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The School Inner-City Asthma Intervention Study: Design, rationale, methods, and lessons learned

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Abstract

Asthma is the most common chronic disease of childhood in the United States, causes significant morbidity, particularly in the inner-city, and accounts for billions of dollars in health care utilization. Home environments are established sources of exposure that exacerbate symptoms and home-based interventions are effective. However, elementary school children spend 7 to 12 h a day in school, primarily in one classroom. From the observational School Inner-City Asthma Study we

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learned that student classroom-specific exposures are associated with worsening asthma symptoms and decline in lung function. We now embark on a randomized, blinded, sham-controlled school environmental intervention trial, built on our extensively established school/community partnerships, to determine the efficacy of a school-based intervention to improve asthma control. This factorial school/classroom based environmental intervention will plan to enroll 300 students with asthma from multiple classrooms in 40 northeastern inner-city elementary schools. Schools will be randomized to receive either integrated pest management versus control and classrooms within these schools to receive either air purifiers or sham control. The primary outcome is asthma symptoms during the school year. This study is an unprecedented opportunity to test whether a community of children can benefit from school or classroom environmental interventions. If effective, this will have great impact as an efficient, cost-effective intervention for inner city children with asthma and may have broad public policy implications.

Keywords

Asthma; School; Mouse; Inner-city; Environmental exposure

1. Introduction

Asthma affects 12–15% of children in urban United States, accounts for over 14 million missed school days per year,[1] and costs billions of dollars in health care utilization despite aggressive measures to identify remediable causes.[2] Elementary school children spend 7 to 12 h a day in school (primarily in one classroom), making school classrooms akin to an occupational exposure for children. The School Inner-City Asthma Study-1 (SICAS-1) (R01 AI 073964, Phipatanakul) was the first observational American study to comprehensively evaluate the role of urban exposures in school, classroom and home environments and asthma morbidity.[3,4] SICAS-1 showed that classroom-specific mouse allergen,[5] mold, and pollutant exposures are associated with asthma morbidity, adjusting for exposure in the home.[6–8] Until SICAS-1, most studies have focused on home exposures to allergenic and pollutant exposures and their associations with asthma morbidity.[9] Home-based trials have demonstrated that targeted interventions (including air filtration) are effective in decreasing asthma morbidity.[10–13] We used established integrated pest management (IPM) measures that have been shown to reduce mouse allergen exposures in homes.[14,15] We then demonstrated that we could effectively decrease classroom-specific toxic exposures during the academic school year by utilizing classroom-suitable High Efficiency Particulate Air (HEPA) air filters specifically adapted to maximize flow while minimizing noise.[16]

In this paper we describe the School Inner-City Asthma intervention Study (SICAS 2), the next logical step to apply successful school/community-based strategies to determine whether a school/classroom intervention to reduce harmful exposures will efficiently and effectively improve asthma morbidity. We use a two-pronged intervention using classroom particle air filter units and school-wide targeted IPM/cleaning to reduce asthma morbidity in urban school children. Herein, we describe our study design, sampling and intervention methods, analytic approach, and anticipated outcomes. In addition, we discuss the importance of our established, successful community relationships over the past decade,

which made us uniquely positioned to give back to the community that, after participation in SICAS-1,[17] want this trial.

Our school-based IPM and air filtration trial to remove particles will have particular relevance to long-term public policy and planning for urban U.S. schools with similar indoor environments. In SICAS1, 17% of elementary school children reported nighttime awakenings due to asthma and 15% had asthma-related school absences in the past year. We expect cost-effectiveness where implementation costs are offset by fewer symptom-days and improved quality of life for children, less health care utilization and less loss of work-days (greater economic productivity) for caregivers. If reduction of classroom-specific exposures leads to improved asthma outcomes, then this approach can be implemented as an efficient and cost-effective strategy to benefit communities of children by improving the school environment.

2. Study design and methods

2.1. Description of study design

SICAS-2 is a factorial, randomized, placebo-controlled, parallel group phase II clinical trial designed to assess the efficacy of classroom air filtration and, randomized, controlled, parallel group school (IPM) environmental intervention in improving asthma control in children with asthma. SICAS-2 is a single-Center environmental intervention study. Three hundred children attending any one of the ~40 participating schools in the northeast from September through June in grades K to 8th (generally ages 4–15) will be enrolled into one of the four random intervention groups (75 per group) as outlined in Table 1

2.2. Intervention

2.2.1. Classroom environmental intervention—After randomization, active or sham (placebo) HEPA air filters are placed in the primary home classroom, where elementary students spend the majority of their day. The students and investigators will be blinded to active versus sham. The Air Filtration System (Coway Co., Ltd., Model AP1013A) efficiently captures particles down to < 0.1 μm in size. To achieve maximum effectiveness with an acceptable noise level (52db), custom modification was made to get a dust-free air delivery rate (CADR) of 106 ft[3]/min (CFM). The air filtration system is designed for rooms up to 400 ft,[2] was effective in reducing particles in our Pilot (4 filters/classroom),[16] and was well-received in the classroom/school setting.

