultimately, missing values for three variables (access to basic drinking water, density of nurses and midwives and DTP3 immunisation coverage) were imputed.[7] MICE was conducted using predictive mean matching (pmm) with five nearest neighbours (knn(5)). (64, 67, 68) The imputation model included all full data variables intended for potential use in the final regression model as predictors,[8] which ensured that the imputation was carried out under the same assumptions as the main regression model. (66, 67) Additionally, the imputation was stratified by WB income group (low, lower-middle, and upper-middle), ensuring that missing values were only imputed within the same group. A total of 20 imputed datasets (m=20) were generated. (68)

Regression Model

To examine the associations between proximate determinants and neonatal sepsis mortality within LMICs over time, a linear panel-data regression model with country and year fixed effects (FE) was specified. (69, 70) This approach controls for global health trends over time as well as for "unobserved, time invariant heterogeneities" (69, p. 234) across countries. The fixed effects model was selected instead of random effects after the Hausman test was found to be significant at a p-value < 0.05. (71)

The specified regression equation takes the following form:

$$\boldsymbol{y_{it}} = \beta_1 \boldsymbol{x_{1it}} + \beta_2 \boldsymbol{x_{2it}} + \cdots + \beta_k \boldsymbol{x_{kit}} + \boldsymbol{\lambda_t} + \boldsymbol{\alpha_i} + \boldsymbol{\varepsilon_{it}}$$

***Equation 1** - y_{it} denotes the neonatal sepsis mortality rate in country i and year t, x represents the independent variable (proximate determinant) with its corresponding coefficient ß, λ_t are year fixed effects to account for time trends, α_i are country fixed effects to control for unobserved heterogeneity between countries, and ε_{it} is the idiosyncratic error term.*

Multicollinearity was assessed using the variance inflation factors (VIF) and calculated from separate simple OLS regressions on each of the imputed datasets. Following standard econometric practice, variables with a consistently high VIF > 5 were excluded in a stepwise process to reduce collinearity and improve the model stability. (72, 73) To ensure

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[7] Following the exclusion of Nicaragua, maternal anaemia was no longer missing data

[8] See *Appendix 3* for predictor variables

interpretability and policy relevance, (74) a final set of 10 determinants – two from each category – were included in the final regression model. [9]

1. **Maternal Factors:** Prevalence of maternal sepsis, Prevalence of HIV / STI
2. **Environmental Exposure Risks**: Disease burden due to lack of handwashing access (DALY), Population with access to basic drinking water (%)
3. **Nutrient Vulnerability:** Prevalence of maternal anaemia (%), Prevalence of neonatal nutritional deficiencies
4. **Intrapartum and neonatal Complications:** Prevalence of neonatal jaundice, Prevalence of obstructed labour and uterine rupture (OL/UR)
5. **Personal Illness control:** Density of nurses and midwives, DTP3 immunisation coverage (%)

The final multivariable FE regression was run using the *mi estimate: xtreg* command for panel in Stata, including both country and year fixed effects as well as clustered standard errors at the country level. (75-78) Parameter estimates and standard errors were automatically pooled across the 20 imputed datasets following Rubin's rule. (67, 79) Additionally, two separate models stratified by WB income groups were estimated. Following Griffiths *et al.*'s (80) approach, low-and lower-middle-income countries were combined into a single group, as the low-income group alone comprised only 26 countries and corresponding clustered standard errors, which was considered too few for reliable results.[10] (81)

3.6 Ethical considerations

All data used in this analysis are secondary and aggregated at the country level. It was obtained from publicly available and reputable sources such as the GBD and the WHO. Therefore, the use of this data does not pose significant ethical risks. Nonetheless, ethical clearance was granted through departmental review, and all data have been handled responsibly regarding academic integrity and appropriate citation of sources.

[9] See *Appendix 5* for more details
[10] Angrist and Pischke recommend at least 42 clusters

4. Results

4.1 Descriptive statistics

The final model included 1920 country-year observations from 128 LMICs, spanning over a 15-year period from 2007 to 2021. Descriptive statistics are presented in *Table 1*. The mean neonatal sepsis mortality rate was 2329.8 deaths per 100,000 population. Among the proximate determinants, the highest prevalence was observed for neonatal nutritional deficiencies, with an average of 56,242 cases per 100,000 population, followed by HIV / STI prevalence, which reached an average of 39,130 cases per 100,000 population. The mean percentage of population with access to at least basic drinking water was 80.2% and the mean DTP3 immunisation coverage was 84.74%. The density of nurses and midwives reached an average of 28.0 per 10,000 workers.

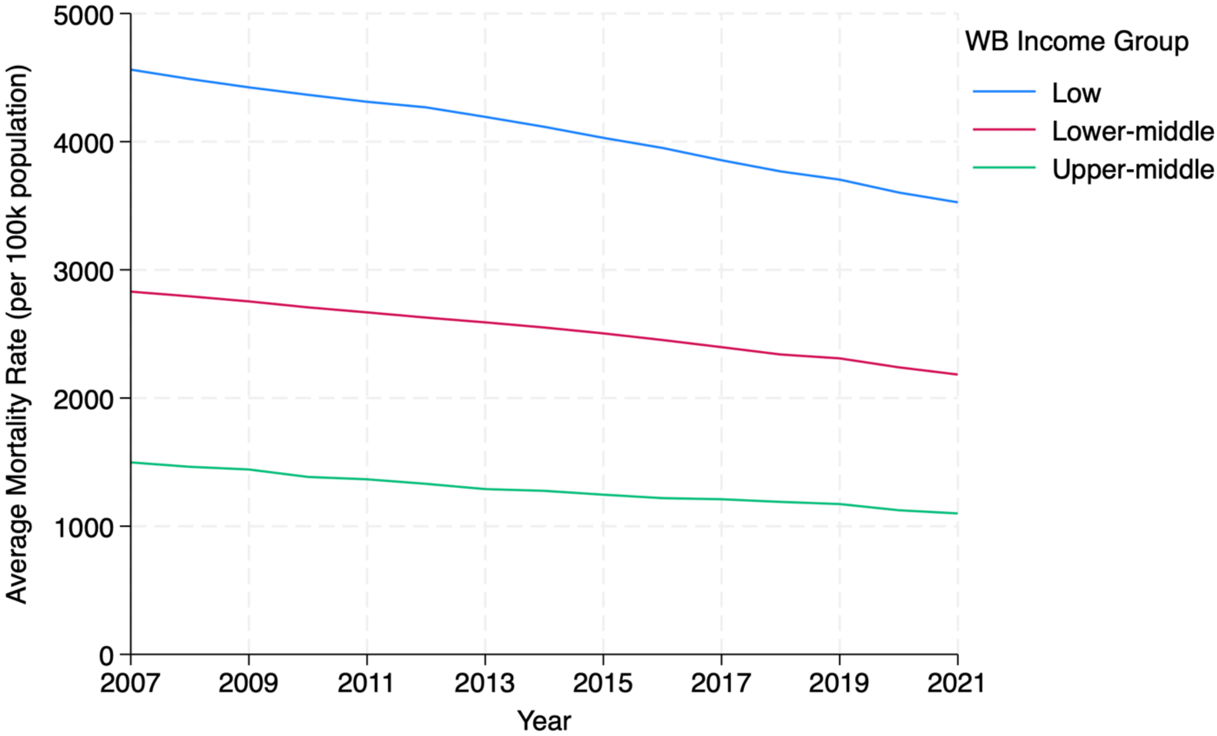
Table 1 *Descriptive Statistics – Estimates adjusted across 20 Imputations*

	Mean	Std. err.	[95% conf. interval]	
Neonatal Sepsis Mortality	2329.786	43.0494	2245.357	2414.214
Maternal Sepsis	156.6872	1.46422	153.8156	159.5588
HIV/STI	39130.37	318.0021	38506.71	39754.04
Neonatal Nutritional Deficiencies	56242.13	277.4112	55698.07	56786.19
Maternal Anaemia	35.18661	.2350444	34.72565	35.64758
Neonatal Jaundice	533.2557	7.678834	518.1959	548.3154
OL/UR	87.21949	3.264479	80.81719	93.6218
Lack of handwashing access	150.7466	4.168652	142.5711	158.9222
Access to Basic Drinking Water	80.18887	.4132514	79.3784	80.99934
Density of Nurses and Midwives	27.97031	.5675979	26.85671	29.08392
DTP3 immunisation Coverage	84.74268	.3437196	84.06849	85.41687

Note*: Variables are reported as prevalence per 100,000 total population unless otherwise specified. Maternal anaemia, access to basic drinking water, and DTP3 immunisation coverage are expressed as percentages. Lack of handwashing access is expressed as DALYs per 100,000 total population. The density of nurses and midwives is expressed as workers per 10,000 population.*

In addition, neonatal sepsis mortality time trends were disaggregated by WB income groups (*Figure 4*). While mortality rates have consistently declined within all three income groups over the 15-year period, substantial disparities remain. Low-income countries persistently experienced the highest mean neonatal sepsis mortality rates, followed by lower-middle-income and upper-middle-income countries. Although the greatest absolute decline occurred in the low-income group (from 4,562 deaths per 100,000 population in 2007 to 3,526.9 in 2021), these countries continue to bear the highest sepsis-related mortality. Notably, the lowest recorded mortality rates in low-income settings (3,526.9 in 2021) still exceeded the highest rates observed in lower-middle or upper-middle income settings. (at 2,830 and 1,497.9 per 100,000 population in 2007, respectively).

Figure 4 *Mean Neonatal Sepsis Mortality Trends by Income Group from 2007 to 2021*



Note: *Own Calculations*

4.2. Main findings

Table 2 presents the results of the main regression model, which estimated the associations between 10 proximate determinants and neonatal sepsis mortality rates within 128 LMICs from 2007 to 2021. As the model includes both country and year fixed effects, all reported associations reflect solely within-country changes over time, rather than differences between countries. (82)

Of the 10 determinants, three – prevalence of neonatal jaundice, prevalence of OL/UR and disease burden due to the lack of handwashing facilities – were found to be statistically significant at the 5% level, while the percentage of population using basic drinking water services showed marginal significance at the 10% level. These four variables fall within only two of the five framework categories: intrapartum and neonatal complications and environmental exposure risk. None of the variables in the other categories were found to have significant associations with neonatal sepsis mortality rates in this model.

Birth and Neonatal Complications: Both variables – OL/UR and neonatal jaundice - were associated with changes in neonatal sepsis mortality. An increase in the prevalence of OL/UR was significantly associated with an increase in neonatal sepsis deaths. In fact, each additional case of OL/UR per 100,000 population was associated with 1.49 additional neonatal sepsis deaths per 100,000 population (95% CI: 0.53 to 2.44, $p = 0.002$). Although the effect size is modest, a higher prevalence of neonatal jaundice was significantly associated with a decrease in sepsis mortality rates (Coefficient = -0.35, 95% CI: -0.57 to -0.13, $p = 0.002$).

