NIAID, NIEHS, NHLBI, MCAN Workshop Report: The Indoor Environment and Childhood Asthma: Implications for Home Environmental Intervention in Asthma Prevention and Management

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Abstract

Environmental exposures have been recognized as critical in the initiation and exacerbation of asthma, one of the most common chronic childhood diseases. The National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Environmental Health Sciences (NIEHS), National Heart, Lung, and Blood Institute (NHLBI), and Merck Childhood Asthma Network (MCAN) sponsored a joint workshop to discuss the current state of the science with respect to the indoor environment and its effects on the development and morbidity of childhood asthma. The workshop included U.S. and international experts with backgrounds in allergy/allergens, immunology, asthma, environmental health, environmental exposures and pollutants, epidemiology, public health, and bioinformatics. Workshop participants provided new insights into the biologic properties of indoor exposures, indoor exposure assessment and exposure reduction techniques. This informed a primary focus of the workshop— to critically review trials and research relevant to the prevention or control of asthma through environmental intervention. The participants identified important limitations and gaps in the scientific methodologies and knowledge, and proposed and prioritized areas for future research. The group reviewed socioeconomic and structural challenges to changing environmental exposure and offered
recommendations for creative study design to overcome these challenges in trials to improve asthma management. The recommendations of this workshop can serve as guidance for future research in the study of the indoor environment and on environmental interventions as they pertain to the prevention and management of asthma and airway allergies.

**Keywords**

asthma; allergy; child health; indoor allergens; pollutants; environmental intervention; clinical trials

**Introduction**

Many trials aiming to improve asthma outcomes by altering the indoor environment have been conducted over the past two decades in response to observational studies suggesting that indoor environmental exposures influenced childhood asthma incidence and morbidity. The NIH Institutes NIAID, NIEHS and NHLBI, in collaboration with the MCAN, sponsored a joint workshop to discuss the current state of the science with respect to the indoor environment and its effects on the development and morbidity of childhood asthma. The workshop included US and international experts from a variety of relevant disciplines and addressed the unmet need to critically review environmental intervention asthma trials aiming at reducing asthma incidence and improving asthma control. In addition, workshop participants discussed indoor exposure assessment methodologies, and the biologic properties of allergens and indoor pollutants as they relate to the risk of asthma and asthma morbidity, as well as to possible protective effects that some of those exposures may have. This report, authored by all participants, presents the deliberations of the workshop with specific recommendations for current research needs in the field. The workshop was held in 2014, but all authors contributed current updates in both recommendations and key publications. The authors hope that the report will stimulate the next generation of scientific projects and clinical trials related to the role of the environment in childhood asthma and respiratory allergy.

**New insights into indoor exposure assessment**

The indoor environment contains numerous exposures with the potential to influence asthma development and morbidity. Exposures include biologics (allergens, bacteria, or fungi), pollutant gases and particulate matter from indoor (e.g. gas stoves and cigarette smoke) and outdoor sources. Infiltrating ambient particulate matter contains a heterogeneous mix of inorganic, organic, and biologic components. (1, 2) Indoor particle sampling can include collection of house dust (vacuumed or swiped from surfaces) or air samples (collected actively or by passive settling). Experience with nasal samplers and other personal monitoring devices for assessment of bioaerosol inhalation exposure is limited. (3–5)

The gold standard for measurement of exposure to individual allergens in dust or air samples has been enzyme-linked immunosorbent assays (ELISA), which have been improved with reduction of assay time and use of amplification to increase sensitivity. In the past decade, for standardized measurement of multiple allergens in epidemiologic studies, ELISA has
largely been replaced by fluorescent multiplex array technology, with measurements shown to be reproducible within and between laboratories. (6–8) New laboratory approaches, advances in field sampling equipment and real-time data monitoring, including rapid tests for allergens (9–11) may contribute insight into the spectrum of indoor exposures (Table 1). (6, 7) Technologies for allergen measurement including qPCR, mass spectrometry and allergen biosensors are in development, including those supported by the NIH PRISMS (Pediatric Research using Integrated Sensor Monitoring Systems) program. (12) Mass spectrometry has been used as a high sensitivity method for detection of grass pollen allergens, and is also being evaluated for food allergen detection. (13–15) A first generation of allergen biosensors can measure Der p 1, Der p 2, Asp f 1 and Ara h 1, and advances in personal air sampling methodology have led to new insight into critical allergen exposure locations. (16–19)

For the characterization of indoor microbial communities in dust and air, prior to the availability of culture independent technology enabling metagenomics, environmental microbial taxa were measured either by culture, qPCR of select taxa, or quantification of presence or activity of bioactive indoor pathogen-associated molecular patterns (PAMPs). Gram negative bacteria endotoxin bioactivity has been quantified using both kinetic Limulus amebocyte lysate (LAL) and recombinant Factor C (rFC) assays. (20–22) Endotoxin and the gram positive PAMP biomarker, peptidoglycan (N-acetyl muramic acid) have been also measured by gas chromatography/mass spectrometry (GC/MS). These methods are now complemented by culture independent metagenomic characterization of communities of microbes originating from a multitude of sources (e. g., humans, pets, mice, cockroaches, dust mites, water, soil, plants, building materials). (23, 24) Amplification and sequencing of select regions (16S rDNA for bacteria; 18S or ITS for fungi) of ribosomal DNA (rDNA), the gene that encodes for ribosomal RNA, yields information on the taxonomic composition of the environmental microbiome. (23–32) Alternatively, rDNA microarrays can be used to characterize bacterial taxonomic abundance. Microarrays are less agnostic than rDNA sequencing, and may require larger quantities of 16S rDNA. (33) Whole genome shotgun sequencing of all DNA extracted from an environmental sample also yields information on taxonomic composition of bacteria, fungi and viruses, although depth of coverage may be less than for rDNA amplification and sequencing. It also provides characterization of potential function through metagenomics estimation of the proportion of genes detected for given microbial metabolic pathways. (34) All of these metagenomic techniques generate relative abundance data for taxonomic composition or representation of functional pathways, but do not measure total bacterial or fungal microbial load, a task that requires qPCR. Also, they do not adequately address the actual function of household bacteria, and the relevance to that function to metabolic products (including breakdown of household chemicals) that could influence human health, or to colonization of the human microbiome.

