ORIGINAL ARTICLE

Liquefied Petroleum Gas or Biomass Cooking and Severe Infant Pneumonia

E.D. McCollum, J.P. McCracken, M.A. Kirby, L.M. Grajeda, S. Hossen, L.H. Moulton, S.M. Simkovich, D. Goodman-Palmer, G. Rosa, A. Mukeshimana, K. Balakrishnan, G. Thangavel, S.S. Garg, A. Castañaza, L.M. Thompson, A. Diaz-Artiga, A.T. Papageorghiou, V.G. Davila-Roman, L.J. Underhill, S.M. Hartinger, K.N. Williams, L. Nicolaou, H.H. Chang, A.E. Lovvorn, J.P. Rosenthal, A. Pillarisetti, W. Ye, L.P. Naeher, M.A. Johnson, L.A. Waller, S. Jabbarzadeh, J. Wang, Y. Chen, K. Steenland, T.F. Clasen, J.L. Peel, and W. Checkley, for the HAPIN Investigators*

ABSTRACT

BACKGROUND

Exposure to household air pollution is a risk factor for severe pneumonia. The effect of replacing biomass cookstoves with liquefied petroleum gas (LPG) cookstoves on the incidence of severe infant pneumonia is uncertain.

METHODS

We conducted a randomized, controlled trial involving pregnant women 18 to 34 years of age and between 9 to less than 20 weeks' gestation in India, Guatemala, Peru, and Rwanda from May 2018 through September 2021. The women were assigned to cook with unvented LPG stoves and fuel (intervention group) or to continue cooking with biomass fuel (control group). In each trial group, we monitored adherence to the use of the assigned cookstove and measured 24-hour personal exposure to fine particulate matter (particles with an aerodynamic diameter of ≤2.5 μm [$PM_{2.5}$]) in the women and their offspring. The trial had four primary outcomes; the primary outcome for which data are presented in the current report was severe pneumonia in the first year of life, as identified through facility surveillance or on verbal autopsy.

RESULTS

Among 3200 pregnant women who had undergone randomization, 3195 remained eligible and gave birth to 3061 infants (1536 in the intervention group and 1525 in the control group). High uptake of the intervention led to a reduction in personal exposure to $PM_{2.5}$ among the children, with a median exposure of 24.2 μg per cubic meter (interquartile range, 17.8 to 36.4) in the intervention group and 66.0 μg per cubic meter (interquartile range, 35.2 to 132.0) in the control group. A total of 175 episodes of severe pneumonia were identified during the first year of life, with an incidence of 5.67 cases per 100 child-years (95% confidence interval [CI], 4.55 to 7.07) in the intervention group and 6.06 cases per 100 child-years (95% CI, 4.81 to 7.62) in the control group (incidence rate ratio, 0.96; 98.75% CI, 0.64 to 1.44; P=0.81). No severe adverse events were reported to be associated with the intervention, as determined by the trial investigators.

CONCLUSIONS

The incidence of severe pneumonia among infants did not differ significantly between those whose mothers were assigned to cook with LPG stoves and fuel and those whose mothers were assigned to continue cooking with biomass stoves. (Funded by the National Institutes of Health and the Bill and Melinda Gates Foundation; HAPIN ClinicalTrials.gov number, NCT02944682.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. McCollum can be contacted at emccoll3@jhmi.edu or at Global Program in Pediatric Respiratory Sciences, Eudowood Division of Pediatric Respiratory Sciences, Johns Hopkins University, 200 N. Wolfe St., Ste. 3071, Baltimore, MD 21287. Dr. Checkley can be contacted at wcheckl1@jhmi.edu or at the Division of Pulmonary and Critical Care, Johns Hopkins University, 1830 E. Monument St., Ste. 555, Baltimore, MD 21287.

*A complete list of the HAPIN Investigators is provided in the Supplementary Appendix, available at NEJM.org.

Drs. McCollum and McCracken contributed equally to this article.

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Pneumonia is a leading cause of death among children worldwide, with most deaths occurring in infants younger than 1 year of age.[1] Approximately 83% of the 808,000 annual deaths from pneumonia among children occur in sub-Saharan Africa, South Asia, and Latin America.[1] Observational studies suggest that exposure to fine particulate matter with an aerodynamic diameter of 2.5 μm or less ($PM_{2.5}$) from incomplete combustion of solid fuel is a risk factor for pneumonia.[1] Nearly 30% of the global pediatric deaths from pneumonia are attributed to household air pollution.[1] Approximately 2.4 billion people — predominantly in low- and middle-income countries — use biomass (e.g., wood, charcoal, animal dung, and coal) daily for cooking or for heating their households.[2]

Data from randomized, controlled trials showing an effect of cleaner cooking interventions on primary outcomes of child pneumonia are lacking.[3-6] However, it is unclear if the lack of benefit stemmed from insufficiently lowered pollutant levels because of inadequate uptake or performance of the cookstove intervention, nonspecific case definitions of pneumonia, or low statistical power. The Household Air Pollution Intervention Network (HAPIN) trial was designed to address these limitations in order to assess whether cooking with an unvented liquefied petroleum gas (LPG) stove and fuel during pregnancy and the offspring's first year of life would lead to a lower incidence of infant pneumonia and other health outcomes than biomass cooking.[7] We reported previously that there was no evidence of an effect of the LPG cookstove intervention on birth weight.[8] Here, we report the effects of the intervention on the incidence of severe pneumonia during the first year of life, one of four primary trial outcomes.

