

EDITORIAL

Reducing Exposure to Mouse Allergen Among Children and Adolescents With Asthma Is Achievable, but Is It Enough?

Leonard B. Bacharier, MD

Exposure to indoor allergens contributes significantly to asthma morbidity, with children raised in inner-city areas particularly affected by such exposures. Most inner-city homes have evidence of mouse infestation,¹ with a linear dose-response relationship between mouse allergen exposure and asthma morbidity among mouse-sensitized children and adolescents.² Furthermore, a threshold exposure level of greater than 0.5 µg of the major mouse allergen (Mus m1) per gram of house dust has been identified as clinically relevant. Preschool children with asthma living in inner-city Baltimore, Maryland, who were sensitized to mouse allergen and exposed to greater than 0.5 µg/g of Mus m1 experienced 50% more symptom days, 80% more days of β-agonist use, and increased risks of emergency department visits and hospitalizations compared with children with lower levels of exposure.³

Given these relationships between the degree of exposure to mouse allergen and asthma morbidity, several studies explored the efficacy of strategies to reduce mouse allergen exposure, generally finding a lack of clinical benefit.^{4,5} A randomized, sham-controlled trial used individualized and multifaceted indoor allergen avoidance measures that targeted furry pets, cockroaches, house dust mites, rodents (mice and rats), and mold.⁶ Even though the intervention group experienced significant reductions in levels of all measured allergens, the sham intervention (control) group also had significant reductions in mouse and house dust mite allergens in the bedroom and cockroach allergen in the kitchen. Despite these reductions, there were no differences between the groups in level of pharmacological therapy required for asthma or any other asthma outcomes.

In this issue of *JAMA*, Matsui and colleagues⁷ report the findings of the Mouse Allergen and Asthma Intervention Trial (MAAIT), a year-long, parallel group, randomized clinical trial focusing on reduction of mouse allergen exposure. Participants included 361 children and adolescents aged 5 to 17 years with persistent asthma who experienced an exacerbation in the previous year, lived in metropolitan Baltimore, Maryland, or Boston, Massachusetts, and had evidence of both allergic sensitization and confirmed exposure to mouse allergen (>0.4 µg/g of Mus m1 in bed dust or >0.5 µg/g in bedroom floor dust). All participants received education on pest management. Participants were randomized to receive an integrated pest management (IPM) intervention or no additional intervention.

The IPM intervention included professionally delivered treatments composed of targeted cleaning to remove aller-

gen reservoirs, placement of traps and rodenticide, sealing of holes and cracks, installing allergen-proof mattress and pillow encasements, and provision of 2 portable air purifiers. Pest management education was provided at 1 home visit at the beginning of the study to all participants, and IPM was performed once with the potential for up to 3 additional booster visits depending on persistence or recurrence of infestation.

The levels of mouse allergen in the bedroom floor dust at the beginning of the study were quite high (geometric mean levels of 6.1 µg/g in the IPM plus pest management education group and 6.6 µg/g in the pest management education alone group). There were substantial but comparable degrees of reduction of mouse allergen in both groups. The magnitude of reduction was much greater than expected, with follow-up geometric mean levels of 2.0 µg/g in the IPM plus pest management education group and 2.5 µg/g in the pest management education alone group, with 46% and 41%, respectively, experiencing mouse allergen reductions of at least 90%.

Despite these impressive reductions in mouse allergen levels, there were no between-group differences in any clinical outcome, including the primary outcome of maximum symptom days over the previous 2 weeks from 6 to 12 months (median, 2.0 days [interquartile range, 0.7-4.7 days] in the IPM plus pest management education group vs 2.7 days [interquartile range, 1.3-5.0 days] in the pest management education alone group). In addition, none of the 18 reported secondary outcomes were significantly different between the groups.

In prespecified exploratory analyses combining both study groups, the authors demonstrated statistically significant, albeit clinically small, associations between the magnitude of mouse allergen reduction and several markers of asthma activity. Each 50% reduction in bedroom floor mouse allergen level was associated with a 4% decrease in β-agonist use, 3% to 11% decreases in asthma symptoms, a 7% decrease in acute care visits, and a 6% decrease in emergency department visits; however, no associations were found with oral corticosteroid use, lung function, or hospitalization. The authors concluded that there was no between-group difference in the number of maximum symptom days from 6 to 12 months and suggested that pest management education alone may be effective in reducing mouse allergen levels.