2.2.2. School intervention—The Integrated Pest Management (IPM) schools receive an IPM strategy (extermination with rodenticide, traps, and sealing of holes and cracks), air filters, cleaning reservoirs, and education regarding pest control measures. The intervention procedures will be those that were used in the Boston pilot home intervention study,[14] and the Inner-City Asthma Study (ICAS) Study,[11] and the NIAID funded Mouse Allergen Asthma Intervention Trial (MAAIT).[15] The school-specific IPM will focus on surrounding areas that feed into the classroom and harbor infestation by food and water sources (i.e. cafeteria). This is modeled after the home interventions that work by focusing on the child's bedroom, surrounding areas, and the kitchen. The home-based strategies have been proven

as effective strategies for reducing pertinent allergen exposure and a low-cost means of improving health outcomes.[10] Our school-based strategies focus on the child's primary classroom, surrounding areas, and the cafeteria. Unlike home intervention strategies, where it is impossible to blind, the School IPM strategies may also be single blinded, because the students attend school during the day, and the IPM will be conducted after hours when the students are not present. Therefore, staff know which school is randomized to IPM but the subjects will be blinded.

2.2.3. Advantages of interventions to be tested—SICAS-2 will be a factorial design with the classroom randomized double-blind, placebo controlled to air filter/purifier and school being randomized in a parallel fashion to an intervention of IPM/Education/Cleaning versus Control School. This allows us to demonstrate the ability of the air filter/purifier in improving classroom air quality and the school-wide effects (classroom/cafeteria, and surrounding supporting areas) of the IPM intervention. Factorial designs have been validated and established[18,19] as an efficient use of resources to determine the effects of two interventions on similar health outcomes within a cohort. The classroom intervention with the parallel school wide intervention allows us to maximize impact and efficiency in one trial.

2.3. Study population

2.3.1. Inclusion criteria

1. Individuals who meet all of the following criteria are eligible for enrollment as study participants:
2. Subject and/or parent guardian must be able to understand and provide informed consent
3. Males and females who are grades K-8 (age 4–15) during the subsequent academic school year after spring screening
4. Attend one of the schools that study team have permission to obtain classroom/school environmental samples for the subsequent academic school year
5. Have no plans to move schools within the upcoming 12 months
6. Have physician-diagnosed asthma at least 1 year prior to the screening visit; and
7. Have evidence of active, asthma as defined by at least one of the following:
8. Wheezing symptoms in the past 12 months
9. On daily controller medications for asthma
10. One asthma-related unscheduled visit to an emergency department (ED), clinic or urgent care facility in the previous 12 months
11. One asthma-related overnight hospitalization in the previous 12 months
12. One or more bursts of oral or injectable corticosteroids in the previous 12 months

(Criteria modeled from the NIAID funded Inner-City Asthma Consortium inclusion/exclusion criteria and SICAS).[10,17,20,21]

2.3.2. Exclusion criteria—Individuals who meet any of these criteria are not eligible for enrollment as study participants:

1. Inability or unwillingness of a participant to give written informed consent or comply with study protocol
2. Lung disease, other than asthma, that requires daily medication
3. Inability to perform lung function testing
4. Cardiovascular disease that requires daily medication, excluding hypertension
5. Taking a beta-blocker
6. Currently receiving escalation (has not reached maintenance) of Immunotherapy (allergy shots)
7. Switching to a school where staff are not doing environmental sampling for that academic school year
8. Current, diagnosed, mental illness or current, diagnosed or self-reported drug or alcohol abuse that, in the opinion of the investigator, would interfere with the participant's ability to comply with study requirements
9. Past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study

2.3.3. Exclusion criteria for school

1. Unable to access areas of school necessary to conduct extermination
2. School in extensive state of disrepair/damage as determined by Study PI

2.4. Study procedures

Clinical and environmental evaluations will occur during five types of study events: clinic visits, telephone questionnaires, school/home visits, and school subject follow-up visit.

2.5. Enrollment

We will use, as we have done successfully in SICAS-1, validated screening surveys[22] (collected under a screening survey protocol) that are distributed to 8–10 elementary schools per year, to be filled out by students and teachers the spring prior to the study year. From SICAS-1, we received 1000 to 1500 surveys returned each spring.

Potential study participants will be screened by telephone. Those who meet study criteria and fulfill inclusion/exclusion criteria will be explained the study and invited to schedule a baseline enrollment study visit in the clinic.

2.6. Screening visit

Screening visits take place at the Asthma Clinical Research Center (ACRC) in order to confirm eligibility and phenotypically characterized participants' asthma before randomization at the start of the school year. The procedures will be performed and timeline in Supplementary Fig. 1 and Tables 2–4 are described in the following: The study is approved by the Boston Children's Hospital Committee on Clinical Investigation Institutional Review Board (IRB).