Environmental Exposure Risks: Each additional DALY per 100,000 population attributable to a lack of access to handwashing facilities among women of reproductive age was associated with an estimated 2.1 additional neonatal sepsis deaths per 100,000 population (95% CI: 0.18 to 3.99, $p = 0.032$). Having access to at least basic drinking water demonstrated a protective effect, albeit with marginal statistical significance. The negative coefficient suggests an inverse relationship, where a one percentage point increase in the population using basic drinking water services was associated with an estimated 11 fewer neonatal sepsis deaths per 100,000 population. (95% CI: -22.95 to 0.63, $p = 0.063$)

Temporal Trends: The results show a consistent downward trend in neonatal sepsis mortality rates over time. Statistical significance at the 10% level to the baseline year 2007 was observed beginning in 2010, and at the 5% level from 2013 onwards. By 2021, neonatal sepsis mortality rates were estimated to be, on average, 343.8 deaths per 100,000 population, lower than in the baseline year 2007. (95% CI: -546.11 to -141.51, $p = 0.001$)

Non-Significant Findings: No statistically significant associations with neonatal sepsis mortality were found for any of the other determinants, including prevalence of maternal sepsis, HIV / STI, nutritional deficiencies, maternal anaemia, density of nurses and midwives and DTP3 coverage.

***Table 2** Pooled Results across 20 Imputations and 128 LMICs*

Neonatal sepsis mortality	Coefficient	Std. err.	t	P>|t|	[95% conf. interval]	
Maternal Sepsis	-0.0219998	1.826846	-0.01	0.990	-3.637571	3.593572
HIV/STI	-0.020004	0.0166406	-1.20	0.232	-0.0529381	0.0129301
Neonatal Nutritional Deficiencies	0.0024845	0.0139016	0.18	0.858	-0.0250288	0.0299979
Maternal Anaemia	13.33742	13.9909	0.95	0.342	-14.3524	41.02724
Neonatal Jaundice	-0.3501639	0.1127516	-3.11	0.002	-0.5733265	-0.1270014
OL/UR	1.490323	0.4815281	3.09	0.002	0.5372794	2.443366
Lack of handwashing access	2.087996	0.963176	2.17	0.032	0.1817413	3.994925
Access to basic drinking water	-11.15904	5.955395	-1.87	0.063	-22.94684	0.6287512
Nurses and Midwives	1.035019	1.138317	0.91	0.367	-1.247961	3.317998
DTP3 immunisation coverage	0.5934393	1.086632	0.55	0.586	-1.559624	2.746502
year						
2008	-18.5862	11.62268	-1.60	0.112	-41.59096	4.418572
2009	-31.16061	21.80822	-1.43	0.156	-74.3238	12.00258
2010	-59.84033	31.17282	-1.92	0.057	-121.5379	1.857285
2011	-68.40939	38.24694	-1.79	0.074	-144.1081	7.289371
2012	-84.83643	44.83047	-1.89	0.061	-173.5662	3.893331
2013	-111.8387	51.78417	-2.16	0.033	-214.3314	-9.34594
2014	-131.5157	58.90266	-2.23	0.027	-248.0972	-14.93423
2015	-158.2951	65.65589	-2.41	0.017	-288.1488	-28.34139
2016	-188.3034	72.16645	-2.61	0.010	-331.1377	-45.46903
2017	-213.9423	77.86308	-2.75	0.007	-368.0517	-59.83297
2018	-244.8275	84.52794	-2.90	0.004	-412.1278	-77.52724
2019	-261.7036	91.02265	-2.88	0.004	-441.8593	-81.54783
2020	-307.5316	97.04352	-3.17	0.002	-499.6796	-115.4554
2021	-343.8066	102.2085	-3.36	0.001	-546.1065	-141.5068

***Note:** Dependent Variable: Neonatal Sepsis Mortality. Variables are reported as prevalence per 100,000 total population unless otherwise specified. Maternal anaemia, access to basic drinking water, and DTP3 immunisation coverage are expressed as percentages. Lack of handwashing access is expressed as DALYs per 100,000 total population. Density of nurses and midwives is expressed as workers per 10,000 population. Standard errors are clustered at the country level. Results are pooled using Rubin's Rule.*

4.3 Findings stratified by income group

The stratified analyses included 1125 observations (75 countries) in the low- and lower-middle income group and 795 observations (54 countries) in the upper-middle income group. The results are presented in *Table 3*.

Table 3 *Pooled Results across 20 Imputations, Stratified by Income Group*

Neonatal sepsis mortality	Low & Lower-Middle Income	Upper-Middle Income
Maternal Sepsis	-0.731 2.570	4.917** 1.841
HIV/STI	-0.0287 0.0211	-0.0121 (0.0182)
Neonatal nutritional deficiencies	0.00487 (0.0178)	-0.00435 0.0216
Maternal Anaemia	6.940 17.48	5.638 19.38
Neonatal Jaundice	-0.950*** (0.349)	-0.294** (0.128)
OL/UR	1.305*** (0.476)	-8.017** 3.424
Lack of handwashing access	2.377** 1.147	1.000** (0.491)
Access to basic drinking water	-11.77* 6.746	-7.592 7.379
Nurses and Midwives	5.277** 2.523	-0.152 1.156
DTP3 immunisation coverage	-0.754 1.337	2.387 1.951
Observations	**1125**	**795**

Note: *Standard errors in parentheses * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$. Variables are reported as prevalence per 100,000 total population unless otherwise specified. Maternal anaemia, access to basic drinking water, and DTP3 immunisation coverage are expressed as percentages. Lack of handwashing access is expressed as DALYs per 100,000 total population. Density of nurses and midwives is expressed as workers per 10,000 population. Standard errors are clustered at the country level. Results are pooled using Rubin's Rule.*

Low-and lower-middle-income countries: Prevalence of neonatal jaundice and prevalence of OL/UR were both strongly associated with neonatal sepsis mortality. Whereas for OL/UR, each additional case per 100,000 population was associated with an increase of 1.31 neonatal sepsis deaths per 100,000 population, a higher prevalence of neonatal jaundice was associated with lower neonatal sepsis mortality rates (both p<0.01). Each additional DALY per 100,000 population attributable to a lack of handwashing access was associated with an increase of 2.38 neonatal sepsis deaths per 100,000 population (p<0.05) whereas a one percentage point increase in the population with access to basic drinking water was marginally associated with a reduction of 11.77 neonatal sepsis deaths per 100,000 population ($p<0.10$). In this income subgroup, a higher density of nurses and midwives was associated with an increase in sepsis mortality rates. Each additional healthcare worker per 10,000 population was associated with 5.28 additional neonatal sepsis deaths per 100,000 population ($p<0.05$).

Upper-middle-income countries: The results show that an increase in prevalence of neonatal jaundice as well as an increase in prevalence of OL/UR were both significantly associated with a decrease in neonatal sepsis mortality per 100,000 population (Coefficient = -0.294, $p<0.05$ and Coefficient = -8.02, $p<0.05$, respectively). Additionally, each additional case of maternal sepsis per 100,000 population within upper-middle-income countries was associated with 4.9 additional neonatal sepsis deaths per 100,000 population. Each additional DALY due to the lack of handwashing access was associated with 1.0 additional neonatal sepsis death (both $p<0.05$).

Prevalence of HIV / STI, neonatal nutritional deficiencies, maternal anaemia, and DTP3 coverage were not significantly associated with neonatal sepsis mortality rates in either stratified model.

4.3 Robustness Check

To assess the robustness of the main findings, several additional analyses were conducted.

Imputation: Although MI is a widely recognised method for handling missing data, (83) concerns regarding the plausibility of imputed datasets persist. (64, 65) As Li *et al*. (65, p. 3) remind us, “the validity of MI depends on the validity of its assumptions”. In the context of this dissertation, this primarily includes the assumption that the data are MAR and that the variables included in the imputation model serve as strong predictors. To evaluate the plausibility and quality of the imputed data, means and standard deviations were compared between observed and imputed data. Histograms were generated to visually compare the distributional shape.[11] (68, 84) Additionally, a complete-case analysis was conducted by re-estimating the FE model using the original, unimputed dataset.[12] (83) All variables that were statistically significant in the imputed model remained significant at the 5% level, and the directionality of their coefficient was preserved, supporting the assumption that the imputation procedure did not substantially alter the observed associations. However, one exception was observed for the density of nurses and midwives, which was marginally significant ($p = 0.083$)

[11] See *Appendix 6* for means and standard deviations and histograms of observed and imputed data
[12] See *Appendix 7* for results

in the non-imputed model but not significant in the imputed model. This discrepancy could be attributed to the level of missingness, imputation quality, or reflect a potential bias introduced by restricting the analysis to complete cases only. In the end, MI was considered the most appropriate and robust method to address missing data, as alternative strategies carry their own limitations that are often even more restrictive in their assumptions and may lead to greater bias. (65, 83)

Fixed Effects model: Other scholars have argued that a "well-specified RE model" (85) is superior to a FE one, particularly for panel datasets where including time-invariant variables can provide valuable insight towards the broader context. However, the decision to use a FE model was based on the result of the Hausman test, which was significant at $p<0.05$, indicating that the assumption underlying the RE model is most likely violated, making the FE model a more appropriate choice. (86) Nonetheless, to account for unobserved structural heterogeneity across countries, a mixed-effects model with random intercepts for each country was estimated as a robustness check.[13] (87) This model is more flexible than a conventional RE approach, as it allows each country to have its own baseline (random intercept), while still allowing population-level FE over time. (88) All key variables remained statistically significant, which supports the robustness of the original findings and suggests that within-country associations remain significant even after including random country-specific intercepts and accounting for unobserved heterogeneity across countries.

Selected Variables: The selection of appropriate independent variables is particularly important when analysing longitudinal data, where high correlation among determinants is often a concern. (89, 90) Although numerous different data-driven variable selection methods have been described elsewhere (89, 90), this dissertation follows the general recommendations by Heinze *et al.* (74, p. 441) who caution against giving these methods the "exclusive control over model building". Instead, a simpler approach, grounded in theoretical knowledge gained through this dissertation's scoping literature review, was prioritised over more complex data-driven approaches. (74) Nonetheless, the robustness of the observed associations was examined by estimating an additional FE model and incorporating all initially considered variables[14] (except those with high multicollinearity). The results indicate that, even after controlling for

[13] See *Appendix 8* for Mixed Effects model results
[14] See *Appendix 9* for Full Variable FE regression model results

the additional variables, the key determinants remained significant, with coefficients showing a consistent direction.

5. Discussion

This dissertation is, to the best of my knowledge, among the first to investigate proximate determinants of neonatal sepsis mortality within all LMICs. While a recent publication by Mu *et al.* (23) also examined different risk factors of neonatal sepsis, their model only included four variables, whereas this dissertation extended the number of possible determinants to a set of ten. It therefore builds upon existing hospital-based clinical studies conducted in LMICs and extends clinical insights to a wider analysis.

First of all, the observed downward trend in overall neonatal sepsis mortality between 2007 and 2021 is consistent with Mu *et al.*'s (23) sepsis estimates and a general decrease in neonatal disorder-related mortality. (91) These improvements are frequently attributed to an increase in public health interventions, such as vaccination campaigns, maternal and newborn care programmes, improved WASH conditions, and enhanced healthcare access. (23, 92, 93) However, despite the gradual decline observed within all three income groups, income-related disparities persist. Low-income countries continue to experience the highest mortality rates, likely due to associations between lower socioeconomic status and increased infection risks, which have been highlighted in previous research. (94, 95)

The findings highlight two categories within this dissertation's conceptual framework that show particularly relevant associations with neonatal sepsis mortality: intrapartum and neonatal complications, as well as environmental exposure risks. While this does not detract from the theoretical and clinical significance of the remaining three categories, as each is supported by individual-level evidence in previous literature, it rather suggests that, on a broader scale, birth and neonatal complications, and environmental factors emerge as the predominant determinants associated with changes in neonatal sepsis mortality.

