Research project proposal:
"Intrapartum-related Neonatal Encephalopathy in Africa: Defining burden, risk and outcomes"

Background

Newborn brain injury, secondary to intrapartum complications, otherwise known as 'Intrapartum-related Neonatal Encephalopathy' (IP-NE), is the third leading cause of under-5 child mortality worldwide, and substantially contributes to long-term disability (neurodevelopmental impairment; NDI) and intrapartum stillbirths.[1] Neonatal Encephalopathy (NE) is a clinical syndrome defined as a "disturbance of neurological function in the earliest days of life in the term infant, manifested by difficulty initiating and maintaining respiration, depression of tone or reflexes, abnormal level of consciousness, and often by seizures". NE increases the risk of adverse outcomes of death, or long-term NDI; this encompasses motor impairment, cognitive impairment, visual loss, hearing loss, and epilepsy, and is diagnosed on clinical assessment at 18 months to 2 years of age. The most common cause of NE is hypoxia-ischaemia due to intrapartum-related events, hence the term 'Intrapartum-related NE' (IP-NE) being increasingly used, although there are many variations on terminology used globally.[2] Likely, NE is a multifactorial disease with a complex causal pathway; there is increasing evidence for the sensitising/ contributory role of perinatal infection to IP-NE.

The only global estimates were published in 2013, based on data from over a decade ago; the incidence of IP-NE in high-income settings was estimated to be 1.6/1000 live births compared to 12.1/1000 in low-income settings, and approximately 717,000 deaths and 233,000 cases of moderate-severe NDI occur each year; over 95% of this burden in low- and middle- income countries (LMICs).[2] These estimates were limited not only by lack of data from the highest-burden settings ("inverse data law"), but specifically by lack of application of case definitions for IP-NE. A lack of consensus on definitions affects reliable estimates, and also limits NE research by affecting comparison of observational and interventional research study outcomes. Through updating these estimates, based on improved data collection systems over the last decade, and developing globally acceptable definitions of NE, resources and efforts can be more effectively mobilised and targeted, and progress accelerated towards reducing the huge burden of NE worldwide. This is key to achieving the Sustainable Development Goals (SDGs) for child mortality, and the 'United Nations Global Strategy for Women's, Children's and Adolescents' Health (2016-2030)' which advocates that children should not only "survive" but "thrive".

There are a variety of neonatal scores to identify those who have NE and are at highest risk of death or NDI, based on clinical examination of the neonate; these include the widely used Sarnat and Sarnat staging which classifies NE into mild, moderate or severe categories.[3] The Sarnat score was developed in the 1970s and validated in a high-income setting, and requires clinical training and equipment to be effectively administered; thus its relevance and feasibility in low-resource settings is limited. A simplified and effective risk score to identify those with NE at highest risk of adverse outcomes that is applicable and feasible in LMICs, is urgently needed. This would enable targeting of timely interventions which can improve outcomes, and identify those to target for follow-up which is particularly important for low-resource settings with limited follow-up services; it could also be used in the recruitment of participants for future NE trials aiming to further our understanding of the aetiology of NE, and develop novel interventions.

This PhD project aims to estimate the regional and global burden of IP-NE, achieve global consensus on standardised definitions, and develop and validate a simplified risk score

feasible for use in LMICs, to effectively identify those with NE at greatest risk of an adverse outcome.

Objectives

1. Conduct regional and global level estimates for incidence of intrapartum-related NE, deaths and long-term NDI, and contribution of perinatal infection to adverse outcomes through systematic review and meta-analysis.
2. Develop globally acceptable definitions for NE with local and regional stakeholders.
3. Develop a risk score practicable for use in LMICs to identify neonates with NE at highest risk, using existing data from NE cohorts in sub-Saharan Africa.
4. Validate the newly developed NE risk score in a sub-Saharan African population of neonates.

Methodology

1) Regional and global estimates for NE

Guided by the methodology used in the last global estimates by Lee et al (2013) 2, I will conduct a systematic literature search for data on incidence of NE and NDI using the following databases: MEDLINE, Embase, Popline, Cochrane, Web of Science, LILACS (Latin American and Caribbean Health Sciences Literature), African Index Medicus and Eastern Mediterranean Region Index Medicus. The date of the median birth year of the cohort will be restricted to 1980 and onwards, with no language restrictions. Search terms will comprise variants of terms related to “neonatal encephalopathy”, using MeSH terms where possible. I will undertake ‘snowball searching’, reviewing reference lists in key papers and abstracts from paediatric conferences. I will make efforts to contact investigators for unpublished data, particularly from LMICs.

