STATISTICAL ANALYSIS PLAN

Intention-to-Treat Analysis for HAPIN Pneumonia

Version 1.1
September 23, 2022

Household air pollution and health: A multi-country LPG stove intervention trial (HAPIN)

Trial Registration: NCT02944682
Protocol Version: HAPIN - Main Study Protocol v15.0

Modification History:

Version	Date	Changes
1.0	August 26, 2022	
1.1	September 23, 2022	• Updated primary analysis plan to a GEE analysis due to quasilikelihood anomalies identified during blinded replication analysis. Justification documentation available. • Corrected minor error in secondary outcome definition. • Added sensitivity analysis of neonates <1 month of age

1. INTRODUCTION

This document contains the statistical analysis plan (SAP) for severe pneumonia of the HAPIN Study. Severe pneumonia is one of the four primary outcomes. The goal of the SAP is to avoid data-driven analyses during and at the end of the study to the extent possible.

1.1. Background and Rationale

Globally, nearly 3 billion people rely on solid fuels for cooking and heating, the vast majority in low- and middle-income countries (LMICs). The resulting household air pollution (HAP) is the most important environmental risk factor in the 2019 global burden of disease, accounting for an estimated 2.3 million premature deaths annually, largely among women and young children. Previous interventions have provided cleaner biomass-based cookstoves but have failed to reduce exposure to levels that produce meaningful health improvements. There have been no large-scale field trials with liquefied petroleum gas (LPG) cookstoves, likely the cleanest scalable intervention.

This study will provide evidence, including costs and implementation strategies, to inform national and global policies on scaling up LPG stoves among vulnerable populations. Ultimately, this will facilitate deeper policy-level discussions as well as identify requirements for initiating and sustaining HAP interventions globally.

1.2. HAPIN Study Overview

The aim of the HAPIN study is to conduct a randomized controlled trial of LPG stove and fuel distribution in 3200 households in four LMICs (India, Guatemala, Peru, and Rwanda) to deliver rigorous evidence regarding potential health benefits across the lifespan. Each intervention site will recruit 800 pregnant women (aged 18-<35 years, 9 to <20 weeks gestation), and will randomly assign half their households to receive LPG stoves and an 18-month supply of LPG. Controls will not receive the intervention at the commencement of the trial and are anticipated to continue cooking with solid biomass fuels; they will be compensated for their participation in the study. The mother will be followed along with her child until the child is 1 year old. In households with a second, non-pregnant older adult woman (aged 40 to <80 years) we will also enrol and follow her during the 18-month follow-up period in order to assess cardiopulmonary, metabolic, and cancer

outcomes. To optimize intervention use, we will implement behavior change strategies. We will assess cookstove use, conduct repeated personal exposure assessments to HAP ($PM_{2.5}$, black carbon, carbon monoxide), and collect dried blood spots (DBS) and urinary samples for biomarker analysis and biospecimen storage on all participants at multiple time points. The primary outcomes are birth weight, severe pneumonia, and stunting at age 1 year in the child, and blood pressure in the older adult woman.

1.3. Study Objectives

The HAPIN study will address the following specific aims: (1) using an intent-to-treat analysis, determine the effect of a randomized LPG stove and fuel intervention on health in four diverse LMIC populations using a common protocol; (2) determine the exposure-response relationships for HAP and health outcomes; and (3) determine relationships between LPG intervention and both targeted and exploratory biomarkers of exposure/health effects.

2. STUDY METHODS

2.1. Trial Design

HAPIN is a randomized, 2-arm intervention trial with parallel assignment. Study sites in the four countries (Guatemala, India, Peru, Rwanda) have been selected and evaluated based on activities conducted in the formative research. HAPIN uses a rolling recruitment process whereby each International Research Center (IRC) will enroll 800 pregnant women (one per household) and an additional approximately 120 older adult women (this will vary by IRC) from the same households who meet inclusion/exclusion criteria (Section 4.1). Key characteristics of each study site is given in Table 2 of the HAPIN design publication (Clasen et al. 2020).

Recruitment and enrollment will occur over approximately 15 months at ~53 pregnant women/8 older adult women per month per IRC. All participants will be followed longitudinally for ~18 months (until the child is age 1).

2.2. Randomization

To ensue balance between arms, households have been randomly allocated to intervention or control arms at the time of consent. To maintain balance of treatment assignments within each study site at the IRCs, a total of 10 randomization strata are implemented as follows.