METHODS

TRIAL DESIGN AND OVERSIGHT

The HAPIN trial was a randomized, controlled trial in which unvented LPG cookstoves with free, uninterrupted fuel supply were compared with usual cooking practices (primarily or exclusively with biomass fuels). The trial was conducted from May 2018 through September 2021 in Tamil Nadu, India; Jalapa, Guatemala; Puno, Peru; and Kayonza, Rwanda.[7] The trial sites were selected to cover a range of geographic settings on four continents where biomass is used for cooking.

The protocol, available with the full text of this article at NEJM.org, was approved by all investigator-affiliated institutional review boards (see the Supplementary Appendix, available at NEJM.org). All the participants provided written informed consent. An independent data and safety monitoring board monitored safety and efficacy and received unblinded data from interim analyses. No prespecified rules for stopping the trial were formulated owing to the low risk related to the intervention. The sponsors played an active role in the trial design and conduct decisions but did not participate or influence the preparation of this report. The first, second, and last three authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The third through sixth authors conducted the statistical analyses.

PARTICIPANTS

Women 18 to 34 years of age were eligible for participation if they were pregnant with a viable, singleton fetus at 9 to less than 20 weeks' gestation (as confirmed on pregnancy testing and ultrasonography), used a biomass stove at least 4 days a week, and lived in a trial area. Pregnant women who smoked tobacco, planned to migrate from the trial area during the trial, or used or planned to switch to LPG cookstoves were excluded. One pregnant woman per household could be enrolled.

RANDOMIZATION

We randomly assigned the participants in a 1:1 ratio to cook with LPG stoves and fuel (intervention group) or to continue cooking with biomass fuel (control group). Randomization was stratified according to geographic region, of which there were 10 in the trial: one district in Jalapa, Guatemala; two districts in Tamil Nadu, India; six provinces in Puno, Peru; and one district in Kayonza, Rwanda. Although the trial-group assignments could not be concealed from the participants and field staff, all the investigators were unaware of the assignments at the time of data cleaning, image interpretation, and data analysis.

INTERVENTION

The unvented LPG cookstoves had at least two burners and met local safety standards. Behavioral-based messaging was provided to reinforce exclusive and safe use of the LPG stoves.[9] Trial staff used stove temperature sensors to monitor

adherence to the trial-group assignment in both groups.[10] The participants in the control group were provided nonmonetary compensation to counterbalance the intervention incentive of free fuel provision and mitigate attrition.[11] Because cooking fuel delivery was considered to be an essential service, the intervention was generally uninterrupted by restrictions related to the coronavirus disease 2019 (Covid-19) pandemic, and the delivery times before and during the Covid-19 lockdown restrictions were similar.[12]

EXPOSURE ASSESSMENT

We used monitoring devices to directly measure 24-hour personal exposure to $PM_{2.5}$ (RTI Enhanced Children's MicroPEM, RTI International), carbon monoxide (Lascar EL-USB-300, Lascar Electronics), and black carbon (SootScan Model OT-21 Optical Transmissometers, Magee Scientific) in pregnant women at baseline (<20 weeks' gestation).[10] Estimates of the infants' exposure to $PM_{2.5}$ and carbon monoxide were made at the ages of 3 months, 6 months, and 12 months by means of an indirect method. In brief, the same $PM_{2.5}$- and carbon-monoxide–monitoring devices used to measure personal exposure in the pregnant women were used to monitor the most commonly occupied household areas. Area monitor data for $PM_{2.5}$ and carbon monoxide levels were then combined with data from locator devices worn by the infants to reconstruct the infants' personal exposure to these two pollutants (see the Supplementary Appendix).[13]

OUTCOME SURVEILLANCE

We conducted active surveillance of severe pneumonia cases at preselected community hospitals and health centers. During formative pneumonia surveillance work, these facilities had been identified as centers where patients with severe cases receive care.[14] Passive facility and household surveillance was also conducted to identify missed facility visits, missed hospitalizations, ventilatory support, and deaths. A standard approach was used for training trial staff in the evaluation for severe pneumonia in children[15]; in brief, they passed certification examinations and received annual retraining. If medical care was needed, mothers could notify trial staff by telephone to facilitate appropriate care. In India, Peru, and Rwanda, trial staff were available in person on weekdays at sentinel facilities and by telephone any time; in Guatemala, staff were available in person continuously at the sentinel hospital. We reviewed medical charts of infant deaths and conducted a verbal autopsy to determine whether the death was related to severe pneumonia. Beginning in November 2019, sites in Rwanda increased trial staff presence at outpatient clinics because during surveillance, some patients with cases were identified as not having been hospitalized. In March 2020, Covid-19–related public health measures commenced at all sites, which limited active in-person surveillance and care-seeking during lockdown periods. Trial staff also telephoned facility contacts to surveil for possible cases; telephone surveillance was uninterrupted during the trial.

