Asthma: NHLBI Workshop on the Primary Prevention of Chronic Lung Diseases

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Abstract

Asthma is a common disease with enormous public health costs, and its primary prevention is an ambitious and important goal. Understanding of how host and environmental factors interact to cause asthma is incomplete, but persistent questions about mechanisms should not stop clinical research efforts aimed at reducing the prevalence of childhood asthma. Achieving the goal of primary prevention of asthma will involve integrated and parallel sets of research activities in which mechanism-oriented studies of asthma inception proceed alongside clinical intervention studies to test biologically plausible prevention ideas. For example, continued research is needed, particularly in young children, to uncover biomarkers that identify asthma risk and provide potential targets of intervention, and to improve understanding of the role of microbial factors in asthma risk and disease initiation. In terms of clinical trials

that could be initiated now or in the near future, we recommend three interventions for testing: (1) preventing asthma through prophylaxis against respiratory syncytial virus and human rhinovirus infections of the airway; (2) immune modulation, using prebiotics, probiotics, and bacterial lysates; and (3) prevention of allergen sensitization and allergic inflammation, using anti-IgE. These interventions should be tested while other, more universal prevention measures that may promote lung health are also investigated. These potential universal lung health measures include prevention of preterm delivery; reduced exposure of the fetus and young infant to environmental pollutants, including tobacco smoke; prevention of maternal and child obesity; and management of psychosocial stress.

Keywords: asthma; primary prevention; allergy; respiratory syncytial virus; rhinovirus

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Asthma is a chronic disease characterized by reversible airflow obstruction, airway hyperresponsiveness, and airway inflammation producing symptoms of shortness of breath, cough, wheezing, and chest tightness. The estimated worldwide prevalence of asthma is 300 million persons. In the United States, childhood asthma prevalence more than doubled between 1980 and the mid-1990s, and the prevalence in 2007 was 8% (1, 2). The public health burden is high, with a significant

proportion of the cost and morbidity resulting from acute care for asthma exacerbations.

As part of the NHLBI 2013 workshop on the primary prevention of chronic lung diseases, the asthma group reports on the state of primary prevention research in asthma, with emphasis on specific recommendations for research priorities and interventions that could be undertaken now. The emphasis of our work was on prevention of disease onset, and because the

majority of asthma begins during the preschool years (Figure 1), this document focuses on childhood asthma.

Framing the Issues around Primary Prevention of Asthma

It is an accepted framework that genetic susceptibilities interact with environmental exposures to cause asthma. Understanding of the details of this framework is

Figure 1. The risk for developing asthma is age dependent, with the majority of incident asthma beginning in the preschool years. Box sizes represent estimates of the relative importance of each developmental period in childhood.

incomplete, however, and there is not consensus on the relative importance of various genetic, environmental, or immune dysfunction factors. The marked differences in rates of asthma across the world, changes over short periods, and with migrating populations suggest that asthma is not the inevitable consequence of genetic predisposition. This is important, as the ability to modify early life environment, diet, and lifestyle means that lower rates of asthma might be attained without medications or sophisticated medical infrastructures and could therefore be achieved worldwide.

Consideration of primary prevention of asthma raises multiple questions, including the following:

1. *What is the optimal timing of prevention interventions?* To have the greatest public health impact, it may be necessary to intervene *in utero* or in early postnatal life. This creates important issues regarding timing and duration of the intervention. It also raises important practical and ethical issues that arise when research studies are needed in pregnant women and/or infants.
2. *When is evidence sufficient to support that an intervention is rational, safe, and should be tested?* Human data about risk factors for asthma have limitations and model systems too have their flaws, so that intervention studies will necessarily be based on hypotheses that may have few supporting data. The research and patient communities will need to consider the levels of evidence needed as the basis for interventions in highly vulnerable patient groups. The level of evidence required will likely relate to the safety of the proposed intervention.

3. *Risk factors—cause or association?* Are purported risk factors true risk factors that cause disease, which, if modified, will prevent disease, or are they merely disease associations, which, if modified, will not prevent disease?
4. *Can biomarkers of asthma risk aid prevention measures?* Primary prevention strategies for asthma will need to precede disease expression, and biomarkers of disease risk are needed to enable this. Advances have been made in biomarker development for asthma but not specifically in the area of risk biomarkers. Systems biology and genomic approaches will likely prove critical to achieving this goal. Further studies are also needed to determine whether biomarkers identified in adults are useful in children and vice versa.
5. *What is the relative importance of host susceptibility factors versus environmental risk factors in asthma inception?* Both host susceptibility factors and environmental risk factors impact disease development, and modifiable risk factors, of both types, need to be identified, recognizing that the impact in groups with specific susceptibility factors may differ.

