# EXECUTIVE SUMMARY

## BIRTH ASPHYXIA BURDEN ASSESSMENT & LANDSCAPING

**UNIVERSITY OF WASHINGTON STRATEGIC ANALYSIS, RESEARCH & TRAINING (START) CENTER**

REPORT TO THE BILL & MELINDA GATES FOUNDATION

**PRODUCED BY: GRAYSON S, SECOR A, HERGOTT D, & LINGAPPA J**

**MAY 2019**

START CENTER
STRATEGIC ANALYSIS, RESEARCH & TRAINING CENTER
Department of Global Health | University of Washington

# Contents

# Introduction

## Report Summary

This report summarizes work conducted by the University of Washington's Global Health Strategic Analysis and Research Training Program (START) team in response to the Bill and Melinda Gates Foundation's (BMGF) work order "Birth Asphyxia Burden Assessment and Landscaping." The intent of this report is to contextualize the data assembled in the final workbook deliverable by detailing the research methodologies and resources consulted to fulfill this research request. The final deliverables are designed to serve as informational resources to support the strategic planning and future investments relevant to the current Birth Asphyxia workstream pursed by BMGF.

## Work Order Objectives

Our team was asked to perform a literature review to support ongoing work at BMGF to conduct a comprehensive landscape of neonatal hypoxic ischemic encephalopathy (HIE) and develop HIE burden models that forecast trends in target geographies in 2019-2040. The original research request outlined two prioritized research aims:

- **Aim 1: Intervention Effect Size**
  To determine the effect size (efficacy and effectiveness; mortality & morbidity) of implementation of known interventions/programs including labor & delivery management, basic and advanced neonatal resuscitation, and therapeutic hypothermia. (*"Drug-based interventions" was added to this list on 4/3/19).*

- **Aim 2: Burden Estimate Studies**
  To determine the incidence of mild, moderate, and severe neonatal HIE by level of care facility and by geography (HIC vs. LMIC). *(Aim 2 was updated and replaced on May 15, 2019- See Updated Project Scope).*

The work order specified that the final deliverable should consist of a populated Excel spreadsheet that included all the resources consulted, as well as copies of the papers reviewed uploaded to Dropbox. Due to the ambitious project timeline, we were asked to initiate our search by reviewing 40 papers shared via Dropbox and then supplement our research with additional targeted searches.

## Subject Matter Expert

Our Program Officer (PO), Dr. Farhad Imam, connected us with Dr. Dmitry Dukhovny, a neonatologist at Oregon Health Sciences University (OHSU), to serve as a subject matter expert throughout the project. We consulted with him by phone on two occasions (on April 15 and May 13, 2019), to address technical questions related to the project scope, clinical definitions, and our research methodology. He contributed valuable feedback on our work-in-progress deliverable formats and recommended several resources to help streamline our research approach.

## Updated Project Scope

On May 15, 2019, our team was asked to complete project Aim 1 and replace project Aim 2 with a new workstream to assess a list of 13 drug interventions prioritized by BMGF. Specifically, we were asked to undertake a focused review of the 13 candidate drug interventions to better understand if

the drugs had been or are currently being tested in children, neonates, and/or pregnant women, with a particular interest in toxicology, PK/PD, and safety information. Thus, the final workbook and this report reflect information relevant to the following aims:

- **Aim 1: Intervention Effect Size**
  To determine the effect size (efficacy and effectiveness; mortality & morbidity) of implementation of known interventions/programs including labor & delivery management, basic and advanced neonatal resuscitation, therapeutic hypothermia, and drug-based interventions.

- **Aim 2: Candidate Drug Studies** *(Updated on May,15)*
  To undertake a focused review of 13 candidate drug interventions identified by BMGF to better understand if the drugs had been or are currently being tested in children, neonates, and/or pregnant women, with a particular interest in toxicology, PK/PD, and safety information.

