

Effect of reduction in household air pollution on childhood pneumonia in Guatemala (RESPIRE): a randomised controlled trial



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Summary

Background Pneumonia causes more child deaths than does any other disease. Observational studies have indicated that smoke from household solid fuel is a significant risk factor that affects about half the world's children. We investigated whether an intervention to lower indoor wood smoke emissions would reduce pneumonia in children.

Methods We undertook a parallel randomised controlled trial in highland Guatemala, in a population using open indoor wood fires for cooking. We randomly assigned 534 households with a pregnant woman or young infant to receive a woodstove with chimney ($n=269$) or to remain as controls using open woodfires ($n=265$), by concealed permuted blocks of ten homes. Fieldworkers visited homes every week until children were aged 18 months to record the child's health status. Sick children with cough and fast breathing, or signs of severe illness were referred to study physicians, masked to intervention status, for clinical examination. The primary outcome was physician-diagnosed pneumonia, without use of a chest radiograph. Analysis was by intention to treat (ITT). Infant 48-h carbon monoxide measurements were used for exposure-response analysis after adjustment for covariates. This trial is registered, number ISRCTN29007941.

Findings During 29 125 child-weeks of surveillance of 265 intervention and 253 control children, there were 124 physician-diagnosed pneumonia cases in intervention households and 139 in control households (rate ratio [RR] 0.84, 95% CI 0.63–1.13; $p=0.257$). After multiple imputation, there were 149 cases in intervention households and 180 in controls (0.78, 0.59–1.06, $p=0.095$; reduction 22%, 95% CI –6% to 41%). ITT analysis was undertaken for secondary outcomes: all and severe fieldworker-assessed pneumonia; severe (hypoxaemic) physician-diagnosed pneumonia; and radiologically confirmed, RSV-negative, and RSV-positive pneumonia, both total and severe. We recorded significant reductions in the intervention group for three severe outcomes—fieldworker-assessed, physician-diagnosed, and RSV-negative pneumonia—but not for others. We identified no adverse effects from the intervention. The chimney stove reduced exposure by 50% on average (from 2.2 to 1.1 ppm carbon monoxide), but exposure distributions for the two groups overlapped substantially. In exposure-response analysis, a 50% exposure reduction was significantly associated with physician-diagnosed pneumonia (RR 0.82, 0.70–0.98), the greater precision resulting from less exposure misclassification compared with use of stove type alone in ITT analysis.

Interpretation In a population heavily exposed to wood smoke from cooking, a reduction in exposure achieved with chimney stoves did not significantly reduce physician-diagnosed pneumonia for children younger than 18 months. The significant reduction of a third in severe pneumonia, however, if confirmed, could have important implications for reduction of child mortality. The significant exposure-response associations contribute to causal inference and suggest that stove or fuel interventions producing lower average exposures than these chimney stoves might be needed to substantially reduce pneumonia in populations heavily exposed to biomass fuel air pollution.

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Introduction

Acute lower respiratory infection (ALRI) is the leading cause of death in children, with most fatal cases occurring as pneumonia in children younger than 5 years in developing countries.¹ Poverty is thought to be the primary cause, which manifests as malnutrition, including micronutrient deficiencies, and limited access to medical care.² Another attribute of poverty is household air pollution from use of unprocessed biomass fuels (wood, animal dung, and crop wastes) and coal in simple stoves.³ Findings from a meta-analysis of published observational studies showed that young

children exposed to smoke from use of household biomass fuel had a rate of ALRI twice that of children not exposed or when cleaner fuels were used.⁴ Furthermore, studies have shown that ALRI risks are associated with short-term air pollution measurements⁵ and other indicators of exposure.^{6–8}

The substantial indoor concentrations of important health-damaging pollutants that result from the use of these fuels are thought to explain the relation with ALRI. As with tobacco smoke, there are thousands of compounds in gaseous and aerosol forms in biomass fuel smoke, including several with effects that include

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immune system suppression, severe irritation, inflammation, ciliary dysfunction, and carcinogenicity.⁹ Small particles are typically used as an indicator of the health risk for these mixtures, and are commonly present in households using biomass fuels without effective chimneys at concentrations ten to 100 times higher than is recommended in health-based guidelines.^{10,11}

Viral agents have an important role in ALRI, although most deaths are thought to arise through bacterial infection, which can occur with or without initial viral infection.¹² Of the viral agents, respiratory syncytial virus (RSV) is the most common in young children, although its incidence varies by season.^{13,14} Evidence about the relation between exposure to biomass fuel smoke and risk of RSV illness is conflicting.¹⁵ One study from The Gambia¹⁶ reported reduced risk of severe RSV illness with increased exposure to cooking smoke, raising the possibility of a differential effect of household air pollution on viral and bacterial ALRI.

The evidence of ALRI risk associated with biomass fuel use is limited by several methodological issues.^{15,17} Previous studies used observational designs, which have the inherent difficulty of residual confounding from the association between biomass fuel use and other poverty-related ALRI risk factors, particularly nutrition. Studies used hospital-based or community-based case-finding; those using hospital-based case-finding were susceptible to selection bias because of differences in health-care seeking behaviour, whereas those using community-based case-finding probably misclassified as ALRI many upper respiratory tract infections, which are more common, can have a different relation with air pollution, and do not cause substantial morbidity or mortality.¹⁸ Since few studies have assessed indicators of ALRI severity (eg, hypoxaemia), and none has attempted to differentiate all ALRI by aetiological agent (viral vs bacterial), the effect of household air pollution on factors that are known to increase case fatality has not been possible to assess.¹⁹ None of the studies directly assessed long-term air pollution exposures, relying instead on indirect exposure indicators such as fuel or stove type, or whether a child is carried on the mother's back during cooking—methods that are inevitably associated with substantial exposure misclassification. Finally, the absence of masking could have led to bias—eg, when interviewing parents about exposure history in case-control studies. Although studies have shown associations between ambient air pollution and child ALRI, most were set in developed countries, where the epidemiology of child pneumonia and associated risk factors differs greatly from that in developing countries.²⁰

We report on RESPIRE (Randomised Exposure Study of Pollution Indoors and Respiratory Effects), a randomised controlled trial to assess whether a specific intervention to lower indoor wood smoke emissions would reduce child pneumonia.