- The India IRC randomization list is stratified by the two study sites
- The Peru IRC randomization list is stratified by the six study sites
- Guatemala and Rwanda have one site each.

Separate randomization lists have been generated for each field team conducting randomization at each IRC. Two randomization lists are produced for each of those field teams: one for households that include an older adult woman (OAW), and one for households that do not. Additional details on randomization of households can be found in the HAPIN protocol.

2.3. Sample Size Considerations

The power for the hypothesis test for relative risk of pneumonia is approximated by

$$\Phi\left(-Z_{1-\alpha/2}+\frac{|logRR|}{\sqrt{\frac{1-p_1}{np_1}+\frac{1-p_2}{np_2}}}\right)$$

where p_1 is the risk of pneumonia among the control group, p_2 is the risk of pneumonia among the intervention group, RR is the true relative risk (i.e. p_2/p_1), and n is the common sample size for each of the treatment group and the control group. For pneumonia, power for Poisson regression is also approximated by the equation for relative risk above assuming that follow-up times are the same for all participants.

The following assumptions, based on previous studies, are made for power calculations.

- For pneumonia, we assume a 1-year cumulative incidence rate among the control group as $p_1 = 0.06$ [a weighted average from Mackenzie et al. 2014, Gupta et al. 2010, Mortimer et al. 2007, Broor et al. 2017, Farooqi et al. 2015]. The actual incidence rate accounting for multiple events over the entire follow-up period is expected to be higher.

We assume a 10% attribution over the 1-year follow-up period, resulting in an effective sample size of $n = 1440$ per treatment arm for pneumonia.

2.4. Trial Framework
HAPIN is a superiority trial. The primary intention-to-treat analysis is a test of statistical significance to evaluate whether the outcome data are consistent with the assumption of there being no difference between the intervention and control arms.

2.5. Statistical Interim Analyses and Stopping Guidance
No interim analysis will be conducted.

2.6. Timing of Analysis
All analysis will be conducted once data collection are complete and the SAP has been approved and registered.

2.7. Timing of Outcome and Covariate Assessments
Each participating household are to be followed from enrollment until the index child reaches (or would have reached, assuming a live birth and continued vitality) his/her first birthday. For the purposes of this analysis plan severe pneumonia follow-up is through the first year of life.

3. STATISTICAL PRINCIPLES

3.1. Confidence Intervals and P-Values
All confidence intervals will be presented at 95% confidence.
Intention-to-treat analysis of the primary outcome will utilize a two-sided test at an α-level of 0.0125. The Bonferroni correction for multiple testing, while conservative, is used to control for family-wise type I error rate to be 0.05 under any dependence structure among the four HAPIN primary outcomes.
Subgroup analysis will use an α-level 0.05 to identify statistically significant effect modifications. If the effect modifiers have more than two categories, simultaneous hypothesis tests will be used.

Analysis of secondary outcomes will use an α-level 0.05 to identify statistical significance.

3.2. Adherence and Protocol Deviations
All homes in the intervention arm will be equipped with Stove Use Monitoring Systems (SUMS) on their traditional stoves, as well as a subset of approximately 80 homes in the control arm. Compliance will be checked every two weeks when SUMS data is downloaded.

Behavioral reinforcements (messages and materials) will be delivered when intervention households show any use of their traditional stoves. We will flag households that are using their traditional stove one or more times over the previous two-week monitoring period. After flagging these households, we will probe members of the participating household to ascertain reasons for non-compliance and intervene as necessary. At all behavioral reinforcement visits, a brief questionnaire will be conducted to identify the barriers to LPG stove use in the household and document the messages and materials used to address those barriers. Once specific reasons/factors are determined, personalized behavior change reinforcements will be delivered.

The intention-to-treat analysis of severe pneumonia will not consider adherence.

3.3. Analysis Populations
The primary analysis of primary outcome and secondary outcomes will be intention-to-treat (ITT). For each outcome, the analysis will include all recruited pregnancies that have a valid outcome measurement for whether the child did or did not have one or more illnesses that met criteria for the pneumonia endpoint

(*complete-case*). We define loss to follow-up as any reason that contributes to a missing outcome value, including death of the mother prior to birth, miscarriage, stillbirth, and withdrawal from study *prior to birth*. Secondary analysis may use various subsets of the study to examine effect modification.