OUTCOMES

The primary outcome was severe pneumonia in the first year of life among the participants' offspring. The case definition used for severe pneumonia was adapted from World Health Organization (WHO) guidelines on the basis of external expert input.[16] In July 2019, when less than 1% of the planned follow-up time for the infants had elapsed, we implemented additional expert recommendations to amend the case definition to improve specificity and objectivity and to be responsive to formative data that had been collected (see the Supplementary Appendix).[17,18] Severe pneumonia was defined as the presence of cough or difficulty breathing with at least one general danger sign (i.e., inability to drink or breast-feed, convulsions, stridor at rest, lethargy, unconsciousness, or vomiting all ingested food, fluid, and medications) or at least one neonatal danger sign (i.e., unable to feed well, not moving at all or movement only when stimulated, grunting, or severe indrawing of the chest wall) and confirmation of pneumonia on imaging; the presence of cough or difficulty breathing along with hypoxemia; or confirmation of death from pneumonia on verbal autopsy.[15] Subsequent symptoms in the same child were considered to be separate episodes if onset was more than 14 days after hospital discharge or more than 30 days after outpatient diagnosis. For a case of pneumonia to be eligible for inclusion in the analyses, the affected child had to have been examined by trial staff, except for children who were receiving ventilatory support or who died.

Chest imaging was performed by means of ultrasonography (Sonosite Edge)[15,19] or radiography if ultrasonography was unavailable. In the

diagnosis of pneumonia in children, lung ultrasonography was reported to have a sensitivity of 95.5% and a specificity of 95.3%, and the corresponding values for chest radiography were reported to be 86.8% and 98.2%.[20] All images were interpreted by adjudication panels, the members of which were unaware of the trial-group assignments and clinical status.[15,19,21] Two panelists independently followed prespecified interpretation procedures and were required to agree on the presence of pneumonia for the image to be classified as pneumonia. Pneumonia on imaging was defined as a consolidation alone (meeting prespecified size dimensions) or a pleural effusion near an infiltrate that was shown on ultrasonography or radiography or as pleural abnormalities that were shown on ultrasonography.[15,19,21]

Hypoxemia was defined as a peripheral arterial oxyhemoglobin saturation (SpO_2) of 92% or less at an altitude lower than 2500 m (in Guatemala, India, and Rwanda) or 86% or less at an altitude of 2500 m or higher (Peru)[15] or receipt of invasive or noninvasive ventilation or high-flow oxygen. Trial staff at the facilities measured SpO_2 by applying a pulse oximeter (Rad-G, Masimo) and pediatric probe to the big toe of the infants while they were breathing ambient air. Staff collected three measurements over 2 minutes, and these were averaged. SpO_2 measurements were extracted from medical charts when available.

Trained, local medical staff performed verbal autopsies with the caregivers of the deceased infants using a validated protocol.[22] A physician verbal-autopsy panel assigned primary and secondary causes of death using *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*, codes published by the WHO in 2016. Two nontrial physicians from one of the four low- and middle-income countries, who were unaware of the trial-group assignments and other documented death classifications, independently reviewed the open-narrative and closed-question parts of the verbal autopsy. When the assigned primary cause of death was discordant between the two physicians, a pediatrician panelist arbitrated the discrepancy to reach consensus. Cases for which a consensus was not reached were classified as "undetermined." The final verbal-autopsy classification was pneumonia if it was the primary or secondary cause of death.

Secondary outcomes were pneumonia according to the WHO Integrated Management of Childhood Illness guidelines[23] and according to the WHO Pocketbook guidelines,[24] hypoxemia or imaging-confirmed pneumonia (or both), and any hospitalization for respiratory illness. Definitions of the secondary outcome are provided in Table S1 in the Supplementary Appendix.

STATISTICAL ANALYSIS

On the basis of available evidence,[5,6,25-28] we estimated that a sample of 3200 pregnant women would provide the trial with 80% power at an alpha level of 0.0125 (an adjustment for multiple hypothesis testing for four trial outcomes) to detect a between-group difference of 36% in incidence of severe pneumonia, assuming a baseline rate of 9 cases per 100 infant-years.[7] The primary analysis was performed according to the intention-to-treat principle and was conducted independently by two teams. We used Poisson regression with generalized estimating equations (GEEs) to model the incidence of all episodes of severe pneumonia and used infant-days at risk as the denominator to derive incidence rate ratios. The intervention group was the main covariate, and the models were adjusted for 10 randomization strata (one site in Guatemala and in Rwanda, two sites in India, and six sites in Peru). When an outcome could not be classified owing to incomplete data, we assumed that the event did not occur.

In secondary analyses, the effect of the intervention on the time to the first episode of pneumonia was estimated by means of Cox proportional-hazards models. Subgroup analyses were performed with the use of GEE–Poisson regression models. Additional analyses were performed to assess whether the effect of the intervention changed over time because of modifications made to outpatient surveillance in Rwanda (after November 2019) and, in analyses that accounted for age, the occurrence of the Covid-19 pandemic (after March 2020). Given the clustering of deaths very early in life and that diagnostic accuracy may be lower in neonates, we also conducted sensitivity analyses of the primary outcome in which children with pneumonia younger than 7 days of age and those younger than 30 days of age were excluded.