Host and Environment Interactions in Asthma Inception

Wheezing associated with viral and bacterial infections during the preschool years is extremely common. While the majority of asthma begins during these years, many children who wheeze do not develop asthma by school age (3). Multiple wheezing phenotypes have been identified and

refined in birth cohort studies. The wheezing phenotypes most strongly linked to childhood asthma development (persistent, intermediate onset, and late onset) share the common feature of highly prevalent helper T-cell type 2 (Th2) inflammatory markers in peripheral blood (3, 4). Studies of airway structure and function have been limited in young children, and the development of noninvasive biomarkers, including nonionizing imaging techniques, is needed to help expand our understanding of wheezing phenotypes and asthma inception in early life. Development of these tools will also help identify distinct endotypes of preschool wheezing that will likely respond to different therapy.

Host Factors That Influence Risk of Asthma

1. *Genetics:* Multiple genetic polymorphisms have been associated with asthma development, most notably the chromosome 17q21 locus containing ORMDL3, GSDMB, and ZPBP2, and other genes identified by genome-wide association (IL1RL1/IL18, TSLP, HLADQ, IL2RB, SLC22A5, RORA, IL33, and SMAD3) (5, 6).
2. *Parental history of asthma:* A history of maternal asthma is a stronger predictor of asthma in children than paternal asthma, which suggests the *in utero* environment contributes to asthma susceptibility (7).
3. *Sex:* Preadolescent boys have greater asthma prevalence than girls, but postadolescent girls have greater asthma prevalence and severity compared with boys (8).
4. *Race:* African Americans and Puerto Rican Hispanics are at particularly high risk for asthma (9).
5. *Obesity:* Obesity has been identified as a risk factor for asthma inception, and likely has both host and environmental components (10, 11).

Environmental Factors That Influence Risk of Asthma

1. *Aeroallergen sensitization:* The vast majority of school age children and adults with asthma have concomitant allergic sensitization. Early sensitization to aeroallergens (first 1–2 yr of life) is