4. TRIAL POPULATION

4.1. Eligibility

Pregnant women will be eligible to participate in the study if they fulfill the following inclusion and exclusion criteria at screening:

Inclusion criteria:

- Confirmed pregnancy (hCG positive blood or urine test)
- Aged 18 to <35 years (via self-report)
- Uses biomass stove predominantly
- Lives in study area
- 9 – <20 weeks gestation confirmed by ultrasound
- Singleton pregnancy (one fetus)
- Viable fetus with normal fetal heart rate (120-180 beats per minute) at time of ultrasound
- Continued pregnancy at the time of randomization confirmed by self-report
- Agrees to participate with informed consent

Exclusion criteria:

- Currently smokes cigarettes or other tobacco products
- Plans to move permanently outside study area in the next 12 months
- Uses LPG stove predominantly, or is likely to use LPG predominantly, in the near future

If two pregnant women live in the same household and are interested in participating, the one with the earliest gestational age will be chosen to participate.

4.2. Recruitment

The following information will be included in the CONSORT flow diagram. All counts will be reported as total and by IRC.

- Reasons for exclusion when assessed for eligibility
  - Not pregnant/no viable fetus
  - Mother outside of age range
  - Does not/will not primarily cook with biomass
  - Planned to move/moved away
  - Unwilling to participate
  - Gestational age out of range
  - Not a singleton
  - Smoker
  - Not in study area
  - Withdrawn by study team/not pursued further
- Participants determined to be ineligible after randomization
- Reasons for exits after randomization
  - Voluntary withdrawal prior to birth and after birth
  - Withdrawn by study team prior to birth and after birth
  - Moved away prior to birth and after birth
  - Pregnancy loss (termination/miscarriage/stillbirth)

4.3. Withdrawal/follow-up

The study will record reasons for exit classified into several categories:

- Not eligible
- Participant voluntary withdrawal
- Withdrawn by study team
- Moved away from study area

- Child deceased
- Lost to follow up
- Mother abortion/miscarriage/stillbirth/child death
- Other

For exits due to eligibility, voluntary withdrawal and withdrawal by study team, several pre-specified reasons will be used, as well as the option to fill in other reasons. The last completed visit will also be recorded. Reasons for withdrawal and loss to follow-up will be ascertained as soon as possible.

4.4. Baseline Participant Characteristics

For the ITT analysis, baseline characteristics restricted to liveborn children will be summarized by intervention versus control arms, separately by each IRC as defined by Table 1. A separate Table 2 will report additional key descriptive variables that may not be available at baseline. We will also report on characteristics of pneumonia cases as defined by Table 3. Means and standard deviations will be calculated for continuous variables and percentages will be calculated for categorical variables. Missing data will be reported as a separate category.

Table 1. Baseline characteristics to be reported of liveborn children

Variables	Type	Definition/Assessment Methods
International Research Center	Categorical	Guatemala, India, Peru, Rwanda
Gestational age (weeks) at intervention	Continuous	Calculated as the date of LPG installation minus the date of screening ultrasound plus gestational age at screening
Child sex	Categorical	Male/Female
Number of siblings in the house	Continuous	
Second-hand smoking	Binary	Whether someone other than the pregnant woman in household smokes (smoking of the pregnant mother was an exclusion criteria) (yes/no/missing)
Household food insecurity score	Categorical	Categories (corresponding score): • Food secure (0) • Mild (1,2,3) • Moderate (4,5,6) / Severe (7,8) • Missing See http://www.fao.org/3/as583e/as583e.pdf
Household assets	Categorical	• Color TV • Radio • Mobile phone • Bicycle • Bank account

Table 2. Other key characteristics of study population of liveborn children

Variables	Type	Definition/Assessment Methods
Maternal variables		
Mother's age (years) at baseline	Continuous	Calculated as the date at baseline minus the date of birth. Date at baseline is assigned by the date of visit if not missing.