Methods

Study design and setting

The study was undertaken between October, 2002, and December, 2004, in the San Marcos region of highland Guatemala. This site was chosen after assessment of ten options in Asia, Africa, and Latin America, on the basis of criteria related to child health (high infant mortality, ALRI incidence), high exposure to household air pollution, feasible host country logistics, and strong local institutional support. Pilot studies were undertaken to obtain data needed to design the randomised controlled trial.^{21–31} The site has already been described.³² Briefly, it is home to a primarily agricultural indigenous population living at 2200–3000 m above sea level, within 23 villages spread over about 94 km² in the western Guatemalan highlands. Nearly all households use only wood for cooking and space heating, with small amounts of crop residues such as corn stalks dependent on season. Pre-intervention pneumonia rates in young children were estimated at 0·5 episodes per child-year.³³ Average daily temperatures vary little throughout the year, at 10–13°C. Cold season night-time temperatures, however, sometimes fall below freezing, so families expect a stove to provide modest space heating.

Malaria is not endemic at this elevation, and HIV and tuberculosis are rare. All but two study households reported exclusive breastfeeding of children younger than 4 months. Anthropometric assessment confirmed severe undernutrition in this population, with substantial growth retardation in most study children; by 17 months, the average height-for-age Z scores as a measure of stunting were three SDs below normal.³⁴

The primary objective was to establish whether a reduction in smoke pollution with use of a chimney stove would reduce the risk of pneumonia in children up to 18 months of age. The secondary objective was to investigate whether there is an increased effect on pneumonia that is more severe or more likely of bacterial cause, as indicated by RSV-negative status. Results for the third objective, to describe the exposure-response function for household air pollution and ALRI, are reported briefly here to assess consistency and support causal inference, and will be described fully elsewhere.

Rapid assessment was undertaken in 5365 households to screen for recruitment on the basis of eligibility criteria of use of an open fire for cooking in an enclosed kitchen and presence of a pregnant woman or child younger than 4 months. Older children were excluded to have at least 12 months of follow up after stove installation and because in this population children begin walking by 18 months, which alters their exposure patterns. Households were excluded if they expected to migrate for seasonal work for more than 6 weeks.

Human participant approvals were obtained from University of California (Berkeley, CA, USA), Universidad del Valle (Guatemala City, Guatemala), the US Centers for Disease Control and Prevention (Atlanta, GA, USA),

the University of Liverpool (Liverpool, UK), and WHO (Geneva, Switzerland). An independent data safety monitoring board was sent reports of project activities, cases, and deaths every 3 months, and had authority to stop the trial if there had been evidence of harm or of the impossibility of showing an effect. Local, trained fieldworkers visited each recruited household and obtained oral informed consent from the primary adult care-giver (usually the mother) of the household.

Randomisation and masking

Half of households were randomly assigned to receive a locally developed chimney stove and the other half to act as controls using open wood fires (figure 1). Randomisation was generated electronically at University of California, Berkeley, with permuted blocks of size 10, with a ratio of 1:1, to ensure equal control and intervention household numbers within communities. Recruitment was done by the field team proceeding from village to village, and was managed by Universidad del Valle. The allocation sequence was concealed from the recruiting field team, and was applied only after consent was obtained. Stoves were produced and installed by an experienced local company (Tasprovi, Quetzaltenango, Guatemala). During follow-up, control homes continued to use the traditional open fire in the usual way, and were offered a chimney stove on completion of follow-up when the child reached 18 months or on leaving the study for any reason (death of child, emigration, or declined to continue follow-up).

Procedures

Follow-up and health outcome assessment methods have also been described in detail.³² The primary outcome was physician-diagnosed pneumonia, without use of a chest radiograph. Secondary outcomes were fieldworker-assessed pneumonia (all and severe) and seven other conditions of physician-diagnosed pneumonia: severe (hypoxaemic); radiograph confirmed (all and severe); RSV-negative (all and severe); and RSV-positive (all and severe). Household visits were undertaken every week by fieldworkers who were trained with standard Integrated Management of Childhood Illness (IMCI) materials to identify ill children. On the basis of fieldworker assessments, ill children were classified according to the IMCI algorithm as WHO pneumonia, which was defined as cough or difficulty breathing plus age-specific raised respiratory rate, or WHO severe pneumonia, which was defined as cough or difficulty breathing and the presence of lower chest wall indrawing or inability to breastfeed or drink, both of which were analysed as secondary outcomes.³⁵ These children were then referred to study physicians who underwent monthly standardisation training for diagnosis and treatment. Although fieldworkers assessing children in homes could not be masked, the physicians examined children in community centres near each village to maintain masking to intervention