- a critical risk factor for asthma inception (12–15). In support of a causal role for allergic sensitization in asthma inception, a sequential relationship of allergic sensitization preceding virus-induced wheezing in preschool children has been identified (14). A “dose-dependent” relationship between allergic sensitization and asthma has been identified, with greater degrees of allergic sensitization (increased numbers of allergens and increased level of allergen-specific IgE) conferring much greater risk for asthma inception and severe exacerbations (15, 16).
2. *Respiratory viruses*: Both respiratory syncytial virus (RSV) and human rhinovirus (RV) lower respiratory tract infections in early life are strongly associated with increased risk of asthma.
 - a. *RSV*. A number of studies support a causal relationship between RSV infection and recurrent wheezing, and also associate severity of infants’ RSV lower respiratory tract infection with asthma risk and severity (17, 18). Further, animal studies provide evidence for a mechanism through which RSV may cause asthma (19). In addition, a randomized controlled trial of palivizumab versus placebo in late preterm infants demonstrated a significant reduction in recurrent wheezing in the treatment group (20). It is not known whether this will translate to prevention of childhood asthma.
 - b. *RV*. In the first several years of life, RV wheezing illnesses and RV bronchiolitis requiring hospitalization are associated with an approximately 10-fold increase in asthma risk at age 6 years. This risk is increased further in children with precedent allergic sensitization (13, 14, 21). Further, mechanisms by which RV infections may promote asthma development have been reported (22). There are RV species (and types) that result in more pathogenic disease in infants (23, 24), but their relationship to asthma inception is currently unknown. There have been no intervention studies to evaluate the effect of RV prevention on asthma inception because of a lack of prevention or treatment options.
 3. *Early life microbial exposures*: The original finding that children raised on animal farms in Central Europe are at markedly decreased risk of developing asthma (25) has now been confirmed by several subsequent studies (26). The mechanism(s) of this protective effect is not known, but exposure to bacterial products is thought to play a major role (27). Exposure to farms is associated with the prevention of both allergic sensitization and transient early wheezing, unrelated to allergic sensitization (28). Therefore, it may be possible that bacterial products could prevent asthma by influencing immune responses not only to allergens but to microbes as well (29). Similarly, evidence is solidifying that exposures to furred pets before the age of 1 year, most consistently dogs, may be protective for asthma development, and these findings may also relate to altered microbial exposures (30, 31).
 4. *Cigarette smoke*: The *in utero* period is a critical phase of lung development, and maternal cigarette smoking is known to influence lung growth and development and to increase risk for asthma (32, 33). In addition, exposure of infants and preschoolers to second-hand tobacco smoke is an important risk factor for wheezing and asthma (34). Efforts to diminish tobacco smoke exposure *in utero* and throughout life remain important means of universal promotion of lung health and prevention of a variety of diseases.
 5. *Air pollution*: Exposure to outdoor air pollutants such as ozone, sulfur dioxide, particulate matter, and nitrogen oxide is associated with increased risk of asthma (35). Tailpipe exhaust and burning of coal, crude oil, and wood are all significant sources of pollutants. In addition, there is evidence that indoor air quality, including exposures to mold, are associated with asthma onset (36).
 6. *Diet and the host microbiome*: Experimental data in mouse models of asthma clearly show that manipulation of the gut microbiome through diet can influence the development of asthma-like phenotypes (37). These data have heightened interest in the role of early life diet in shaping allergic immune responses in children and in the possibility that modifying diet and the gut microbiome may be a novel strategy to prevent asthma.
 7. *Vitamin D deficiency*: Positional cloning shows that the vitamin D receptor gene is associated with asthma, an association replicated in some studies but not others (38–40). Vitamin D plays an immunoregulatory role, and low vitamin D is associated with immune dysfunction (41). Further, vitamin D is associated with improved alveolarization of the lung and surfactant production (42). In observational birth cohort studies, the offspring of women who reported taking vitamin D during pregnancy had 40–50% less early life wheezing than babies of women who did not report taking vitamin D (43, 44). A randomized controlled prevention trial (NCT00920621; ClinicalTrials.gov) giving vitamin D to pregnant women and assessing asthma incidence in their offspring is currently underway.
 8. *Antioxidants*: Observational studies have reported associations between both asthma inception and control and dietary antioxidants (vitamin E, vitamin C, carotenoids, selenium, polyphenols, and fruit) and polyunsaturated fatty acids (45, 46). Although supplementing the diets of adults with prevalent asthma with antioxidants and n-3 polyunsaturated fatty acids has had marginal clinical benefit, little is known about their potential role in disease prevention.
 9. *Stress*: Poverty, violence, maternal anxiety, and child anxiety represent early life stresses that may alter the normal course of lung morphogenesis and maturation, leading to asthma inception and exacerbation (47). Maternal stress during pregnancy influences programming of integrated physiological systems in their infants (e.g., neuroendocrine, autonomic, immune function), may be transgenerational, and is associated with increased asthma risk (48, 49).

Primary Prevention Strategies for Asthma: General Considerations

Asthma is not caused by a single gene, nor is it a disease that results from a single environmental exposure. Therefore, a single intervention is unlikely to prevent all asthma. A multifaceted prevention approach, as with cardiovascular disease, will likely have the greatest overall impact. In addition, providing a biologic mechanism and demonstration of

a causal effect beyond association studies will greatly strengthen the scientific rationale for studying an intervention. The weight of epidemiologic evidence points to aeroallergen sensitization and viral respiratory tract infections as key modifiable factors for asthma inception in young children.

Recommendations for Specific Clinical Studies/Trials to Realize the Goal of Implementing Primary Prevention Strategies for Asthma

Achieving the goal of primary prevention of asthma will involve integrated and parallel sets of research activities in which mechanism-oriented studies of asthma inception proceed alongside clinical trials to test biologically plausible prevention ideas (Figure 2).

Mechanism-oriented Studies of Asthma Inception

Continued research to identify biomarkers (including genotypes) that predict asthma are needed to properly enable efficient and cost-effective intervention trials that are based on accurate identification of at risk populations. Leveraging existing cohorts by using previously collected biospecimens may be a cost-effective means to uncover novel biomarkers of asthma risk. However, newly initiated studies are likely still needed to apply integrated systems biology and genomics approaches and to examine the usefulness of new technologies (e.g., imaging) as a biomarker in young children. Also of relevance to asthma prevention is research

into how early life exposures to microbes shape immune responses, including allergen sensitization and type 2 immune responses in the lower airway. Studies of the airway and gut microbiome in asthma are currently in their infancy, and more research is needed to determine whether treatment with microbes can prevent asthma, or whether suppression of specific microbial species can improve asthma control in established disease.

