

## Respiratory allergy caused by house dust mites: What do we really know?

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**The house dust mite (HDM) is a major perennial allergen source and a significant cause of allergic rhinitis and allergic asthma. However, awareness of the condition remains generally low. This review assesses the links between exposure to HDM, development of the allergic response, and pathologic consequences in patients with respiratory allergic diseases. We investigate the epidemiology of HDM allergy to explore the interaction between mites and human subjects at the population, individual, and molecular levels. Core and recent publications were identified by using “house dust mite” as a key**

**search term to evaluate the current knowledge of HDM epidemiology and pathophysiology. Prevalence data for HDM allergen sensitization vary from 65 to 130 million persons in the general population worldwide to as many as 50% among asthmatic patients. Heterogeneity of populations, terminology, and end points in the literature confound estimates, indicating the need for greater standardization in epidemiologic research. Exposure to allergens depends on multiple ecological strata, including climate and mite microhabitats within the domestic environment, with the latter providing opportunity for intervention measures to reduce allergen load. Inhaled mite aeroallergens are unusually virulent: they are able to activate both the adaptive and innate immune responses, potentially offering new avenues for intervention. The role of HDM allergens is crucial in the development of allergic rhinitis and asthma, but the translation of silent sensitization into symptomatic disease is still incompletely understood. Improved understanding of HDMs, their allergens, and their microhabitats will enable development of more effective outcomes for patients with HDM allergy. (J Allergy Clin Immunol 2014;■■■■:■■■-■■■.)**

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The house dust mite (HDM) is globally ubiquitous in human habitats and a significant factor underlying allergic rhinitis and allergic asthma. These features make it one of the most important sources of indoor allergens.<sup>1,2</sup> Sensitization to mite allergens in the first years of life has a significant clinical effect on lung function in pediatric populations with wheeze and associates in the long term with poorer clinical outcomes in respiratory health.<sup>3</sup> This might explain why the approach advocated by current guidelines for allergic rhinitis (Allergic Rhinitis and its Impact on Asthma)<sup>4</sup> and allergic asthma (Global Initiative for Asthma)<sup>5</sup> classifies disease based on the severity of symptoms, often leaving the underlying allergic cause unaddressed. Although comprehensive reviews of HDM allergy exist, consideration of the link between exposure, allergenicity, and the pathologic consequences for the entire airway has yet to be thoroughly explored. This review seeks to provide a complete picture of the epidemiology of HDM allergy and the effect of HDM allergens on the human immune system.

### EPIDEMIOLOGY: SCOPING THE PROBLEM

Throughout the published literature, studies frequently cite the high prevalence of HDM allergy,<sup>6,7</sup> yet an accurate global

*Abbreviation used*

HDM: House dust mite

estimate has proved elusive. A comprehensive thesis of HDM allergy suggests that 1% to 2% of the world's population might be affected, which is equivalent to 65 to 130 million persons.<sup>8</sup> Geographic variation complicates the picture: although HDM allergy is consistently found in Western nations, variation between countries, regions, and even individual test centers is significant.<sup>9</sup> One fundamental issue is the diversity of terminology and end points used in the literature, which can obscure the relationship between silent sensitization to HDM allergens and clinical disease. When evaluating data, a clear distinction must be made between epidemiologic studies conducted across a population selected at random and studies targeting sensitized symptomatic subjects selected from a group with diagnosed allergy.<sup>10</sup>

Focusing specifically on the proportion of patients with HDM allergen sensitization and rhinitis, asthma, or both, interpopulation differences are high. Among patients from 15 developed countries in the European Community Respiratory Health Survey I, the mean prevalence of sensitization to HDM was 21.7%.<sup>9</sup> Among Latino women in the United States of various ages, the prevalence of sensitization to *Dermatophagoides pteronyssinus* was 37% and to *D farinae* was 34%,<sup>11</sup> whereas the prevalence was greater than 80% in a pediatric study in Taiwan.<sup>12</sup> Given that study groups can be sampled from across continents, countries, ethnic groups, sexes, and/or age ranges, the heterogeneity of populations might confound potential comparisons of observed differences.