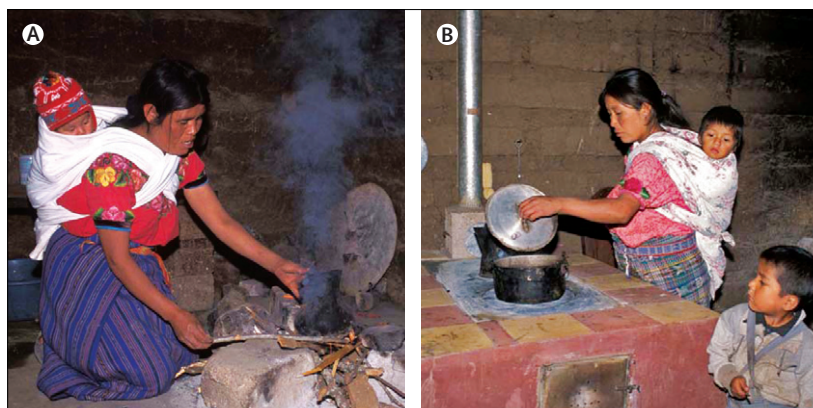


Figure 1: Traditional open fire used for cooking (A) and the locally developed and constructed high-mass chimney woodstove (B)

The chimney woodstove has a thick metal heating surface for cooking tortillas and holes with removable concentric rings for pots, a firebrick combustion chamber with baffling, a concrete and brick body, tile surfaces around the cooking area, dirt and pumice stone insulation, a metal fuel door, and a metal chimney with damper. Printed with permission of the women pictured.

status. Treatment for pneumonia and other diseases was begun immediately by the study physicians and, if severely ill, the child was referred to a local hospital. Children were defined as not at risk for a new episode of a specific pneumonia classification until at least 21 days had passed since a previous episode of that same type was recorded, unless the child had already been seen at least 7 days after that previous episode and was classified at that time as being free of any pneumonia by the fieldworker or physician.

Oxygen saturation was measured by pulse oximetry, and hypoxaemia defined as less than 87%, which was two SDs below the mean value for well children in our study population.³² We use hypoxaemia as the criterion for severe physician-diagnosed pneumonia. Subject to parental consent, all children diagnosed with pneumonia had an RSV enzyme immunoassay test (Becton-Dickinson Directigen RSV, Sparks, MD, USA), and were offered transport to a clinic 45 min away for a chest radiograph. This radiograph was taken up to 2 days after clinical examination, and films were not available to the physician at the time of diagnosis. Not all children received an RSV test or chest radiograph, because some parents refused. Films were assessed in a masked manner by two physicians, following a standardised method for pneumonia interpretation developed by WHO.³⁶ There were ten different outcome assessments planned (two fieldworker assessed and eight physician diagnosed), spanning a range of sensitivity, specificity, and objectivity. Verbal autopsies were undertaken on all child deaths by an independent panel that was unaware of the intervention status and with the standard instrument and procedure developed by WHO.³⁷

Weekly fieldworker home visits included assessment of how well the chimney stove was functioning and arrangement of repair if needed. Personal 48-h carbon monoxide exposures—serving as an indicator for wood

smoke^{31,38}—were obtained with diffusion tubes (Gastec Corp, Fukayanaka, Ayase-City, Japan) every 3 months for all study children, and are used here for preliminary reporting of exposure-response analysis. The results of these monitoring efforts are reported separately.^{39,40}

Follow-up ended in December, 2004, because the number of child weeks of follow-up needed to meet sample size requirements had been achieved, and few children younger than 18 months remained in the study.

Statistical analysis

Sample size was calculated to detect a 25% reduction in the primary outcome, with a baseline incidence of 0.5 episodes per child per year, two-sided $\alpha=0.05$, power=0.80, and a 20% dropout rate from migration, death, and project fatigue. This sample size yielded a requirement for 630 child-years, which would be feasible if 500 children were recruited for the expected period of follow-up. 534 of 777 eligible households (69% response) were eventually recruited, 518 (97%) of which contributed to the final ALRI dataset.

Data entry, compilation, and interim simple statistics were done by investigators who were masked to intervention status throughout the project. The

intervention codes were merged only after all surveillance was complete. SAS (version 9.1) software was used to calculate descriptive statistics for household and participant characteristics by randomised groups.

Rate ratios (equivalent here to relative risks) were estimated in intention-to-treat analysis for new episodes with pooled logistic regression (webappendix pp 1–2). A generalised estimating equation approach and empirical SEs were used to account for multiple episodes within a child.⁴¹

About a third of children with new illness episodes meeting criteria for WHO pneumonia on the basis of fieldworker assessments were not seen by the physician, and of those seen by the physician, not all received RSV testing or had chest radiographs taken. Missing data were more common in the control than in the intervention group.³² Therefore, we used multiple imputation to reduce bias attributable to incomplete outcome assessment. With use of the available respiratory signs and symptoms, as well as household and child baseline characteristics, season, and child age, we created logistic regression models to predict the missing pneumonia observations. Separate models, stratified by intervention status, were created for each of the eight pneumonia classifications involving physician diagnosis. Independent variables with *p* values less than 0.1 in either stratum were maintained in the imputation models (webappendix p 3).

We used Proc MI in SAS (version 9.1) to do multiple imputation on the basis of these models and created 100 complete datasets for each outcome. Generalised estimating equations were then used, as in the primary case analysis, with one log rate ratio estimate for each dataset, which were combined with SAS Proc Mianalyze. Since the Proc MI procedure does not account for correlation among repeated observations within a child, bootstrap CIs were calculated by application of the bias-corrected method to estimates from 2000 random samples of children selected with replacement.⁴² We calculated two-sided *p* values by dividing the multiple-imputation estimate from the original sample by the bootstrap SD and comparing this estimate to the standard normal distribution.