Prevalence of OL/UR served as a proxy indicator for birth complications, which not only represent a leading cause of maternal mortality (96) but also increase the risk of neonatal infections due to vertical transmission from the mother to the newborn. (97, 98) This association was supported in the analysis, which demonstrated that an increase in within-country prevalence of OL/UR was associated with higher sepsis mortality rates. In the stratified analyses, the associations remained strongly significant within low-and lower-middle-income countries, whereas within upper-middle-income countries higher prevalence of OL/UR was associated with lower sepsis mortality. This could be explained with prior research findings, indicating that upper-middle-income countries generally provide better MNCH care compared to low-and lower-middle-income countries. (99) This result also reinforces calls made by previous scholars advocating for further improvements of pregnancy and intrapartum care, especially in lower-resource settings. These include a minimum number of ANC checkups, enhanced availability of medical technologies, and equitable access to healthcare. (100) Neonatal jaundice prevalence revealed an inverse association at the population level, whereby increases within LMICs over time were associated with lower sepsis mortality rates. While this finding may initially seem counterintuitive, it is important to keep in mind that this dissertation analysed mortality and not incidence rates, which is in contrast to other clinical studies that examine sepsis incidence or prevalence. (101, 102) Additionally, some scholars and national guidelines characterise jaundice not as a determinant of neonatal sepsis but rather as an indicator of an underlying infection. (103, 104) Overall, enhanced recognition of subtle or non-specific signs of illness, such as neonatal jaundice, is crucial to identify infants at risk. (105)

Overall, the strong observed associations between intrapartum and neonatal complications and sepsis outcomes once again highlight the need to improve birth conditions, reduce complication rates, and ensure access to appropriate postnatal care. Furthermore, MNCH interventions should prioritise enhancing education on newborn care and sepsis manifestations, particularly in neonates. To achieve this, it is essential that policymakers explicitly incorporate neonatal sepsis prevention and education strategies into national maternal and newborn care policies.

Environmental exposure risks, particularly poor WASH conditions, emerged as the second relevant category. The association between inadequate WASH infrastructure and infectious diseases is well established in the literature, due to faecal-oral and faecal-skin transmission pathways. (106) Importantly, this association has also been established for neonatal sepsis. A study from Uganda identified good maternal hand hygiene as a protective factor (107) consistent with the present analysis, which indicates that increases in within-country disease burden among women of reproductive age attributable to inadequate handwashing access are associated with increases in neonatal sepsis mortality. This association was maintained in the stratified analyses, suggesting that a lack of access to handwashing facilities continues to contribute to the sepsis burden within both low-and lower-middle-income, as well as upper-middle-income countries. Other scholars have demonstrated that interventions promoting the use of soap have been shown to be effective in reducing respiratory infections (108); however, further research is needed to examine the specific impact of similar interventions on neonatal sepsis. Similarly, having access to basic drinking water showed a marginal association with a decrease in neonatal sepsis mortality rates in the overall model and within low-and lower-middle-income settings in the stratified model. The mechanism underlying this relationship most likely includes direct effects, such as improved hygiene and reduced exposure to pathogens, and indirect effects, including reducing time collecting clean water and increased time for childcare and work. (106, 109, 110) Given that income inequalities present a major barrier to the access of safe drinking water, (111) expanding coverage of basic drinking water services is particularly critical for women of reproductive age within low-and lower-and middle-income countries. Such efforts would not only improve WASH conditions in general but simultaneously exert a protective effect against sepsis-related neonatal mortality.

Another well-documented theme in the literature is the strong association between maternal risk factors and neonatal health outcomes. (112-114) However, in this analysis, these associations were less evident. In the main model, neither maternal sepsis nor HIV/STI prevalence showed a statistically significant association with neonatal sepsis mortality over time, indicating that shifts in maternal infectious disease patterns are not strongly associated with changes in neonatal sepsis mortality. The stratified analyses revealed a significant association between higher prevalence of maternal sepsis and neonatal sepsis mortality within upper-middle-income countries, which is consistent with clinical theory and other research predominantly from high-income settings. (114) Additionally, two important considerations should be noted when interpreting the results. First, previous literature itself presents mixed evidence, as not all clinical studies support a strong link between maternal and neonatal infections. For instance, Okomo *et al.* (115) have reported low vertical transmission rates among culture-confirmed EOS cases in Gambia. Second, the findings presented here are based on aggregated country-level data, which may not accurately reflect individual-level transmission pathways. Thus, the results do not contradict clinical evidence and hospital-based individual studies per se but rather reflect a relationship that is mediated through more indirect pathways, such as maternal exposure to poor hygiene conditions.

The absence of statistically significant associations for DTP3 immunisation coverage and density of nurses and midwives is unexpected, particularly given the well-documented protective effects of both routine childhood vaccinations (116) and the role of skilled health personnel in reducing neonatal mortality. (117) However, it is possible that the FE model's ability to detect associations was limited because of "too little within-unit variation for fixed effects analysis" (118, p. 441). In other words, the within-country variation over time of the two determinants may not have been enough for a measurable effect at the population level. One exception to this pattern was observed within low-and lower-middle-income countries, where increases in the density of health workers were marginally associated with higher neonatal sepsis mortality rates. This result contrasts with previous research, which links healthcare staff shortages to higher mortality rates. (119) However, skilled healthcare personnel have demonstrated to diagnose infections in infants with high sensitivity (87%), (120) suggesting that the higher reported mortality rates within low-and lower-middle-income countries may, in fact, reflect improved detection.

Despite previous evidence indicating that nutrient vulnerability and malnutrition contribute to an increased infection risk and adverse health outcomes in children (121, 122), a specific association with neonatal sepsis mortality could not be observed in any of the models. Given that malnutrition in children is often linked to suboptimal breastfeeding practices (123, 124), future research may benefit from examining potential associations between neonatal sepsis mortality and breastfeeding practices directly, rather than focusing on neonatal malnutrition as an outcome.

To summarise, various external influences emerged as critical proximate determinants associated with neonatal sepsis mortality within LMICs. The findings underscore two key points: First is imperative to continue to improve intrapartum and newborn care. Additionally, such efforts should not merely aim to reduce maternal and neonatal morbidity and mortality in general, but rather, they need to explicitly prioritise the prevention of neonatal sepsis deaths by recognising sepsis as a preventable outcome of poor birth conditions. Second, WASH interventions also need to address the interconnections between maternal exposure to poor hygiene conditions and neonatal sepsis outcomes. This includes targeting women of reproductive age and teaching them about potential transmission pathways related to their hygiene practices and the potential impact on their child's health.

Coming back to the second research question, although the findings of this dissertation cannot be directly translated into concrete modifications or improvements of current sepsis scores, they can inform future policies and research aimed at the development of more context-sensitive tools for LMICs. The observed associations contribute to a deeper understanding of neonatal sepsis mortality within LMICs by providing valuable insights into broader risk pathways and neonatal vulnerabilities.

Current scoring systems predominantly rely on immediate determinants and often require confirmation through laboratory testing, which is limited, especially in LMICs. (4, 125) Expanding sepsis scores to incorporate proximate determinants, such as inadequate WASH conditions, intrapartum complications or neonatal vulnerabilities, as additional criteria, could help improve current limitations regarding their applicability in low-resource settings. In previous research, expanding the SOFA score with socio-demographic variables has yielded highly promising results. (9) As emphasised by Neal *et al.* (126, p. 10), there is an urgent need for "models that do not require laboratory parameters", and the identified proximate determinants offer a promising opportunity for future research to refine and adapt existing sepsis scores to enhance their applicability in LMICs. Furthermore, understanding the associations between the determinants identified in this analysis and neonatal sepsis mortality not only guides future sepsis score research but also equips healthcare providers and policymakers within LMICs with evidence to design diagnostic tools, interventions and policies that address sepsis through a wider lens. This is particularly relevant in light of a recently published WHO report (July 2025) emphasising the importance of "accessible and affordable" (127, p. 1) in vitro diagnostic tests for neonatal sepsis. While such clinical tests are critical for timely diagnosis and treatment, this dissertation highlights that the burden of neonatal sepsis is not solely clinical but also a manifestation of external factors, including environmental conditions, birth circumstances and the broader neonatal health context. Addressing these upstream determinants is a necessary step to ultimately effectively reduce neonatal sepsis mortality rates within LMICs.

6. Limitations

This dissertation has several limitations, corresponding to each step of the methodological approach and analysis.

Sepsis definition: Several limitations stem from one overarching issue: the lack of consensus on how neonatal sepsis should be clinically defined, diagnosed, or operationalised in research and practice, which has created a lot of ongoing uncertainty and debates. (4, 128, 129) In the scoping review, no strict sepsis definition was applied to screen studies, as different studies used different definitions, which inevitably led to considerable differences in study populations and reported outcomes, and hindered comparability. Additionally, neonatal sepsis mortality data were collected from the GBD, which defines sepsis purely based on a set of ICD-10 codes. This coding system, although standardised, is reliant on correct diagnoses, categorisation, and documentation by trained healthcare professionals, which, given the lack of consensus, represents a common limitation. (2, 4, 130) The absence of a standardised definition has resulted in a lack of universally applicable diagnostic criteria for neonatal sepsis, which has, in turn, contributed to substantial data quality issues. (131)

Literature Review: Although the scoping literature review was deliberately conducted to avoid the common limitation of over-relying on other secondary analyses and to ensure that variable selection was based on context-specific, clinical evidence from LMICs themselves, the geographical distribution of neonatal sepsis research was very uneven across low-income settings, as only a minority of LMICs have published studies on neonatal sepsis and its broader determinants. (see *Figure 2*) This introduces a risk of selection bias. Important determinants that may be relevant in underrepresented settings could have been missed simply because no sepsis-specific studies exist or could be identified from those regions in the review. Ghani *et al.* (132) reported similar limitations. In their study, nearly half (49.9%) of all LMIC-based publications originated from the African region, compared to 11% from the Southeast Asia region. Although they acknowledge that this mirrors the proportional percentage of LIC/LMICs globally, it does not reflect the distribution of population, nor does it capture the full heterogeneity of LMIC contexts or allow results to be generalised across contexts. (132) Lastly, due to time and word limit constraints of this dissertation, the identified distal determinants were not incorporated into the quantitative analysis. Further research should therefore investigate how distal determinants exert their influence via proximate pathways.