Research Priorities

- Analytical/Technological Improvements
  - Personal monitoring devices for allergen, pollutant, and microbial exposures, including capacity for continuous monitoring, real-time data capture and spatial mapping
Development of techniques for uncontaminated and unbiased collection, extraction and processing of environmental microbiome samples in air and dust

Expansion of methods to measure environmental microbial functional potential and viability

Assessment of the metabolism of household chemicals by environmental microbes

- Development of methods for:
  - Quantification of multiple combined as well as individual indoor environmental allergens, microbes, pollutants, and household chemicals (“the exposome”)
  - Assessment of their relevance to human compartmental (e.g., upper airway, lower airway, gut) exposures during critical life stages

Insights into biologic properties of indoor exposures and associations with respiratory allergy and asthma outcomes

**Molecular studies of allergens, adjuvants and other environmental stimuli**—
Allergy is classically manifested by an IgE antibody response to something that is normally considered harmless, typically a protein. The role of allergens in cross-linking pre-formed IgE on mast cells followed by the recruitment of Th2 cells, basophils and eosinophils and resulting in immediate and late allergic responses, is well understood. Given that not all proteins are allergenic, other biologic properties of allergens that are less understood may be responsible for their allergenic potential. Recent studies focus on the importance of allergen proteases (37) in disrupting airway epithelial barrier integrity and function and allowing for more effective antigen uptake by innate immune cells. (38–40) Also, non-antigenic stimulation of pattern recognition receptors on epithelial cells can produce alarmins like TSLP, IL-33, IL-25 leading to Type 2 immune response polarization. (41, 42)

Human and in-vitro laboratory studies have suggested a variety of adverse or protective airway responses to inhaled allergens modulated by co-exposure to natural adjuvants, (e.g. bacterial components) that depend on dose, timing of exposure and host characteristics. In some mouse models, endotoxin was found to be the primary adjuvant in common house dust for promoting Th17 responses and neutrophilic inflammation characteristic of steroid-resistant asthma, but this microbial product was dispensable for priming the Th2 responses that are associated with allergic asthma. (43) In contrast, bacterial flagellin stimulated strong Th2 responses to ovalbumin, and was an important adjuvant component in some samples of house dust. (44) Thus, in mouse models, microbial ligands found in house dust can act in a dose-dependent manner to direct discrete types of immune responses to inhaled allergens. (45, 46) Human studies support this general notion that concomitant exposure to allergens and microbes can shape the type of immune response to the allergen that develops. (23, 24, 43, 44)
Allergen and microbial exposures may interact with each other and with pollutants, leading to harmful or, in certain cases, beneficial immunologic and clinical effects. (47, 48) Tobacco smoke and other inhalant toxins appear to alter epithelial cell gene expression throughout the respiratory tract and are likely to be important co-factors in immune response to allergens and perpetuation of asthma. (38) Metabolites of microbes and other organisms can also act as adjuvants. For example, chitin, a polysaccharide in allergens, fungi and insects, has been shown to be an adjuvant for Th2 responses. (45, 46, 49)

The effects of allergens, adjuvants and other environmental stimuli on the human airway epithelium can be studied in vitro with the use of primary cell cultures. Nasal brushing yielding upper airway respiratory epithelial cells from the inferior turbinate offers targeted opportunities for epigenetic and gene expression characterization of airway responses potentially relevant to asthma and allergic rhinitis. (50) While it is a minimally invasive procedure, nasal brushing is perceived with variable levels of comfort/discomfort by children and adults. (51) A recent study suggest that gene expression responses to tobacco smoke in the nasal epithelium correlate well with that in lower airway epithelial cells. (52, 53)

**Population level studies of allergen exposure**—While the prospective relation of home allergen levels to allergy development has been well-studied in specific birth cohorts, including those with clinical trial designs (Table 3), the National Survey of Lead and Allergens in Housing and National Health and Nutrition Examination Survey 2005–2006 were the first US population-level studies of cross-sectional associations between allergen exposures, allergic conditions and sensitization. (54, 55) These surveys indicated that almost half of the US population was sensitized to aeroallergens and that exposure to multiple allergens in homes was common. While many prospective as well as cross-sectional studies show adverse associations of allergens or their sources with allergic sensitization, wheeze or asthma, protective associations have also been found with exposures to animal allergens or their mammalian sources, (56–60) and in one multi-city disadvantaged urban U.S. cohort study, to multiple allergens including cockroaches and dust mite. (24) Collectively, these findings underscore the need to understand time windows of susceptibility to allergic sensitization and the complex dose-response relationships between allergen exposure, other heritable or environmental co-exposures (e.g., stress, pollutants) and sensitization.

**Research Priorities**

- Studies on biochemical characteristics, such as protease or lipid binding activity, of a wide variety of allergens, to elucidate their contribution to allergy.

- Studies of individual and combined influences of natural adjuvants, microbial substances, and inhaled irritants and toxicants on immune and airway responses relevant to allergy and asthma, using *in vitro, in vivo*, and human studies that take into account dose, timing, vulnerability and susceptibility.

- Studies of airway respiratory epithelial cell responses to environmental stimuli with further development of more consistently comfortable upper airway
sampling methods yielding outcomes relevant to the lower airways and asthma.

(50)

Exposure reduction techniques: Fundamental concepts/methods and new insights for environmental interventions

Air pollutants found indoors, that can trigger asthma symptoms, originate from outdoor (e.g., traffic) and indoor sources (e.g., secondhand smoke (SHS), gas stove emissions). Elimination of SHS through smoking cessation and home smoking bans should always be considered a first-line indoor environmental intervention for children with asthma. Technologic improvements have been made in the efficacy of High Efficiency Particulate Air (HEPA) particle filtration designed to remove targeted indoor air pollutants such as fine particulate matter (PM$_{2.5}$).(61) Other than replacement of gas stoves with electric stoves, fewer methods are currently available for indoor NO$_2$ reduction of indoor or outdoor origin. (62, 63) In homes with smokers, recent home and school-based intervention trials in children report significant reductions in particulate matter with HEPA filter use, (64–66) but without reduction in indoor gases, without consistent reductions in markers of cigarette smoke, and with mixed success in improving child asthma symptoms. The efficacy in reducing indoor pollutants is dependent on room dimensions and building structure and conditions. While air cleaners have been also been used as adjunct interventions in multipronged environmental intervention trials (67) successful in reducing asthma symptoms, their independent contributions to health is uncertain, and the physical settings in which they may reduce exposure sufficiently to contribute to asthma control are also not well defined.