To explore the consistency with the intention-to-treat analysis, to assess the extent to which exposure misclassification might limit the ability to detect effects in the analysis, and to examine an additional potential contribution to causal inference, we also undertook exposure-response analysis with the child carbon monoxide measurements over 48 h, which had been repeated about every 3 months during participation in the study.⁴⁰ We used the natural log-transformed mean of the carbon monoxide measures for each child as the exposure variable. Although carbon monoxide is not the pollutant in wood smoke that is thought to contribute to ALRI risk, it is highly correlated to fine particles in this setting.^{31,38} Because the exposure metric was no longer randomised, we used multivariate analysis with adjustment for several

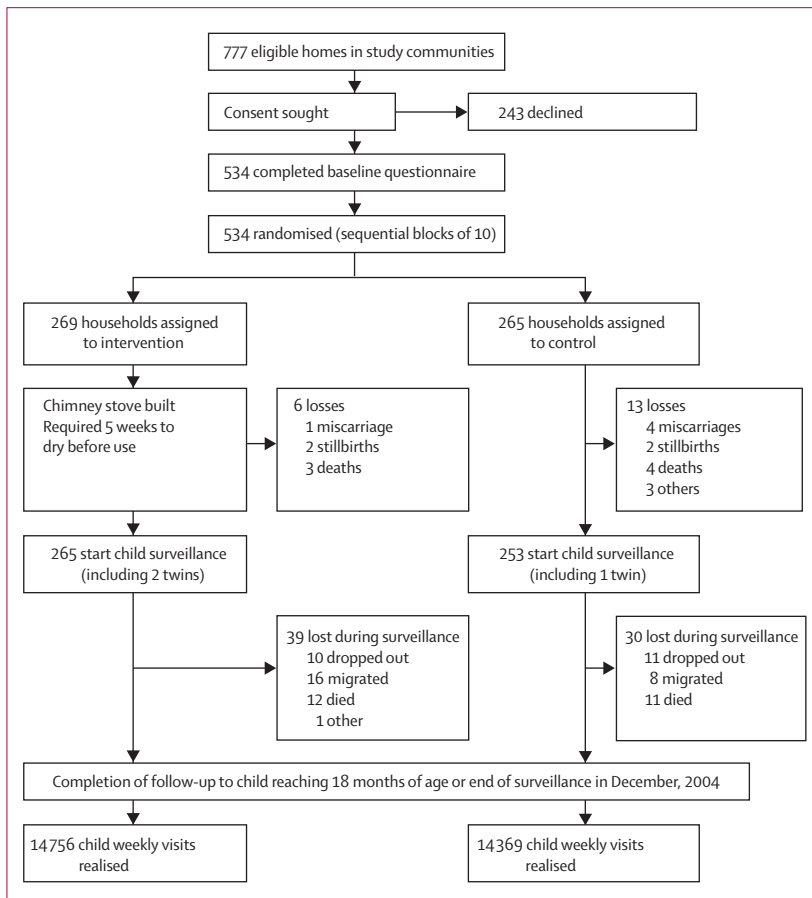


Figure 2: Trial profile

potential confounders. Importantly, stove type, which was randomised, remained the most important covariate, explaining 49% of the exposure variance.³⁹

This trial is registered, number ISRCTN29007941.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data and final responsibility to submit this paper for publication.

Results

Figure 2 shows the trial profile. Recruitment was done in two groups: group A (n=321) was recruited in October–November, 2002, and achieved a 59% acceptance (of 540); group B (n=213) was recruited in April–May, 2003, and achieved a higher level of acceptance (90% of 237), indicating the growing trust that the field team built with the community. Of the 534 study households, 269 were randomised to the intervention group and 265 to the control group. Six from the intervention group and 13 from the control group were lost during the drying period of the chimney stove construction (about 5 weeks), before start of health surveillance (figure 2). Because three sets of twins were born, 265 children were retained in the intervention group and 253 in the control group. After consultation with the project data safety monitoring board, surveillance data from one child with Down's syndrome were excluded before breaking of the code. All other children were retained in the analysis. Baseline characteristics of the households in the intervention and control groups were similar (table 1). There was a smoker in around a quarter of homes, but the intensity of smoking in this population is low, with 91% reporting that cigarettes were rarely smoked in the home. Proportions of children lost to follow-up were slightly higher in intervention than in control households, and were due mainly to internal migration (figure 2). We noted no consistent differences in baseline household characteristics between the dropouts in the intervention and control groups, nor between dropouts and the overall sample (data not shown).

14756 weekly surveillance visits occurred in intervention households and 14369 in control households, together making about 560 child-years. Table 2 shows the numbers of these visits at which the child was at risk for each outcome. There were more observed child weeks defined as at risk for physician-diagnosed outcomes than fieldworker-assessed outcomes because parents occasionally brought children directly to the study physician, despite not being at home during the fieldworker visit. Fieldworker assessment identified 321 new episodes of WHO pneumonia in the intervention households, and 340 in the control households (table 2). Fieldworker assessment identified 26 cases of severe WHO pneumonia in intervention households and 45 in control households (table 2).