## Birth Asphyxia Workbook Format

The first two worksheets in the final Birth Asphyxia Workbook ***[1. Intervention Effect Size]*** and ***[2. Candidate Drug Trials***] correspond to these aims listed above. We performed a cursory literature review of burden estimate studies prior to being informed that this original Aim 2 would be replaced. For completeness, we have included our findings from this cursory literature review of HIE burden in the third worksheet ***[3. Burden Estimate Studies],*** but these should not be interpreted to reflect the output from a comprehensive search strategy. The fourth worksheet ***[4. Candidate Drug Database]*** is a line listing of all identified clinical trials in the National Institutes of Health (NIH) clinical trials database (clinicaltrials.gov) of the BMGF-identified list of 13 candidate drugs in the target populations. Our team has also bolded the studies in the Birth Asphyxia Workbook that we have deemed to be of highest impact and quality.

# Methodology

## Aim 1: Intervention Effect Size

We reviewed studies of clinical interventions given to encephalopathic term infants with evidence of perinatal hypoxic insult. Due to inconsistent and changing definitions for newborns with perinatal hypoxic insult, the following case terms were used in our search strings to ensure we identified the maximum number of relevant studies: *asphyxia neonatorum, birth asphyxia, neonatal encephalopathy, hypoxic ischaemic encephalopathy, hypoxic ischemic encephalopathy, and intrapartum mortality.* The primary search was restricted to articles published in the year 2000 or later, although results from some earlier studies were included as part of systematic reviews (e.g. Jacobs 2003).

We conducted an initial review in PubMed for studies meeting the above criteria and added findings to initial materials provided by BMGF. We then carried out an additional, more targeted PubMed search based on a list of high-priority drug-based interventions obtained from the BMGF team, our review of the literature, and review of the NIH clinical trials database (clinicaltrials.gov). START team members conducted title/abstract and then full-text review of identified articles. Due to the limited number of studies published in this area, particularly for some interventions, highly relevant articles

were reviewed for relevant references (snowball sampling), which were then put through the review process.

# Aim 2: Drug Intervention Studies

We undertook a focused review of 13 candidate drug interventions identified by BMGF to better understand if the drugs had been or currently are being tested in children, neonates, and/or pregnant women. We searched the NIH clinical trials database (clinicaltrials.gov) and PubMed. The specific strategies for each data source are described below:

**Clinicaltrials.gov:** We searched the clinical trial repository for each drug, restricting to study populations that included children only, and then adding "pregnancy" into the search terms to target studies that may have been performed among pregnant women. We reviewed the study overview of the results to determine the age ranges of children included in each study. Studies with drugs tested in neonates were prioritized and results from these studies were added to the ***[2. Candidate Drug Trials]*** worksheet in the Birth Asphyxia Workbook. For drugs that had not been tested in neonates, we noted the lowest age in which the drug had been tested and further reviewed those studies. If results were available in clinicaltrials.gov, that information was extracted and also included in the ***[2. Candidate Drug Trials]*** worksheet in the Birth Asphyxia Workbook. If results were not published, we searched for the clinical trial number in PubMed to look for possible published results. All trials registered in clinicaltrials.gov for the given drugs that were returned from our search, along with basic information such as study population, drug regimen tested, area of study, time period of study, and status of study are included in the ***[4. Candidate Drug Database]*** worksheet of the Birth Asphyxia Workbook.

**PubMed Clinical Trials:** We conducted a restricted search in PubMed for clinical trials conducted in children, infants, or pregnant women for each candidate drug**.** As an additional search, we looked for any clinical trial that had been published in PubMed on each of the 13 candidate drug interventions. We restricted our search to studies in children under five years old. For drugs that had been studied in this population, we reviewed relevant publications and included them in the ***[2. Candidate Drug Studies]*** worksheet in the Birth Asphyxia Workbook. For drugs that had not been studied in this age group, we reviewed any study that had been done in children. We reviewed inclusion and exclusion criteria of drug studies carried out in adult populations to look for any studies that had been carried out in pregnant women. If any were found, we also included them in the worksheet.