RESULTS

PARTICIPANT CHARACTERISTICS

A total of 3200 women underwent randomization; 1593 (49.8%) were assigned to the intervention

group and 1607 (50.2%) to the control group (Fig. 1). After randomization and assignment, 3195 women remained eligible (1590 in the intervention group and 1605 in the control group). The maternal characteristics at baseline were similar in the trial groups (Table 1), and the pregnant women and their offspring were representative of the broader population of women and infants affected by indoor air pollution from biomass cooking (Table S2). Pregnant women received the LPG stoves in the mid-second trimester of their pregnancy at a mean (±SD) of 18.1±3.3 weeks. Overall, 3061 live births occurred, with 1536 in the intervention group and 1525 in the control group. The characteristics, including vaccination status, of the live-born children are shown according to trial group in Table 2.

INTERVENTION ADHERENCE AND EFFECTS ON EXPOSURE

Among the participants in the intervention group, the median frequency of biomass stove use on the days that were monitored was 0.4% (interquartile range, 0.0 to 2.3).[12,29] After randomization, the median 24-hour personal exposure to $PM_{2.5}$ was lower in the intervention group (24.8 μg per cubic meter; interquartile range, 17.0 to 40.5) than in the control group (77.0 μg per cubic meter; interquartile range, 40.7 to 132.8) during the antenatal period, as well as during the postnatal period, with corresponding values of 24.2 μg per cubic meter (interquartile range, 17.8 to 36.4) and 66.0 μg per cubic meter (interquartile range, 35.2 to 132.0).[13,30] The results with respect to carbon monoxide and black carbon are also provided in Tables 1 and 2 and Table S3.

PRIMARY OUTCOME ANALYSIS

We identified 85 episodes of severe pneumonia in the intervention group and 90 episodes in the control group (Fig. 2) during 1243 health care facility visits and 55 verbal autopsies (Fig. S1 and Tables S4 through S8). Among these episodes, 12 deaths were attributed to pneumonia (in 6.9% of the pneumonia cases), with 4 deaths occurring in the intervention group and 8 in the control group (Table S9). The incidence of severe pneumonia in the first year of life was 5.67 per 100 infant-years (95% CI, 4.45 to 7.07) in the intervention group and 6.06 per 100 infant-years (95% CI, 4.81 to 7.62) in the control group (incidence rate ratio, 0.96; 98.7% CI, 0.64 to 1.44; P=0.81) (Fig. 2).

OTHER ANALYSES

No evidence of an intervention effect was observed in the analyses of the secondary outcomes (Fig. 2 and Table S10) or in the subgroup analyses defined according to country location or other subgroup variables (Fig. S2). Although the observed incidence of severe pneumonia across all trial sites decreased by 77% (95% CI, 61 to 86) during the Covid-19 pandemic period (Fig. 3 and Fig. S3 and Table S11), there was no appreciable change in the incidence rate ratio when our models accounted for the pandemic period and child's age (incidence rate ratio, 0.96; 95% CI, 0.70 to 1.31). The incidence rate ratios in Rwanda that were determined for the periods before the surveillance changes (0.71; 95% CI, 0.12 to 4.23) and after the changes (0.80; 95% CI 0.49 to 1.31) that took place in November 2019 were also similar to the result in the primary analysis (Table S12).

ADVERSE EVENTS

Burns were reported in three infants (0.2%) in the intervention group and in seven infants (0.5%) in the control group. None of the burns were classified as a serious adverse event (Table S13).

DISCUSSION

In this multinational trial, despite high uptake of the LPG intervention and substantial reductions in exposure to air pollutants, we found no significant difference in the incidence of severe infant pneumonia between the intervention group and the control group. Our findings are consistent with null findings from a cluster-randomized trial in Ghana of a similar cookstove,[3] which indicated that LPG cookstoves are unlikely to reduce the risk of severe infant pneumonia. Our trial also showed no difference between the trial groups with respect to the other primary outcomes of birth weight[8] and stunting (reported in another article in this issue of the *Journal*).[31]

We propose several potential explanations for our null findings with respect to severe infant pneumonia. First, evidence suggests that household air pollution is more closely linked to bacterial than to viral nasopharyngeal carriage.[32,33]