How could the interventions in this study have not worked? One potential explanation is the simultaneous exposure of children to multiple indoor allergens and irritants, with uncertain contribution of each to asthma morbidity. The most effective trials in environmental modification have included multiallergen-reduction approaches,⁸ suggesting that focus on



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a single allergen is unlikely to provide substantial clinical benefit. In addition, although several studies have demonstrated reduction in mouse allergen levels, the extent of the reduction has often been insufficient to fall below the threshold of 0.5 µg/g of Mus m1, such as in the study by Phipatanakul et al,⁴ in which the mouse allergen levels in nearly all homes remained above this threshold.

A subanalysis⁵ of the Inner-City Asthma Study, in which 150 homes received a multiallergen-reduction intervention, showed very low pretreatment bed floor dust levels of mouse allergen (median, 0.04 µg/g; range, 0-184.8 µg/g). Despite these low levels, homes receiving the tailored intervention showed a 27.3% reduction (compared with a 28% increase in control homes), and 29% of treated homes achieved at least a 50% reduction. There was no effect on asthma symptoms or health care use, even after controlling for cockroach exposure and sensitivity; however, children in treated homes did have fewer school absences, night awakenings, and amount of days caretakers had to change plans. Even though the magnitude of reduction of allergen exposure in MAAIT was substantial and much greater than expected, with the pest management education alone group experiencing a 65% reduction in allergen levels, only 47% of the IPM plus pest management education group and 40% of the pest management education alone group attained levels below the 0.5-µg/g threshold previously reported as clinically relevant.³ Thus, it is possible that interventions that effectively reduce levels more than in this trial might lead to clinical benefits.

Several other potential explanations for the lack of clinically relevant differences between study groups should be considered. If MAAIT included a control group that received either a sham intervention or standard of care, it would have helped to determine the natural course of allergen levels in the homes and the effect of study participation alone (ie, the Hawthorne effect) on outcomes. The study participants demonstrated relatively good asthma control, with low levels of symptoms at baseline (median of 2.5-3.0 days per 2 weeks) in the setting of substantial degrees of asthma therapy (>50% received step 4 or 5 care), potentially making it difficult to improve from this low level of baseline disease activity.

Inclusion of a population with poorer baseline disease control might have revealed greater clinical efficacy of the intervention. Inner-city children are exposed to mouse allergen out-

side the home, including in school classrooms, and these exposures also have been associated with greater asthma morbidity and reduced lung function.⁹ Thus, reduction of exposures in the home without concomitant reductions in the school and other environments may be insufficient to yield clinical improvements. The focus on mouse allergen alone without targeting other allergens may have contributed to these findings.

Large proportions of participants were sensitized, exposed, or both to other relevant indoor allergens, including more than 50% sensitized to cockroach allergen, the levels of which did not change over the trial. Although studied generally in the context of their contribution to asthma development, the composition of house dust-associated microbiota differs between homes of low-income children with asthma and controls,¹⁰ and thus house dust-associated microbiota may also contribute to asthma activity and serve as a potentially modifiable environmental target. In addition, the contributions of other indoor exposures, such as environmental tobacco smoke and pollutants (particulates and nitrogen dioxide) were not assessed, nor was adherence to asthma controller medications.

Based on these findings and the available literature, lingering questions remain. Is there any added value of IPM focused exclusively on mouse allergen, given the cost of the intervention? Would the addition of cockroach or other allergen abatement have been beneficial because previous studies suggest that a professionally delivered intervention targeting multiple allergens and environmental tobacco smoke was effective⁸ in improving asthma symptoms? Why did the pest management education alone group achieve such substantial reductions in mouse allergen levels? Would modification of the dust-associated microbiota enhance the efficacy of strategies that target allergen levels?

Environmental exposures remain major contributors to ongoing asthma morbidity, especially among children living in urban environments. Even though single-allergen targeted approaches may reduce detectable levels of allergen, they appear to exert small clinical effects on indicators of asthma morbidity relative to multifaceted interventions. Further research into multiexposure-reduction strategies is needed to determine if and which combinations of approaches provide the greatest clinical benefit, as well as identification of mitigation strategies that consistently reduce exposures below threshold levels.

