Title: Particulate Air Pollution Exposures and Childhood Acute Respiratory Infections in Guatemala: A Randomized Intervention Trial

Related Projects: Not applicable

Nature and Purpose: Our primary goal is to conduct the first randomized controlled intervention trial ever performed with relation to public air pollution exposures, thus increasing confidence in air pollution risk estimates, which are based now on observational studies. To do so, we randomly introduced a previously proven exposure-reduction technology (an improved cooking stove called a Plancha) in a highly exposed population in rural Guatemala and compare the changes in the incidence of young children’s acute lower respiratory infections (ALRI) in the treatment versus control groups. ALRI is the chief cause of childhood morbidity worldwide and the chief cause of childhood death in less-developed countries (LDCs). The main objective of this study is to quantify the contribution of wood smoke from open fires to the burden of ALRI. All field activities will be implemented and managed by the Medical Entomology Research Unit (MERTU) of the Centers for Disease Control and Prevention located at the Universidad del Valle in Guatemala City. The secondary goal is to extend current knowledge of airborne particulate exposure-response relationships to higher exposures, thus potentially helping develop better understanding of the physiological mechanisms leading to disease from particulate matter (PM). Based on pilot studies at the site, PM exposures in our study households will range from the high end of those found in US ambient studies to the much higher (10-15x) levels commonly seen indoors in LDCs. Exposure assessment is a necessary component of this study to reduce exposure misclassification; to determine PM differences between houses with open fires versus improved stoves; to quantify pollutant concentrations and exposures; and to examine the exposure response relationship.

Subjects: The primary subjects for recruitment are approximately 500 children under 4 mo of age, including those in utero at the time of the household/recruitment survey, who are living in households using a traditional wood-fired open stove. The health status of these children are followed from birth until they reach 18 months because this is the period of greatest ALRI risk and the period during which they spend most of their time with their mothers, thus receiving the greatest air pollution exposures. Their mothers are involved in the study as the chief source of information for the weekly health surveillance interviews and to assist in placement of the carbon monoxide monitoring tubes, which occurs every 12 weeks in each household. The fathers or other adult may be involved at the time of the scoping and recruitment surveys. Based on pilot work in the area, we expect to survey about 5500 households to find 2800 with open-fire stoves from which we expect to be able to recruit about 500 homes each with at least one child. A 20% loss to follow-up (in child-months) from this sample size will still allow us to meet our statistical criteria of 630 child-years.

Recruitment: The project site is an area of about 25 km² containing almost 6000 rural households in 20, mostly Mam-speaking, communities in highland Guatemala. There are three phases of the fieldwork proposed:
A. **Scoping** survey was conducted over about one month by 10 fieldworkers (including supervisors). A short questionnaire (less than one page) was administered serving three basic purposes: to identify households with open fires; to begin to map the area; and to let people know that a child-health study will be carried out soon. It will be preceded by contacts with local leaders, who will be kept informed throughout the project. The intervention was not mentioned to the householders at this point.

B. **Household/recruitment** survey of the approximately 2800 open-fire households identified in Part A. above was conducted by 18 Mam-speaking fieldworkers over about 5 weeks (6 hh/worker-day) starting with questions designed to determine if the household meets the eligibility criteria. If it did, the study was explained and the adult being interviewed was asked whether the household is willing to participate. Allowance was made for revisiting households that did not immediately decide whether to join, for example, because one spouse was absent at the time of the initial interview. An oral consent procedure (Appendix A) was conducted in Mam (pre-tested and back translated to Spanish) whereby a fieldworker visited each recruited household, and informed the participants that it will either receive a *plancha* (improved stove with chimney) at the initiation of the study or when their child reaches 18 months. It was explained that the allocation to one or the other group was based on the concept of a “lottery”. Previous experiences in Guatemala show that this kind of random allocation is acceptable to households. The fieldworker recorded the oral consent.

During this phase, the four communities were mapped by marking the location of each household in the community, the central meeting places, roads, etc. This information is already available for each community, but it was verified and combined into one large map. This facilitates coordination of stove installation, ARI surveillance, and pollution monitoring through the use of a geographic information system.