Mother's highest level of education completed	Categorical	• No formal education or some primary school • Primary school or some secondary school incomplete • Secondary school or vocational or university/college Missing
Gestational age (weeks) at baseline	Continuous	Calculated as the date at baseline minus the date of screening ultrasound plus gestational age at screening, and then divided by 7
Child variables		
Birth weight-for-age z score	Continuous	
Breastfeeding	Binary	Breastfeeding during the first six months of life (yes/no/missing)
Up-to-date vaccination status	Binary	Number of respiratory vaccine doses by vaccine type by one year of age, including number of doses of pneumococcal conjugate vaccine (PCV) (*note*: PCV not available in India site), number of doses of haemophilus influenzae (HiB) vaccine, dose of measles vaccine Categorized as age <8 weeks & 1 dose PCV & HiB; age 8 to <12 weeks & 2 doses of PCV & HiB, age 12 to 32 weeks & 3 doses of PCV & HiB, age >32 weeks & 3 doses of PCV & HiB and 1 dose measles Yes/no

Table 3. Pneumonia case characteristics to be reported		
Variables	**Type**	**Definition/Assessment Methods**
Demographic information		
International Research Center, n (%)	Categorical	Guatemala, India, Peru, Rwanda
Child's age (months)	Continuous	Calculated as the date at diagnosis minus the date of birth. Date at diagnosis is assigned by the date of visit if not missing. Categorized as <2, 3-5, 6-11
Child sex, n (%)	Categorical	Male/Female
Weight (kg)	Continuous	
Severe acute malnutrition, n (%)	Binary	Weight-for-length or weight-for-age (if length unavailable) z score > -3 (use stata zscore06 at https://www.stata.com/statalist/archive/2011-04/msg01386.html) Yes/no
Up-to-date vaccination status, n (%)	Binary	Number of respiratory vaccine doses by vaccine type by age at diagnosis, including number of doses of PCV (*note*: PCV not available in India site), number of doses of HiB vaccine, dose of measles vaccine Categorized as age <8 weeks & 1 dose PCV & HiB; age 8 to <12 weeks & 2 doses of PCV & HiB, age 12 to 32 weeks & 3 doses of PCV & HiB, age >32 weeks & 3 doses of PCV & HiB and 1 dose measles Yes/no
$PM_{2.5}$, CO, BC	Continuous	
Antenatal $PM_{2.5}$, CO, BC	Continuous	
Postnatal $PM_{2.5}$, CO, BC	Continuous	

Clinical signs		
Temperature >38 C, n (%)	Binary	
Average Heart rate	Continuous	Average of measurements when multiple measurements available Beats per minute
Average Respiratory rate	Continuous	Average of measurements when multiple measurements available Breaths per minute
Average SpO_2	Continuous	Average of measurements when multiple measurements available
Hypoxemia, n (%)	Binary	Categorized as SpO_2 <93% for Guatemala, India, and/or Rwanda. <87% for Peru. Yes/No
Wheeze +/- crackles, n (%)	Binary	Yes/No
At least one respiratory danger sign, n (%)	Binary	Any of the following: chest indrawing, severe chest indrawing, head nodding, persistent nasal flaring, grunting, stridor when calm, audible wheeze, tracheal tugging, intercostal recessions Yes/No
Chest indrawing, n (%)	Binary	Yes/No
Head nodding, n (%)	Binary	Yes/No
Persistent nasal flaring, n (%)	Binary	Yes/No
Grunting, n (%)	Binary	Yes/No
Stridor when calm, n (%)	Binary	Yes/No
Audible wheeze, n (%)	Binary	Yes/No
Tracheal tugging, n (%)	Binary	Yes/No
Intercostal retractions, n (%)	Binary	Yes/No
At least one general danger sign, n (%)	Binary	Any of the following: unable to drink or breastfeed, vomiting everything, convulsions, lethargy or unconscious, unable to feed, not moving at all or moves with stimulation only Yes/No
Unable to drink or breastfeed, n (%)	Binary	Yes/No
Vomiting everything, n (%)	Binary	Yes/No
Convulsions, n (%)	Binary	Yes/No
Lethargy or unconscious, n (%)	Binary	Yes/No
At least one neonatal danger sign, n (%)	Binary	Any of the following: unable to feed well, not moving at all or moves with stimulation only, grunting, severe chest wall indrawing Yes/No
Unable to feed well, n (%)	Binary	Applies to <2 months only. Yes/No

Not moving at all or moves only, n (%)	Binary	Applies to <2 months only. Yes/No
Grunting, n (%)	Binary	Applies to <2 months only. Yes/No
Severe chest indrawing, n (%)	Binary	Applies to <2 months only. Yes/No
Lung Imaging		
Lung ultrasound, n (%)	Binary	Primary endpoint pneumonia Yes/No
Chest radiography, n (%)	Binary	Primary endpoint pneumonia Yes/No
Clinical care		
Hospitalized, n (%)	Binary	Yes/No
Oxygen treatment, n (%)	Binary	Yes/No
Advanced respiratory supportive care, n (%)	Binary	Any of the following: High flow, NIV (CPAP/BiPAP), mechanical ventilation Yes/No
Outcome		
Mortality, n (%)	Binary	Death <30 days since diagnosis and/or Verbal Autopsy positive Yes/No

We plan to include additional supplemental tables reporting more detailed imaging results and verbal autopsy results that will be included in the publication online supplemental information.