Physician clinical diagnosis of pneumonia (the primary outcome) identified 124 cases in intervention households and 139 cases in control households (rate ratio [RR] 0·84, 0·63–1·13, p=0·257). For physician-diagnosed pneumonia, 340 of 518 (66%) children had no episodes, 119 (23%) one episode, and 59 (11%) more than one episode. The range was zero to seven episodes, and the mean number of cases per child was 0·47 (SD 0·73) in the intervention group and 0·55 (0·99) in the control group. For physician-diagnosed severe pneumonia, 413 (80%) had no episodes, 82 (16%) one episode, and 23 (4%) more than one episode. The range was zero to four episodes, and the mean number of cases per child was 0·23 (SD 0·52) in the intervention group and 0·30 (0·66) in the control group.

71% (242/340) of WHO pneumonia cases based on fieldworker assessments were seen by the physician (on the day of referral or subsequently that week) in intervention households and 65% (240/367) in control households. The proportion at risk seen by the physician

	Intervention (N=269)	Control (N=265)
Household characteristics		
Altitude (m)	2601 (179)	2613 (185)
Dirt floor in main home	239 (88·8%)	245 (92·5%)
No electricity in main home	81 (30·1%)	81 (30·6%)
Roof type		
Straw	16 (6·0%)	10 (3·7%)
Aluminum	200 (74·3%)	205 (77·4%)
Tile	53 (19·7%)	50 (18·9%)
Number of rooms in house	1·2 (0·4)	1·2 (0·4)
Number of people in house	7·4 (2·8)	7·3 (2·9)
Cooking area in separate closed room	200 (74·3%)	202 (76·2%)
Leaks in roof	89 (33·1%)	65 (24·5%)
Kitchen volume (m ³)	40·9 (22·2)	40·6 (22·8)
Kitchen eave spaces		
Completely closed	55 (20·4%)	46 (17·4%)
Partially closed	101 (37·5%)	102 (38·5%)
Completely open	113 (42·0%)	117 (44·1%)
Stove in same room as bed	37 (13·8%)	35 (13·2%)
Smoker present in home	55 (20·4%)	71 (26·8%)
Has temazcal wood-fired sauna bath	234 (87·0%)	224 (84·5%)
Maternal characteristics		
Recruited during pregnancy	138 (51·3%)	128 (48·3%)
Maternal age (years)	26·4 (7·2)	27·0 (6·8)
Maternal education		
None	83 (30·8%)	98 (36·9%)
Elementary school	162 (60·2%)	157 (59·2%)
Secondary school	13 (4·8%)	4 (1·5%)
Missing	11 (4·2%)	6 (2·4%)
Data are mean (SD) or number (%).		
Table 1: Baseline characteristics of the 534 participating RESPIRE households, by randomised group		

	Definition	Observed: new cases/ child weeks		Incomplete observations: child weeks		Observed and imputed			
		Intervention	Control	Intervention	Control	New cases/child weeks		RR (95% CI)	p value
						Intervention	Control		
Fieldworker assessed									
All*	Child ill with cough and/or difficult breathing, plus meeting criteria for referral to study physician as possible ALRI (WHO pneumonia): age <2 months with respiratory rate ≥ 60 breaths per min, nasal flaring, grunting, stridor, audible wheeze, or chest wall indrawing; or age ≥ 2 months with fast breathing (≥ 50 breaths per min for children aged 2 months to <12 months, ≥ 40 breaths per min for children aged ≥ 12 months), and/or chest wall indrawing, audible wheeze, stridor	321/14 379	340/13 939	1010	786	0.91 (0.74–1.13)	0.393
Severe*	Severe WHO pneumonia defined as above, but with chest wall indrawing and/or inability to drink or breastfeed	26/14 719	45/14 310	1050	815	0.56 (0.32–0.97)	0.036
Physician diagnosed									
Clinical pneumonia									
All†	Based on history and clinical examination. Pulse oximetry but not chest radiograph was available to the physician at time of diagnosis	124/15 526	139/14 871	95	127	149/15 596	180/14 955	0.78 (0.59–1.06)	0.095
Severe*	As above, with hypoxaemia measured by pulse oximetry, and defined as $\leq 87\%$ (2 SD below mean for well study children) ³²	60/15 553	76/14 891	96	133	72/15 637	101/14 998	0.67 (0.45–0.98)	0.042
Radiological pneumonia									
All*	Subset of clinical pneumonia with chest radiograph confirmation	41/15 558	44/14 886	120	178	59/15 640	76/15 000	0.74 (0.42–1.15)	0.231
Severe*	As above, but also hypoxaemic	25/15 559	28/14 891	109	153	36/15 659	49/15 024	0.68 (0.36–1.33)	0.234
RSV negative									
All*	Subset of clinical pneumonia with negative result on RSV direct antigen test	73/15 542	77/14 877	105	152	95/15 625	115/14 998	0.79 (0.53–1.07)	0.192
Severe*	As above, but also hypoxaemic	27/15 564	42/14 899	100	143	35/15 656	61/15 025	0.54 (0.31–0.91)	0.026
RSV positive									
All*	Subset of clinical pneumonia with positive result on RSV direct antigen test	43/15 556	43/14 879	103	151	54/15 648	67/15 009	0.76 (0.42–1.16)	0.275
Severe*	As above, but also hypoxaemic	30/15 568	27/14 897	99	142	38/15 659	42/15 025	0.87 (0.46–1.51)	0.633

Multiple imputation was used to adjust for effect of missing data for physician-diagnosed outcomes. For full definitions of outcomes, see Bruce et al.³² Denominators are child-weeks at risk, which vary slightly by outcome, and thus should not be compared directly with those in figure 2. ALRI=acute lower respiratory infection. RSV=respiratory syncytial virus. RR=rate ratio. *Secondary outcome. †Primary outcome.