Indoor fungi originate through penetration from outdoors as well as from indoor sources, especially in damp and water damaged buildings.(68–70) They have a multitude of forms, properties and components. Fungi and their irritant or toxicant components can have adverse airway irritant as well as allergenic properties, and asthma symptoms can occur in individuals not sensitized, as well as in those sensitized to fungi.(71, 72) The mechanisms for effects of individual fungal components and interactive effects with other indoor exposures on airway and immune responses are not well-understood. Paradoxically, some observational birth cohort studies suggest that specific microbial communities or early life diversity of microbial agents, including fungi, may protect against allergy development,(73) but this is not a justification for discouraging fungal remediation in water damaged homes or poorly maintained moldy homes.

In symptomatic patients with asthma, fungal prevention and remediation strategies and their success in reducing exposures or improving health in damp or water damaged buildings can vary by housing stock, climatic region, and resident behaviors. New building materials, ventilation systems, and home furnishings, particularly those harboring humidity, may introduce new challenges requiring novel strategies to minimize fungal growth. While a review of studies to reduce mold in buildings and assess health outcomes recommended “better research, preferably with a randomized controlled study design and with more validated outcome measures,” (74–76) imaginative study designs are needed to fit extreme situations investigators and communities are at times confronted with. In disasters with clear-cut mold damage the health risks can be obvious, but building remediation solutions
may be challenging. The post-Hurricane Katrina HEAL study reported improvement of asthma symptoms with implementation of a hybrid intervention with asthma counselors and environmental remediation, but in the midst of post-disaster changes, investigators could not disentangle the extent to which the active study environmental interventions were responsible for the observed fungal reduction or symptom improvement.\(^{(77)}\)

A variety of multi-pronged community-based strategies have been used to decrease indoor allergen exposures \(^{(78, 79)}\) with varying success in reducing exposure and in improving asthma control. This inconsistency may be due to variable levels of intensity of the intervention, provided resources, participant education, social resources or adherence. More confounders include other changes in environmental exposures, differences in tailoring the interventions to individual sensitivities of the participants, baseline levels of allergens, and effect modification of the intervention health effect by the presence of co-exposures like stress or ETS (i.e., SHS).

While many studies have sampled and tested efficacy of interventions in individual indoor homes, effects of the structure and building components of housing, including multi-unit structures, on exposure are less well studied. In Northeastern and mid-Atlantic cities, asthma prevalence is often high in multifamily low-income housing sites where multiple and interrelated housing-related exposures are present. A few studies have evaluated indoor environmental and respiratory health before and after alterations in single or multifamily homes that undergo ‘green’ construction, renovation or weatherization under construction guidelines aimed to conserve energy while maintaining adequate ventilation, using “environmentally friendly” materials. Such studies take advantage of costly interventions already taking place but have the potential limitations of uncontrolled observational study designs.\(^{(80)}\) In one Boston-based study, asthmatic children living in green homes experienced substantially lower risk of asthma symptoms, hospital visits, and asthma-related school absences than children living in conventional public housing.\(^{(80)}\) A study of green housing in the South Bronx \(^{(81)}\) showed improvements in asthma symptoms and urgent care visits for asthma and a Chicago-based study showed self-reported asthma symptom improvements.\(^{(82)}\) However, given the variable application of “green” construction approaches, the potential risks of responding to financial pressures by reduction of air exchange or inadequate maintenance even in new buildings, and study design limitations, uncertainty remains about which aspects of new construction may improve asthma.

Table 2 offers a summary of selected published studies on exposure reduction and on associations between exposure reduction with asthma control.

**Research Priorities**

- Well-designed (and, if feasible, blinded and controlled) trials to test the conditions under which free-standing air filtration systems, structural interventions, and other emerging building-level interventions reduce indoor pollutants, allergens, and other contaminants at home or in schools. This is a precondition to assessing whether exposure reduction improves respiratory health.
• Development of effective mold reduction strategies tailored to specific individual risk factors (e.g., poorly controlled asthma) and building, geographic, and climatic factors.

• Tailoring of multipronged strategies for indoor exposure reduction to the specific physical and social situations of urban families and their housing situations. Effective strategies may require changes in physical infrastructure, as well as in building management practices and occupant behavior.

• Assessment, with engagement of building management and construction engineers, of effects of new building approaches (including 'green' building) and building characteristics (e.g., humidity, structural integrity) on indoor exposures and health.

• Assessment of effects of housing policy interventions, such as housing mobility programs, on indoor exposures.

• For highly mobile populations or for populations with little control over the structure of their homes, testing of low cost interventions easily transferable from home to home or interventions that can be applied to any home without the need for structural changes.

• Development of novel technologies for particle or gas filtration (including NO$_2$ reduction) in home and school environments.

• With community engagement, development of interventions that can be applied to low-income populations with limited resources, especially those with high mobility.

• All environmental interventions should include cost-benefit estimations.

**Indoor environmental interventions for primary prevention of asthma**

Primary prevention of asthma is an enviable goal that, if achieved, could reduce the prevalence of the disease. Of a large number of potentially modifiable risk factors for asthma development identified in the literature, (104) allergen exposure is one that has attracted considerable attention. (105, 106) Observational epidemiologic studies have identified early life allergen exposures as risk factors for subsequent allergic sensitization, and early allergic sensitization is a major risk factor for asthma. (107) However, the concept of allergen avoidance for primary prevention of asthma has been challenged by investigators who argue that this approach is limited by a) the ubiquitous nature of aeroallergens in some ecologic and cultural settings; b) the dominance of genetic factors in influencing the course of asthma; c) the importance of early priming by other factors (microbes or microbial components, in utero smoking, vitamin D, etc.) or, most recently d) the benefits from early allergen exposure as manifested by studies in food allergy and e) the protective effect against wheezing of high aeroallergen exposure in the first years of life. Evidence for potential benefits of early exposure to allergens or their sources for allergic sensitization, wheeze or asthma have been reported by observational birth cohort studies including the Massachusetts-based Epidemiology of Home Allergens and Asthma Study (EHAAS), the Wisconsin Childhood Origins of Asthma Study (COAST), the Detroit Childhood Allergy...
Study (CAS) and the Urban Environment and Childhood Asthma (URECA) Study. (24, 56, 58, 108) Most of these observational studies report protective associations with early-life mammalian exposures, especially dogs and associated allergens or microbes. The URECA data indicated that early-life multiple exposures including cockroach and mouse are protective, (24) whereas EHAAS found these two exposures to be risk factors. Multiple differences in cofactors and exposure levels may be responsible for the contrasts in these observational studies.