- *Informed Consent*: The research study will be explained in lay terms to each potential research participant. The participant's parent/guardian will sign an informed consent form and the participant will sign an assent form before undergoing any study procedures. Once the informed consent and assent have been signed, the participant is considered enrolled in the study and will be assigned a unique participant number.
- *Questionnaires* - assess clinical characteristics (asthma symptoms, health care utilization, home characteristics) and HRQL using the EQ-5D instrument for the U.S. population;
- *Anthropometric Measurements*: Height and weight will be taken.
- *Skin testing*: Allergy skin testing will be performed to 14 allergens, using the MultiTest II device (Lincoln Diagnostics, Decatur, IL). The allergen extracts to be used are: Timothy grass, Penicillium, German Roach, Oak tree pollen, Dog, Cat, Mouse epithelia, Rat epithelia, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, Aspergillus mix, *Alternaria alternata*, Cladosporium, Ragweed pollen mix. Skin tests will be performed according to standard procedures [23]
- *Fractional Exhaled NO (F_ENO)* is a known marker of pulmonary inflammation and will provide a non-invasive means of assessing pulmonary inflammation. Measurement of exhaled nitric oxide will be obtained prior to lung function testing, and will be obtained according to the American Thoracic Society Guidelines.[24] Exhaled nitric oxide concentrations will be measured using an FDA-approved (for clinical use in asthma management) handheld device that uses an electrochemical analyzer to quantify F_ENO levels (NIOX Mino/NIOX Vero System, Aerocrine, Sweden).
- *Spirometry and Bronchodilator reversibility*: Pre- and post-bronchodilator spirometry will be performed according to ATS guidelines.[25] At least three reproducible flow-volume loops will be obtained using the portable Koko spirometer, after which albuterol will be administered via nebulizer. Approximately 10–15 min after completing the nebulized albuterol, spirometry will be repeated to obtain post-bronchodilator FVC, FEV_1, FEF25–75, and PEF.
- *Nasal swab/blow*: This will be obtained by swabbing the nares to clean and blowing into a nasal sample kit to be frozen and saved for future analysis of viral and microbial organisms that could affect clinical response to the intervention.

- *Venipuncture*: A 35 ml venous blood sample will be obtained so that the serum can be used to measure total IgE and allergen-specific IgE levels. Cell count with differential to obtain eosinophils will also be obtained.

If a subject cannot complete all activities at one screening visit, he/she may return within a week to complete the remainder of study activities.

2.7. Home environment dust sampling

Home environmental sampling is done once at any point throughout the subject's participation in the study by dust sampling collection from the participant's bedroom and kitchen. Home samples will be linked to school/class sampling as a surrogate measure for home exposure and for adjusted analyses. Home environmental sampling will also be done to differentiate the effect of home exposure in adjusted analyses with the primary focus of this study on the school/classroom specific exposure and clinical outcomes.

2.8. Randomization

The DCC Data Management System randomizes the classroom to receive active versus sham (placebo) air purifiers and the school to receive the IPM intervention. Randomization will occur by site and with random blocks. The randomization scheme has been developed by the Data Coordinating Center (DCC) and is embedded into the data management system so that schools and classrooms can be randomized and linked to enrolled SICAS-2 students. Study staff do not have access to the randomization codes.

2.9. Integrated Pest management (IPM)

Intervention includes IPM Module of two IPM visits, conducted 4 ± 3 weeks apart.

2.9.1. IPM intervention visit 1—If the School has been randomized to the IPM arm, the study coordinator schedules an IPM visit in the fall after the baseline school sampling. The IPM intervention team includes the Research Assistants (RA) and IPM Technicians (IT). Classroom/School Inspection Form(s) are used to document a walk through the school in order to sketch a layout and document visual evidence of infestation and holes/cracks in the structure. IPM procedures include placement of traps and sealing of holes and cracks.

Our school-based work focuses on the primary exposure school room of interest, the child's primary home classroom, which is where we focused in our observational findings that provided supporting data for this study. We 1) inspect conditions, record observations, 2) identify pests, 3) continue follow up and make adjustments as needed, 4) record observations and activities, 5) and educate staff. Focusing on the classroom/cafeteria will also allow us to isolate and control conditions focused where the child spends the majority of his/her time. We also clean and target IPM on the heating system of the classroom, and evaluate nearby surrounding areas, including cafeteria, and any nearby support areas if they directly feed into the classroom such as storage rooms, boiler rooms, and janitor/storage closets if they have evidence of mouse infestation.

2.9.2. Focused cleaning—At the first visit of the IPM module, the research assistant completes a focused cleaning aimed at[1] removing allergen reservoirs; and[2] removing

clutter to aid the IPM technician. Procedures include removal of dead mice from traps, removal of trash and clutter, removal of mouse droppings, wet mopping of floors with hard surfaces and vacuuming carpeted floors with HEPA filtered vacuum cleaner. Our methods are modeled off of successful intervention work in Boston homes[14] which led to our NIAID funded home based study Mouse Allergen Asthma Intervention Trial.[15] This trial utilized successful strategies targeted to the bedroom, inspection targeted in surrounding areas, and in the kitchen. Our school-based study will focus on the primary exposure school room of interest, the child's classroom, surrounding support areas, and the cafeteria.

2.9.3. IPM intervention visit 2—The second visit of the IPM module serves as a booster visit and includes an assessment of the status of the mouse infestation and repeat setting of traps, and sealing of holes and cracks.