Clinical Trials

Clinical trials of primary prevention are especially needed in infants who are at high risk for asthma. Risk factors for asthma should be considered as inclusion criteria for primary prevention trials to decrease the sample size of intervention trials (Box 1). Early life interventions will require trials that begin from either pregnancy or early infancy through 5–6 years to establish the diagnosis of asthma.

The committee considered a range of pharmacologic, environmental, and behavioral interventions and concluded that three categories of asthma prevention are ready for clinical trials in high-risk infants now or in the near future. These interventions focus on prophylaxis against viral respiratory tract infections; immune modulation using prebiotics, probiotics, and bacterial lysates; and prevention of allergen sensitization and allergic inflammation using anti-IgE (Figure 2).

1. Prevention of RSV and RV early life lower respiratory tract infections

BACKGROUND AND RATIONALE. There is a plausible causal role for RSV and RV in asthma inception. A study of prevention of RSV infection, using RSV immunoprophylaxis,

Box 1: Host risk factors for asthma in infants

1. At least one parent with asthma
2. High-risk genotypes (e.g., 17q21)
3. Prematurity
4. Early sensitization to aeroallergens

demonstrated decreased recurrent wheezing in infancy, but has not yet assessed effects on asthma inception (20). It is not clear whether an anti-RV strategy (vaccine or medication) can be developed in light of the tremendous diversity of RVs. A definitive randomized controlled trial of RSV or RV prevention during early life on asthma inception at age 5–6 years has not been done.

INTERVENTIONS.

1. **Immunoprophylaxis:** Palivizumab is a humanized monoclonal IgG antibody directed against the RSV fusion (F) glycoprotein. There is no currently available immunoprophylaxis for RV.
2. **Vaccines:** Development of vaccines to RSV or RV is challenging, but stabilized variants of perfusion RSV F have shown promise as effective vaccines in animal models (50). For RV, it is not clear whether a vaccine can be developed because of the tremendous viral diversity.
3. **Antivirals:** Ribavirin has been used for treatment, not prevention, of RSV infections and does not significantly reduce the long-term respiratory outcomes associated with RSV. New RSV and RV antivirals are in development.

CHALLENGES. Although RSV immunoprophylaxis is currently available and licensed for use in infants, it is expensive and must be administered monthly during the RSV season by injection, and no studies have been done to demonstrate efficacy in preventing RSV lower respiratory tract infection in healthy term infants.

CONCLUSIONS. We recommend immediate consideration of clinical trials to test the efficacy of RSV immunoprophylaxis as an asthma prevention strategy in infants at high risk for asthma. In addition, we recommend that drug discovery research continue for interventions (small molecules, vaccines, etc.) that prevent RV infections, and that provide more practical approaches to RSV prevention.

Figure 2. An integrated portfolio across the translational research spectrum is needed moving forward toward primary prevention of asthma. The figure illustrates how basic research efforts must continue alongside specific clinical intervention trials. RSV = respiratory syncytial virus; RV = human rhinovirus. *Covariates such as vitamin D should be assessed in asthma prevention trials; additional vitamin D trials may be necessary depending on the results of ongoing trials.

2. Immune modulation using prebiotics, probiotics, immunostimulants, and animal exposures

BACKGROUND AND RATIONALE. Multiple factors have increased interest in the airway and gut microbiome as drivers of the altered immune responses that underlie asthma. There are animal and human studies demonstrating the influence of the microbiome on the immune system and asthma susceptibility as well as evidence of altered microbial communities in patients with established disease. There is some evidence to suggest that the use of probiotics, prebiotics, or immunostimulants may be helpful in reducing allergic sensitization, eczema, respiratory infections, and associated wheezing. However, the evidence for the efficacy of these interventions is generally suboptimal, and efficacy data for asthma are limited.

INTERVENTIONS.

1. Probiotics may enhance gastrointestinal microflora colonization, optimize Th1/Th2 immune balance, and promote immune maturation.
2. Prebiotics can be used selectively by microorganisms such as bifidobacteria or lactobacilli that have positive effects to prevent allergic immune responses (51).
3. Immunostimulants can be derived from various sources, including synthetic, thymic extracts or factors, *Klebsiella* extracts containing lipopolysaccharide, and mixed bacterial lysates. For example, OM-85 BV ("Broncho-Vaxom") is an extract of eight bacterial strains that has been shown to reduce respiratory infections and wheezing in children 1–6 years old with recurrent wheezing (52).
4. Animal exposures, such as on farms or with dogs, have been associated with reduced asthma risk, potentially through alterations in the microbiome.