**Dust mite allergen avoidance and prevention studies**—Long-term follow up in primary allergen prevention trials focused on house dust mite reduction vary in terms of their success in asthma prevention. (109) The first such study was the Isle of Wight primary prevention study which recruited 120 children and used a multifaceted approach to reduce both common food allergens and house dust mite (HDM) exposure during infancy, with follow-up extending to 18 years. This study has shown a consistent reduction of asthma, but not atopy, in the allergen avoidance group (Figure 1).((110–112) A multifaceted approach for infants with a family history of allergic disease was also tested in the Canadian Asthma Primary Prevention Study (Table 3). The intervention, which began during pregnancy, yielded mixed results with a significant reduction in asthma, but not atopy, at 1, 2 and 7 years. At 15 years of age, the reduction in asthma risk was seen only in females.(113, 114) The Manchester Asthma and Allergy Primary Prevention Study (MAAPPs) tested the effect of stringent indoor allergen avoidance measures in a relatively large (n=291) randomized controlled trial. (115) By age 3 years HDM sensitization was more common in the intervention group and there was no difference between the groups in physician-diagnosed asthma.((116, 117) Finally, in the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study, 810 allergic mothers were enrolled during pregnancy and randomized to impermeable mattress- and pillow-covers or placebo covers. Apart from a reduction in asthma prevalence at age 2 years, no preventive effect on asthma or allergic sensitization up to 8 years was observed.(118–121)

There are a number of explanations for the inconsistent findings across studies of HDM allergen avoidance. It might be that only a multifaceted intervention is effective.(122) Another potential explanation is that the baseline mite allergen levels in the PIAMA study were so low that further reduction could not have significant clinical effect.((115, 123) It is also possible, but less likely, that genetic variations in Isle of Wight and Canadian children made them more receptive to allergen avoidance (124) or that genes or environmental co-factors in the home, or outside of the home modify either the magnitude or even the direction of the response. Overall, interpretation of these findings is difficult because the relationships between the levels of allergen exposure and their biologic effects are not clear.

**Other potentially modifiable environmental factors for asthma prevention**—An explanation for protective associations with pets might be that the ecology of the home microbiome is affected by the presence of a pet, which in turn may influence the gastrointestinal microbiome of the infant.((125–127) Whether the microbial ecology of a child’s home is affected by outdoor microbes brought in by the pet, or by the pet’s own microbiome is unknown (Figure 1). The mechanisms through which this protection may
occur are unknown, but the role of the microbiome and its biochemical products as modulators of innate immune system responses that may suppress allergy is an area of intense focus. One recent animal model validated the Detroit birth cohort observation that pet dust could be protective against allergic responses.

Asthma disproportionately affects certain ethnic groups, and patterns of allergen and microbial exposure vary according to socioeconomic status, area of residence, and race or ethnicity. For example, non-Hispanic Blacks and Hispanics in the US Northeast are more likely to be exposed to mouse and cockroach allergens (but less likely to be exposed to HDM, dog, and cat allergens) than non-Hispanic whites. In addition, stressful experiences, such as home or community violence, may contribute to the high prevalence of asthma in these communities. Such experiences can disturb stress regulation and thus adversely influence immune function and increase susceptibility to asthma. Primary prevention studies in asthma should strive to account for relevant social, cultural and demographic factors, as well as for the role of diet, stress and other lifestyle factors.

Other potentially modifiable factors such as micronutrients, antioxidants and others, which are not considered classic environmental pollutants, allergens, or bioaerosols, are beyond the scope of this article. However, such factors are being actively investigated in the context of asthma prevention.

**Research Priorities**

- Additional observational and animal model validation studies to assess the role of dose, route, timing and pattern of single or multiple exposures, as well as genetic inheritance, in determining the relation of exposure to allergy or asthma development. This will optimize design of asthma prevention trials focused on allergen, pollutant, and microbial exposures.

- Sufficiently powered observational study of multiple early-life environmental influences on asthma and allergy development in diverse communities in the United States. The recent collaboration of U.S. birth cohorts through the NIH-sponsored effort “Environmental Influences on Child Health Outcomes” (ECHO) offers a unique opportunity to achieve this goal; ECHO will facilitate characterization of children manifesting a variety of asthma phenotypes or endotypes that may be differentially influenced by indoor environmental exposures.

- Studies to identify early patterns of human microbiome and its metabolic output in the gastrointestinal tract, the airways and the skin that are associated with the development of allergic diseases, and how they are influenced by the indoor environment, including environmental microbes, their metabolic products, and their functional components.

- Randomized multifaceted environmental interventions for asthma prevention designed to account for each element of the intervention and for social, cultural and other demographic factors.
Randomized controlled trials (RCTs) that include primary prevention of asthma, through stress reduction measures tailored to ethnic and cultural diversity, and assessment of interactive effects of stress reduction with environmental interventions on asthma development.

For each of major potentially modifiable factors,

- Identify the subpopulations that would benefit from the intervention, and subpopulations that might be at adverse risk, or not benefit.
- Define, develop, refine and test interventions that would be of benefit to most children (e.g., smoking cessation).

**Indoor Environmental Interventions for Asthma Management**

Although indoor environmental interventions aimed at reducing asthma morbidity have been more successful than those aimed at primary prevention of asthma, questions remain about their role in asthma management. Table 2 provides an overview of the most recent environmental intervention trials and highlights their findings and limitations in influencing exposure reduction and asthma control. Effective environmental interventions are typically multi-faceted, tailored to the specific exposures and sensitivities of the target subject, and intensive.\(^{84, 150}\) Publication bias leads to less publication of unsuccessful intervention trials, but the few that have been published suggest that single-allergen interventions and low-intensity efforts are ineffective. One such negative publication (151) exemplifies the challenge of translating an efficacious intervention from a tightly controlled clinical trial setting to a broader population: when the provision of allergen-proof mattress/pillow encasements to adults with asthma was tested in primary care, no effect was found with this untailored intervention. Although the study population was adults, the notion that health benefits observed in tightly controlled RCTs may not easily translate to more “real-world” settings is applicable to environmental interventions in children, too. In addition, families face a number of barriers to remediating environmental exposures, including costs, preferences, home ownership status, life-long behavioral practices, and education. For example, low-income urban populations are highly mobile and have limited resources with which to address environmental concerns. Also, residents often do not control the structure of their buildings since they rent, rather than those who own their homes.