2.9.4. Additional IPM intervention visits—Subsequent IPM modules are delivered only if there is persistent or recurrent mouse infestation so that IPM is tailored to the infestation status of the school. Mouse infestation is assessed at the follow up school visits and a school is considered to have ongoing or recurrent mouse infestation if there is evidence of mouse infestation during inspection or if staff reports seeing mice, or evidence of mice, during subsequent sampling.

2.9.5. School environmental assessment—Participating schools for the Academic Year will be scheduled for a baseline school visit to determine allergen/mold/particulate exposure status in the fall prior to deploying the randomized intervention. At the school visit, a school environmental assessment will be conducted, and settled dust and table wipes will be collected from SICAS-2 student's home classroom, cafeteria, and gym. The air samples will be collected from the student's home classroom to have a baseline determination of airborne dust. School environmental assessment will include the following procedures:

- Completion of School Assessment/Inspection Form
- Collection of settled dust from cafeteria, primary home classroom and gym.
- Air pollution, air and mold samples are collected from the primary home classroom.

The dust and air samples from home and school will be shipped to the University of Iowa for analysis of endotoxin using a kinetic chromogenic *Limulus* amebocyte lysate assay,[26,27] (1 → 3)-β-glucan using the *Limulus* Factor G assay, and ten inhalant allergens using the MARIA multiplex bead-based assay (Indoor Biotechnologies, Inc.).

Analysis of the collected filter samples will be performed for particulate matter, black carbon, and trace elements at the Harvard T.H. Chan School of Public Health.

A return school visit occurs approximately one week after the first school visit to collect the air sampling equipment and samples. Followup school environmental assessments take place once during the fall school semester and one during the spring school semester.

2.9.6. Telephone surveys—These are performed in order to collect health outcomes (e.g., symptoms, health care use; time-activity) and home environmental information. They are conducted after the start of the school year (baseline), and every 2 months after the intervention is deployed, yielding 3 follow-up measures during the school year, including 1 at the end of the school year.

2.9.7. School subject follow-up visit—Using the same standard procedures performed at the screening visit, we obtain anthropometric measurements (height and weight), spirometry, and F_ENO at the fall and spring follow-up visits. Nasal swab/blow and buccal swabs are only performed during the spring follow-up visit. Follow-up clinical assessments will be linked in timing to the environmental sampling done during the academic year, post randomization. Not only will the timing of the assessments enable us to evaluate the effects of the interventions on these outcomes (lung function, F_ENO,) partway through and near the end of the intervention periods, but will also enable us to do secondary analyses on the relation of these outcomes to short-term measured school exposures in the different treatment arms.

These school environmental and clinical measures will enable us to [1]: estimate the efficacy of the interventions in opposite seasons and [2] conduct secondary analyses linking season-specific health outcomes with exposure measures rather than treatment group.

2.10. Education

An educational module is delivered to IPM Schools. The module reviews the approaches to reducing mouse allergen levels – source removal, prevention of re-entry, and cleaning of allergen reservoirs – with school staff.

2.11. Stratification, randomization, and blinding/masking

2.11.1. Randomization—We randomize the filter interventions at the class level, and the IPM intervention at the school level at the beginning of the school year when the enrolled student's classroom is confirmed. The randomization scheme is developed by the DCC. At each new randomization step, we seek to balance the numbers of students both within the school, but also cumulatively over all schools visited to that time of the current randomization. We match classrooms and schools based on the number of participants to ensure a nearly exact 1:1 randomization ratio. At the classroom level this may involve 1:1 or 2:1 matching, but at the school level it may require 3:1 or 2:2 matching in order to maintain balance. Our experience has shown that this strategy has arms that are balanced as much as possible (i.e. very nearly exact 1:1 randomization ratio) for both interventions.

2.11.2. Masking—Although it may be possible to attempt to mask some study staff by increasing the number of research assistants at each site so that 1–2 research assistants could be dedicated to collection of clinical outcome data, this would substantially increase the budget, so double-blind is not practical or feasible, even in a school-based study. Double-blinding in environmental home-based studies is also not feasible. There are also several aspects of the study that will guard against bias that could result from having unmasked study staff. First, all laboratory assays will be conducted by laboratory technicians who will

be masked to group assignments. Second, some of the clinical data that are collected, including F_ENO and pre- and post- bronchodilator spirometry, are objective measurements that are less subject to influence by the study staff or study participant's. Third, analyses will be conducted to determine if any improvements in clinical outcomes are associated specifically with decreases in school allergen, mold, and pollutant levels, not just to group assignment.

The air filter classroom intervention, however, is double-blind, placebo controlled and randomized. Staff from the Harvard T.H. Chan School of Public Health (HSPH) Environmental Assessment and Intervention Core or IPM technicians who do not have contact with the study participants service and change the air filters every 3 months at the school after school hours, maintaining participants and investigators/study staff blinding.

All laboratory studies (allergen ELISAs, allergen-specific IgE levels, endotoxin levels, $PM_{2.5}$, BC and, NO_2 levels, and mold) are performed in centralized laboratories in batches to minimize variability of the assay.