Significant differences exist not only between surveys but also within them. The European Community Respiratory Health Survey provided an opportunity to explore data from 13,558 subjects from 16 countries, focusing on the relationship among sensitization, allergy, and asthma.<sup>13</sup> A meta-analysis from this study reported a high overall prevalence for asthma with HDM sensitization (21%,  $r = 0.64$ ) but with significant interpopulation heterogeneity ( $P < .001$ ). The proportion of asthma attributed to any allergen had a wide range (4% to 61%) and was highly dependent on the diagnostic technique used.<sup>13</sup> This suggests that discrepancies in the use of diagnostic tools can confound epidemiologic studies.<sup>9</sup> The Environmental Health Risks in European Birth Cohorts project cited a lack of common definitions of exposure, health variables, and monitoring as critically limiting factors for establishing the prevalence of HDM allergy.<sup>14</sup>

## FACTORS INFLUENCING EXPOSURE, SENSITIZATION, AND ALLERGY TO HDM

### Allergen exposure and sensitization

The prevalence of HDM allergy is intricately linked to exposure to the mite itself. The German Multicentre Allergy Study, which followed newborn children ( $n = 1314$ ) through the first 3 years of life, found a cumulative increase in the development of allergy with increasing exposure to the major HDM allergens Der p 1 and Der f 1.<sup>15</sup> This reached a peak level of 5.5% with exposure to greater than 10  $\mu\text{g/g}$  in carpet dust in children from families with a known history of allergy; the corresponding prevalence for those without a family history was 3%. At levels of less than 0.1  $\mu\text{g/g}$ , the risk of allergy was low.<sup>15</sup> Although sensitization is linked to allergen exposure, the correlation does not follow a linear

pattern. A study showed a lower prevalence of mite atopy and asthma in the highest and lowest quintiles of exposure in children aged 0 to 5 years and also in the first 18 months from birth, with the highest prevalence observed at 3.5 to 23.4  $\mu\text{g/g}$ .<sup>16</sup> Other studies have also reported a bell-shaped dose-response curve for HDM exposure versus sensitization.<sup>17-19</sup> The mechanism of the apparent protective effect of high exposure levels remains unclear. It has been proposed that it might be similar to the "high dose tolerance" reported for cat allergen<sup>20</sup>; however, reports of high dose tolerance for aeroallergens are inconsistent between studies.<sup>16</sup> Parental history of allergy and asthma has been reported to influence the relationship between HDM exposure and atopy; exposure to greater than 10  $\mu\text{g/g}$  was associated with a decreased risk of atopic asthma in children with a parental history but with an increased risk in those without.<sup>21</sup> At present, this threshold is not well defined in the literature and is likely to be compounded by the presence of other allergens and some predisposing factors, such as viral infections, exposure to chemicals (eg, formaldehyde), individual susceptibility, and use of medication.<sup>22,23</sup> Studies seeking to quantify a level of exposure that can be considered "safe" suggest that levels of less than 2  $\mu\text{g/g}$  of HDM allergens are the maximum level for the primary prevention of sensitization in atopic children and young adults.<sup>24,25</sup>

A study of HDM sensitization during the first 3 years of life found that sensitization was low during infancy (0.5%), with an increase during the second (1.4%) and third (1.9%) years of life, and concluded that interventions aimed at primary prevention of sensitization should be introduced as early as possible, preferably during infancy.<sup>15</sup>

The quantitative relationship between exposure to HDM allergens and symptoms in asthmatic patients is complex and, similar to sensitization, influenced by environmental and genetic factors. Many asthmatic patients are sensitized to more than 1 allergen, which makes determination of the contribution of a specific allergen to airway inflammation difficult.<sup>26</sup> Although a clear threshold for provocation of asthma symptoms has not been clearly defined, symptoms are likely to be more severe with increasing allergen exposure.<sup>26</sup>