Table 2: Associations between randomised chimney stove intervention and pneumonia by endpoint of ALRI

was greater for severe fieldworker-assessed cases (87% [20/23] in intervention households and 69% [29/42] in controls). Additionally, mothers in the intervention group were somewhat more likely to consent to RSV testing (intervention 94% [116/124] vs controls 86% [120/139]) and to chest radiography (81% [101/124] vs 76% [105/139]) than were those in the control group.

On the basis of the physician assessments and after multiple imputation to account for missing visits, we estimated 149 cases of pneumonia in intervention households and 180 cases in controls (22% reduction, 95% CI –6% to 41%; table 2). For severe (hypoxaemic) pneumonia, there were 72 cases in the intervention group and 101 in the control group (table 2; webappendix p 4 shows detailed results of imputation). Table 2 shows further analyses by RSV status and for

radiological pneumonia. In severe (hypoxaemic) cases, we recorded a significant effect for RSV-negative cases, but not for RSV-positive cases (table 2).

Figure 3 shows effect estimates and 95% CIs for intention-to-treat analysis before and after adjustment by multiple imputation for the differential compliance with fieldworker referral and investigations. Webappendix pp 2 and 4 show RRs and CIs before and after imputation. Effect estimates are stronger for all outcomes after imputation, as anticipated from the lower compliance in the control group than in the intervention group. No imputation was done for fieldworker outcomes.

Nine of the 23 deaths occurring during surveillance were assigned to pneumonia by verbal autopsy. Four of these nine deaths occurred without care being sought from the study physician: two sought alternative local

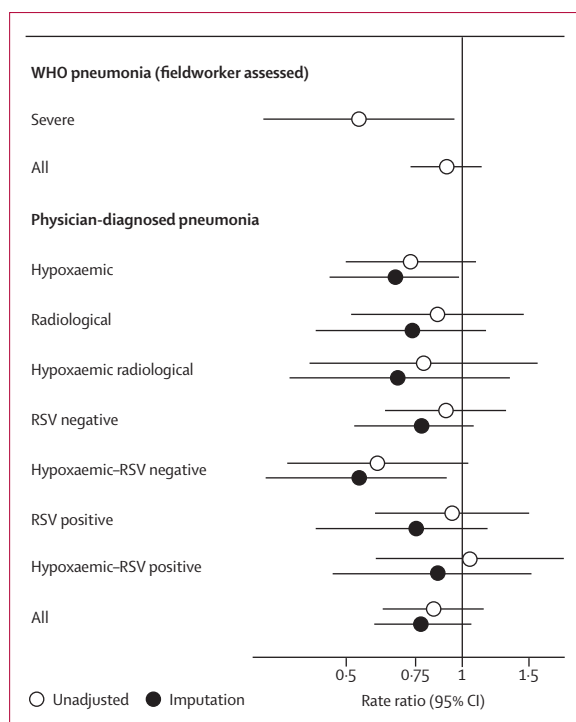


Figure 3: Comparison of effect estimates of chimney stove intervention across the ten outcomes examined (fieldworker-assessed [WHO] pneumonia and severe pneumonia, and the eight outcomes based on physician diagnosis) The results are shown within each physician-diagnosed outcome for unadjusted estimates and those adjusted by multiple imputation for bias attributable to incomplete outcome assessments. RSV=respiratory syncytial virus.

care, and two sought care from outside the study area. Three occurred in children in the intervention group and six in those in the control group (relative risk 0.48, 95% CI 0.12–1.91, $p=0.296$). Use of the intervention stove was not associated with any important adverse events, including burns (data not shown).

Quarterly measurements in a random eighth subsample indicated that 48-h carbon monoxide concentrations in the kitchen were about 90% lower in chimney stove households than in control households,⁴⁰ whereas quarterly personal measurements on all children indicated that the chimney stove was associated with an approximate 50% reduction in personal 48-h exposures from about 2.2 to 1.1 ppm carbon monoxide.^{39,40} Comparison of sociodemographic information collected during the rapid assessment with that of participating households suggested that the sample was similar to the population using open wood fires across the study area (webappendix p 5).

The intention-to-treat analysis used randomised stove type alone as the indicator of exposure. However, data for carbon monoxide exposure showed that classification based on stove type introduces substantial exposure misclassification. Although the mean exposure for children in households assigned to chimney stoves was shifted downwards by about 50%, we noted considerable overlap between the two distributions. Some children in