# Results

## Aim 1 Results: Intervention Effect Size

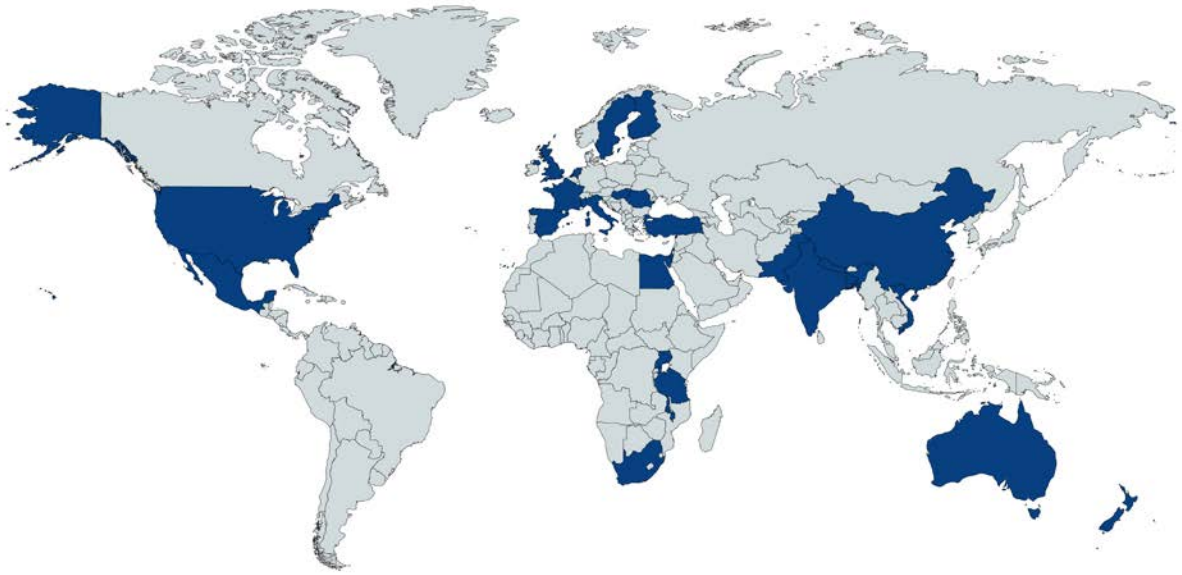
In total, 525 studies were reviewed and 34 were included in the final ***[1. Intervention Effect Size]*** worksheet. An additional 11 relevant review articles were also identified and included in the START_Birth Asphyxia_Literature Dropbox folder. We classified the reviewed effect size studies based on intervention type, geography (High-Income Countries (HIC) or Low and Middle-Income Countries (LMIC)), facility type, HIE severity, and study type shown in ***Table 1.*** The majority of studies included in the workbook measure the effect size of therapeutic hypothermia (47%) or drug-based interventions (29.4%) and were based in tertiary care centers (88.2%). We included a nearly equal number of LMIC-based and HIC-based studies (47% and 44.1%, respectively), with the remaining ~8.8% of studies based in both LMIC and HICs. The specific geographies are listed in the workbook and represented in ***Figure 1***.

***Table 1****. Intervention Effect Size Study Categorization*

| **Intervention Type** | **# Studies (% Total)** |
|---|---|
| Therapeutic Hypothermia | 16 (47%) |
| Drug-based Intervention | 10 (29.4%) |
| Neonatal Resuscitation | 5 (14.7%) |
| Other | 2 (5.9%) |
| Multiple | 1 (2.9%) |
| **Study Geography (HIC/LMIC)** | **# Studies (% Total)** |
| Low and Middle-Income Countries (LMIC) | 16 (47%) |
| High-Income Countries (HIC) | 15 (44.1%) |
| Both | 3 (8.8%) |
| **Facility Type** | **# Studies (% Total)** |
| Tertiary Care | 30 (88.2%) |
| Community-based | 1 (2.9%) |

| | |
|---|---|
| Multiple | 3 (8.8%) |
| **HIE Severity** | **# Studies (% Total)** |
| Low/Moderate | 11 (32.4%) |
| Moderate/Severe | 13 (38.2%) |
| Unknown | 10 (29.4%) |
| **Study Type** | **# Studies (% Total)** |
| RCT | 23 (67.6%) |
| Meta-analysis | 6 (26%) |
| Retrospective | 3 (8.8%) |
| Non-RCT Prospective | 2 (5.9%) |