Data: There are several limitations related to the data used. First, the analysis is based entirely on aggregated country-level data estimates, which do not capture individual-level variation, potentially obscuring important contextual nuances. Second, for some maternal variables, available data were not disaggregated by pregnancy status. As a result, indicators such as 'maternal' sepsis refer to all women of reproductive age rather than specifically to pregnant women, which ultimately compromises the specificity of the results. Third, the dependent variable - *neonatal sepsis mortality* – is itself subject to various data limitations. The GBD estimates sepsis mortality based on ICD-10 codes corresponding to sepsis and other infections. This method only captures those cases that were diagnosed and correctly coded, thereby largely excluding undiagnosed or undocumented sepsis cases, especially if they occur outside the formal health system. (4) Moreover, the GBD aggregates multiple ICD-10 codes under the broader category "Neonatal sepsis and *other neonatal infections"*, which may introduce measuring error by conflating sepsis with other infectious causes of neonatal death. On the other hand, sepsis is a condition resulting from an underlying infection, which is why other scholars argue sepsis is under-reported in mortality data, either because only the infection is coded, sepsis could not be explicitly diagnosed, or because there are ongoing debates about which infections are included in sepsis estimates.[15] (4, 133) To address this, Rudd *et al.* (2) have expanded their estimation approach, aiming to capture deaths likely attributable to undiagnosed sepsis, which yielded a significantly higher number of sepsis-related deaths.

Quantitative Analysis: Variable reduction for the quantitative model was primarily guided by the scoping literature review, theoretical considerations, and data availability. However, quantitative variable selection methods, such as those suggested by Fan *et al.* (89), may have offered a more robust and systematic approach. Moreover, omitted variable bias remains a significant concern in this dissertation, mainly caused by limited data availability. Frequently mentioned determinants from the literature - such as *'Number of ANC visits'* or *'Place of delivery'* – had to be excluded either because appropriate proxy indicators were not available, or due to the extent of missing data. Additional limitations relate to the assumptions underlying the MI procedure. Despite several robustness checks, MI relies on the MAR assumption as well as on the accuracy and validity of the predictors used. Because MAR cannot be empirically verified, Kang (62) recommends further sensitivity analyses to explore potential violations of this assumption. Another key limitation of the FE model is the exclusion of time-invariant variables, such as border distal determinants and cross-country variation (134), which may ultimately limit the model's comprehensiveness. Finally, although stratified analyses were conducted to disaggregate the results by WB income group, the findings do not allow for cross-income group comparison. Further analysis is needed to formally test whether associations between income groups differ significantly.

7. Conclusion

This dissertation examined a range of proximate determinants of neonatal sepsis mortality within LMICs, extending the analytical focus beyond purely clinical manifestations by investigating broader risk pathways. A specifically adapted version of Mosley and Chen's child survival framework was applied, identifying relevant proximate determinants from hospital-based research in LMICs. The determinants and their associations with neonatal sepsis

[15] The GBD for example does not include pneumonia in their sepsis estimates

mortality were then analysed using aggregated national-level panel data from the GBD, the WHO, and the WB. The findings highlighted the relevance of two of the framework's five determinant categories: environmental exposure risks and birth and neonatal complications. Both categories showed significant associations with neonatal sepsis mortality at the population level, exhibiting either protective effects and lower mortality rates or adverse effects associated with higher mortality rates. Stratified analyses similarly showed significant associations within the low- and lower-middle-income, as well as within the upper-middle income subgroup. However, further research is needed to assess if the differences between income groups are significant. The findings also offer valuable insights into broader risk pathways that could guide future research to develop adapted and context-sensitive sepsis scores, as their applicability within most low-resource contexts is currently very limited.

To conclude, I want to highlight two key points: Enhancing clinical testing of immediate determinants to improve timely diagnosis and treatment of neonates with suspected sepsis remains crucial, and the recent WHO targets are a step in the right direction. However, it is equally important for researchers and policy makers to expand their focus, recognise the influence of proximate determinants and explicitly incorporate them into relevant policies, interventions, and ultimately context-sensitive diagnostic tools, echoing former United Nations Secretary-General Ban Ki-moon's call that "it is time to give newborns a more prominent place on the global health agenda" (135, p. 3).

8. AI Statement

I hereby acknowledge the use of ChatGPT (OpenAI, 2025) to identify improvement in my writing style and refine my work's academic language, grammar, and spelling. The content itself, including any arguments and interpretations presented, remains entirely my own.

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Appendix

Appendix 1 *Full PubMed Search String*

(newborn[Title/Abstract] OR neonate[Title/Abstract] OR infant[Title/Abstract] OR pediatric[Title/Abstract] OR paediatric[Title/Abstract] OR child[Title/Abstract] OR children[Title/Abstract] OR childhood[Title/Abstract] OR " under-5" OR "under five")

AND

("low- and middle-income countries"[Title/Abstract] OR LMICs[Title/Abstract] OR "developing countries"[Title/Abstract] OR "resource-limited setting*"[Title/Abstract] OR "low-resource setting*"[Title/Abstract] OR Afghanistan[Title/Abstract] OR Angola[Title/Abstract] OR Albania[Title/Abstract] OR Argentina[Title/Abstract] OR Armenia[Title/Abstract] OR "American Samoa"[Title/Abstract] OR Azerbaijan[Title/Abstract] OR Burundi[Title/Abstract] OR Benin[Title/Abstract] OR "Burkina Faso"[Title/Abstract] OR Bangladesh[Title/Abstract] OR Bulgaria[Title/Abstract] OR Bosnia[Title/Abstract] OR Herzegovina[Title/Abstract] OR Belarus[Title/Abstract] OR Belize[Title/Abstract] OR Bolivia[Title/Abstract] OR Brazil[Title/Abstract] OR Bhutan[Title/Abstract] OR Botswana[Title/Abstract] OR "Central African Republic"[Title/Abstract] OR China[Title/Abstract] OR "Cote d'Ivoire"[Title/Abstract] OR Cameroon[Title/Abstract] OR Congo[Title/Abstract] OR Colombia[Title/Abstract] OR Comoros[Title/Abstract] OR "Cabo Verde"[Title/Abstract] OR "Costa Rica"[Title/Abstract] OR Cuba[Title/Abstract] OR Djibouti[Title/Abstract] OR Dominica[Title/Abstract] OR "Dominican Republic"[Title/Abstract] OR Algeria[Title/Abstract] OR Ecuador[Title/Abstract] OR Egypt[Title/Abstract] OR Eritrea[Title/Abstract] OR Ethiopia[Title/Abstract] OR Fiji[Title/Abstract] OR Micronesia[Title/Abstract] OR Gabon[Title/Abstract] OR Georgia[Title/Abstract] OR Ghana[Title/Abstract] OR Guinea[Title/Abstract] OR Gambia[Title/Abstract] OR Grenada[Title/Abstract] OR Guatemala[Title/Abstract] OR Guyana[Title/Abstract] OR Honduras[Title/Abstract] OR Haiti[Title/Abstract] OR Indonesia[Title/Abstract] OR India[Title/Abstract] OR Iran[Title/Abstract] OR Iraq[Title/Abstract] OR Jamaica[Title/Abstract] OR Jordan[Title/Abstract] OR Kazakhstan[Title/Abstract] OR Kenya[Title/Abstract] OR Kyrgyz[Title/Abstract] OR Cambodia[Title/Abstract] OR Kiribati[Title/Abstract] OR Lao[Title/Abstract] OR Lebanon[Title/Abstract] OR Liberia[Title/Abstract] OR Libya[Title/Abstract] OR "St. Lucia"[Title/Abstract] OR "Sri Lanka"[Title/Abstract] OR Lesotho[Title/Abstract] OR Morocco[Title/Abstract] OR Moldova[Title/Abstract] OR Madagascar[Title/Abstract] OR Maldives[Title/Abstract] OR Mexico[Title/Abstract] OR "Marshall Islands"[Title/Abstract] OR "North Macedonia"[Title/Abstract] OR Mali[Title/Abstract] OR Myanmar[Title/Abstract] OR Montenegro[Title/Abstract] OR Mongolia[Title/Abstract] OR Mozambique[Title/Abstract] OR Mauritania[Title/Abstract] OR Malawi[Title/Abstract] OR Malaysia[Title/Abstract] OR Namibia[Title/Abstract] OR Niger[Title/Abstract] OR Nigeria[Title/Abstract] OR Nicaragua[Title/Abstract] OR Nepal[Title/Abstract] OR Pakistan[Title/Abstract] OR Peru[Title/Abstract] OR Philippines[Title/Abstract] OR Korea[Title/Abstract] OR Paraguay[Title/Abstract] OR "West Bank"[Title/Abstract] OR Gaza[Title/Abstract] OR Russia*[Title/Abstract] OR Rwanda[Title/Abstract] OR Sudan[Title/Abstract] OR Senegal[Title/Abstract] OR "Solomon Islands"[Title/Abstract] OR "Sierra Leone"[Title/Abstract] OR "El Salvador"[Title/Abstract] OR Somalia[Title/Abstract] OR Serbia[Title/Abstract] OR "Sao Tome"[Title/Abstract] OR Suriname[Title/Abstract] OR Eswatini[Title/Abstract] OR Syria[Title/Abstract] OR Chad[Title/Abstract] OR Togo[Title/Abstract] OR Thailand[Title/Abstract] OR Tajikistan[Title/Abstract] OR Turkmenistan[Title/Abstract] OR "Timor-Leste"[Title/Abstract] OR Tonga[Title/Abstract] OR Tunisia[Title/Abstract] OR Turkey[Title/Abstract] OR Tuvalu[Title/Abstract] OR Tanzania[Title/Abstract] OR Uganda[Title/Abstract] OR Ukraine[Title/Abstract] OR Uzbekistan[Title/Abstract] OR Grenadines[Title/Abstract] OR Venezuela[Title/Abstract] OR Vietnam[Title/Abstract] OR Vanuatu[Title/Abstract] OR Samoa[Title/Abstract] OR Kosovo[Title/Abstract] OR Yemen[Title/Abstract] OR Zambia[Title/Abstract] OR Zimbabwe[Title/Abstract] OR "Latin America"[Title/Abstract] OR Africa[Title/Abstract] OR "sub-Saharan"[Title/Abstract] OR Asia[Title/Abstract])