5. DATA ANALYSIS

In this section we provide the analysis approach for the intentional to treat aim. The primary outcome is HAPIN pneumonia. We present the primary analysis along with effect modification and secondary analyses (alternative model specifications, secondary outcomes).

5.1. Outcome Definitions

This section describes each primary and secondary outcomes, including data collection approaches and calculations for derived outcomes.

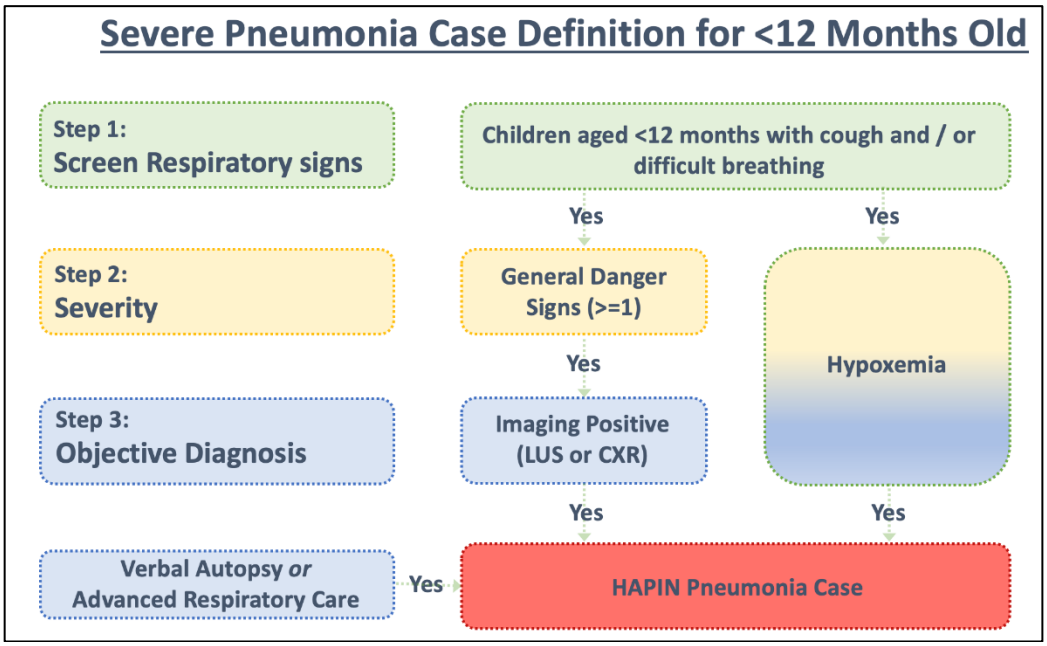
The primary outcome is HAPIN pneumonia.

HAPIN pneumonia Case Definition (see Simkovich SM, et al. ERJ Open Res 2020;6(1))

We will define HAPIN pneumonia as a case of severe pneumonia adapted from the revised WHO classification of childhood pneumonia (World Health Organization, 2014), which includes three algorithms for the case definition: (1) the presence of cough and/or difficult breathing and at least one general danger sign and primary endpoint pneumonia on a lung ultrasound or chest x-ray, or (2) the presence of cough and/or difficult breathing and hypoxemia (measured via pulse oximetry, SpO_2), or (3) children who died and their death is attributed to pneumonia by verbal autopsy. General danger signs for all participants include any of the 5 signs of: (1) unable to drink or breastfeed, (2) vomiting everything, (3) convulsions, (4) lethargy or unconscious, (5) stridor at rest. There are 4 additional general danger signs for participants <2 months of age (neonatal danger signs): (1) unable to feed, (2) grunting, (3) not moving at all or moves with stimulation only, (4) severe chest indrawing. Severe acute malnutrition is also considered a danger sign for all participants, and is defined as a calculated weight-for-length z score < -3 or weight-for-age z score < -3 (if length unavailable or age <60 days).