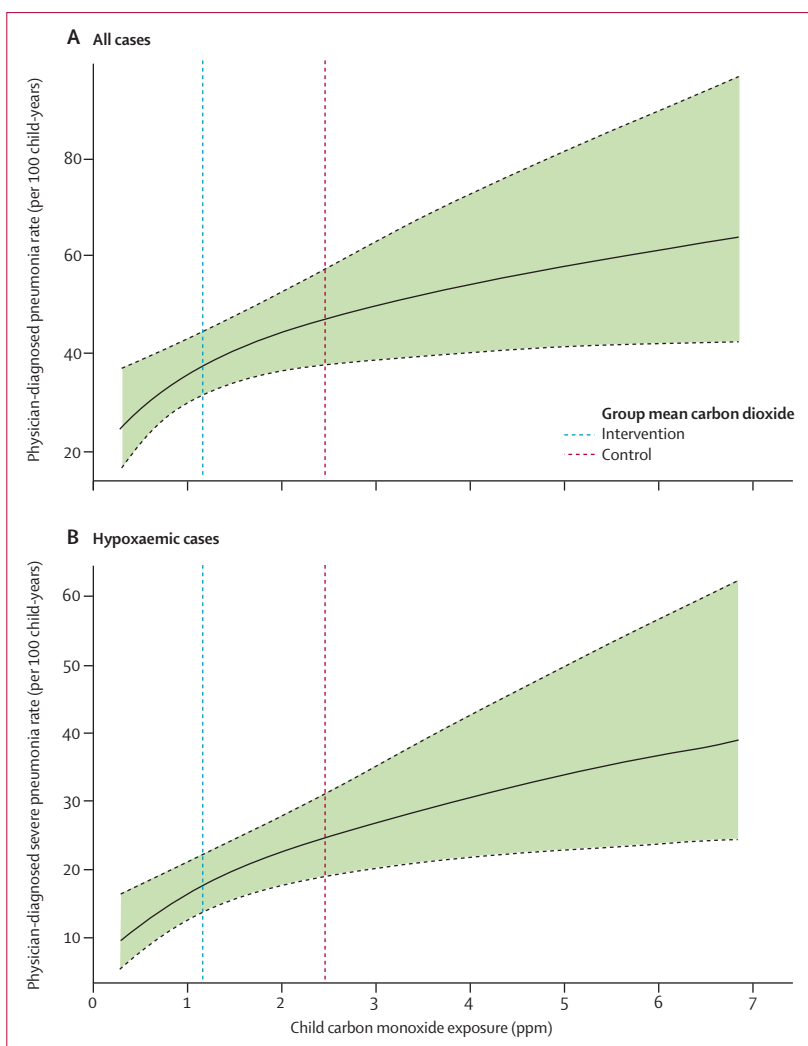


Figure 4: Exposure-response for personal carbon monoxide concentrations in study children for physician-diagnosed pneumonia (A) and physician-diagnosed severe (hypoxaemic) pneumonia (B) Vertical axis shows the adjusted incidence per 100 child-years and horizontal axis shows carbon monoxide exposures for each child. The dotted vertical lines show the mean exposures of children in the intervention and control groups. The shaded areas indicate the 95% confidence bounds. Child-specific average of 48-h personal carbon monoxide measures are repeated roughly every 3 months. Data are adjusted for child's age (quadratic), sex, birth interval less than 2 years (yes vs no), mother's age (quadratic), maternal education and paternal education (none vs primary vs secondary), secondhand tobacco smoke exposure (yes vs no), latrine (yes vs no), piped water (yes vs no), electricity (yes vs no), kerosene lamp (yes vs no), wood-fired sauna (yes vs no), bedroom in kitchen (yes vs no), roof type (metal sheet vs tiles vs straw), earth floor (yes vs no), asset index (linear over range 0–6), animal ownership index (linear over range 0–4), crowding index (people per room), altitude (five categories), occupation (farm other land vs farm own land vs other), and season (cold dry, warm wet, warm dry).

households with open fires, for example, had lower exposures than did many with chimney stoves, and vice-versa.^{39,40} To reduce exposure misclassification, we report an exposure-response analysis for two important physician-diagnosed outcomes: all physician-diagnosed pneumonia and physician-diagnosed hypoxaemic (severe) pneumonia.

For both outcomes, a model with natural log-transformed personal carbon monoxide exposure fitted the data best, and we recorded a significant reduced

pneumonia risk with lower exposures (figure 4). A mean carbon monoxide exposure reduction of 50%, equivalent to that caused by the chimney stove, was associated with a relative risk of 0·82 (95% CI 0·70–0·98) for physician-diagnosed pneumonia and 0·72 (0·59–0·92) for physician-diagnosed hypoxaemic pneumonia. These values are similar to the central estimates for the intention-to-treat analysis (table 2), but are now statistically significant, as were results for all and severe radiologically confirmed pneumonia in exposure-response analysis (data to be presented elsewhere). Exposure reduction to levels below the average achieved by the chimney stove seemed to result in additional reduction in pneumonia risk (figure 4).

Discussion

Findings from the RESPIRE trial have shown that in rural Guatemalan homes traditionally using wood fuel in open fires, a chimney stove did not significantly reduce physician-diagnosed pneumonia in children. The reasons for no effect being detected could be attributable to insufficient exposure reduction or insufficient power, or the fact that the previously observed association might not be causal. The first two of these reasons are closely inter-related, and are most plausible. The sample size for the trial was set for a 25% reduction in a pneumonia incidence of 0·5 episodes per child per year, whereas the effect recorded was a 22% reduction. Exposure misclassification (overlapping distributions) will have introduced additional error; we noted that in exposure-response analysis in which the misclassification is much reduced, similar sized effects on the primary outcome (for a 50% exposure change) were more precisely estimated and statistically significant. The shape of the exposure-response function (figure 4) showed that larger exposure reduction to less than the average in the chimney stove group is associated with a greater reduction in pneumonia risk. Hence, if the chimney stove had reduced exposure more, or more statistical power had been available, a significant effect on all physician-diagnosed pneumonia might have been detected.

The third reason—namely, that the association is not causal—seems unlikely in view of the nature and diversity of the evidence now available, with reference to the Bradford-Hill criteria.⁴³ Our findings of an exposure-response association accord with that reported from Kenya by Ezzati and Kammen,⁴⁴ evidence from ambient air pollution⁴⁵ and secondhand tobacco smoke,⁴⁶ and plausible mechanisms.⁴⁷ Furthermore, although not the outcomes on which sample size were estimated, intention-to-treat analysis in RESPIRE has shown significant reductions in severe fieldworker-assessed and severe physician-diagnosed pneumonia outcomes. That the severe physician-diagnosed cases included an element of objective assessment (pulse oximetry) adds some weight to these findings.