C. **Surveillance**: Once recruited via a baseline survey and born, the child is visited once per week by a trained Mam-speaking fieldworker to determine the child’s health status and, every 12 weeks, to attach a small passive air pollution monitor on the child's clothing that is retrieved after 48 hours (see Procedures below). Fieldworkers will be trained using standard WHO protocols (known as Integrated Management of Childhood Illnesses or IMCI) to identify cases of ALRI and to refer them to the study physicians. The doctors conduct an independent ‘blind’ diagnosis in a nearby community center on the same day and initiate the appropriate medical treatment (see Benefits below). All cases are taken by one of the project doctors to the nearest hospital (San Marcos – about 45 minutes by road) for x-rays, where severe cases are admitted.

D. **Pollution monitoring and Exposure Assessment**: An important component of this study is assessment of the level of exposure to indoor air pollutants from wood smoke. In particular, we focus on small particles (PM) exposure, which has been suggested as the best single measure of the respiratory risk of combustion-related pollution. Because of the inherent difficulties in measuring personal exposure to PM (labor intensive, time-consuming, expensive), in the entire 500-household population we measure carbon monoxide (CO) levels, which provide a very good correlate of PM exposure – extensive monitoring. For a fraction of the study households (N=64, half in each sub-group) we conduct more detailed measurements on the levels of PM concentrations as well as activity patterns of the mother and child, particularly to assess the duration that the child spends near the lit stove. The 64 intensive households were selected randomly from among the recruited households at the time of the baseline survey. A separate consent was administered for this portion of the study (Appendix B). Outdoor pollutant concentrations are measured to determine the degree to which indoor pollution is due to penetration of outdoor pollution from neighboring households (i.e. “neighborhood effect”).

**Screening**: The criteria for recruitment are:
- A household still cooks exclusively with a traditional cookstove (i.e., open fire),
- Does not migrate for a substantial part of the year, and
• Has a child 4 months or younger; or contains a pregnant woman.

In addition, if a mother in a household recruited by the above criteria becomes pregnant again before her eligible child retires from the study, her new child will also be included in the study, if agreeable to the household. No additional benefit will be offered, however. No woman who becomes pregnant during the course of the study but is in a household not eligible from the outset will be included, however. This is to reduce the incentive for women to become pregnant in order to join the study and receive the improved stove. In practice, women less than 4 months pregnant are not likely to be included because, among the Mam, women do not often admit that they are pregnant before 4 months.

Procedures: The household baseline questionnaire (see Appendices) administered at the time of recruitment includes information on:

- Variables used to determine socio-economic status including presence of electricity, running water, TV, radio, bicycle, separate kitchen, and type of toilet, wall-construction material, roof, and floor;
- Cooking facilities and type, source, amount, and price of (or time spent gathering) fuels;
- Household composition including number, age, gender, education, occupation, health history, and kinship of each household member; and
- Use patterns of alternative sources of air pollution, including smoking, garbage burning, lamps, nearby roads, and bath-houses.

Stoves (planchas) are installed in houses that are randomized to the intervention group by a licensed stove manufacturing company that has been actively installing similar stoves in the area for many years. Once the household is randomized they are identified to the stove installer for a convenient appointment date. Installation of the stove takes approximately 6 hours because it has to be built out of bricks and concrete blocks. This is followed by a drying period of 35 days during which it cannot be used otherwise it will develop cracks. Field workers educate and encourage the households to avoid using the new stoves until the 35 days have passed. At the time of installation, training is provided to each household in the proper use and maintenance of the new plancha. Field workers check the condition of the stove during the weekly visits and inspect them for cracks (the main problem encountered for the plancha) and trained masons conduct maintenance and repairs on the stoves. Control households have a plancha installed at the end of the study or when they disenroll for any reason.

The weekly questionnaires (see Appendices) during the surveillance phase uses WHO established queries related to ARI and diarrhea in the subject child since the last weekly visit. A more detailed questionnaire is administered every 12 weeks to see if any of the answers to the original household questionnaire have changed. If the questionnaire or direct observation reveals signs of ARI in the child, the fieldworker also measures respiration rate with a stopwatch and take a nasal aspiration, which involves use of a fine tube to aspirate fluid for lab viral evaluation. Active case finding via trained field worker home visits, referral, and management are summarized in a schematic flowchart in the Appendices. Validation of case findings include repeat home visits by supervisors and checking of home-visit report forms.