Lung ultrasound will be the imaging modality obtained unless there are logistical or regulatory reasons this cannot happen and then we will obtain a chest x-ray. We will define tachypnea based on current World Health Organization thresholds ($\geq$60 breaths/minute for 0-2 month olds and $\geq$50 breaths/minute for 3-11 month olds).

We will determine hypoxemia based on the physiologic threshold of ≤92% for altitudes <2,500 meters above sea level and ≤86% for altitudes ≥2,500 meters above sea level. Children are also considered hypoxemic, regardless of oxygen saturation, and assumed to have cough and/or difficult breathing if they are receiving advanced respiratory support at the time of evaluation, which includes any of the following: intubation and mechanical ventilation, non-invasive ventilation with continuous positive airway pressure support (CPAP), non-invasive ventilation with bi-level positive airway pressure support (BIPAP), or high-flow nasal cannula oxygen. Children who die but are determined to have had pneumonia or symptoms and/or signs of a respiratory illness consistent with pneumonia by verbal autopsy will also be considered a case of severe pneumonia. Children are permitted to meet the above case definition for severe pneumonia multiple times if the repeat event occurs either >14 days after the hospital discharge date or, if the hospital discharge data is not available or the child was not hospitalized, >30 days after the date the child met criteria for severe pneumonia. Implausible values and outliers identified from the variables that comprise the case definition will be considered missing.



Secondary Outcomes are given in Table 4.

Table 4. Secondary Outcomes

Parameter	Definition
Total IMCI pneumonia	IMCI non-severe and severe pneumonia
IMCI (Integrated Management of Child Illnesses) WHO non-severe	Cough and/or difficult breathing and • chest indrawing or fast breathing and • no general danger sign (unable to drink or breastfeed, vomiting everything, convulsions, lethargic or unconscious) and • no stridor at rest and • no severe acute malnutrition and • no HIV infection or exposure and • no hypoxemia (SpO_2 <90%)
IMCI WHO severe	Cough and/or difficult breathing and • any general danger sign (unable to drink or breastfeed, vomiting everything, convulsions, lethargic or unconscious) or • stridor at rest or • severe acute malnutrition or • HIV infection or exposure (if chest indrawing also) or

	• Hypoxemia (SpO_2 <90%)
Total Pocketbook pneumonia	Pocketbook non-severe and severe pneumonia
Pocketbook WHO non-severe	Cough and/or difficult breathing and • chest indrawing or fast breathing and • no sign of Pocketbook WHO severe pneumonia
Pocketbook WHO severe	Cough and/or difficult breathing and • central cyanosis or SpO_2<90% or • severe respiratory distress (grunting, very severe chest indrawing) or • sign of pneumonia (fast breathing, chest indrawing, or lung auscultation signs of decreased or bronchial breath sounds, crackles, abnormal vocal resonance, pleural rub) and at least one general danger sign (unable to drink or breastfeed, vomiting everything, convulsions, lethargic or unconscious) or other high-risk condition (severe acute malnutrition or HIV infection or exposure)
Hospitalization for respiratory illness	Hospitalization for respiratory illness at any time during the follow-up period
Lung ultrasound or chest radiograph pneumonia	Primary endpoint pneumonia Yes/No
Hypoxemic pneumonia	Categorized as SpO_2 <93% for Guatemala, India, and/or Rwanda. <87% for Peru.

5.3. Intention-to-Treat Analysis

For the primary outcome of the incidence of HAPIN pneumonia episodes (see Section 5.2) over a one-year follow-up period, we will use a Generalized Estimating Equations (GEE) Poisson response model based on child-days at risk of follow up, to derive an incidence rate ratio for the intervention vs. control groups. The use of Poisson regression and rate ratios, rather than a relative risk of first occurrence of pneumonia, is motivated by observing that the occurrence of multiple severe pneumonias episodes in the study children, which occurs often enough to warrant taking the multiple events into account. The GEE framework will account for multiple severe pneumonias episodes.

Specifically, the intention-to-treat analysis will be modelled as follows:

$$\log E(y_i) = \beta_0 + \beta_1 \times I(intervention_i) + \sum_{1}^{9} \beta_{k+1} I_{ik} + \log n_i,$$

where y_i is the number of HAPIN pneumonia episodes for the i^{th}child during the first year of follow-up and $y \sim Poisson$, in the GEE framework with a working independence variance structure. $I(intervention_i)$ is an indicator variable that is 0 if the i^{th}child was assigned to the control group and 1 if assigned to intervention, $\hat{\beta}_2$ through $\hat{\beta}_{10}$ are the coefficients for the indicator variables ($I_{i.}$) representing nine strata (with one stratum is reference, for a total of 10 strata), and n_i represents the number of child-days at risk for the i^{th}child. The estimated parameter $\hat{\beta}_1$ is the logarithm of the incidence rate ratio of HAPIN pneumonia between the intervention and control groups.