2.12. HEPA air filter accountability

According to the manufacturer, the Coway portable air filter units have a particle collection efficiency of 99.9% for particles as small as 0.3 μm. Our researchers performed additional laboratory tests that showed collection efficiency of at least 95% for particles as small as 0.1 μm. HEPA filters will be replaced at each school visit, every 3 months, as recommended by the manufacturer's instructions.

For the classroom air filters, a research assistant will assess the units at the school visits to document functionality and whether the unit is on and plugged in at the time of the school visit. Reminders are taped on the units to encourage compliance. If the units are turned off or unplugged, staff will communicate with the school contacts to encourage compliance.

2.13. Primary and secondary outcomes

The primary objective and hypothesis of SICAS-2 is to test the efficacy of School Integrated Pest Management (IPM) and Classroom Air Filters in reducing asthma morbidity in school children with asthma.

The primary and secondary outcomes are presented in Table 5. The primary endpoint is the maximal number of days with asthma symptoms in the previous two weeks before the clinical outcome interview, defined as the largest value among the following three variables: number of days with wheezing, tightness in the chest, or cough; number of nights with disturbed sleep as a result of asthma; and number of days on which the child had to slow down or discontinue play activities because of asthma. The primary endpoint is the longitudinal vector of symptom-days at each of the visits for each subject ascertained at baseline and every two months follow up during the school year after randomization.

2.14. Secondary endpoint

Secondary outcomes specified in Table 5 will be standardized according to the recent Asthma Outcomes Workshop guidelines.[28,29] They include school absences, Health Care

Utilization; pulmonary function tests (PFT's), health related quality of life (HRQL), and degree of exposure reduction. The Composite Asthma Severity Index will also be included. A number of these outcomes will be used in estimating the net cost and cost-effectiveness of the intervention.

2.15. Analysis plan

Analyses will be performed using an intent-to-treat (ITT) dataset which will include all participants who are randomized. The primary analysis will be an ITT analysis. After ensuring that any dropout is missing completely at random (see Missing data considerations section), the ITT dataset will include all participants who are randomized. A per-protocol (PP) dataset will include only participants who have completed at least one intervention visit (one IPM/Air Purifier visit) and one follow up clinical outcome visit.

2.16. Primary analysis of primary endpoint(s)

2.16.1. Multi-level modeling—We will employ multi-level models[30] to quantify the effects of interventions (both class-specific filters and school-wide IPM) on the clinical outcomes, while accounting for the multiple levels (school, classroom, student, time point) of data. Specifically, we will employ non-linear mixed effects models, which intrinsically handle unbalanced data (unequal number of classrooms within schools and unequal number of children with asthma within classrooms) while accounting for child, class, and school-level variability (clustering) in the outcome by treating these factors as random effects. SICAS-1 generally had no more than one to two SICAS asthma students per classroom, so that clustering by classroom will be minimal and classroom random effects are likely not necessary. Count data (such as our primary symptom outcome) will be analyzed by negative binomial regression and continuous outcomes by linear mixed models. Our primary analysis will contrast outcome levels in the intervention and control arms. (Please see Statistical supplement for additional details).

2.17. Sample size considerations sample size estimates: (please see statistical supplement for further details)

2.17.1. Power and sample size calculations: (a) primary clinical outcome—We powered the study focusing on the primary endpoint in the study. For the primary clinical outcome, assumptions for the sample size estimate for the symptom outcome are based on classroom/exposure and symptom data from SICAS-1. The proposed primary statistical analysis assessing the impact of the interventions (school- and classroom-based) is based on a multilevel negative binomial regression model, which simultaneously accounts for correlation among clustered observations while accounting for over-dispersion in the symptom counts. We calculated power using a simulation-based approach that repeatedly generated data under this model, and calculating the proportion of time we reject the null hypothesis of no school-wide IPM effect and no classroom filter effect. The amount of overdispersion in the negative binomial distribution was set equal to that estimated in SICAS-1. All power calculations were run assuming a two-sided alpha = 0.05 level test, and all power estimates are based on 1000 simulated datasets. Results in Table 6 show that with a total n = 240, we have > 80% power to detect a difference of at least 0.6 days of symptoms

and > 90% power to detect a difference of 0.75 days between the two groups. Taking into account a conservative projected 20% dropout rate (SICAS-1 > 90% retention), we will enroll 300 participants to ensure that 240 will complete the study. To check our power to detect associations among quintiles of the exposure distribution (as a continuous variable), we used the same simulation strategy based on a multilevel negative binomial regression model but with exposure quintile as a covariate.

Using this approach, we estimate that we will have 90% power to detect the slope estimated in SICAS-1 of 0.173 (the effect size in seen in SICAS 1), which represents the log relative rate per increase in exposure quintile, in as little of 40 subjects. This result demonstrates the increase in power that results in using the continuous exposure concentrations, when such an effect in fact exists, and suggests that we will be able to detect such associations even if this effect exists only in subjects sensitized to mouse and mold (our SICAS-1 data supports that we will have > 40 sensitized subjects).