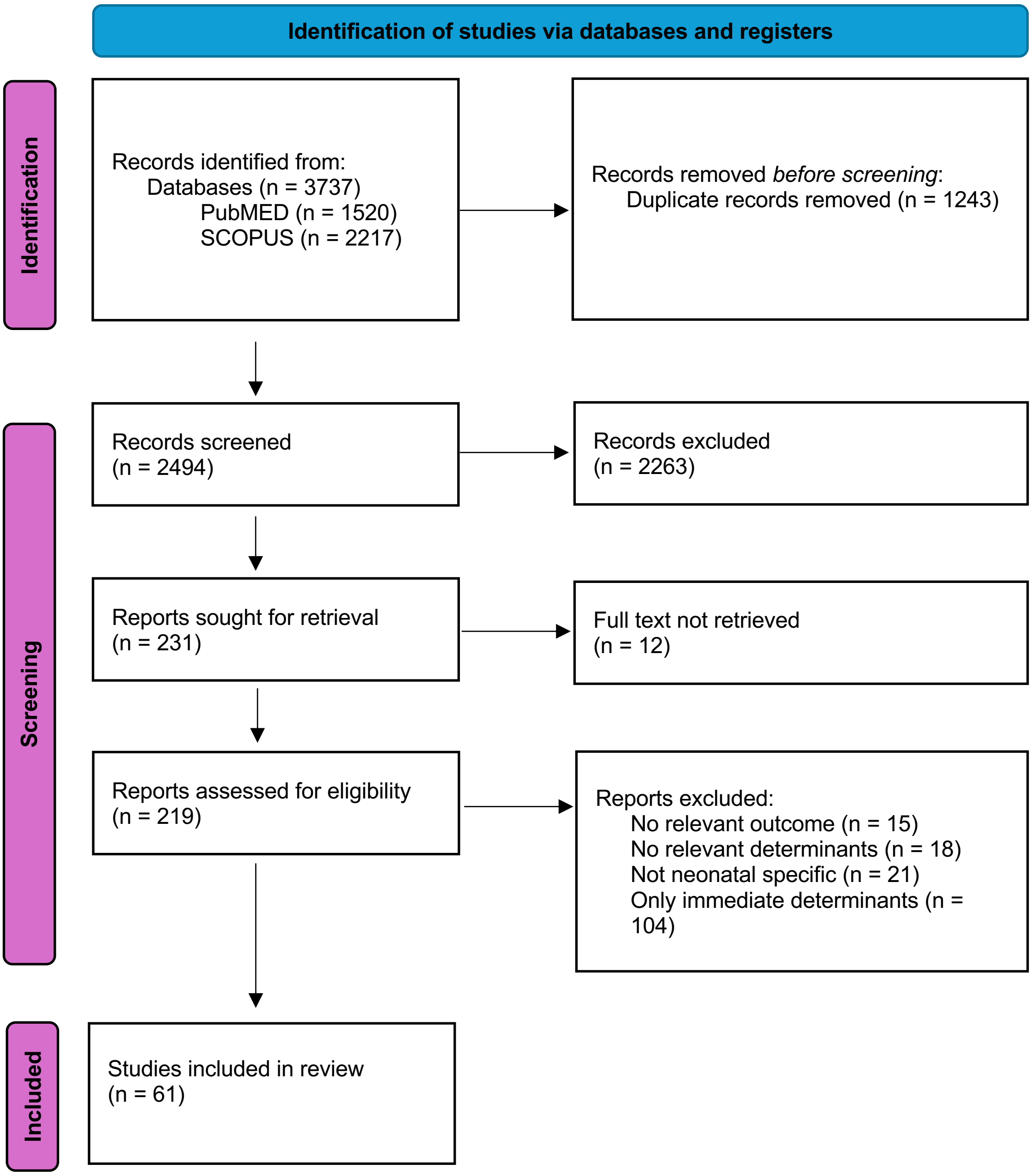
AND

(sepsis[Title/Abstract] OR septic[Title/Abstract] OR "blood poisoning"[Title/Abstract])

AND

("risk factor*"[Title/Abstract] OR determinant*[Title/Abstract] OR predictor*[Title/Abstract] OR "associated factor*"[Title/Abstract] OR barrier*[Title/Abstract] OR cause*[Title/Abstract])

***Appendix 2** PRISMA chart*



Note: The PRISMA chart is adapted from the PRISMA 2020 statement (136)

Appendix 3 *Original and Adapted Framework – Full List of Proxy Variables and Step-by-Step Variable Selection Process*

Mosley & Chen Framework	Original determinants	Adapated proximate determinants	Determinants identified through the scoping review	Proxy set of exposure variables		STEP 1		STEP 2	STEP 3	STEP 4
				Variable name	Source	Match		Missing data	Included in Imputation Model	Included / Excluded in final model
Maternal factors	Age, parity, birth interval	Maternal Factors	Maternal age			No match - Individual variable				
			Parity			No match - Individual variable				
			Maternal hypertension	Prevalence of maternal hypertensive disorders	GBD	Exact match		0.00%	Yes - Predictor Variable	Excluded - Multicollinearity
			Maternal Infections during pregnancy	Prevalence of maternal sepsis and other maternal infections	GBD	Close match		0.00%	Yes - Predictor Variable	Included
			Maternal History of HIV/STI	Prevalence of HIV in women aged 15-49	GBD	Close match - not mother specific		0.00%	Yes - Predictor Variable	Included
			Maternal History of UTI	Prevalence of Urinary Tract infections and interstitial nephritis among women of reproductive age (15-49)	GBD	Close match - not mother specific		0.00%	Yes - Predictor Variable	Excluded
			Maternal History of abortions, stillbirth, and early neonatal deaths	Abortion rate estimate	WHO	Exact match expect for early neonatal births		88.80%	No	
			Previous maternal hospitalisation			No match				
Environmental contamination	air; food/water/fingers; skin/soil/inanimate objects; insect vectors	Environmental Expsoure Risks	Use of oxygen / Mechanical ventilation			No match				
			Nasogastric tube insertion			No match				
			Endotracheal intubation			No match				
			Use of intravenous fluids / medication			No match				
			Use of parental nutrition			No match				
			Frequency of vaginal exams during birth			No match				
			Mode of delivery (C-Section, vaginal, instrumental / assisted)	Births by caesarean section (%)	WHO	Close match - only accounts for C-Sections		93.60%		
			Place of delivery	Proportion of births delivered in a health facility (%)	WHO	Exact match		82.90%	No	
			Maternal hand-washing	DALYs - No access to handwashing faciity	GBD	Close - Captures Household environment but does not measure maternal behaviour directly		0.00%	Yes - Predictor Variable	Included
			Source of water	Population using at least basic drinking-water services	WHO	Close match - Reflects environmental exposure risks		2.30%	Yes - Imputed Variable	Included
			Duration of stay in the facility			No match				
			Ward type / size			No match				
			Season of birth / Climate	Number of deaths due to Non-optimal temperature	GBD	Fair match - Environmental proxy, however not birth specific				
				Number of Deaths due to air pollution	GBD	Fair match - Environmental proxy, however not birth specific				
Nutrient deficiency	calories; protein, micronutrients (vitamins and minerals)	Nutrient Vulnerability (including both mother and neonate during pregnancy and lactation)	Maternal anaemia	Prevalence of anaemia in women aged 15-49, by pregnancy status (%)	WHO	Exact match (if filtered for pregnant women)		0.80%	Yes - Predictor Variable	Included
			Undernutrition	Prevalence of neonatal nutritional deficiencies (<28 days) Including prevalence of Iodine deficiency, Dietary iron deficency, Protein-energy malnutrition, and Vitamin A deficiency	GBD	Exact match		0.00%	Yes - Predictor Variable	Included
			Low birth weight	Low birthweight	GBD	Exact match		0.00%	Yes - Predictor Variable	Excluded - Multicollinearity
			Breastfeeding Practice	Deaths due to non-exclusive breastfeeding	GBD	Close match		0.00%	Yes - Predictor Variable	Excluded
				Exclusively breastfed for the first two days after birth (children born in the last 24 months)	WHO	Exact match		85.70%	No	
				Proportion of newborns put to the breast within one hour of birth	WHO	Exact match		83%	No	
Injury	accidental, intentional	Injury (Including birth and neonatal complications)	Birth asphyxia	Prevalence of encephalopathy due to birth asphyxia and trauma (<28 days)	GBD	Exact match		0.00%	Yes - Predictor Variable	Excluded
			Prematurity / Gestational age	Prevalence of neonatal preterm birth (<37 weeks of gestation)	GBD	Exact match		0.00%	Yes - Predictor Variable	Excluded
			APGAR score			No match - Individual variable				
			Neonatal resuscitation			No match - Individual variable				
			Respiratory distress syndrom			No match - Individual variable				
			Convulsions			No match - Individual variable				
			Meconium aspiration syndrom			No match - Individual variable				
			Jaundice	Prevalence of Hemolytic disease and other neonatal jaundice (<28 days)	GBD	Exact match		0.00%	Yes - Predictor Variable	Included
			Induced labour			No match - Individual variable				
			Duration of labour			No match - Individual variable				
			Not crying immediately after birth			No match - Individual variable				

			Foul-Smelling Liquor			No match - Individual variable				
			Fould-Smelling Vaginal Discharge			No match - Individual variable				
			Meconium-stained amniotic fluid			No match - Individual variable				
			PROM - Premature Rupture of Membrane			No match - Individual variable				
			Birth Trauma	Prevalence of maternal obstructed labour and uterine rupture	GBD	Close Match		0.00%	Yes - Predictor Variable	Included
Personal illness control	personal preventive measures; medical treatment	**Personal illness control (including care during and after pregnancy and childbirth)**	Number of ANC visits	Antenatal care coverage - at least four visits (%)	WHO	Exact match		77.80%	No	
			Late registration of pregnancy (after 8 weeks)	Law requriring birth registration	WHO	Fair match - Structural indicator, however does not capture actual timing of registration				
			Vaccination with Tetanus toxoid	Diphteria tetanus toxoid and pertussis (DTP3) immunization coverage among 1-year-olds	WHO / Unicef	Exact match		20.15%	Yes - Imputed Variable	Included
			Delay in seeking care / treatment	*See Health System Variables*						
			Delays in receiving care / referral							
			Lack of training of health workers (on resuscitation / infection prevention)			No match				
			Timing of birth during on-call hours			No match - Not available in national data				
			Type of birth attendant	Births attended by skilled health personnel (%)	WHO	Exact match		85.40%	No	
				Nursing and midwifery personnel (per 10 000 population)	WHO	Close match		13.95%	Yes - Imputed Variable	Included

Mosley & Chen Framework		Identified socioeconomic/distal determinants	
Socioeconomic determinants	**Individual-level Variables**	**Individual-level Variables**	Maternal education
			Employment Status
			Cultural and religious beliefs
			Relationship Status (Unmarried / Single Motherhood)
	Household Level Variables	**Household Level Variables**	Income / Wealth
			Household food insecurity
			Financial support (from father)
			Urban / Rural Residence
	Community-Level variables (not directly identfied through the literature review but adapted from the original conceptual framework and consided analytically relevant)	**Ecological Setting**	Climate
			Temperature
			Rainfall
			Seasonality
		Political Economy	Physical infrastructre
			Policy and Environment (not directly identified in literature review but important for health challenges)
		Health System	Institutionalised Health Measures
			Cost Subsidies / Service Financing (not directly identified in literature review but important for health challenges)
			Health System Structure / Health Capacity