The same GEE/Poisson regression model will be used for subgroup analyses and secondary outcomes.

Subgroup Analysis. Effect modification analyses will be conducted using interaction terms between the indicator variable for the intervention (study arm, control or intervention) and the effect modifiers. A joint statistical test will be conducted to detect effect modification at a type I error rate of 0.05. Potential effect modifiers to be assessed are listed in Table 5.

Table 5. Subgroup analysis variables of liveborn children (effect modifiers)

Variables	Type	Definition/Assessment Methods
International Research Center and randomization stratification	Categorical	Randomization strata within Guatemala, India, Peru, Rwanda
Mother's age (years) at baseline	Continuous and Categorical	Calculated as the date at baseline minus the date of birth. Date at baseline is assigned by the date of visit if not missing. Will also include age categories.
Mother's highest level of education completed	Categorical	• No formal education or some primary school • Primary school or some secondary school incomplete • Secondary school or vocational or university/college • Missing
Gestational age (weeks) at intervention	Continuous and Categorical	Calculated as the date at baseline minus the date of screening ultrasound plus gestational age at screening. Will also include gestational age categories.
Breastfeeding	Binary	Breastfeeding during the first six months of life, non-exclusive (yes/no/missing)
Up-to-date vaccination status	Binary	Receipt of 3 respiratory vaccines by one year of life, including 3 doses of PCV (*note*: PCV not available in India site), 3 doses of Hib vaccine, one dose of measles vaccine (yes/no/missing)

Secondary analyses. Secondary analyses include time-to-event analysis for estimating the intervention effect on the time to first pneumonia incidence and analysis of secondary outcome definitions as listed in Table 4 (section 5.2).

Additional Analysis. If imbalance between control and intervention groups for a baseline covariate (Section 4.4, Table 1) suggests problems with randomization, and the covariate is a potential confounder, covariate-adjusted effects will be evaluated as a sensitivity analysis.

We will also plan to assess the influence of (1) a marked *increase* of pneumonia cases in Rwanda from November 2019 due to surveillance strengthening at outpatient clinics, and (2) the COVID-19 pandemic, which started in April 2020 and may have contributed to an observed *decrease* in cases in all study sites. We may do this by following the analytical approach prescribed for the primary analysis with two indicator variables to time periods, with pre-November 1, 2019 as referent, November 1, 2019 to March 31, 2020 as the first indicator, and from April 1, 2020 as the second indicator, and/or evaluate using another appropriate modelling approach. We plan to include interaction terms with treatment arm and these time periods to assess whether the effect of intervention changed over time. (3) We will conduct a sensitivity analysis of the primary analysis where we do not consider neonatal cases (<30 days old) and newborn cases (<7 days old).

Incomplete Outcome Data. Our primary approach to incomplete outcome data that precludes assessment of a possible HAPIN pneumonia event will be to conservatively assume that such events are non-outcome events. For example, if the child's oxygen saturation and/or image is missing we assume that child is not a case, but keep the child in the denominator-at-risk rather than censor them. It is anticipated that incomplete outcome data will be rare and when present balanced between intervention arms. We will conduct additional analyses to evaluate the potential influence of any missing outcome data.

5.4. Analysis Replication Plan

Selected components of the intention-to-treat will be replicated by an independent analyst. Secondary analyses of any outcome related to sensitivity analyses (i.e., alternative health model specifications, alternative covariate specification) will not be replicated.

The replication team will receive the following from the Data Management Core (DMC).

1. A cleaned analytic dataset where exclusions have been applied following the CONSORT diagram. The dataset will also include baseline variables and covariates for subgroup analysis.
2. A table summarizing baseline characteristics (overall and by IRC).
3. The set of outcomes (primary and secondary) and subgroup analysis to be replicated.

Specific replication tasks include:

1. Replicate summary statistics (e.g., mean, standard deviation, percentages, proportion missing) in the baseline characteristic table.
2. Replicate intention-to-treat analyses for primary and secondary outcomes according to models specified in Section 5.3.
3. Replicate results from effect modification analyses (intention-to-treat only).