Our power calculations for our primary outcome were determined by the SICAS-1 data on exposure, sensitization and symptoms for mouse and mold, and the pollutant exposures for the entire population and supports that the SICAS-2 population will have adequate power to test our primary hypotheses.

We also estimated our power to detect intervention effects on secondary outcomes, specifically FEV_1 reflecting pulmonary function. We used the same simulation approach outlined above for symptoms, but simulating from a linear mixed effects model for a continuous outcome instead of a negative binomial regression model for counts.

Analysis will compare IPM versus Control Schools and Air Filter Versus Sham Classrooms, and efficiently test the effectiveness of the intervention in real life. Since IPM likely affects school wide exposures, while air filters affect classroom specific exposures, these interventions will be analyzed separately. The power calculations are based on a two-sided 0.05 alpha level test.

2.17.2. Cost-effectiveness analysis (CEA) plan—We will estimate incremental costs and effects, and the incremental cost-effectiveness ratios (ICERs) between trial arms. Intervention costs include IPM evaluation and extermination (for technicians hired to conduct IPM), annualized capital equipment costs (total air filter costs divided by years of useful life), pest control education and targeted cleaning. We will therefore record the (self-reported) time that it takes for education and targeted cleaning which will be multiplied by the US Bureau of Labor Statistics average wages (by area and occupation). We will then calculate health care costs[31] and potential savings that might result from lower rates of outpatient medical care (including scheduled and unscheduled visits and school nurse visits), inpatient, ED, and reduced use of rescue medications. Utilization data collected through our surveys will be monetized using state-specific average costs by setting. The number of days that parents and children missed from work and school, respectively, will be recorded at each data collection opportunity. For parents we will use the human capital approach (lost wages); school absence will be valued using caregiver's daily wages. We will use two measures of effectiveness that are widely used in CEA of asthma interventions, symptom-

free days (SFDs using self-reports), and gains in quality-adjusted life years (QALYs). QALYs capture the full impact of interventions on life expectancy and health-related quality of life. SFDs strongly correlate with QALYs.[31,32] We set clear criteria for interpretation of our results. We hypothesize that the interventions will be effective and will also reduce total societal costs. If is the intervention costs are more expensive than savings in health care use including medications, we will be guided by widely accepted (e.g. 50,000/QALY) as well as more recent estimates of the threshold societal willingness to pay for an additional QALY proposed by Braithwaite.[33]

3. Discussion

The School Inner-City Asthma Intervention Study was built on a decade of ongoing school and community trusting relationship between the investigators and administrators, facilities management, teachers, students, principals, and families.[17] We first built commitment from the senior school administrators as necessary to introduce our research program in the schools.[17] We then fostered local community support from the individual principals, teachers, school nurses, administrative staff, facilities management, medical directors, and the students and their families. This commitment was born out of trust that the investigators will give back to the community in some capacity, through education, health care accessibility, or some other mechanism.[17] The second means for establishing trust is by raising awareness for the study, or the issue being studied, in a way that demonstrates the investigator's commitment to the community. For example, our ongoing work utilized investigator-led neighborhood asthma initiatives, advocacy groups, informational parent's nights, and involved high school students in research mentorship programs to bolster interest and awareness.[17] Work in schools was only made possible because of longstanding community trust and relationships developed from these experiences.[17] We also had a school champion in the facilities management department at the school that supported our work. The initial phase of our work enabled us to build the community trust necessary to objectively evaluate the school environment and the effects on health, independent of home exposures. We first had to demonstrate that we were able to comprehensively understand the role of the school environment on asthma morbidity, adjusting for exposures in the home. [5] We then piloted in a school-based setting that we could feasibly bring down asthma-based triggers in schools.[16] This utilized classroom-suitable HEPA air filters[16] specifically adapted to maximize flow while minimizing noise.

The investigative team developed strong community buy-in, and included thoughtful attention to the barriers to study participation and retention, commonly encountered in all inner-city studies, such as lack of transportation, unstable housing, neighborhood violence, language barriers, and lack of access to care.[34–37] We adapted study materials to the languages of the participants and committed, multi-lingual, multi-cultural study staff are needed to maintain trust among participants' families and the community.[34,36] Minimizing staff turnover and providing incentives to participants are resource intensive measures, but are ongoing and necessary for success in these studies.

We continually work to retain study participants. The phenomena leading to study drop-out have been studied in various other inner-city studies.[34–37] Based on our earlier work, it

was found that lack of social support, having few contacts, out-of-date contact information, and caretaker stress were predictors for study drop-out.[34,36] School-based studies provide the additional challenge that students may change to a school outside the study.[17] Unlike home based studies, in which subjects may frequently be lost to follow up, schools generally know where children are and have state mandated enrollment and attendance records. In our experience, buy-in from the schools enables staff to maintain participation by the families and students, and as a result we have been successful in maintaining excellent engagement and follow-up from our families.