Additional short questionnaires are administered during the course of the study to obtain more detailed data pertinent to the study exposures and outcomes. These include fuel use patterns, use of the temascal (household sauna or sweat bath), pregnancy related confounders, and hospital medical charts. Any new study instruments will be forwarded to CPHS as soon as final versions are available in English and Spanish.

The collection method for aspirates (nasal washes) is to use a few drops of normal saline in each nostril (one at a time) and aspirate the secretions with a soft feeding tube attached to a 20 cc syringe. The parent will be asked to help with holding the child, in particular holding the head still and the hands out of the way.
If the illness is present, as determined by the WHO protocol, the fieldworker will refer the child to the local clinic attended by the study doctor for medical diagnosis and, if appropriate, antibiotic treatment. If the family does not take the child in within 24 hours, a second visit will be made to urge the family to take the child to the clinic. All diagnosed cases at the clinic will be taken by the doctor to the nearest hospital for further diagnosis, including chest x-rays, and admission to the hospital if required. These services, including transport, are provided at no cost to the families. Two project physicians are available to make sure that clinical assessment of the children, treatment, and referral of sick children take place with due speed. One physician also assists with validation of fieldwork by visiting a random sub-sample of homes to confirm fieldworker diagnosis. They will also follow-up severe cases. One of the project doctors is blinded to the intervention status of the children, by doing all their work in the clinics and not visiting households.

Once every 6 months, the fieldworkers weigh and measure (anthropometry) the child as part of a standard nutrition evaluation protocols. At the time a pregnant woman enrolled in the study gives birth, she will send a representative (usually a household member) to the study headquarters or local field worker’s home to inform us of the birth. This is to ensure that a fieldworker is able to visit the household within 24 hours after birth to weigh the baby and get an accurate birth weight, which is a confounding factor that must be adjusted in the analyses. An incentive payment equivalent to about $3 is provided.

Because of the high child mortality rate in the region there will be deaths in the study population during the surveillance period. A standard verbal autopsy procedure, involving interview of the mother after a period of at least 6 weeks by one of the study doctors, will be used along with clinic and hospital records to determine the cause of death. This technique has been used quite extensively in recent years, and when applied sensitively has not been found to cause undue distress to the family. The verbal autopsy form (see Appendices) was developed by WHO and is a satisfactorily valid method of assessing cause of death for pneumonia. The form will contain demographic information (from the database); questions to ensure at the correct household; open-ended section for mother’s description of illness; pre-coded section about specific symptoms; and section for data from death certificate.

To meet the secondary objectives of the study we monitor indoor pollutant levels and individual exposures for the study subjects. For each of the 500 children enrolled in the study, personal CO exposure are monitored for a 48-hours period at the start of the study and once per 3 months thereafter, with 5% done in duplicate for quality control. This is done by placing a small tube in a tough, non-toxic plastic holder, which is then pinned to the outer garment of the child. These tubes are very light and, in previous studies among children, have been found to work well. The tubes are checked the next day by the surveillance team and picked up the second day, sealed with a rubber cap and transported back to study headquarters to be read by another team member who is masked to the assignment of the household from which the tube was collected. The times at which the tubes are deployed and collected will be recorded on sheets with a short questionnaire to determine if there were any abnormal activities during the monitoring period. In Fall 2003, a small passive particle monitor (proprietary device identified in application coversheet) placed on the kitchen wall was added to these 3-month extensive measurements. In addition, a small box the size of a book of matches and weighing less than half an ounce will be placed along with the tube on baby and mother during personal monitoring. Using low energy ultrasound, it signals the kitchen particle monitor when the person is in the room. Neither it nor the tube is in the size range to be at risk of choking small children. Informed consent is obtained before placing the sensor on the individual as is done for the CO tubes.

For the 64 households in which intensive exposure assessment takes place, the kitchen and bedrooms are monitored for particle and CO concentrations every three months Portable battery-operated, air pollution monitoring equipment is placed in these homes for periods of 24-48 hours by the trained exposure monitoring team. Personal monitoring on the mothers is done using small light quiet devices for particles and CO placed in a small bag with a shoulder strap. Outdoor monitors are also placed in
villages for 48-hr periods and rotated among the study villages. Laboratory analysis of the filters is done at Harvard University and the University of California.