ARTICLE INFORMATION

Author Affiliations: Division of Allergy, Immunology and Pulmonary Medicine, Department of Pediatrics, School of Medicine, Washington University, St Louis, Missouri; St Louis Children's Hospital, St Louis, Missouri.

Corresponding Author: Leonard B. Bacharier, MD, School of Medicine, Washington University, 660 S Euclid Ave, Campus Box 8116, St Louis, MO 63110 (bacharier_l@kids.wustl.edu).

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Unproven Technologies in Maternal-Fetal Medicine and the High Cost of US Health Care

Steven L. Bloom, MD; Kenneth J. Leveno, MD

Preterm birth is one of the leading health indicators among nations, as it is the most frequent cause of neonatal death and the second most frequent cause of death in children younger



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than 5 years worldwide.¹⁻³ In the United States alone, complications related to preterm birth account for approximately two-thirds of all infant deaths.⁴ Infants born preterm who do survive have significantly higher risks of long-term morbidity, including serious neurologic and developmental disabilities. In 2005, the Institute of Medicine estimated that the annual societal cost of preterm birth in the United States was \$26 billion.^{1,5}

In this issue of *JAMA*, Esplin and colleagues⁶ report the results of a large, multisite, prospective study of 9410 nulliparous women with singleton pregnancies. The purpose of their study was to assess whether universal screening of cervical length measured with transvaginal ultrasound, quantitative measurement of vaginal fetal fibronectin, or both could identify women who would spontaneously deliver preterm (before 37 weeks' gestation). Such screening has gained considerable momentum because of reports suggesting that women found to be at risk for preterm birth benefit from treatment with vaginal progesterone.^{7,8}

Central to understanding the utility of screening tests for disease—in this case, preterm birth—is measuring the relationship between the true-positive rate (sensitivity) and the false-positive rate (1–specificity). This relationship is known as a receiver operator characteristic (ROC), and the accuracy of the screening test is measured by the area under the ROC curve. In the analysis by Esplin and colleagues,⁶ 3 key ROC curves were presented: one for cervical length, one for fetal fibronectin level, and one using the combination of both tests. The areas under the curve were 0.67, 0.59, and 0.67, respectively, indicating that these screening tests had low predictive accuracy for preterm birth.⁶ An area under the curve of 0.50 indicates that the accuracy of the diagnostic test is no better than chance, whereas an area under the curve greater than 0.90 is associated with very good diagnostic accuracy.

The report by Esplin and colleagues⁶ is important for at least 2 reasons. First, this large and well-executed prospec-

tive study provides compelling data that 2 popular screening modalities, either alone or in combination, do not accurately predict which women will deliver preterm. Second, this report provides provocative insights as to how medical practice determined through consensus, rather than reproducible evidence, contributes to the narrative in the United States regarding the cost and quality of health care.

In a 2016 article, President Barack Obama discussed the problems of the substantial cost of health care and the need for improvements in quality.⁹ For example, the Centers for Medicare & Medicaid Services estimated that spending on health care in the United States in 2015 accounted for 17.8% of the country's total gross domestic product (GDP).¹⁰ The total amount of health care spending—\$3.2 trillion—equated to an estimated \$10 000 per person. Moreover, compared with 12 other high-income countries (Australia, Canada, Denmark, France, Germany, Japan, the Netherlands, New Zealand, Norway, Sweden, Switzerland, and the United Kingdom), health care spending in the United States as a proportion of GDP was approximately 50% more than the next-highest spender (France, 11.6% of GDP) and double the amount spent in the United Kingdom (8.8% of GDP).¹¹ Despite having the highest expenditure, health care outcomes—including infant mortality rates—were worse in the United States (6.1 infant deaths per 1000 live births) compared with these other countries (2.1-5.2 infant deaths per 1000 live births).¹¹ Causes for the excessive health care costs in the United States have been attributed in part to greater use of medical technology and higher prices.¹¹

Transvaginal ultrasound cervical length screening for low-risk women illustrates the problem. In 2012, the publications committee of the Society for Maternal-Fetal Medicine provided a consensus clinical guideline for use of progesterone for the prevention of preterm birth.¹² The guideline indicated that vaginal progesterone was beneficial for women at low risk for preterm birth who were discovered to have short cervical length during an ultrasound examination. This recommendation raised the issue of universal testing for short cervix in women such as those screened in the study by Esplin and colleagues.⁶ The authors of the clinical guideline, which was