The Inner-City Asthma Study (ICAS) may be the most successful environmental intervention study conducted to date; the intervention was targeted at specific allergen reduction in asthmatic children who were both sensitized and exposed to those allergens, but the intervention was also multi-faceted including integrated pest management targeted to specific allergen sensitivities, provision of HEPA vacuum cleaners, free standing bedroom HEPA filter air cleaners, and allergen-impermeable mattress and pillow covers. Primary trial results reported in 2004 found that the environmental intervention group experienced significant and clinically meaningful reductions in a range of asthma outcomes compared to controls.\(^{84}\) Benefits were seen up to 12 months after the environmental intervention and cost-effectiveness analysis derived a cost of $750 to $1000 per year per family to implement, a cost they estimated was equivalent to cost of mid-range inhaled corticosteroid and albuterol for a child with moderately severe asthma. This translated to almost $28 per gained...
symptom-free day. (152) Because a multi-faceted, patient-tailored, intervention was tested in ICAS, and direct measures of environmental tobacco smoke exposure reduction were not made, it is not possible to determine the relative contribution of individual components of the environmental intervention and exposure reduction to the successful outcome. Notably, both arms of the ICAS (environmental intervention and physician feedback) were successful without other interaction with the health care systems, but optimally environmental control trials should be designed in the context of optimal access to health care, access to medications, and appropriate clinical asthma management.

Research Priorities

- Further define the role of environmental interventions in asthma management by conducting randomized, multifaceted clinical trials designed to account for each element of the intervention and for social, cultural and other demographic factors.

- Determine the most feasible, and cost- and clinically-effective approach to environmental interventions by conducting head-to-head comparisons of various forms of environmental intervention.

- Determine which environmental intervention components can be effectively implemented and the best approaches to implementation. Studies are needed that will test how to effectively implement optimal environmental control schemes into healthcare, public health policy, housing policy, and clinical practice.

Specific, detailed research questions for each priority area in environmental interventions for asthma management described above are listed in Table 4. Addressing these research priorities will have clear implications for how healthcare providers, public health agencies, healthcare systems, communities, and insurers implement and support environmental intervention as an integral component of asthma management.

Conclusions

With a focus on indoor allergens, microbes and pollutants, workshop participants assessed current methods, and prioritized new method development for measurement of indoor environmental exposures potentially relevant to asthma development and asthma management. We assessed new insights into the biologic properties of many of these exposures, and prioritized needs for future elucidation of these properties. We reviewed the state-of-knowledge of the efficacy of targeted and multi-pronged environmental interventions in changing environmental exposures, and the social and structural challenges in influencing environment interventions, with recommendations for future directions. Finally, we reviewed the efficacy of primary prevention trials to reduce asthma development by altering the indoor biologic or physical environment, and the efficacy of trials to improve asthma management and asthma control by improving the indoor home or school environment. For each covered topic, the workshop offered recommendations on research priorities to inform the next generation of asthma prevention or asthma management trials that include environmental components. There was uncertainty as to whether efforts at primary intervention should include a trial of changes in the indoor environment. It is
anticipated that the newly funded, U.S.-wide NIH-initiative Environmental Influences on Child Health Outcomes (ECHO) as well as complementary mechanistic studies with functional validation of observational findings might further inform future directions. Ultimately, new trials and translation of trial findings into public policy will need to take into account the family, social, economic and neighborhood context of participants and, for children with established asthma, their access to adequate health care, including appropriate asthma medications.

Acknowledgments

This workshop was supported by funds from the Division of Allergy, Immunology, and Transplantation, National Institute of Allergy and Infectious Diseases, the Division of Lung Diseases, National Heart, Lung, and Blood Institute, the Division of Intramural Research, National Institute of Environmental Health Sciences, and the Merck Childhood Asthma Network (MCAN), Inc. The authors would like to give special thanks to Dr. Floyd Malveaux for his MCAN leadership and support of this workshop. The findings and conclusions in this manuscript are those of the authors and do not necessarily represent the official position of any of the above-referenced NIH Institutes or the CDC.

References


Figure 1.
A schematic model describing presumed relationships between the microbiome and allergic asthma. Adapted with permission from (153)
## Table 1

Recent and Emerging Technologies for Indoor Exposure Assessment of Biologic Environmental Exposures

<table>
<thead>
<tr>
<th><strong>Allergens</strong></th>
<th>Description/Comments</th>
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<tbody>
<tr>
<td>Fluorescent Multiplex Array (6–8)</td>
<td>Bead-based fluorescent suspension array allows for simultaneous detection of up to 11 allergens. Also being developed for food allergens.</td>
</tr>
<tr>
<td>Biosensors (16–19)</td>
<td>Variety of sensor technologies (AAO film, gold nanoparticle, magnetic beads, DNA-stem loop probe). High sensitivity; could be smart phone enabled for personal exposure measures.</td>
</tr>
<tr>
<td>Mass Spectrometry (13–15)</td>
<td>Fragmentation of analyte and quantification of mass to charge units. Methods developed for grass pollen, food allergens. High sensitivity, but high throughput capacity is limited; measurements are expensive</td>
</tr>
</tbody>
</table>

### Bacteria

| **16S rDNA microarrays (33)** | Requires higher quantities (~500ng) of 16S rDNA compared to sequencing. Broad range of taxa identifiable, but some rare microorganisms may be missed. |

### Fungi

| **18S/28S/ITS rDNA sequencing (29, 30, 36)** | rDNA from 18S, 28S, or ITS regions is amplified and sequenced. Sequencing technologies: Roche 454 pyrosequencing, Illumina HiSeq, MiSeq, Ion Torrent, PacBio. Reference databases (SILVA, FMP) limited but increasing. |

### All Biologics

| **Whole genome shotgun sequencing (34)** | All DNA from an environmental sample is extracted and sequenced. More expensive than rDNA methods, often less depth taxonomically for lower abundance microbes. Offers potential for functional metagenomics (i.e. abundance of microbial metabolic pathway genes). |