***Figure 1.*** *Geographic Distribution of Effect Size Studies*



# Aim 2 Results: Drug Intervention Studies

A total of 31 clinical trials of the 13 candidate drugs identified by BMGF were included. These studies are detailed in the ***[2. Candidate Drug Trials]*** worksheet in the Birth Asphyxia Workbook and summarized in ***Table 2*** below. The studies returned from our clinicaltrials.gov search for each of the 13 candidate drugs prioritized by BMGF are categorized below in ***Table 3.*** The clinical trials identified in neonates among the 13 candidate drugs from our clinicaltrials.gov searches are categorized in *Table 4* below.

***Table 2:*** *Summary of Relevant Candidate Drug Trials Included in [2. Candidate Drug Trials] Worksheet*

| Drug Name | # Studies |
|---|---|
| Azithromycin | 6 |
| B-hydroxy butyrate (ketone body equivalents) | 0 |
| Cannabinoids | 5 |
| Carnitine | 0 |
| Edaravone | 2 |
| Iodide | 0 |
| Isrib | 0 |
| Lactoferrin | 6 |
| Mitro-Q | 0 |
| N-acetylcysteine/dendrimer | 5 |
| Selective NOS inhibition | 0 |
| Thiorphan | 4 |
| Uridine (triacetate)+/- GRAS partner | 3 |
| **Total** | 31 |

***Table 3:*** *Clinicaltrials.gov Search Results of Candidate Drugs Used in Children, Pregnant Women, or "Neither"*

| | # Studies in Children | # Studies in Pregnant Women | # Studies in "Neither" | Total |
|---|---|---|---|---|
| Azithromycin | 186 | 32 | 0 | 218 |
| B-hydroxy butyrate (Ketone body equivalents) | 18 | 4 | 0 | 22 |
| Cannabinoids | 22 | 4 | 0 | 26 |
| Carnitine | 55 | 17 | 0 | 72 |
| Edaravone | 1 | 0 | 0 | 1 |
| Iodide | 6 | 3 | 0 | 9 |
| Isrib | 0 | 0 | 0 | 0 |
| Lactoferrin | 41 | 16 | 0 | 57 |
| Mito-Q | 0 | 0 | 7 | 7 |
| N-acetylcysteine | 71 | 16 | 0 | 87 |
| NOS inhibition | 0 | 0 | 4 | 4 |
| Thirophan | 4 | 0 | 0 | 4 |
| Uridine | 12 | 0 | 0 | 12 |
| **Grand total** | 416 | 92 | 11 | 519 |

***Table 4:*** *Clinicaltrials.gov Search Results of Candidate Drugs Used in Neonates*

| Drug Name | # Studies |
|---|---|
| Azithromycin | 6 |
| Cannabinoids | 1 |
| Carnitine | 6 |
| Lactoferrin | 20 |
| N-acetylcysteine | 1 |
| Uridine | 1 |
| **Total** | 35 |

# Conclusion

In conclusion, we identified a total of 34 intervention studies among encephalopathic term infants with evidence of perinatal hypoxic insult, spanning therapeutic hypothermia, resuscitation, and drug-based therapies. While we were unable to find effect size studies among the 13 candidate drugs prioritized by BMGF, we identified 31 studies with reported adverse events, toxicology, or pharmacokinetic/pharmacodynamic information. In addition, we identified eight studies with disease burden estimates of intrapartum-related neonatal health, with a general focus on hypoxic ischemic encephalopathy. Details of these studies, as well as their PDFs, have been delivered to the BMGF team as the final deliverable for this project.