Implementing environmental interventions in schools is not a simple process. Using HEPA filters as an example, similar to the environmental assessment tools, the filters themselves must be physically unobtrusive. They must be placed carefully such that they can function effectively yet are not inadvertently turned off or altered by curious students.[38] The filters must be large enough to purify the air of an entire classroom, which may be much larger than the bedrooms studied in most home-based intervention studies. The filters must be acoustically tolerable, which may be challenging at the high flow rates required to filter the air in a large classroom. Furthermore, previous studies have shown that air filters are affected by the volume and air exchange rates of a given room.[39] Filters themselves should be replaced and serviced taking into account these variables. While integrated pest management strategies[10,40–43] in homes have been well-developed, implementing what works in a school setting has additional challenges, given limitations on strategies allowed in a school setting, and even baits (synthetic products, as opposed to peanut/food products).

Despite these challenges, blinding is possible for select school-based interventions. For example, students may be blinded to sham and active filters in the classrooms. The school-based integrated pest management intervention may be done after hours so that the students, teachers, and parents are likely to be blinded. Additionally, interventions that cannot be randomized from classroom to classroom, such as integrated pest management, may be randomized between schools and focused on cafeterias. Large scaled interventions may be more difficult to blind, such as heavy duty building maintenance to remove mold and repair cracks.

Despite the logistical challenges of implementing comprehensive school-based interventions, evidence provides support towards the importance of school and classroom exposures and health outcomes. [5,16,44–53] Our ongoing efforts are evaluating the additive role of the school environment, adjusting for home environment on health outcomes, and may provide additional support for school-based environmental intervention as a next step. The school may eventually be considered an effective target for asthma morbidity prevention. School-based interventions have the potential to reduce exposures for many symptomatic children, in contrast to the individual families impacted by home-based interventions. If effective, results from school-based interventional studies could inform public policy change, funding, and initiatives. Unlike home intervention strategies, these efforts would likely not be dependent on individual family practice and funds, privately or through health insurance.

While our SICAS2 trial may seem to be an expensive undertaking for cities, preliminary studies suggest that environmental interventions may be cost effective.[54] A recent study found that education regarding such things as allergen-impermeable covers and pest management yielded a net savings of over $14 million when accounting for direct medical expenses and indirect expenses, such as lost work productivity in the state of Maryland.[54] In inner cities where the burden of disease is so great, interventions may reduce the cost to the community even further. We have focused this perspective on inner-city school environments because the majority of previous home-based interventions have focused on inner-cities, which have a disproportionately high asthma burden.[21,55–61] Non-urban school environments may also be important if these interventions prove effective. While we do not intend to suggest that school-based interventions should replace home-based interventions, but that a comprehensive school-based environmental intervention would be an important first step to provide information on the additional or independent role of school-based environmental interventions. Finally, if the benefits from school-based interventions last beyond when the intervention is performed, as they did in the home-based study from Morgan et al., the impact will be even greater.[10]

Our school-based IPM and air cleaning filtration trial will have particular relevance to long-term public policy and planning for urban U.S. schools with similar indoor environments. We anticipate the proposed interventions will result in net savings, where implementation costs are offset by fewer symptom-days and improved quality of life for children, less health care utilization and less loss of work-days (greater economic productivity) for caregivers. Previous indoor environment intervention trials focused on individuals in single homes. If we demonstrate that reduction of classroom-specific exposures leads to improved asthma outcomes, then our findings can be translated into efficient and cost-effective strategies[62] to benefit communities of children through improving the school environment, where children in America spend the majority of their day.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ACT	Asthma Control Test
CADR	Clean Air Delivery Rate
CASI	Composite Asthma Severity Index
CFM	Cubic feet per meter
Db	decibels
DCC	Data Coordinating Center
FDA	Food and Drug Administration
F_ENO	Fractional Exhaled Nitric Oxide
FEF25–75%	Forced expiratory flow between 25 and 75% of vital capacity
FEV_1	Forced expiratory volume in 1 s
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
HEPA	High Efficiency Particulate Air
HRQL	Health related quality of life
HSPH	Harvard T. H. Chan School of Public Health
ICAS	Inner-City Asthma Study
ICAC	Inner-City Asthma Consortium
IgE	Immunoglobulin E
IPM	Integrated Pest Management
IRB	Institutional Review Board
IT	IPM Technician
MAAIT	Mouse Allergen Asthma Intervention Trial
MARIA	Multiplex array for indoor allergens
µg/g	microgram per gram
µm	micrometer
NIH	National Institutes of Health
NIAID	National Institute of Allergy and Infectious Diseases
PEF	Peak expiratory flow

PFT	Pulmonary Function Test
PI	Principal Investigator
PM	Particulate Matter
QALYs	quality-adjusted life years
RA	Research Assistant
SACCC	Statistical and Clinical Coordinating Center
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SICAS	School Inner-City Asthma Study- observational study
SICAS-1	School Inner-City Asthma Study-observational study
SICAS-2	School Inner-City Asthma Intervention Study – clinical trial

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Table 1

Arms of the Study.

Groups	N	Assigned intervention
Cohort A - ARM 1	75	School: IPM intervention Classroom: air filter
Cohort B - ARM 2	75	School: IPM intervention Classroom: sham (placebo) air filter
Cohort C - ARM 3	75	School: control Classroom: air filter
Cohort D - ARM 4	75	School: control Classroom: sham (placebo) air filter

Table 2

Schedule of events: surveys.