In addition, because of the importance of personal activities in determining actual exposures, particularly the duration that the child spends near the lit stove, it is important to obtain a measure of actual exposure as well as indoor and outdoor area concentrations. The same 64 households for which intensive air pollution monitoring is being conducted will be involved in time-activity assessments. Time-activity measurement instruments will be modeled along the lines of previously developed ones (see Appendices). These have been adapted during the first few months of the intervention using direct observation techniques and estimation of activities and time spent by study subjects so that they are specific to our study population.

**Benefits:** The benefits of participation in the study include receipt of an improved cook stove or plancha (worth approximately $125), weekly child health surveillance, and, when necessary, ALRI and other medical treatment by study doctors at no cost to the household at a local clinic, or in severe cases, in the hospital in San Marcos, the nearest town.

Although the presence of the study will inevitably help strengthen local health services, we will work carefully with local agencies to ensure that expectations are not raised unreasonably and that when we finish and leave the area any improvements are sustainable.

The plancha improved stove represents a long-term sustainable benefit to the households. It uses the same fuel as they use now, i.e. wood, and has a lifetime exceeding 20 years for its key components. It can be repaired and maintained locally. Pilot studies have shown that the planchas are highly desired by households in the area, but are not spreading rapidly on their own because of their initial cost. Participants will receive support in using and maintaining the plancha if this is required. All eligible households will be offered an improved cookstove, although the control group will receive them as they leave rather than join the study. Households will be free to withdraw from the study at any time without prejudice or coercion. A control household that leaves early will still be offered an improved stove.

It is anticipated that one outcome of stronger evidence linking indoor air quality and health, however, might well be accelerated government and NGO efforts to develop and disseminate improved stoves widely in the study area as well as elsewhere.

**Risks:** The drawbacks to participation are the weekly visits by project personnel, which may be viewed as inconvenient or an invasion of privacy, although none of the procedures are invasive. The small CO monitoring tube placed on the outer garment of each child once every 12 weeks for 48 hours will be protected from breakage by a strong plastic sleeve and the glass tube itself is coated with plastic to prevent shattering. (A CO tube is about the size and weight of a ballpoint pen.) Being a passive device, it has no battery or pump. Being battery-operated, none of the other monitoring equipment, which will be used in just 5% of households to measure room concentrations, represent electrical or fire risks. As described, the new ultrasound sensor (see Procedures above) is not in the size range to be a choking hazard to small children. Devices left overnight are placed in sound-dampening cases to reduce the irritation associated with pump operation. The nasal washes use a soft tube that has been found to be easily tolerated by infants and pose no risk of breakage or scraping/cutting.

The households will be assured that the instruments pose no personal risk, e.g., do not take blood or emit radiation. Demonstration of the use of the CO tube will be performed during the recruitment interview. In addition, the household will be told that they will not be held responsible if the instruments become lost or damaged while being deployed in their household.

Care has been taken in the design of the study not to inadvertently create pro-natalist incentives in the population. The value of an improved stove is sufficiently high in the local context that it is quite
conceivable that couples who saw their neighbors being recruited into the study when they became pregnant, might be encouraged to shorten the birth interval for their next child. Since shortening birth intervals has a negative health impact, this raises ethical questions about the design. This is the reason that recruitment occurred in two short intense periods close in time so that only those pregnant at the time of the first period were recruited.

Confidentiality: Local maps and census reports are used for background information and for designing the initial scoping survey, but the project expects to develop much more accurate and up-to-date information directly from the community during the course of the study. Strict confidentiality will be maintained. During training, fieldworkers receive instruction not discuss subject information with community members or non-project personnel. We assign village, family, and individual codes to the data. No names appear in the study reports or publications and study codes will be used to link data files. All data are kept in a locked room at the project field headquarters. The key that links names and codes will be locked in a desk in a separate building. Analyses will be done at MERTU/Universidad del Valle (Guatemala City), Liverpool University, and UCB where similar precautions will be taken, e.g., the key will not be kept with the data and data for analysis are be stripped of personal identifying information.

The heads of the household are informed at the time of recruitment that all data are kept confidential and that they may direct complaints to the project field director or contact MERTU at any time during the study. MERTU and Universidad del Valle have been conducting medical research in the area for a decade or more.