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<th>Reference</th>
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<tr>
<td>Carter et al. (2017)</td>
<td>104 enrolled 6-16 y/o inner-city children with asthma (Atlanta, GA, US)</td>
<td>RCT Single-blinded</td>
<td>Dust mite and cockroach allergens</td>
<td>Intervention 1 (n=35): allergen impermeable covers + effective reach bait, instructions to wash bedding weekly, in hot water, and education on dust mite and cockroach cleaning measures Intervention 2 (placebo): n=34, instructions to wash bedding once/ wk, in cold water</td>
<td>No difference between intervention vs placebo in percent achieving 70% decrease in allergen reduction; cockroach allergen reduction measures ineffective</td>
<td>• Decreased asthma visits for asthma in home visited</td>
<td>Applying allergen avoidance challenging in poor communities because of multiple sensitizations and problems applying protocols in this environment</td>
</tr>
<tr>
<td>Morgan et al. (2004)</td>
<td>937 5–11 y/o inner-city children with asthma sensitized to ≥ 111 indoor allergens (7 US cities: ICAS)</td>
<td>RCT Indoor allergens, ETS</td>
<td>Intervention (n=469): Multifaceted: 1 yr. of education + allergen impermeable covers + HEPA vacuum cleaner + bedroom HEPA air cleaner + remediation with IPM tailored to each child’s sensitization/exposure profile</td>
<td>Reduction in dust mite and cockroach allergen levels</td>
<td>• Decreased asthma symptoms during the intervention year (3.39 vs. 4.20 days) and the year after</td>
<td>Separate effects of each component of intervention unknown</td>
<td>Cost: $1500 to $2000/child—similar to cost of total-range ICS &amp; albuterol for a child with moderately severe asthma</td>
</tr>
<tr>
<td>Phipatanakul et al. (2004)</td>
<td>18 mouse-sensitized homes of mouse-sensitized inner city asthma children (Boston, US)</td>
<td>RCT Mouse allergen</td>
<td>Intervention (n=12): Professionally delivered IPM</td>
<td>Reduction (~75%) in settled dust mouse allergen levels</td>
<td>• No differences in asthma outcomes, exposure to mouse allergen, or other mouse allergens (focus on cockroach, mouse)</td>
<td>No direct ETS exposure measures</td>
<td></td>
</tr>
<tr>
<td>Krieger et al. (2005)</td>
<td>274 4–12 y/o children with asthma from low-income families (Seattle-King County, WA, US)</td>
<td>RCT Multiple asthma “triggers”</td>
<td>Intervention (n=138): Multifaceted: 1 yr. of education + allergen impermeable covers + HEPA vacuum cleaner + bedroom HEPA air cleaner + remediation with IPM tailored to each child’s sensitization/exposure profile</td>
<td>Reduction of ~75% in PM2.5 &amp; PM10; indoor allergens (focus on cockroach, mouse)</td>
<td>• Decreased daytime, nighttime, and other asthma symptoms between groups</td>
<td>Insufficient power to detect long-term or clinical responses</td>
<td></td>
</tr>
<tr>
<td>Eggleston et al. (2015b)</td>
<td>100 6–12 y/o children with asthma from low-income families (Baltimore, MD, US)</td>
<td>RCT PM2.5 &amp; PM10, indoor allergens (focus on cockroach, mouse)</td>
<td>Intervention (n=50): Multifaceted 1 yr. of education + allergen impermeable covers + HEPA vacuum cleaner + remediation with IPM for mice and for cockroach (if infestation signs or if child sensitized)</td>
<td>Reduction of ~39% in PM2.5 &amp; PM10, and ~90% in cockroach allergens</td>
<td>• Decreased daytime asthma symptoms</td>
<td>Separate effects of each component of intervention unknown</td>
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</tbody>
</table>