***Appendix 4** Full List of Included/Excluded LMICs*

Economy	Income group	GBD name	Included in quantitative analysis ?
Afghanistan	Low income	Afghanistan	Yes
Albania	Upper middle income	Albania	Yes
Algeria	Upper middle income	Algeria	Yes
Angola	Lower middle income	Angola	Yes
Argentina	Upper middle income	Argentina	Yes
Armenia	Upper middle income	Armenia	Yes
Azerbaijan	Upper middle income	Azerbaijan	Yes
Bangladesh	Lower middle income	Bangladesh	Yes
Belarus	Upper middle income	Belarus	Yes
Belize	Upper middle income	Belize	Yes
Benin	Lower middle income	Benin	Yes
Bhutan	Lower middle income	Bhutan	Yes
Bolivia	Lower middle income	Bolivia (Plurinational State of)	Yes
Bosnia and Herzegovina	Upper middle income	Bosnia and Herzegovina	Yes
Botswana	Upper middle income	Botswana	Yes
Brazil	Upper middle income	Brazil	Yes
Burkina Faso	Low income	Burkina Faso	Yes
Burundi	Low income	Burundi	Yes
Cabo Verde	Lower middle income	Cabo Verde	Yes
Cambodia	Lower middle income	Cambodia	Yes
Cameroon	Lower middle income	Cameroon	Yes
Central African Republic	Low income	Central African Republic	Yes
Chad	Low income	Chad	Yes
China	Upper middle income	China	Yes
Colombia	Upper middle income	Colombia	Yes
Comoros	Lower middle income	Comoros	Yes
Congo, Dem. Rep.	Low income	Democratic Republic of the Congo	Yes
Congo, Rep.	Lower middle income	Congo	Yes
Costa Rica	Upper middle income	Costa Rica	Yes - but in the new income income classification for FY26 (effective July 1, 2025 – June 2026) Costa Rica has been newly classified as a high-income country
Côte d'Ivoire	Lower middle income	Côte d'Ivoire	No - missing data
Cuba	Upper middle income	Cuba	Yes
Djibouti	Lower middle income	Djibouti	Yes
Dominica	Upper middle income	Dominica	Yes
Dominican Republic	Upper middle income	Dominican Republic	Yes
Ecuador	Upper middle income	Ecuador	Yes
Egypt, Arab Rep.	Lower middle income	Egypt	Yes
El Salvador	Upper middle income	El Salvador	Yes
Equatorial Guinea	Upper middle income	Equatorial Guinea	Yes
Eritrea	Low income	Eritrea	Yes
Eswatini	Lower middle income	Eswatini	Yes
Ethiopia	Low income	Ethiopia	Yes - but in the new income income classification for FY26 (effective July 1, 2025 – June 2026) Ethiopia was unclassified
Fiji	Upper middle income	Fiji	Yes
Gabon	Upper middle income	Gabon	Yes
Gambia, The	Low income	Gambia	Yes
Georgia	Upper middle income	Georgia	Yes
Ghana	Lower middle income	Ghana	Yes
Grenada	Upper middle income	Grenada	Yes
Guatemala	Upper middle income	Guatemala	Yes
Guinea	Lower middle income	Guinea	Yes
Guinea-Bissau	Low income	Guinea-Bissau	Yes
Haiti	Lower middle income	Haiti	Yes
Honduras	Lower middle income	Honduras	Yes
India	Lower middle income	India	Yes
Indonesia	Upper middle income	Indonesia	Yes
Iran, Islamic Rep.	Upper middle income	Iran (Islamic Republic of)	Yes
Iraq	Upper middle income	Iraq	Yes
Jamaica	Upper middle income	Jamaica	Yes
Jordan	Lower middle income	Jordan	Yes
Kazakhstan	Upper middle income	Kazakhstan	Yes
Kenya	Lower middle income	Kenya	Yes
Kiribati	Lower middle income	Kiribati	Yes
Korea, Dem. People's Rep.	Low income	Democratic People's Republic of Korea	Yes
Kosovo	Upper middle income	Not listed	No - not included in the GBD / IHME data
Kyrgyz Republic	Lower middle income	Kyrgyzstan	Yes
Lao PDR	Lower middle income	Lao People's Democratic Republic	Yes
Lebanon	Lower middle income	Lebanon	Yes
Lesotho	Lower middle income	Lesotho	Yes
Liberia	Low income	Liberia	Yes
Libya	Upper middle income	Libya	Yes
Madagascar	Low income	Madagascar	Yes
Malawi	Low income	Malawi	Yes
Malaysia	Upper middle income	Malaysia	Yes
Maldives	Upper middle income	Maldives	Yes
Mali	Low income	Mali	Yes
Marshall Islands	Upper middle income	Marshall Islands	Yes
Mauritania	Lower middle income	Mauritania	Yes
Mauritius	Upper middle income	Mauritius	Yes

Mexico	Upper middle income	Mexico	Yes
Micronesia, Fed. Sts.	Lower middle income	Micronesia (Federated States of)	Yes
Moldova	Upper middle income	Republic of Moldova	Yes
Mongolia	Upper middle income	Mongolia	Yes
Montenegro	Upper middle income	Montenegro	Yes
Morocco	Lower middle income	Morocco	Yes
Mozambique	Low income	Mozambique	Yes
Myanmar	Lower middle income	Myanmar	Yes
Namibia	Upper middle income	Namibia	Yes
Nepal	Lower middle income	Nepal	Yes
Nicaragua	Lower middle income	Nicaragua	No - missing data
Niger	Low income	Niger	Yes
Nigeria	Lower middle income	Nigeria	Yes
North Macedonia	Upper middle income	North Macedonia	Yes
Pakistan	Lower middle income	Pakistan	Yes
Papua New Guinea	Lower middle income	Papua New Guinea	Yes
Paraguay	Upper middle income	Paraguay	Yes
Peru	Upper middle income	Peru	Yes
Philippines	Lower middle income	Philippines	Yes
Rwanda	Low income	Rwanda	Yes
Samoa	Lower middle income	Samoa	Yes
São Tomé and Príncipe	Lower middle income	Sao Tome and Principe	Yes
Senegal	Lower middle income	Senegal	Yes
Serbia	Upper middle income	Serbia	Yes
Sierra Leone	Low income	Sierra Leone	Yes
Solomon Islands	Lower middle income	Solomon Islands	Yes
Somalia	Low income	Somalia	Yes
South Africa	Upper middle income	South Africa	Yes
South Sudan	Low income	South Sudan	Yes
Sri Lanka	Lower middle income	Sri Lanka	Yes
St. Lucia	Upper middle income	Saint Lucia	Yes
St. Vincent and the Grenadines	Upper middle income	Saint Vincent and the Grenadines	Yes
Sudan	Low income	Sudan	Yes
Suriname	Upper middle income	Suriname	Yes
Syrian Arab Republic	Low income	Syrian Arab Republic	Yes
Tajikistan	Lower middle income	Tajikistan	Yes
Tanzania	Lower middle income	United Republic of Tanzania	Yes
Thailand	Upper middle income	Thailand	Yes
Timor-Leste	Lower middle income	Timor-Leste	Yes
Togo	Low income	Togo	Yes
Tonga	Upper middle income	Tonga	Yes
Tunisia	Lower middle income	Tunisia	Yes
Türkiye	Upper middle income	Türkiye	Yes
Turkmenistan	Upper middle income	Turkmenistan	Yes
Tuvalu	Upper middle income	Tuvalu	Yes
Uganda	Low income	Uganda	Yes
Ukraine	Upper middle income	Ukraine	Yes
Uzbekistan	Lower middle income	Uzbekistan	Yes
Vanuatu	Lower middle income	Vanuatu	Yes
Venezuela, RB		Venezuela (Bolivarian Republic of)	No - unclassified by the WB due to the unavailability of data
Vietnam	Lower middle income	Viet Nam	Yes
West Bank and Gaza	Lower middle income	Palestine	Yes
Yemen, Rep.	Low income	Yemen	Yes
Zambia	Lower middle income	Zambia	Yes
Zimbabwe	Lower middle income	Zimbabwe	Yes

Appendix 5 *List of Proximate Determinants Retained for the Final Quantitative Model*

Final list of Proximate Determinants

Category	Variable	Indicator Name	Source	Year(s)	Countries	Measure	Metric / Unit	Age	Sex	Missing Data	Description	URL
Maternal factors	Prevalence of maternal sepsis	Maternal sepsis and other maternal infections - Level 4 cause	GBD / IHME	2007-2021	130	Prevalence	Rate per 100 000 women of reproductive age	15-49	Female	No	Further information can be found in: Institute for Health Metrics and Evaluation (IHME). GBD 2021 Cause and Risk Summary: Maternal Sepsis and other maternal infections - Level 4 cause. Accessed (June 22, 2025). Seattle, USA: IHME, University of Washington, 2024.	https://www.healthdata.org/research-analysis/diseases-injuries-risks/factsheets/2021-maternal-sepsis-and-other-maternal
	Prevalence of HIV/STI	HIV/AIDS and sexually transmitted infections - Level 2 cause	GBD/IHME	2007-2021	130	Prevalence	Rate per 100 000 women of reproductive age	15-49	Female	No	Further information can be found in: Institute for Health Metrics and Evaluation (IHME). GBD 2021 Cause and Risk Summary: HIV/AIDS and sexually transmitted infections - Level 2 cause. Accessed (June 22, 2025). Seattle, USA: IHME, University of Washington, 2024.	https://www.healthdata.org/research-analysis/diseases-injuries-risks/factsheets/2021-hivaids-and-sexually-transmitted
Environmental Exposure Risks	Disease burden due to lack of handwashing access	No access to handwashing facility	GBD / IHME	2007-2021	130	DALYs	Rate per 100 000 women of reproductive age	15-49	Female	No	Defined as "lack of access to a handwashing facility, which includes soap (bar, liquid, or powder/detergent), water and wash station (either permant or mobile. Furhter information can be found in: Institute for Health Metrics and Evaluation (IHME). GBD 2021 Cause and Risk Summary: No access to handwashing facility - Level 3 risk. Accessed (June 22, 2025). Seattle, USA: IHME, University of Washington, 2024.	https://www.healthdata.org/research-analysis/diseases-injuries-risks/factsheets/2021-no-access-handwashing-facility-level-3
	Access to basic drinking water	Population using at least basic drinking-water services	WHO	2007-2021	130	Coverage	% of total population	n.a.	n.a	Yes	Basic drinking water services is defined as water from an "improved source, provided collection time is not more than 30 minutesfor a round trip". Further information can be found in: WHO. The Global Health Observatory. 2025. Indicator Metadata Registry List	https://www.who.int/data/gho/indicator-metadata-registry/imr-details/4818
Nutrient Vulnerability (mother and neonate)	Prevalence of maternal anaemia	Prevalence of anaemia in women aged 15-49, by pregnancy status (%)	WHO	2007-2021	129	Prevalence	% (of women of reproductive age)	15-49	female	Yes	Filtered by pregnancy status / includes only pregnant women (aged 15-49) Further information can be found in: WHO. The Global Health Observatory.2025. Indicator Metadata Registry List.Prevalence of anaemia in women aged 15-49, by pregnancy status (%)	https://www.who.int/data/gho/data/indicators/indicator-details/GHO/prevalence-of-anaemia-in-women-of-reproductive-age-(-)
	Prevalence of neonatal nutritional deficienices	(Neonatal) Nutritional deficiences - Level 2 cause	GBD /IHME	2007-2021	130	Prevalence	Rate per 100 000 women of reproductive age	<28 days	Both	No	Inclues protein-energy malnutrtion, iodine deficincy, vitamin A deficiency, iron deficiency, and other nutritional deficiences. Further information can be found in: Institute for Health Metrics and Evaluation (IHME). GBD 2021 Cause and Risk Summary: Nutritional deficiences - Level 2 cause. Accessed (June 22, 2025). Seattle, USA: IHME, University of Washington, 2024.	https://www.healthdata.org/research-analysis/diseases-injuries-risks/factsheets/2021-nutritional-deficiencies-level-2-disease
Intrapartum / Neonatal Complications	Prevalence of neonatal jaundice	Hemolytic disease and other neonatal jaundice - Level 4 cause	GBD / IHME	2007-2021	130	Prevalence	Rate per 100 000 population	<28 days	Both	No	Further information can be found in: Institute for Health Metrics and Evaluation (IHME). GBD 2021 Cause and Risk Summary: Hemolytic disease and other neonatal jaundice - Level 4 cause. Accessed (June 22, 2025). Seattle, USA: IHME, University of Washington, 2024.	https://www.healthdata.org/research-analysis/diseases-injuries-risks/factsheets/2021-hemolytic-disease-and-other-neonatal
	Prevalence of obstructed labor and uterine rupture (OL/UR)	Maternal obstructed labor and uterine rupture - Level 4 cause	GBD / IHME	2007-2021	130	Prevalence	Rate per 100 000 women of reproductive age	15-49	Female	No	Includes obstructed labour, uterine rupture, and fistula . Further information can be found in: Institute for Health Metrics and Evaluation (IHME). GBD 2021 Cause and Risk Summary: [CAUSE/RISK/IMPAIRMENT NAME]. Accessed (June 22, 2025). Seattle, USA: IHME, University of Washington, 2024.	https://www.healthdata.org/research-analysis/diseases-injuries-risks/factsheets/2021-maternal-obstructed-labor-and-uterine
Personal Illness Control	Density of nurses and midwives	Nursing & Midwifery Professionals	GBD / IHME	2007-2021	130	Health workforce desnsity	Workers (per 10 000 population)	n.a.	n.a.	Yes	Further information can be found in: Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019) Human Resources for Health 1990-2019. Seattle, United States of America: Institute for Health Metrics and Evaluation (IHME), 2022.	https://ghdx.healthdata.org/record/ihme-data/gbd-2019-human-resources-health-1990-2019
	DTP3 immunisation coverage	Diphteria tetanus toxoid and pertussis (DTP3) immunization coverage among 1-year-olds	WHO / UNICEF	2007-2021	130	Coverage	% (of 1-year-olds)	1-year-olds	both	Yes	The percentage of surviving infants who received the 3 doses of diphtheria and tetanus toxoid with pertussis containing vaccine (DTP3) in a given year Further information can be found in: Maternal, Newborn, Child and Adolescent Health and Ageing . 2025. Diptheria tetanus toxoid and pertussis (DTP3) immunization coverage among 1-year-olds (%)	https://platform.who.int/data/maternal-newborn-child-adolescent-ageing/indicator-explorer-new/MCA/diphtheria-tetanus-toxoid-and-pertussis-(dtp3)-immunization-coverage-among-1-year-olds-(-)