Although the mean concentrations of carbon monoxide in the kitchen were lowered by a factor of ten, child exposures were lowered by only a factor of two.^{39,40} This difference results from the chimney stoves not greatly reducing emissions but merely venting smoke to the immediate outdoors, some of which re-enters the homes and generally contaminates both outdoor and indoor environments where children spend some of their time. Additionally, children are exposed to smoke from open fires when in neighbours' homes and from other wood combustion in the area. The modest reduction in total carbon monoxide exposure occurred even with the high stove use that was achieved in this efficacy trial through weekly visits to the households, during which fieldworkers encouraged use of the chimney stove and provided repairs and maintenance if needed.

RSV testing was included to investigate the a-priori hypothesis of a differential effect of household air pollution reduction on pneumonia by RSV status, particularly for severe cases.¹⁶ We recorded no evidence of a differential effect of the intervention on RSV-positive and RSV-negative cases for all pneumonias. For severe (hypoxaemic) pneumonia, however, we noted a significant and larger reduction for RSV-negative than for RSV-positive cases. This result is intriguing, consistent with our a-priori hypothesis, and potentially important because severe RSV-negative cases are those most likely to be of bacterial cause and have a higher mortality.

The mechanisms and respiratory tract compartments involved with RSV infection differ from those involved with bacterial infection. RSV infects the airway epithelium and is cleared largely by T-cell-dependent immune processes.⁴⁸ By contrast, bacteria invade the alveoli and lung parenchyma, and macrophages have a central role in the defence against bacterial pneumonia. Alveolar macrophages have decreased phagocytic function when laden with soot, as occurs with increased amounts of household air pollution.⁴⁹

Less than 50% of clinically diagnosed pneumonia cases show infiltrates on chest radiograph,^{17,50} and our data accord with this finding. The trial was not powered to detect differences in radiologically diagnosed pneumonia, and additional power was lost because of parental refusal to allow chest radiographs to be taken. Furthermore, the trial was not designed to study mortality, but the non-significant reduction for pneumonia deaths based on verbal autopsy in the chimney stove group is consistent with what was recorded for severe pneumonia.

Although the chimney stove was chosen mainly to reduce kitchen air pollution and child exposure, health effects could have been mediated through other stove effects—eg, for nutrition and hygiene. Although an improved stove might change household nutrition, there was no intervention effect on child growth rates.³⁴ The only important difference attributable to the chimney stove would therefore seem to be reduced air pollution for children, mainly after birth. Although 50% (266 of 534) of

the children were recruited while in utero, the median prenatal exposure to the chimney stove of intervention children was only 40 days (IQR 0–78).

The main limitation in study design was that it could not be double-blinded at the household level. As discussed by Bruce and colleagues,³² there was no evidence of a difference by intervention status in fieldworkers' referral decisions based on presence or absence of pneumonia symptoms and signs at the weekly home visits. Nor was there consistent evidence of a significant difference in clinical criteria used for pneumonia diagnosis by the physicians, who did not visit homes and, as far as could be ascertained, remained masked to intervention status when seeing children in the community centres.

Clearly, however, awareness of intervention status did affect the households themselves, because homes with chimney stoves had higher acceptance of study medical procedures than did those without stoves. Our results show that the unadjusted effect estimates for RSV-negative and RSV-positive cases are both smaller (closer to the null) than is that for physician-diagnosed pneumonia overall (figure 3). These unadjusted results are difficult to interpret because they are biased by the differential compliance of the parents in consenting to have their child tested. The imputed results reported in table 2 and shown in figure 3 yield more consistent results for physician outcomes. Consequently, we regard these outcomes based on imputation as being the more reliable estimates of the chimney stove effect.

The study results, and in particular the findings from exposure-response analysis, imply that if prevention of child pneumonia is to be achieved through the control of household air pollution from biomass fuel use, larger exposure reduction will be needed. Such exposure reduction may require either clean fuels or biomass stoves with cleaner combustion than this chimney stove.

The RESPIRE sample was similar to the wider population of households using open wood fires in the study area, which is typical of poor rural communities with high biomass fuel use throughout the Americas and elsewhere. We therefore conclude that the findings of this trial are, broadly speaking, generalisable to other settings, but intervention-based studies in other populations are needed for verification. The findings for severe pneumonia would have important implications for prevention of child pneumonia mortality in view of the high case-fatality associated with hypoxaemia.

Contributors

KRS was principal investigator for the trial and the pilot studies, participated in site identification and proposal preparation leading up to it, spent 3 months supervising field operation each year at the site during data collection, wrote the first draft of most sections of the report, and coordinated inputs from others for it. JPM supervised exposure measurements and other data collection in the field, did the primary data analysis, and participated in writing of the report. MWW assisted in study design, IMCI training of fieldworkers and project physicians, data interpretation, and writing of the report. AH provided data analysis and interpretation. AJ was project coordinator and provided input into questionnaire design, data analysis and interpretation, and writing.

LMT assisted with data collection and analysis, and coordinated the standardisation and database for the radiographs. JB read all radiographs and participated in radiograph quality assurance, interpretation of clinical outcomes, and assisted in data interpretation and writing. AD was field manager and supervised all questionnaire development, data taking, and data management. BA was Guatemalan principal investigator and assisted in IMCI training and interpretation of clinical outcomes. NB was co-principal investigator for the entire project and assisted in proposal development, site identification, and pilot studies, as well as all stages of the study implementation including data interpretation and writing.

Conflicts of interest

We declare that we have no conflicts of interest.

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