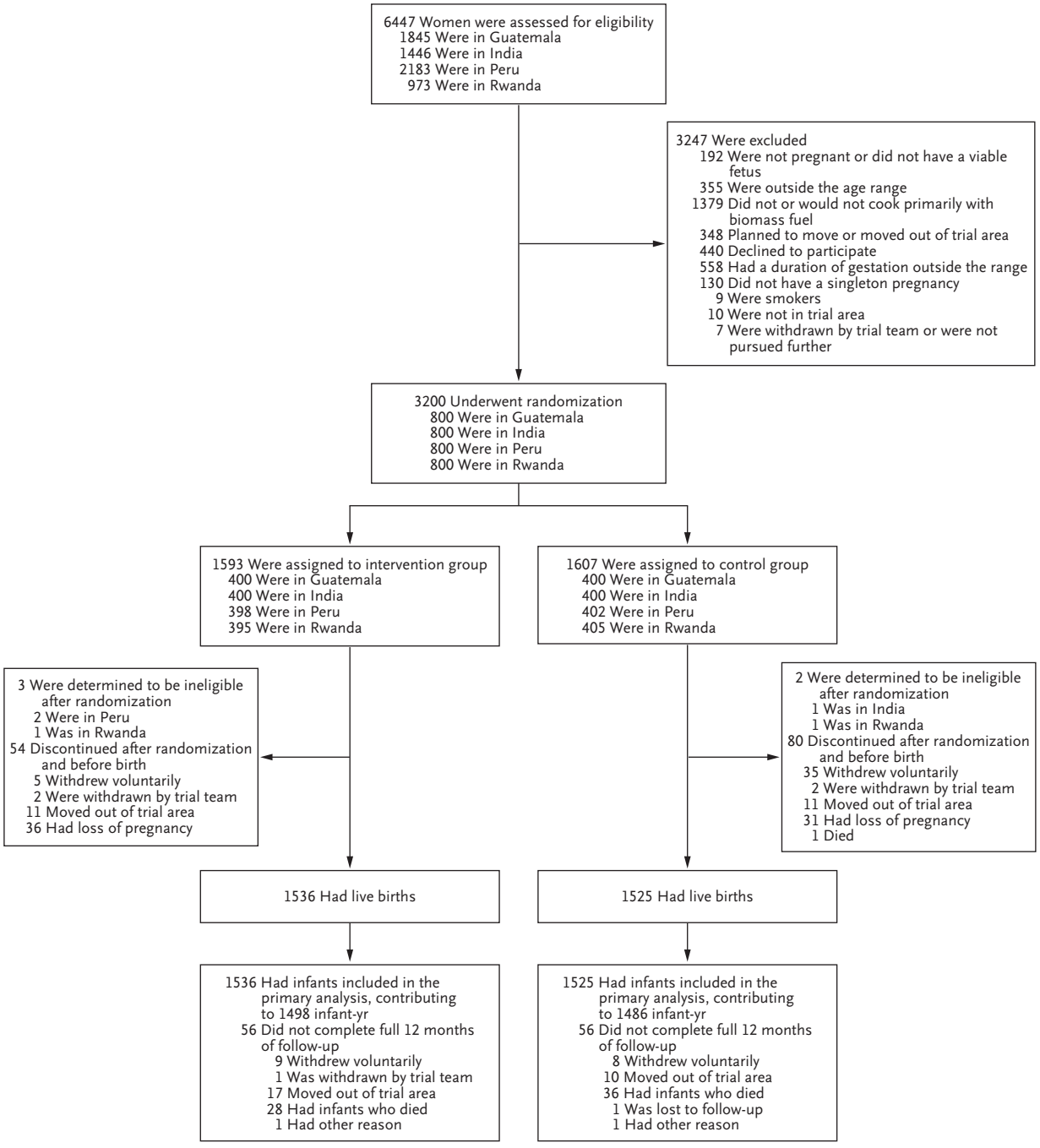

Figure 1. Screening, Randomization, and Analysis.

Participants may have had more than one reason for exclusion.

Nasopharyngeal carriage is considered to be a key pathway for the development of invasive or mucosal bacterial diseases such as pneumonia,[34] and populations vaccinated against *Haemophilus influenzae* type B and *Streptococcus pneumoniae* (pneumococcus) are well protected against disease resulting from nasopharyngeal carriage.[35] A high percentage of participants in our trial popula-

Table 1. Characteristics of the Pregnant Women with Live-Born Children at Baseline.*

Characteristic	Intervention (N=1536)	Control (N=1525)
Country of residence — no./total no. (%)		
Guatemala	384/1536 (25.0)	386/1525 (25.3)
India	388/1536 (25.3)	387/1525 (25.4)
Peru	385/1536 (25.1)	358/1525 (23.5)
Rwanda	379/1536 (24.7)	394/1525 (25.8)
Age at baseline		
Mean — yr	25.3±4.4	25.4±4.5
Distribution — no./total no. (%)		
18 to <25 yr	787/1536 (51.2)	758/1525 (49.7)
25 to <30 yr	484/1536 (31.5)	488/1525 (32.0)
30 to <35 yr	265/1536 (17.3)	279/1525 (18.3)
Highest level of education completed — no./total no. (%)		
None or some primary	461/1536 (30.0)	540/1525 (35.4)
Primary or some secondary	538/1536 (35.0)	514/1525 (33.7)
Secondary, vocational, or university or college	537/1536 (35.0)	471/1525 (30.9)
Gestation at baseline — wk	15.5±3.1	15.3±3.2
Gestation at stove installation†		
Mean — wk	18.1±3.3	17.9±3.2
Distribution — no./total no. (%)		
10 to <18 wk	767/1536 (49.9)	791/1525 (51.9)
18 to <30 wk	769/1536 (50.1)	734/1525 (48.1)
No. of siblings in household	1.0±1.1	1.1±1.2
Exposure to second-hand smoke in household — no./total no. (%)	146/1535 (9.5)	174/1525 (11.4)
Household food insecurity score — no./total no. (%)‡		
0: food secure	904/1515 (59.7)	820/1503 (54.6)
1–3: mild insecurity	403/1515 (26.6)	424/1503 (28.2)
4–8: moderate or severe insecurity	208/1515 (13.7)	259/1503 (17.2)
Socioeconomic status index score§	−0.1±1.1	0.1±1.0
Median personal exposure to pollutants (IQR)¶		
$PM_{2.5}$ — $\mu g/m^3$	81.6 (45.9 to 150.7)	84.2 (46.5 to 143.0)
Black carbon — $\mu g/m^3$	10.5 (6.2 to 15.4)	10.9 (6.9 to 15.5)
Carbon monoxide — ppm	1.3 (0.5 to 3.0)	1.2 (0.5 to 2.5)

* Plus–minus values are means ±SD. IQR denotes interquartile range, and $PM_{2.5}$ particulate matter with an aerodynamic diameter of 2.5 μm or less.