Form	Pre-screening (spring)	Screening (summer) June–Sep	Baseline phone survey (fall) Sep–Oct	Intervention implementation	2 mo follow up (fall-winter) Jan–Feb	4 mo follow up (winter-spring) Mar–Apr	Exit/final survey (end of school) May–June
Form 01: Student Screening Survey	3						
Form 02: Subject Screening and Eligibility Form	1						
Form 03: Baseline Questionnaire		2					
Form 04: Personal Care Products Usage Form		3	1[a]				1
Form 05: Participant Contact Information	1	3	1		1	1	1
Form 07: Adherence to Asthma Medication Schedule		2	1		1	1	1
Form 08: Asthma and Allergy Medication Form		2	1		1	1	1
Form 10: CASI		2			1	1	1
Form 11: Food Allergies Form		3	1[a]			1	
Form 12: Medical Visits/Safety Form		2	1		1	1	1
Form 13: Neighborhood Questions Form[a]		3	1[a]				1
Form 14a: PROMIS Parent Proxy v20 Profile 25		1	1[a]		1		
Form 32: PROMIS Parent Proxy Short Form v20-Asthma Impact 8a		3	1[a]			1	
PROMIS Parent Proxy Scale v10-Global Health-7		3	1[a]			1	
PROMIS Parent Proxy Short Form v10-Psychological Stress Experiences 4a		3	1[a]			1	
Form 15: Pediatric Asthma Caregivers Quality of Life Questionnaire		1			1		
Form 17: Sleep and TV Watching Form		3	1[a]			1	
Form 18: Time Spent Outside Home Form		3	1[a]			1	
Form 19: EQ5D-Y Parent Interview		1					1
Form 20: WPAI-General Health Interviewer Version		3	1[a]		1		
Form 30: Follow-Up Questionnaire			1		1	1	1
Form 31: Health Outcomes Form		2	1		1	1	1

1 = Interview-phone 2 = Interview-in person 3 = Self-administered 1[a] = only if self-administered form was not received

[a]Completed for interim follow-ups only if child moved or changed schools

Table 3

Clinical procedures.

	Screening (Jun–Sep)	Randomization	School follow-up 1 (Dec–Feb)	School follow-up 2 (Mar–Jun)
Participant Baseline Visit Data and Sample Collection	X			
• CBC/Allergen specific IgE				
• Serum, plasma, urine and saliva for storage				
• Nasal swab and blow				
• Buccal Swab (optional)				
• Height, Weight, Heart rate, Pulse Oximetry				
• Skin Allergy Test				
• Pre/Post Albuterol Spirometry				
• Nasal Brush (optional)				
Participant Follow-up Visit Data Collection	X		X	X
• Spirometry				
• FeNO				
• CO-oximetry				
Participant Follow-up Visit Sample Collection at School				X
• Nasal Swab and Blow				
• Buccal Swab				

Table 4

Environmental measures and forms (school, classroom, and home).

Measure	Baseline (Oct–Nov)	Randomization	Follow-up 1 (Dec–Feb)	Follow-up 2 (Mar–Jun)
School Contact and Demographics Form	X			
School/Classroom Evaluation	X		X	X
School Environmental Samples	X		X	X
Home Environmental Samples-Vacuum Dust[a]	⟵		–	⟶

[a]One home dust sample is taken at any time during the year as a surrogate measure for home exposure

Table 5

Primary and secondary clinical outcomes.

Primary clinical outcomes	**Primary indices**
Maximum asthma symptom days in past two weeks	Maximum number of **1** Days with wheezing, tightness in the chest, or cough and/or **2** Nights with disturbed sleep as a result of asthma and/or **3** Days on which the child had to slow down or discontinue play activities because of asthma
Secondary Clinical and Economic Outcomes	**Primary indices**
School Absences	Number of school days missed because of asthma/2 weeks
Health Care Utilization	Total asthma-related unscheduled visits (UVs) defined as sum of unscheduled clinic visits and emergency department visits, and asthma-related overnight hospitalizations/school year[a]
Composite Asthma Severity Index[a]	Day symptoms and albuterol use, night symptoms and albuterol use, controller treatment, lung function, and exacerbations (defined as systemic steroids for asthma)[a]
Pulmonary Function (PFT)	FEV_1; FEV_1/FVC[a] [Secondary indices: (a) FEF25–75 (b) Bronchodlilater responsiveness (% change in FEV_1 post albuterol)]
Degree of Exposure Reduction	Health Outcomes (Primary and Secondary)
Health-related quality of life (HRQL)	ranges 0–100 and will also be converted to quality-adjusted life years

[a]Standardized core asthma outcomes from Asthma Outcomes Workshop

Table 6

Sample size estimates.

Δ sx days/2 weeks	Total N	Power: IPM school	Power: class
060	240	84	89
	280	91	92
075	240	96	98
	280	99	99
090	240	99	100
	280	100	100