Because data are encoded and entered while the surveillance phase is continuing, it is possible to carry out an interim analysis at the end of the first year of surveillance of the intervention’s effectiveness. This allows us to monitor the safety and effectiveness of the intervention in preventing ARI in children, and to evaluate the integrity and validity of the data collected during the course of the study. A data safety and monitoring board (DSMB) consisting of independent experts from around the world has also been set up for this project. The chair is Prof. Mark Steinhoff of the School of Public Health, Johns Hopkins University.

Informed Consent: The study is explained to the households as a child health study focusing on ARI and diarrhea, the two most important causes of childhood illness in poor countries. The improved stove is represented as compensation for their participation and the different timings for installation in different households necessitated mostly because of cost, i.e., the project cannot afford to give everyone a stove at the start (in fact, this is true, since some 500 stoves at $125 each is a substantial cost). This way of presenting the study is designed to reduce the chance for bias and changed behavior with regard to pollution exposures in the households. We need to do this because, although we can perform a randomized trial, we cannot do a double-blind one, i.e., there can be no “placebo” improved stoves. The delay in implementation for the control group also allows more thorough evaluation of stove performance, fuel efficiency, maintenance requirements, etc., which has not been done on large scale, nor in randomized comparison with traditional stoves.

The primary adult care-giver (usually the mother) of the household must give their informed consent during the initial visit. The premise of the study, and the risks and benefits to the enrollees will be explained to the adult care-giver in her/his appropriate local language. We clearly communicate that participation in the study is voluntary and that they may withdraw from the study at anytime without any penalties. English and Spanish versions of the consent form for the study used (see accompanying documents). Because of the low level of literacy in the study community, the consent form is orally presented to the participants.

We asked adults who were at home at the time of the recruitment visit to consent for the entire family. We believe this is appropriate based on four criteria. First, that the research involves no more than minimal risk to the subjects as described in the previous section. Second, that the form of consent does
not adversely affect the rights and welfare of the subjects. We anticipate that there will be community level and family discussion of participation, both before study enrollment and after. We will make clear that study subjects are free to drop out of the study, once it has begun, so study subject rights will not be compromised. Third, the research would not be practical if carried out with individual consents. Given the level of literacy and social organization, written informed consent from each individual is not practicable in this cultural setting. Therefore, it is planned that the elements of informed consent will be presented orally to the subject’s legally authorized representative. Fourth, pertinent information is provided, when appropriate, after participation. In this study, ongoing communication between the study implementers and the study subjects is part of the study. Study workers are able to provide information on risks and benefits of participation at regular intervals.

Financial Aspects: Other than the (substantial) non-monetary benefits outlined above, no monetary or other compensation will be offered for participation.

Written Materials: The attached English version of the informed consent form, which has been translated to Spanish, does

- List all the organizations involved in the study (see cover sheet) with MERTU being most prominent because of its long-term role in the area. A list of contact names and numbers at the local MERTU office located at the Universidad del Valle will be given to the household.
- Explain briefly that these organizations are starting a child health study that will run for about two years and for which they would like to recruit households with a pregnancy or having a child under one-year. Households are being asked to stay involved until their child reaches 18 months of age.
- Explain the benefits of agreeing to be involved, 1) a *plancha* stove either at the start or end of participation, 2) weekly health checks by trained health workers to see if the baby has any problems with breathing or has diarrhea and that will include weighing the baby every 3 months or so, 3) better information about diarrhea and respiratory infections that may help all people in rural areas.
- Explain the downsides of participation, 1) necessity of answering a short questionnaire about their child’s health every week; 2) place a CO tube on their child’s clothing for 24 hours once every 8 weeks (which will be demonstrated); 3) possible need to allow 24-hour use of small battery-operated equipment to measure the quality of the air in their house 2-3 times over the period. (Photos of the equipment will be shown.)
- Assure participants that:
  --They can leave the study at any time
  --They will not be held responsible for lost or broken equipment at their house,
  --If for any reason someone is hurt or property is damaged in the household due to the study, medical care and compensation will be provided by MERTU, and
  --That they can contact the project director or the MERTU office at any time with questions or complaints.

The oral administration of the consent form is done in Mam, if necessary, using a standardized and tested translation read by the fieldworker, who fills in the name and date, and personally signs the form if the household agrees to participate.

Signature:  Kirk R. Smith___________________________

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