† In the control group, gestational age at stove installation was calculated as the age at baseline plus 2.6 weeks, which is the mean time between baseline and stove installation in the intervention group.

‡ Household food insecurity is measured by the Food Insecurity Experience Scale (FIES), which was applied with a 30-day reference period. In the FIES, higher scores represent increasingly severe food insecurity.

§ Socioeconomic status was assessed by means of principal component analysis of data on the number of persons in the household, the participant's education level, the quality of water and sanitation, access to electricity, housing materials, ownership of 24 specific household assets, and food insecurity score at the start of the trial. Multiple imputation with chained equations was used to handle missing data. The socioeconomic status index scores among the participants ranged from −2.2 to 2.1; a higher score indicates worse socioeconomic status. Data on the socioeconomic status index score were missing for 277 participants (144 in the intervention group and 133 in the control group).

¶ Data on exposure to $PM_{2.5}$ were missing for 184 pregnant women in the intervention group and 173 in the control group; data on exposure to black carbon were missing for 313 and 314, respectively; and data on exposure to carbon monoxide were missing for 152 and 150, respectively. Invalid samples that had failed to pass quantitative quality checks, including samples with unacceptable flow rates, filter damage, and measurement durations outside 24±4 hours, were considered to be missing data.

Table 2. Characteristics of the Live-Born Children.*

Characteristic	Intervention (N=1536)	Control (N=1525)
Sex — no./total no. (%)		
Male	800/1536 (52.1)	787/1525 (51.6)
Female	736/1536 (47.9)	738/1525 (48.4)
Birth weight-for-age z score†	−0.8±1.0	−0.8±1.0
Exclusive breast-feeding — no./total no. (%)‡	702/1436 (48.9)	747/1424 (52.5)
Up-to-date vaccination at trial exit — no./total no. (%)§		
Pentavalent vaccine	1306/1369 (95.4)	1311/1377 (95.2)
Pneumococcal conjugate vaccine	999/1023 (97.7)	1000/1033 (96.8)
Median personal exposure to pollutants during the trial period (IQR)¶		
$PM_{2.5}$ — $\mu g/m^3$‖		
Antenatal period	24.8 (17.0 to 40.5)	77.0 (40.7 to 132.8)
Postnatal period	24.2 (17.8 to 36.4)	66.0 (35.2 to 132.0)
Black carbon during the antenatal period — $\mu g/m^3$**	2.9 (1.7 to 4.8)	10.0 (5.9 to 14.1)
Carbon monoxide — ppm††		
Antenatal period	0.3 (0.1 to 0.8)	1.2 (0.5 to 2.4)
Postnatal period	0.3 (0.0 to 0.8)	1.3 (0.4 to 3.0)

* Plus–minus values are means ±SD.
† Data were missing for 24 participants in the intervention group and 3 in the control group.
‡ Exclusive breast-feeding was defined as feeding only breast milk, without any other foods or liquids including infant formula or water, during the first 6 months of life.
§ At all the international research centers in the trial, up-to-date vaccination with the pentavalent vaccine was considered to be receipt of three doses by 1 year of age. Up-to-date vaccination with the pneumococcal conjugate vaccine was considered to be receipt of three doses by 1 year of age (in Rwanda) or the receipt of two doses by 1 year of age (in Guatemala and Peru); the pneumococcal conjugate vaccine was not available in India.
¶ Median personal exposure to pollutants during the trial period (antenatal or postnatal) refers to the median of the mean postrandomization measurements across the participants in the trial. Invalid samples that had failed to pass quantitative quality checks, including samples with unacceptable flow rates, filter damage, and measurement durations outside of 24±4 hours, were considered to be missing data. Antenatal measurements were determined directly from the personal-exposure measurements in the pregnant women, and postnatal measurements were estimated with the use of an indirect method in which data from the area monitors and the locator devices that were worn by the children were combined.
‖ Data on exposure to $PM_{2.5}$ during the antenatal period were missing for 99 participants in the intervention group and 116 in the control group; data on exposure to $PM_{2.5}$ during the postnatal period were missing for 688 and 592, respectively.
** Data on exposure to black carbon during the antenatal period were missing for 123 participants in the intervention group and 149 in the control group; measurements of exposure to black carbon during the postnatal period were not available.
†† Data on exposure to carbon monoxide during the antenatal period were missing for 86 participants in the intervention group and 95 in the control group; data on exposure to carbon monoxide during the postnatal period were missing for 571 and 609, respectively.

tion had been vaccinated against *H. influenzae* type B and pneumococcal pneumonia, thereby making severe bacterial pneumonia less likely to occur. Second, as observed in this trial and elsewhere, the fact that mitigation efforts during the Covid-19 pandemic dramatically reduced both respiratory virus circulation and pediatric hospitalizations provides indirect evidence regarding the central role of viruses in causing severe childhood respiratory disease.[36,37] However, definitively determining the cause of severe childhood pneumonia is challenging, and we do not have information on respiratory pathogens in these infants. Third, the levels of personal exposure to $PM_{2.5}$ that were achieved in this trial were lower than the levels in other trials[3-6] but remained above the WHO

recommended levels.[38] Although uncertain, it is possible that lower $PM_{2.5}$ exposure levels than those achieved in this trial may be required to reduce the risk of severe pneumonia, and greater reductions may require broader community interventions rather than household strategies as we used. Fourth, even though unvented LPG cookstoves produce nitrogen dioxide at levels lower than biomass cookstoves, these levels are nevertheless above those recommended.[39] Elevated nitrogen dioxide concentrations have been associated with asthma in children[40] and may have contributed to our null results.