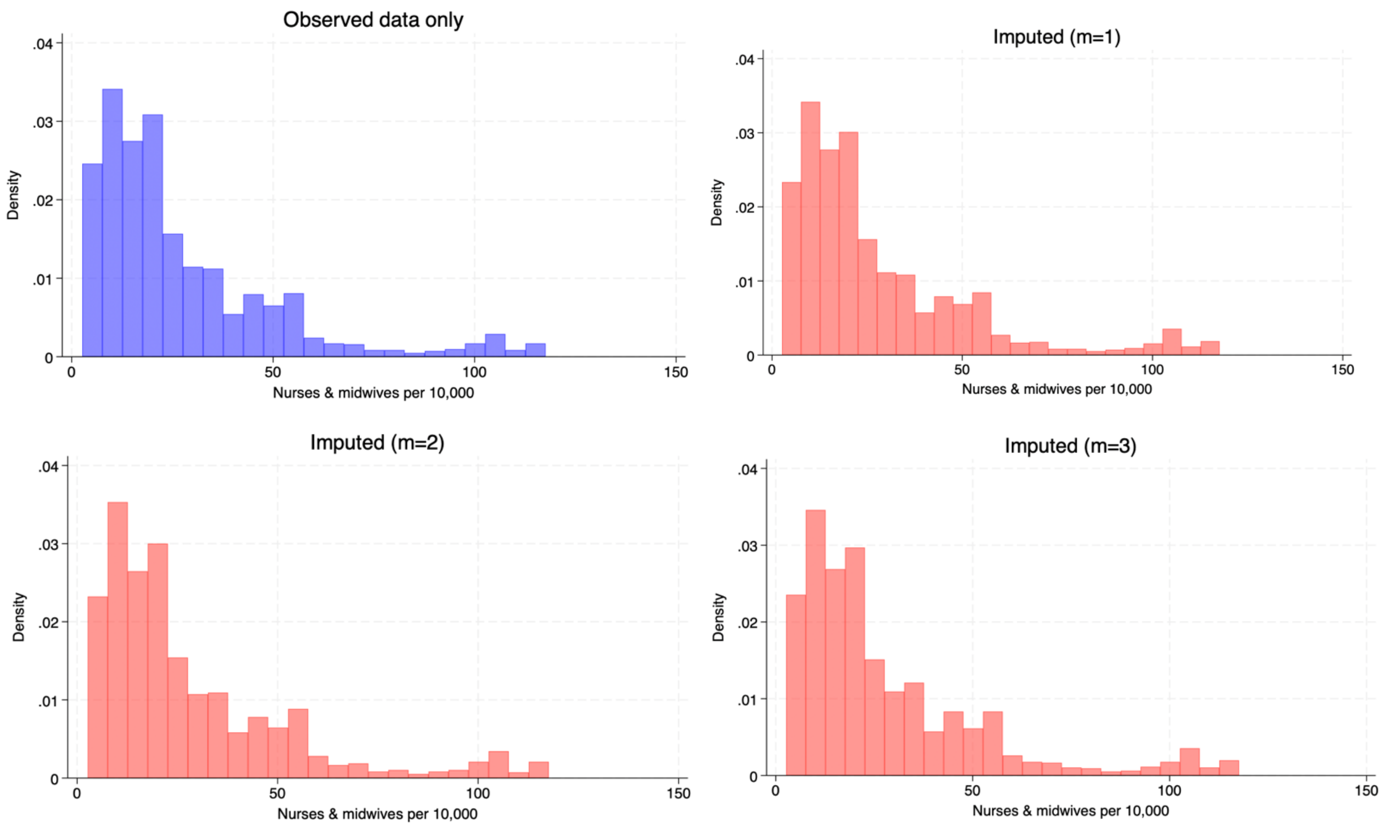
Appendix 6 *Plausibility of Imputation Model*

1. Comparison of Means and SD

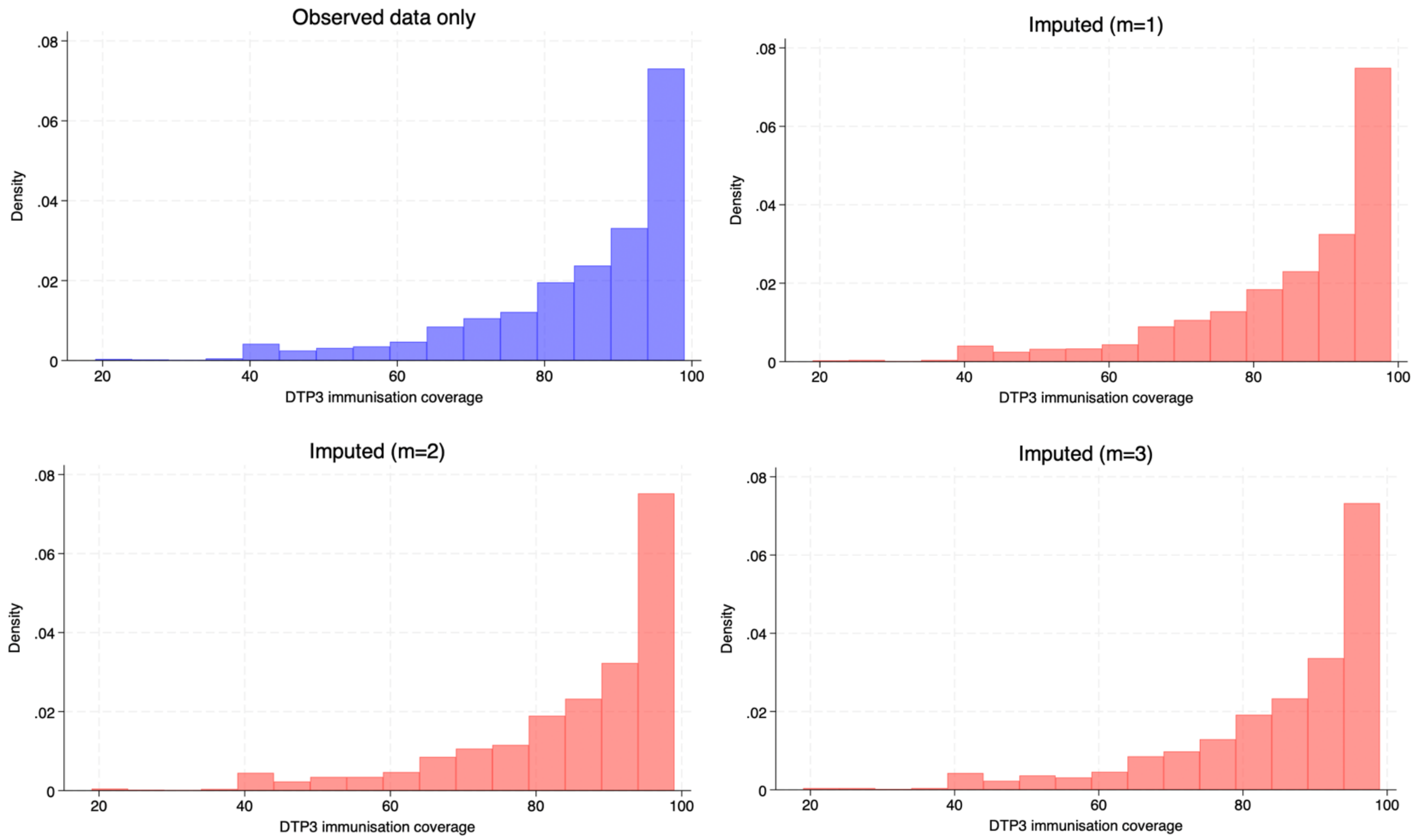
	Unimputed Complete Case dataset			Pooled Imputed Datasets		
Variable	**Obs (m=0)**	**Mean (m=0)**	**SD (m=0)**	**Obs (m>0)**	**Mean (m>0)**	**SD (m>0)**
Density of Nurses and Midwives	1254	27.50	23.54	405	26.25	22.17
DTP3 immunisation coverage	1254	85.21	14.66	279	82.23	14.73
Access to basic drinking water	1254	79.97	18.08	623	80.57	18.05