Note: PM = particulate matter; ICS = inhaled corticosteroids; QOL = quality of life; IPM = integrated pest management.
<table>
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<tr>
<th>Reference</th>
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<th>Intervention</th>
<th>Exposure outcome</th>
<th>Asthma outcome</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Chew et al. (2014) (88)</td>
<td>3 uninhabited water-damaged homes (New Orleans, LA, US)</td>
<td>Pre-post treatment comparison</td>
<td>Mold (spore counts, cultures, PCR analyses, glucan, endotoxin, and PM)</td>
<td>Intervention: Removal of drywall, carpet, insulation, and all water-damaged furnishings. Reductions in mold and endotoxin pre- and during treatment mold and PM.</td>
<td>N/A</td>
<td>NA</td>
<td>Pre- and during treatment mold and PM reduction levels were orders of magnitudes above those in homes without water damage. Adequate respiratory recommended during clean-up.</td>
</tr>
<tr>
<td>Kercsmar et al. (2006) (74)</td>
<td>62 2–17 y/o children with asthma in homes with mold (Cuyahoga County, IL, US)</td>
<td>RCT</td>
<td>Mold scores, allergen levels</td>
<td>Intervention (n=20) and Control (n=20), outcome action plan, education, individualized problem solving. Intervention group only + household repairs and modifications</td>
<td>Decreased asthma symptom days and prevalence of exacerbations in intervention group compared to control.</td>
<td>N/A</td>
<td>Low sample size, limited power - Frequency of families moving - Complexity of applying for household repairs and working with landlords.</td>
</tr>
<tr>
<td>Sever et al. (2007) (89)</td>
<td>60 cockroach infested homes (NC, US)</td>
<td>3-arm RCT</td>
<td>Cockroach/Bla g 1</td>
<td>Intervention 1 (n=20): 12-mo professional entomological pest control. Intervention 2 (n=20):12-mo contract based at times performed by pest control companies. Control (n=20).</td>
<td>Compared to control: • Intervention 1: reduction in Bla g 1 (~90%). • Intervention 2: No reduction.</td>
<td>N/A</td>
<td>Suggest increase education of commercial pest control companies on efficient eradication methods and dedication of families.</td>
</tr>
<tr>
<td>Pongracic et al. (2008) (90)</td>
<td>312 5–11 y/o inner-city children with asthma and sensitization to a incident subset of ICAS; 7 US cities</td>
<td>RCT</td>
<td>Bedding allergen/Mix 1</td>
<td>Intervention (n=42): ICAS (inner-city children study) rodent module: 1 yr. of education + allergen impermeable covers + HEPA vacuum cleaner + bedroom HEPA air cleaner + filling rodent access points and setting traps throughout home. Control (n=159): 97% received at least 1 other module.</td>
<td>80% bed rooms had detectable mouse allergens. • Intervention: reduction in mouse allergen (~27%) in bedroom floor but not bed. • Control: Increase in mouse allergen (~28%).</td>
<td>N/A</td>
<td>Did not measure rat allergen, cannot evaluate whether findings relate to change in this exposure.</td>
</tr>
<tr>
<td>Howden-Chapman et al. (2008) (91)</td>
<td>489 households of 6–12 y/o children with asthma (5 New Zealand communities)</td>
<td>RCT</td>
<td>Nitrogen dioxide</td>
<td>Intervention (n=240): Installation of a non-polluting more effective heater (heat pump, wood pellet burner, or flued gas) before winter. Control (n=249). Give replacement heater at end of 1 yr. trial.</td>
<td>Reduction in NO2 levels in living rooms and bedrooms.</td>
<td>N/A</td>
<td>Engagement with asthma coordinators - Multiethnic, including Maori, who have greater burden of respiratory diseases - Challenges include: Complex communication - Technical difficulties with Piko (for lung function measurement).</td>
</tr>
<tr>
<td>Bryant-Shepherd et al. (2009) (92)</td>
<td>264 2–16 y/o children with asthma (Philadelphia, PA, US)</td>
<td>Randomized 1:1 crossover</td>
<td>Dust, pests, pet ETS</td>
<td>Intervention (n=144) [or delayed] Immediate (n=144) intervention: family education + supplies for trigger reduction (allergen impermeable covers, each bait, mouse traps, cleaning aids, storage bins, replacement for curtains/bedspread given by lay health educators.</td>
<td>Reduction in rodents. Increased use of impermeable covers (measured at 2.5 mo. post intervention).</td>
<td>N/A</td>
<td>Separate effects of individual interventions unknown - High drop out in the delay intervention group - The longer in the study, the better the outcome - No skin testing.</td>
</tr>
<tr>
<td>Reference</td>
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<tr>
<td>Breyec et al. (2011)</td>
<td>49 adults, 29 children</td>
<td>Cross-sectional health survey</td>
<td>Green specifications targeting ventilation, moisture, mold, pests, radon</td>
<td>Intervention: Renovation according to Enterprise Green Communities green specifications, using “Healthy Housing” features. New mechanical ventilation installed (94)</td>
<td>Reduction in energy use (45%)</td>
<td>No change in symptom-free days</td>
<td>No formal cost effectiveness analysis (cost ~ $500/home)</td>
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<tr>
<td></td>
<td>from 31 units in a low-income 3-building, 96-unit apartment complex (MN, US)</td>
<td>pre-immediately post renovation</td>
<td></td>
<td>Immediate post renovation</td>
<td>Self-care of cleaners, more comfortable, safer housing</td>
<td>No change in symptom-free days</td>
<td>Potential recall bias</td>
</tr>
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<td>Breysse et al. (2011)</td>
<td>49 adults, 29 children</td>
<td>Cross-sectional health survey</td>
<td>Reduction in energy use (45%)</td>
<td>Improvement in overall adult health, in non-smoking adults (adults + children) and in asthma health (adults)</td>
<td>Lack of improvement in asthma controller use</td>
<td>Potential communication problems with non-English speaking residents</td>
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<td>from 31 units in a low-income 3-building, 60-unit apartment complex (MN, US)</td>
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<td>Reduction in radon</td>
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<tr>
<td>Bryson et al. (2014, 90)</td>
<td>182 low income households in rental properties with 1 or more children with not well-controlled asthma (King Country W A, US)</td>
<td>Observational, pre-post intervention study with historical comparison group</td>
<td>Move from conventional to new buildings designed to green standards, smoke-free policies and IPM practices employed</td>
<td>Fewer reports of mold, pests, inadequate ventilation, and stuffiness</td>
<td>Fewer sick building syndrome symptoms</td>
<td>Fewer asthma symptoms, hospital visits, school absences for children in green compared to conventional public housing</td>
<td>Suggested benefits of move to green housing need further assessment; Numbers of controls limit pre-post analysis</td>
</tr>
<tr>
<td>Colton et al. (2015, 96)</td>
<td>235 households in 3 Boston public housing 188 residents (80%) with 2 visits</td>
<td>Observational comparison of conditions and health in green vs conventional housing. Visits included home inspection and questionnaire</td>
<td>Visits to Green Units (n = 201) and conventional Public Housing Units (n = 222)</td>
<td>Fewer reports and observations of mold, pests, inadequate ventilation, and stuffiness compared to conventional housing.</td>
<td>Fewer asthma symptoms, hospital visits, school absences for children in green compared to conventional public housing</td>
<td>Suggested benefits of move to green housing; Effects observed only for children in with asthma; effects on adults not certain.</td>
<td></td>
</tr>
<tr>
<td>DiMango et al. (2016, 100)</td>
<td>110 adults and 137 children with asthma sensitized and exposed to at least 1 indoor allergen</td>
<td>RCT</td>
<td>Key allergens in vacuumed settled dust (cat, dog, dust mite, aspergillus and mouse)</td>
<td>Following optimization of asthma management and control, randomization to: Intervention (n=125): Multifaceted allergen avoidance + allergen impermeable covers + HEPA vacum cleaner + bedroom HEPA air cleaner</td>
<td>Improvement in asthma control in both arms, with no difference between groups.</td>
<td>Lack of difference between intervention and control groups in achieved allergen reduction may explain lack of effect of active intervention on asthma outcomes; Intervention did not include intensive targeted IPM; post hoc analyses suggested improvement when mouse allergen was reduced; Not powered to assess effects in adults vs children</td>
<td></td>
</tr>
<tr>
<td>Matsui et al. (2017, 101)</td>
<td>389 children and adolescents with asthma sensitized and exposed to mouse</td>
<td>RCT</td>
<td>Mouse allergen</td>
<td>IPM + Education Group (n=183): application of rodenticide, sealing holes that could serve as entry points for mice, trap placement,</td>
<td>No difference in mouse allergen levels between groups.</td>
<td>Large reduction in mouse allergen observed in education group was unexpected.</td>
<td></td>
</tr>
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<tr>
<td>Gold et al. (2017)(101)</td>
<td>5–7 y/o children with moderate to severe asthma in cockroach-infested homes (New Orleans, LA, US)</td>
<td>RCT</td>
<td>Dust mite allergen</td>
<td>Intervention (n=50): 12-mo with trapping &amp; bait placement at baseline, 1, 3, 6, 9, and 12 mo.</td>
<td>Fewer cockroaches in intervention homes.</td>
<td>Fewer asthma symptoms and unscheduled health care utilization.</td>
<td>Results suggest education alone may be effective in some populations, but study did not include control group that received no education about pest management.</td>
</tr>
<tr>
<td>Rabito et al. (2017)(102)</td>
<td>5–7 y/o children with moderate to severe asthma in cockroach-infested homes (New Orleans, LA, US)</td>
<td>RCT</td>
<td>Dust mite allergen</td>
<td>Intervention (n=50): 12-mo with trapping &amp; bait placement at baseline, 1, 3, 6, 9, and 12 mo.</td>
<td>Fewer cockroaches in intervention homes.</td>
<td>Fewer asthma symptoms and unscheduled health care utilization.</td>
<td>Suggested benefits of single intervention with strategic insecticidal bait placement.</td>
</tr>
<tr>
<td>Murray et al. (2017)(103)</td>
<td>3–17 y/o mite-sensitized children with emergency hospital attendance for asthma exacerbation (North-West England)</td>
<td>RCT [Age group (3–10 y; 11–17 y) stratified]</td>
<td>Dust mite allergen</td>
<td>Intervention (n=146): 12-mo with mite-impermeable bed encasings. Control (n=138): 12-mo with no encasings.</td>
<td>Lower dust mite (Der p 1) levels.</td>
<td>Fewer hospital visits with an exacerbation.</td>
<td>Limited in that all data on exacerbations and oral corticosteroids were reported by parents/caregivers. No measured adherence to meds or asthma trigger data.</td>
</tr>
</tbody>
</table>