Myself and a second reviewer will review titles and abstracts; those reporting data on NE incidence, prevalence, staging, case fatality, or NE-related NDI will be included. If studies report only numbers of NE cases, I will attempt to contact the principal investigator for data on the size of the original birth cohort. Studies will be excluded if there was clear selection bias (intervention studies will be excluded for incidence and case fatality), if the same data is reported in another included study, or if the NE case definition was not clear, did not specify term infants, or comprised only the Apgar score. I will extract data using a standard form which will be rechecked by a second investigator. Study characteristics will be collected including study identifiers, context, design, and limitations. NE data will be summarised including: case definition, evidence of intrapartum-related events, exclusion criteria, incidence (numerator of NE cases, denominator of total live births in the same period), proportion of NE cases classified into mild/moderate/severe stages, neonatal case fatality (overall and by stage), and NDI (overall and by stage). Data on perinatal infection will be collected where available; defined as a positive neonatal blood or cerebrospinal fluid culture, or chorioamnionitis/ funisitis on placental histology.

All statistical analyses will be performed using Stata (College Station, TX: StataCorp LLC). I will complete relevant courses at LSHTM including Statistical Methods in Epidemiology (SME) and Advanced Statistical Methods in Epidemiology (ASME), and will conduct this work with the support of a senior statistician. For estimation of NE incidence, regression modelling will be applied. Considerations for hierarchies in the data will be explored by fitting random effect models as appropriate. Variables that could plausibly predict the risk of NE will be evaluated, including demographic factors, health care access (e.g. skilled birth attendance); and

socioeconomic factors (e.g. female literacy). For estimation of NE-related NDI, a compartmental model will estimate NE survivors depending on access to care, and the proportion of survivors with NDI. A meta-analysis with random effects will be used to estimate NE risk (pooled proportions) according to sex, neonatal case fatality rate, NDI risk, and association with infection. In addition, I will explore models to estimate disability adjusted life years (DALYs), years of life with disability (YLDs), and years of life lost (YLLs) attributed to IP-NE.

2) Consensus on definitions

To pursue a consensus on globally acceptable definitions for NE, I will utilise the Delphi method, the gold standard for consensus statements, after attending a relevant training course. I will design an online survey based on a list of variables that could potentially be included in definitions of NE and potential challenges around diagnosis particularly in low-resource settings, as identified through systematic review of the literature. I will disseminate this to relevant stakeholders including healthcare professionals of diverse cadres in newborn care across all settings particularly in LMICs. I will utilise the Child Healthcare Information For All (CHIFA), a moderated global discussion forum utilising the Dgroups platform with >3500 members in over 140 countries with which I am a steering group member, as well as senior researchers at international institutions including WHO and UNICEF. Findings from the first 'round' will be shared anonymously with all participants in a summary report; questions for the second 'round' of the survey will be informed by feedback from the first round, after which a summary report on the findings will be shared. Repeated 'rounds' will be continued until consensus is achieved.

3) Development of NE risk score

For the development of the risk score, I will perform retrospective secondary analysis on de-identified and anonymised data from existing observational NE study datasets; the ABAaNA study4 (Uganda, 2010-2014, n= 210) and the Baby BRAiN study (Uganda, 2019-2022, n=51). To develop the model, I will adapt the approach used by Medvedev and colleagues, on the development and validation of a simplified mortality risk score for neonates weighing ≤2kg.5 I will generate a list of potential variables associated with both NE and adverse outcomes (death/ NDI); from current published literature on risk factors these may include pregnancy-induced hypertension, non-cephalic presentation, chorioamnionitis/funisitis, early neonatal sepsis, seizures, and hypoglycaemia.4 These will be included in a complete multivariable model, which will be progressively simplified using reverse stepwise selection, with the least statistically significant variable being removed at each step. Discrimination will be assessed using the c-index, equivalent to the area under the receiver operating characteristic (ROC) curve; a value of 0.5 will indicate no predictive ability, 0.8 will indicate good ability, and 1.0 will indicate perfect ability. Overall goodness-of-fit will be assessed using the Brier score, and calibration assessed by plotting observed versus predicted risk. The logistic regression model will be executed across the imputed datasets, and the β coefficients and c-index will be compared with original estimates. To develop the score, I will assign points to the variables in the final model proportional to their β regression coefficient values. To assess calibration of the score to the model using regression coefficients, observed risks in groups and population deciles of scores will be derived and compared with mean predicted risks in each group/ population decile. I will assess overall predictive ability of the score using the c-index.