2. Histograms illustrating the distributional shape of observed and imputed data

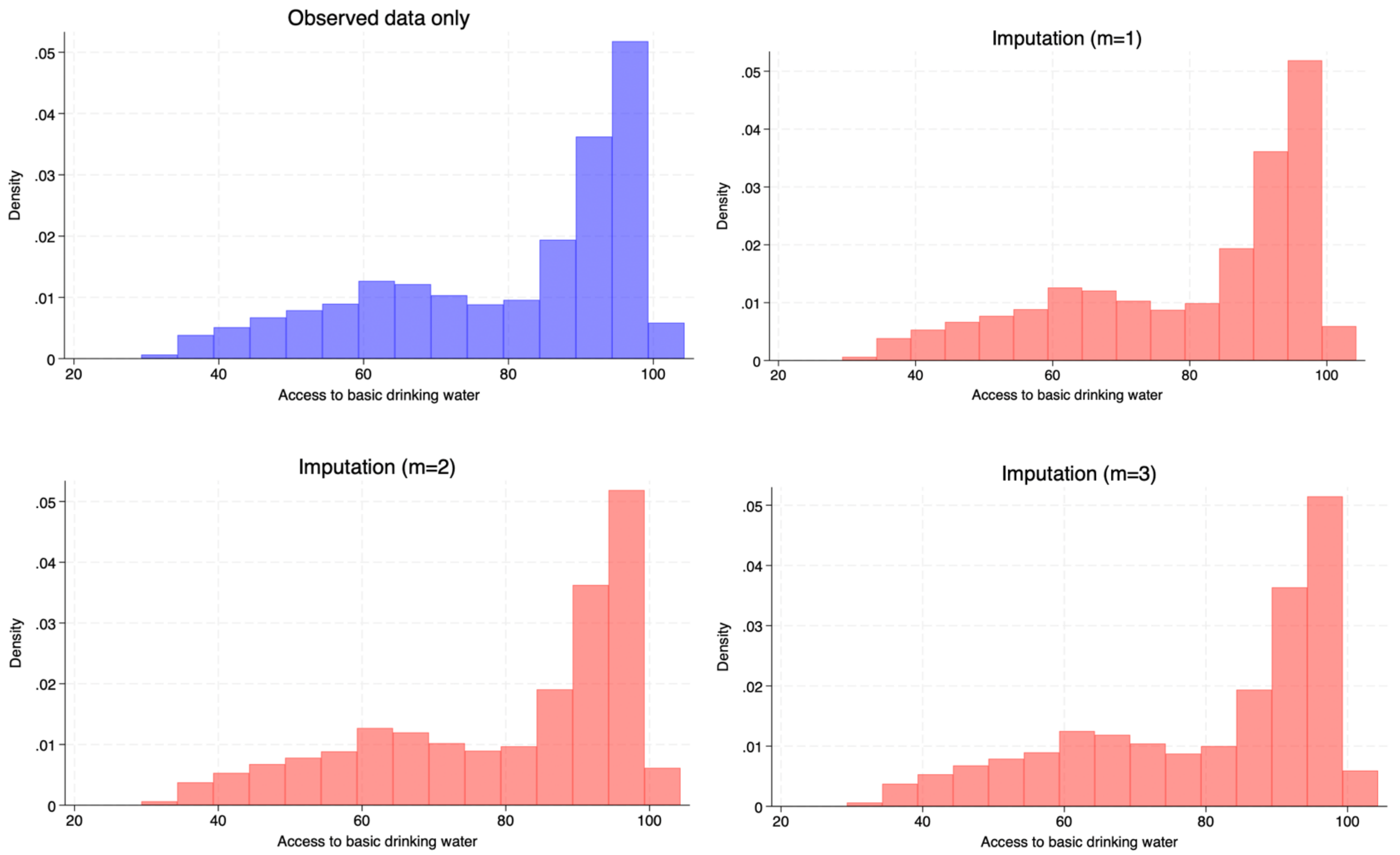
Nurses & Midwives per 10,000



DTP3 immunisation coverage



Access to basic drinking water



***Appendix** 7 Robustness Check: Fixed effects regression on the original / unimputed data*

Number of observations = 1,254

Number of groups = 128

Neonatal Sepsis Mortality	Coefficient	Std. Err.	t	P>|t|	95% CI Lower	95% CI Upper
Maternal Sepsis	0.3750	1.8678	0.20	0.841	-3.3211	4.0711
HIV/STI	-0.0201	0.0143	-1.41	0.161	-0.0483	0.0081
Neonatal Nutritional Deficiencies	-0.0039	0.0128	-0.31	0.759	-0.0292	0.0213
Maternal Anaemia	13.5406	14.0350	0.96	0.336	-14.2320	41.3133
Neonatal Jaundice	-0.2538	0.1211	-2.09	0.038	-0.4935	-0.0140
OL/UR	1.1437	0.5364	2.13	0.035	0.0823	2.2050
Lack of handwashing access	1.8862	0.9159	2.06	0.042	0.0738	3.6986
Access to basic drinking water	-13.8906	6.6620	-2.09	0.039	-27.0734	-0.7077
Nurses and Midwives	7.5601	4.3246	1.75	0.083	-0.9976	16.1178
DTP3 immunisation coverage	-1.1818	1.6242	-0.73	0.468	-4.3958	2.0322
year						
2009	-42.4330	20.6921	-2.05	0.042	-83.3790	-1.4871
2010	-77.0724	29.1050	-2.65	0.009	-134.6659	-19.4789
2012	-108.7642	41.5777	-2.62	0.010	-191.0390	-26.4893
2013	-141.8850	48.5160	-2.92	0.004	-237.8893	-45.8806
2015	-199.6149	62.8258	-3.18	0.002	-323.9358	-75.2940
2016	-232.6052	70.0664	-3.32	0.001	-371.2541	-93.9564
2017	-271.1862	75.5663	-3.59	0.000	-420.7184	-121.6541
2018	-303.5322	82.3169	-3.69	0.000	-466.4226	-140.6419
2019	-325.0041	89.0348	-3.65	0.000	-501.1879	-148.8203
_cons	3737.1550	1170.7550	3.19	0.002	1420.4420	6053.8680

***Note:** Dependent Variable: Neonatal Sepsis Mortality. Variables are reported as prevalence per 100,000 total population unless otherwise specified. Maternal anaemia, access to basic drinking water, and DTP3 immunisation coverage are expressed as percentages. Lack of handwashing access is expressed as DALYs per 100,000 total population. Density of nurses and midwives is expressed as workers per 10,000 population. Standard errors are clustered at the country level. Complete Cases only*

***Appendix 8** Robustness Check: Mixed effect model with random intercepts at the country level*

Neonatal Sepsis Mortality	Coefficient	Std. Err.	t	P>|t|	95% CI Lower	95% CI Upper
Maternal Sepsis	0.2375	1.7546	0.14	0.892	-3.2014	3.6765
HIV/STI	-0.0081	0.0123	-0.65	0.513	-0.0322	0.0161
Neonatal Nutritional Deficiencies	0.0038	0.0127	0.30	0.765	-0.0211	0.0287
Maternal Anaemia	21.1679	12.2469	1.73	0.084	-2.8356	45.1715
Neonatal Jaundice	-0.2864	0.1007	-2.84	0.004	-0.4838	-0.0890
OL/UR	1.4775	0.5002	2.95	0.003	0.4972	2.4579
Lack of handwashing access	2.2263	0.9686	2.30	0.022	0.3278	4.1248
Access to basic drinking water	-11.4703	5.9386	-1.93	0.053	-23.1099	0.1693
Nurses and Midwives	0.5441	1.1004	0.49	0.622	-1.6304	2.7186
DTP3 immunisation coverage	0.7552	1.0792	0.70	0.484	-1.3613	2.8716
year						
2008	-11.2678	10.0364	-1.12	0.262	-30.9389	8.4034
2009	-17.2539	18.5268	-0.93	0.352	-53.5658	19.0580
2010	-40.6315	26.6509	-1.52	0.127	-92.8664	11.6034
2011	-44.8217	32.5503	-1.38	0.169	-108.6191	18.9757
2012	-57.1103	38.2613	-1.49	0.136	-132.1011	17.8806
2013	-80.1563	44.3680	-1.81	0.071	-167.1162	6.8035
2014	-96.8086	50.6459	-1.91	0.056	-196.0729	2.4556
2015	-121.3458	56.7829	-2.14	0.033	-232.6386	-10.0531
2016	-149.5610	62.6276	-2.39	0.017	-272.3091	-26.8130
2017	-173.0466	67.6453	-2.56	0.011	-305.6293	-40.4638
2018	-201.6575	73.7002	-2.74	0.006	-346.1076	-57.2074
2019	-216.8281	79.5758	-2.72	0.006	-372.7941	-60.8620
2020	-259.2432	84.8470	-3.06	0.002	-425.5411	-92.9452
2021	-293.8268	89.4553	-3.28	0.001	-469.1567	-118.4970

***Note:** Dependent Variable: Neonatal Sepsis Mortality. Variables are reported as prevalence per 100,000 total population unless otherwise specified. Maternal anaemia, access to basic drinking water, and DTP3 immunisation coverage are expressed as percentages. Lack of handwashing access is expressed as DALYs per 100,000 total population. Density of nurses and midwives is expressed as workers per 10,000 population. Fixed year effects. Random intercepts for each country. Standard errors are clustered at the country level.*

Appendix 9 *Robustness Check: Full Variable FE regression model*

Neonatal Sepsis Mortality	Coefficient	Std. Err.	t	P>|t|	95% CI Lower	95% CI Upper
Maternal Sepsis	0.1570	1.7945	0.09	0.930	-3.3947	3.7086
HIV/STI	-0.0217	0.0168	-1.29	0.198	-0.0550	0.0115
UTI	-0.8499	2.1095	-0.40	0.688	-5.0248	3.3250
Neonatal Nutritional Deficiencies	0.0005	0.0136	0.04	0.969	-0.0263	0.0274
Maternal Anaemia	8.4608	14.7481	0.57	0.567	-20.7274	37.6491
Non-exclusive breastfeeding	0.0032	0.0023	1.38	0.169	-0.0014	0.0077
Preterm Birth	0.2170	0.4219	0.51	0.608	-0.6180	1.0521
Neonatal Jaundice	-0.3267	0.1208	-2.70	0.008	-0.5658	-0.0875
Birth asphyxia	0.3246	0.6314	0.51	0.608	-0.9250	1.5743
OL/UR	1.2912	0.4591	2.81	0.006	0.3825	2.1998
Lack of handwashing access	1.8589	1.0595	1.75	0.082	-0.2379	3.9557
Access to basic drinking water	-9.9371	5.7673	-1.72	0.087	-21.3526	1.4784
Density of Nurses and Midwives	0.8182	1.1011	0.74	0.461	-1.3916	3.0281
DTP3 immunisation coverage	0.8963	1.0803	0.83	0.409	-1.2459	3.0385
year						
2008	-16.5186	12.1814	-1.36	0.178	-40.6292	7.5920
2009	-26.5370	23.0206	-1.15	0.251	-72.0993	19.0253
2010	-52.7092	32.6412	-1.61	0.109	-117.3126	11.8942
2011	-60.0471	39.5756	-1.52	0.132	-138.3749	18.2807
2012	-73.1125	46.1496	-1.58	0.116	-164.4523	18.2274
2013	-97.3744	53.1449	-1.83	0.069	-202.5596	7.8108
2014	-113.4015	60.4791	-1.88	0.063	-233.1024	6.2995
2015	-137.3593	66.9091	-2.05	0.042	-269.7867	-4.9320
2016	-163.5045	72.9788	-2.24	0.027	-307.9457	-19.0633
2017	-183.7285	78.2689	-2.35	0.020	-338.6405	-28.8165
2018	-209.0072	84.7822	-2.47	0.015	-376.8104	-41.2039
2019	-221.6899	91.1754	-2.43	0.016	-402.1475	-41.2323
2020	-259.2339	98.1376	-2.64	0.009	-453.4748	-64.9931
2021	-290.9515	103.7416	-2.80	0.006	-496.2843	-85.6188

Note: *Dependent Variable: Neonatal Sepsis Mortality. Variables are reported as prevalence per 100,000 total population unless otherwise specified. Maternal anaemia, access to basic drinking water, and DTP3 immunisation coverage are expressed as percentages. Lack of handwashing access is expressed as DALYs per 100,000 total population. Density of nurses and midwives is expressed as workers per 10,000 population. Standard errors are clustered at the country level.*