RCT=Randomized controlled trial; ETS=environmental tobacco smoke; IPM=integrated pest management; PM=particulate mass; ICS=inhaled corticosteroids; QOL=quality of life; ICAS=Inner City Asthma Study. References (2000–2016) selected by Workshop participants as representative and illustrative of asthma management intervention studies in children.
## Table 3

Randomized controlled trials in primary prevention of asthma using HDM allergen avoidance

<table>
<thead>
<tr>
<th>Studies</th>
<th>Year/s recruited</th>
<th>N</th>
<th>Assessments (Years)</th>
<th>Major findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isle of Wight (110–112)</td>
<td>1990</td>
<td>120</td>
<td>1, 2, 4, 8, 18</td>
<td>Reduced asthma and atopy at all ages 1–18</td>
</tr>
<tr>
<td>MAAPS *(109, 115, 116)</td>
<td>1995–1997</td>
<td>291</td>
<td>1, 3, 5, 8, 16</td>
<td>Reduced severe wheezing (infancy)</td>
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<tr>
<td></td>
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<td></td>
<td>Increased mite sensitization (age 3 years)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Improved lung function (age 3 years)</td>
</tr>
<tr>
<td>CaPPS(113, 114, 149)</td>
<td>1995</td>
<td>545</td>
<td>1, 2, 7, 15</td>
<td>Reduced asthma (up to age 7 and at age 15 in females only)</td>
</tr>
<tr>
<td>PIAMA(118–120)</td>
<td>1996/97</td>
<td>810</td>
<td>1, 2, 3, 4, 5, 6, 7, 8</td>
<td>Reduced asthma at age 2. No effect at other ages.</td>
</tr>
<tr>
<td>CAPS(121)</td>
<td>1997–1999</td>
<td>616</td>
<td>18 mo., 3, 5</td>
<td>No difference in asthma, wheeze or atopy. Eczema higher in intervention group.</td>
</tr>
</tbody>
</table>

* Published outcomes of the intervention in MAAPPS available for ages one and three years only
Table 4

Research Questions for Priority Areas for Environmental Interventions and Asthma Management in Children

<table>
<thead>
<tr>
<th>Priority: Further define the role of environmental interventions (EI) in asthma management</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Are the findings from positive trials replicable? Scalable?</td>
</tr>
<tr>
<td>• Are there behavioral interventions that can improve adherence to EI behaviors?</td>
</tr>
<tr>
<td>• How, and in which settings, should EI be implemented? Are EIs effective as a public health intervention delivered at the community or school, rather than health care, level?</td>
</tr>
<tr>
<td>• What populations benefit most from EIs? Should EIs be targeted primarily only to high morbidity populations, such as low-income and minority children with uncontrolled disease? Are EIs effective in populations that have not been studied (e.g., adults, suburban, rural)?</td>
</tr>
<tr>
<td>• Is further tailoring of the intervention, considering the whole environment (e.g., social stressors) as well as environments not typically studied (e.g., outdoor allergens) more effective than focusing on home and indoor allergens?</td>
</tr>
<tr>
<td>• Do EIs improve asthma outcomes by lowering indoor allergens, by their “bystander” effect on other factors related to asthma (e.g., medication adherence, second hand smoke exposure) or both?</td>
</tr>
<tr>
<td>• Do EIs have beneficial effects above and beyond those obtained by the use of controller medications?</td>
</tr>
<tr>
<td>• Do EIs reduce controller medication requirements/needs?</td>
</tr>
<tr>
<td>• Does EI mitigate the costs and side effects of controller medications?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Priority: Determine the most feasible, and cost- and clinically-effective approach to EI</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Which component(s) of EI are clinically effective and cost-effective, in order to maximize clinical effectiveness and limit costs?</td>
</tr>
<tr>
<td>• What is the minimal EI that retains efficacy and what components are required to retain efficacy (e.g., minimum frequency of visits, location of visits, activities performed at visits, duration of intervention)?</td>
</tr>
<tr>
<td>• Are there specific populations for whom the cost-benefit balance is favorable?</td>
</tr>
<tr>
<td>• How would coverage of EI by a healthcare system affect asthma morbidity and costs among its pediatric patients with asthma?</td>
</tr>
<tr>
<td>• In consideration of cost-effectiveness, which environmental intervention measures are most appropriate for specific populations and what is the optimal duration of a specific intervention?</td>
</tr>
<tr>
<td>• What are the benefits of one size fits all EIs, how do they compare to tailored EIs, and how do the cost-benefits compare?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Priority: Determine which EI components can be effectively implemented and the best approaches to implementation (Implementation Science)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• What are the systems obstacles to implementing EIs and how can they best be overcome?</td>
</tr>
<tr>
<td>• How should the population that will receive EIs be defined and identified in a non-research setting?</td>
</tr>
<tr>
<td>• How should staff be identified and trained (Are community health workers enough? Are more advanced credentials needed? Is professional integrated pest management necessary? How does training used in a clinical trial setting translate to the healthcare or community setting?)</td>
</tr>
<tr>
<td>• How can the intervention be supported financially?</td>
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<tr>
<td>• How should tools developed for clinical trials be replicated/developed/adapted for use beyond the clinical trial EI?</td>
</tr>
<tr>
<td>• When do adaptations no longer make the EI evidence-based, and what study designs are sufficient to evaluate continued efficacy?</td>
</tr>
</tbody>
</table>