CHALLENGES. There are regulatory challenges because these product(s) may not be manufactured according to good manufacturing practice (GMP) standards. It is difficult to determine from the literature which intervention warrants testing in larger and more rigorous prevention trials for asthma. A randomized trial of dog exposure carries low potential risk, but raises multiple logistical challenges. Further,

a greater understanding of how microbial exposures specifically influence early life immune development to cause asthma (or protect from it) will be needed to fully take advantage of these approaches to prevention.

CONCLUSIONS. Administering prebiotics, probiotics, or immunostimulants to infants at risk of allergic disease may prevent eczema and sensitization, but evidence that they prevent asthma is weak (53). The premise that these interventions may prevent asthma is plausible, however, and prior studies may have been negative because they were underresourced, underpowered, or used the wrong bacterial product. An National Institutes of Health–funded placebo-controlled study (NCT00113659; ClinicalTrials.gov) is underway to determine whether *Lactobacillus* GG in the first 6 months of life can prevent or delay asthma, and it will inform future trial designs. Meanwhile, the committee recommends additional studies of OM-85 BV (Broncho-Vaxom) for two reasons. First, OM-85 BV is available as a drug in capsule form, and it has a long record of use in children. Second, OM-85 BV has shown efficacy in preventing acute respiratory tract infections and wheezing attacks in preschool children, and this provides preliminary evidence supporting larger trials.

3. Prevention of allergen sensitization and allergic inflammation, using anti-IgE

BACKGROUND AND RATIONALE. As described previously, the majority of school age children and adults with asthma have concomitant allergic sensitization, and a number of studies have associated allergic sensitization with asthma inception and severity. To date, efforts to decrease allergen exposures as a strategy to prevent allergen sensitization or asthma have been generally unsuccessful (54). This may be because of the difficulty in eliminating aeroallergen exposures, concomitant elimination of helpful microbial exposures, or because allergic sensitization is associated with the disease pathway but not causal. Strategies may be more successful if they focus on preventing aberrant host responses. In addition, the processes involved in allergic sensitization may represent immune events that are intrinsic to asthma and not dependent on single aeroallergens, but rather a Th2-like pattern of immune response.

INTERVENTIONS.

1. *Specific immunotherapy (SIT):* Allergen immunotherapy with allergen extracts (SIT) has shown some promise as a strategy to prevent new allergic sensitizations in children (55) and may reduce the risk of the development of asthma in children with allergic rhinitis (56).
2. *Anti-IgE:* Omalizumab is an approved drug that is a nonanaphylactogenic monoclonal antibody directed against IgE. Quilizumab is an experimental drug currently in clinical trials, and it reduces IgE by targeting a segment of membrane IgE on human IgE-switched B cells.
3. *Other Th2 inhibitors:* Other biologic agents directed toward Th2 inflammation have shown promise in asthma treatment (57–59), but have not been studied yet in children under 12 years.

CHALLENGES. There is extensive experience with omalizumab in children 6 years and older, but its application to prevent allergic sensitization and inflammation will require that it be approved for use in preschool children.

CONCLUSIONS. Preventing allergen sensitization using SIT or anti-IgE shows promise to prevent asthma. There is a rationale for using either specific immunotherapy or anti-IgE in clinical trials. The committee recommends anti-IgE as a more comprehensive and more likely intervention to work. Secondary prevention studies demonstrating safety in preschool children may be required before primary prevention studies can be undertaken.

4. Environment and behavior. Environmental and behavioral factors associated with asthma risk include air pollutants (e.g., cigarette smoke, ozone, particulates) and obesity in late childhood/adolescence. Interventions to address these risk factors may promote healthy lungs, as discussed in the PROMOTION OF LUNG HEALTH article in this issue (pp. S125–S138), which also addresses the idea that promotion and maintenance of optimal lung health may prevent chronic lung diseases, such as asthma.

Summary

Asthma is a common disease with a large personal, social, and economic impact.

Although we have an incomplete understanding of how genetic and environmental factors combine to cause asthma, and the mechanisms of disease are not fully understood, this should not prevent an increased emphasis on primary

prevention research in asthma. Asthma research is clearly at the point that it is imperative to test several biologically plausible interventions, such as those identified here, while continuing to investigate mechanisms, biomarkers, and

potential approaches to inform the development of additional asthma prevention interventions. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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