Our trial has several limitations. Incomplete

Pneumonia Outcome	Intervention	Control	Incidence Rate Ratio (98.75% or 95% CI)
	no./total no.		
Severe pneumonia (primary outcome)	85/1498	90/1486	0.96 (0.64–1.44)
Pneumonia according to the WHO IMCI guidelines	182/1498	197/1486	0.94 (0.76–1.17)
Severe pneumonia according to the WHO IMCI guidelines	129/1498	138/1486	0.95 (0.74–1.22)
Pneumonia according to the WHO Pocketbook guidelines	178/1498	182/1486	1.00 (0.80–1.25)
Severe pneumonia according to the WHO Pocketbook guidelines	121/1498	122/1486	1.01 (0.78–1.30)
Hypoxemia	69/1498	72/1486	0.99 (0.70–1.41)
Positive imaging	28/1498	29/1486	0.99 (0.57–1.71)
Hypoxemia and positive imaging	16/1498	16/1486	1.03 (0.50–2.13)
Respiratory hospitalization	104/1498	95/1486	1.11 (0.83–1.47)

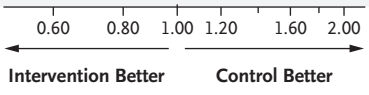

Figure 2. Effects of the Intervention on Primary and Secondary Outcomes.

The 98.75% confidence interval for the incidence rate ratio for severe pneumonia (primary outcome) was adjusted for multiplicity. The 95% confidence intervals of the other outcomes were not adjusted for multiplicity and should not be used to infer definitive treatment effects. Secondary outcome case definitions are provided in Table S1 in the Supplementary Appendix. IMCI denotes Integrated Management of Childhood Illnesses, and WHO World Health Organization.

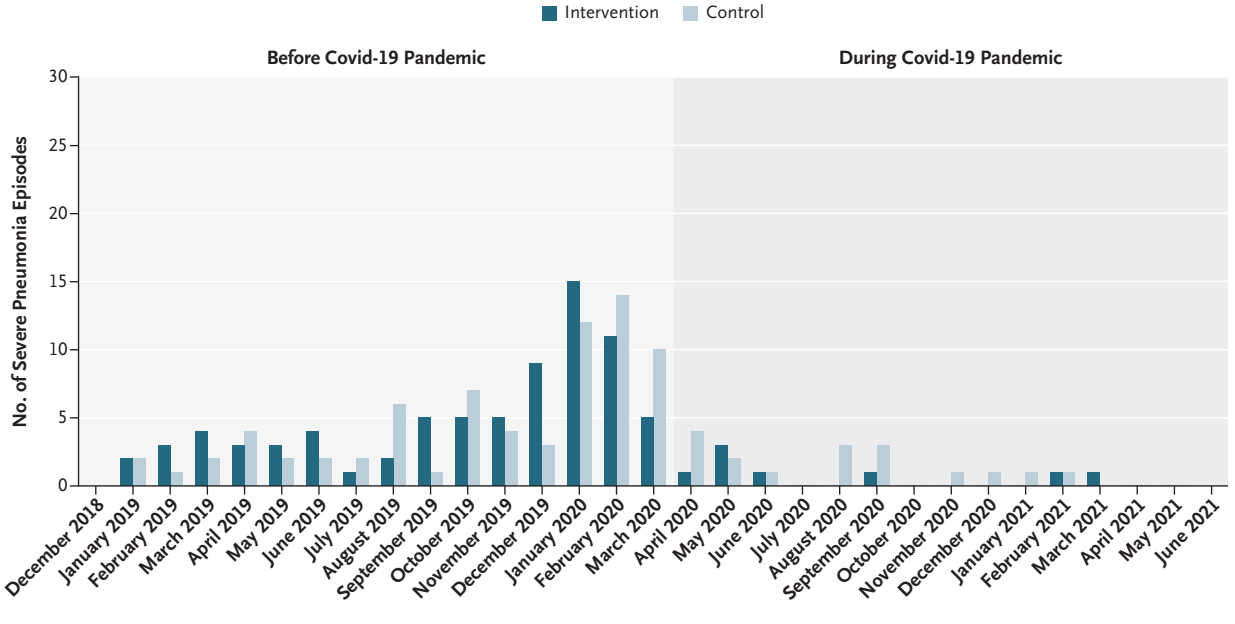

Figure 3. Episodes of Severe Pneumonia over Time.