4) Validation of NE risk score

To evaluate external validity, the model will be applied to data from ongoing large NE cohorts. Existing cohorts that could be utilised include NEST 360 (Newborn Essential Solutions and Technologies), a multi-country study across facilities in sub-Saharan Africa (2019-2024), the NESHIE (Neonatal Encephalopathy Suspected Hypoxic Ischaemic Encephalopathy) cohort in

South Africa (2020-2025, n=5000), and NNRD (UK, 2008-current, 187 neonatal units). Other historical and future databases may be identified during my initial systematic review for the global estimates (objective 1). As recruitment to these cohorts is ongoing, I will contact the study investigators in a timely manner to ensure that data on the variables included in the risk score are being collected, and if not, request that they be added to the Case Report Forms. Collaborative meetings will be held 6-monthly for data quality management and progress reporting. Discrimination will be evaluated using the c-index, and goodness-of-fit evaluated using the Brier score. Calibration will be assessed by plotting observed versus predicted risk, and overall predictive ability of the risk score will be assessed using the c-index.

Project timeline

	YEAR 1				YEAR 2				YEAR 3				YEAR 4			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
PhD Progression																
Upgrading																
Write-up of thesis																
Submit thesis, dissemination and engagement																
Research Training																
Statistics & Epidemiology (SME, AME, systematic review)																
Transferable skills																
3 month placement outside project																
Objective 1: Global and regional estimates																
Ethics approval, protocol development																
Systematic review and meta-analysis																
Manuscript preparation, submit for publication																
Objective 2: Consensus on definitions																
Ethics approval, protocol development																
Dissemination of survey, discussions with stakeholders																
Objective 3: Development of NE risk score																
Secondary analysis of existing data (ABAaNA, BRAiNS)																
Manuscript preparation, submit for publication																
Objective 4: Validation of NE risk score																
Ethics approval, protocol development																
Data collection (NEST360, NESHIE, NNRD databases)																
Data cleaning																
Data analysis																
Manuscript preparation, submit for publication																

Personal experience

Over the last seven years I have developed a passionate interest and specific experience in neonatal diseases (particularly NE) and childhood outcomes, particularly in LMICs. In

pursuing every opportunity to develop my experience and skills in this field alongside {applicant-specific training deleted], I have been involved in a wide range of research and programmes spanning epidemiology, observational studies, trial experience and public engagement. As a [deleted] at [deleted] over several years, I have been privileged to work with and learn from international experts in the field including statisticians, public health/ child health researchers, social scientists, and policymakers. I have specific experience in [applicant-specific experience set out in detail here, to validate skills claims, deleted], and am currently conducting [applicant-specific work, related to skills for this project, deleted]. I have had a substantial role in several Ugandan studies from the initial protocol development through to implementation, data analysis and evaluation. I also co-led a collaboration with [deleted] in [deleted], facilitating dialogue amongst the global child health community around implementation and measurement challenges, and aiming to achieve consensus on definitions for different levels of newborn care. My experiences working in sub-Saharan Africa have strengthened my understanding of the challenges of both clinical work and research in low-resource settings, enhancing my resilience, flexibility and problem-solving abilities. Through this programme, I will develop key research and personal skills that will crucially inform my future career as [deleted]. My experiences and established collaborations with senior researchers at [deleted] and in [deleted], my love of learning and passion for this field, will enable me to deliver this PhD successfully. I would be thrilled to lead this project which aligns perfectly with my current and future research interests, and has immense potential to inform research, policy, and clinical practice, improving outcomes for a leading cause of child death and disability globally.

References

1) UN-IGME. Levels and trends in child mortality report 2020. *United Nations*: New York 2020.
2) Lee AC, Kozuki N, Blencowe H.... Lawn JE. Intrapartum-related neonatal encephalopathy incidence and impairment at regional and global levels for 2010 with trends from 1990. Pediatr Res. 2013 Dec;74 Suppl 1(Suppl 1):50-72.
3) Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. Arc Neurol 1976; 33: 698-705. 23.
4) Tann CJ, Webb EL, Lassman R… Cowan FM. Early Childhood Outcomes After Neonatal Encephalopathy in Uganda: A Cohort Study. EClinicalMedicine. 2018 Dec;6:26-35.
5) Medvedev MM, Brotherton H, Gai A, Tann C, Gale C, Waiswa P, Elbourne D, Lawn JE, Allen E. Development and validation of a simplified score to predict neonatal mortality risk among neonates weighing 2000 g or less (NMR-2000): an analysis using data from the UK and The Gambia. Lancet Child Adolesc Health. 2020 Apr;4(4):299-311.

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