Covid-19 denotes coronavirus disease 2019.

assessments at facility visits may have led to missed cases, although this is unlikely to have affected our results because the percentage of missingness of data from children who had undergone screening was low. It is also possible that incomplete case ascertainment occurred because care for some children had been sought at clinics outside the surveillance area or had not been sought at all. Missed cases may have been more common during the Covid-19 pandemic period, particularly in the first months during lockdowns. We accounted for the pandemic in our analysis but did not find evidence of differential effects of the pandemic on our results. The wide confidence intervals around our effect estimates mean that we cannot exclude clinically important reductions or increases in the risk of severe pneumonia with the use of LPG cookstoves as compared with biomass cookstoves. Also because there is no gold standard for the diagnosis of pneumonia, the accuracy of our primary case definition of severe pneumonia is undetermined. However, we sought and incorporated external expert recommendations intended to improve the objectivity and specificity of the definition. The results for pneumonia outcomes in which alternative definitions were used were also consistent with the results for the primary outcome.

In this multicenter trial conducted in four low- to middle-income countries, the incidence of severe infant pneumonia was not significantly lower with the use of LPG cookstoves than with biomass cookstoves.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the National Institutes of Health or Department of Health and Human Services.

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APPENDIX

The authors' full names and academic degrees are as follows: Eric D. McCollum, M.D., M.P.H., John P. McCracken, Sc.D., Miles A. Kirby, Ph.D., Laura M. Grajeda, M.S.P.H., Shakir Hossen, M.B., B.S., M.S.P.H., Lawrence H. Moulton, Ph.D., Suzanne M. Simkovich, M.D., Dina Goodman-Palmer, Ph.D., Ghislaine Rosa, Ph.D., Alexie Mukeshimana, Adv.Dip., Kalpana Balakrishnan, Ph.D., Gurusamy Thangavel, M.Sc., Sarada S. Garg, D.N.P., Adly Castañaza, M.D., Lisa M. Thompson, R.N., Ph.D., Anaite Diaz-Artiga, M.P.H., Aris T. Papageorghiou, M.D., Victor G. Davila-Roman, M.D., Lindsay J. Underhill, Ph.D., Stella M. Hartinger, Ph.D., Kendra N. Williams, Ph.D., Laura Nicolaou, Ph.D., Howard H. Chang, Ph.D., Amy E. Lovvorn, M.P.H., Joshua P. Rosenthal, Ph.D., Ajay Pillarisetti, Ph.D., Wenlu Ye, Ph.D., Luke P. Naeher, Ph.D., Michael A. Johnson, Ph.D., Lance A. Waller, Ph.D., Shirin Jabbarzadeh, M.D., M.S.P.H., Jiantong Wang, M.S., Yunyun Chen, M.S.P.H., Kyle Steenland, Ph.D., Thomas F. Clasen, J.D., Ph.D., Jennifer L. Peel, Ph.D., and William Checkley, M.D., Ph.D.

The authors' affiliations are as follows: the Global Program in Pediatric Respiratory Sciences, Eudowood Division of Pediatric Respiratory Sciences (E.D.M.), the Division of Pulmonary and Critical Care (S.H., S.M.S., D.G.-P., S.M.H., K.N.W., L.N., W.C.), and the Center for Global Non-Communicable Disease Research and Training, School of Medicine (S.H., S.M.S., D.G.-P., S.M.H., K.N.W., L.N., W.C.), and the Department of International Health (E.D.M.) and the Program in Global Disease Epidemiology and Control, Department of International Health (L.H.M.), Bloomberg School of Public Health, Johns Hopkins University, Baltimore, the Division of Healthcare Delivery Research, MedStar Health Research Institute, Hyattsville (S.M.S.), and Fogarty International Center, National Institutes of Health, Bethesda (J.P.R.) — all in Maryland; the Global Health Institute, Department of Epidemiology and Biostatistics (J.P.M., L.M.G.), and the Department of Environmental Health Science, College of Public Health (L.P.N.), University of Georgia, Athens, and the Department of Biostatistics and Bioinformatics (H.H.C., L.A.W., S.J., J.W., Y.C.) and the Gangarosa Department of Environmental Health (A.E.L., K.S., T.F.C.), Rollins School of Public Health, and the Nell Hodgson Woodruff School of Nursing (L.M.T.), Emory University, Atlanta — both in Georgia; the Center for Health Studies, Universidad del Valle de Guatemala, Guatemala City (J.P.M., L.M.G., A.C., A.D.-A.); the Department of Global Health and Population, Harvard T.H. Chan School of Public Health, Boston (M.A.K.); the Division of Pulmonary and Critical Care Medicine, Georgetown University, Washington DC (S.M.S.); the Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London (G.R.), and Nuffield Department of Women's and Reproductive Health, University of Oxford, Oxford (A.T.P.) — both in the United Kingdom; Eagle Research Center, Kigali, Rwanda (A.M.); the Indian Council of Medical Research Center for Advanced Research on Air Quality, Climate and Health, Department of Environmental Health Engineering, Sri Ramachandra Institute for Higher Education and Research, Chennai, India (K.B., G.T., S.S.G.); the

Global Health Center, Institute for Public Health and Cardiovascular Division, Department of Medicine, Washington University, St. Louis, MO (V.G.D.-R., L.J.U.); the Division of Environmental Health Sciences, School of Public Health, University of California, Berkeley (A.P., W.Y.), and Berkeley Air Monitoring Group (M.A.J.) — both in Berkeley, CA; and the Department of Environmental and Radiological Health Sciences, Colorado State University, Fort Collins (J.L.P.).

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