Assessing HDM exposure presents a challenge to the physician. In the clinical trial setting exposure has been expressed as the maximum level found in the home, the percentage of sites with greater than 2  $\mu\text{g/g}$ , and the mean value at the site with the maximum level.<sup>27</sup> However, a recent practice parameter on the environmental assessment and exposure control of HDM recommends the use of a hygrometer to estimate the amount of moisture available for propagation of HDM in the home and contains questions on home characteristics to assess the probability of HDM exposure.<sup>28</sup> This complexity could explain the relatively low predictive value of questionnaires in diagnosing sensitized subjects in the general population compared with other allergens (ie, 22% vs 64%, HDM vs pollen).<sup>29</sup> Moreover, HDM populations can also fluctuate seasonally,<sup>30,31</sup> exhibiting corresponding patterns of symptomatic response in patients.<sup>32</sup>

### Environmental factors

The key species of HDM involved in allergy are shown in Table 1,<sup>8</sup> along with a corresponding median value of the climatic variants with which they associate. Humidity is a critical factor for mite prevalence both inside and outside the home, with higher concentrations found in damp homes.<sup>33</sup> Relative humidity

**TABLE I.** Climatic features associated with the global distribution of 11 major HDM species

Species	Elevation, median height (m)	Rainfall, per month (mm)	Temperature (°C)		Relative humidity (%)		Relative frequency and locations present
			Maximum median temperature	Minimum median temperature	In the morning, 09 AM	In the afternoon, 15 PM	
<i>Dermatophagoides pteronyssinus</i>	46	66.0	18.4	8.9	82.0	65.0	85% Occurrence; most frequent species recorded; present at all localities representing extremes of altitude and latitude and at the wettest locality
<i>Dermatophagoides farinae</i>	45	66.0	18.9	9.4	82.0	64.0	47% Occurrence; second most frequently occurring species worldwide; most frequently found in the United States, Japan, and continental Europe; considerably rarer than <i>D pteronyssinus</i> in Australia, the United Kingdom, and Latin America
<i>Euroglyphus maynei</i>	61	62.5	17.2	7.8	82.0	63.0	27% Occurrence; third most frequent species globally; most records are from coastal localities or areas of high rainfall; also found at high latitudes in conditions of low temperature and rainfall
<i>Blomia tropicalis</i>	34	96.5	30.0	20.3	85.0	66.7	20% Occurrence; predominantly found in the tropics at low elevations that are hot and wet, with high summer rainfall (Asia, southern United States, and Latin America)
<i>Chortoglyphus arcuatus</i>	41	77.0	17.5	8.1	84.5	64.8	17% Occurrence; found at localities with a high seasonal variation in rainfall, some of which have most rain during the winter months
<i>Lepidoglyphus destructor</i>	65	56.0	16.7	6.7	82.0	65.0	16% Occurrence; found at high latitudes with low temperatures and rainfall (low seasonal variation) in both the Northern and Southern Hemispheres
<i>Glycophagus domesticus</i>	45	56.0	16.1	6.3	83.0	64.0	14% Occurrence; found at high latitudes with low temperatures and rainfall, with little seasonal variation in rainfall; mostly Europe, Russia, and Japan; not recorded in North America, Africa, Australia, or Southeast Asia
<i>Gohieria fusca</i>	95	53.0	16.5	6.3	83.0	64.8	9% Occurrence; found at relatively high elevation (mostly Europe but has been recorded in the tropics)
<i>Hirstia domicola</i>	20	98.0	21.1	11.4	83.0	60.5	8% Occurrence; mainly found at Northern Hemisphere locations with strong seasonal variation in temperature and rainfall (mainly Japan and Southeast Asia)
<i>Dermatophagoides microceras</i>	94	58.0	15.9	5.9	84.0	64.5	4% Occurrence, although misidentification likely means that species is more abundant; recorded in the Northern Hemisphere only, mostly at high latitudes, with the exception of localities in India and Malaysia

(Continued)

TABLE I. (Continued)

Species	Elevation, median height (m)	Rainfall, per month (mm)	Temperature (°C)		Relative humidity (%)		Relative frequency and locations present
			Maximum median temperature	Minimum median temperature	In the morning, 09 AM	In the afternoon, 15 PM	
<i>Malayoglyphus intermedius</i>	33	137.0	31.1	22.8	83.0	68.0	4% Occurrence; mainly found in the Northern Hemisphere in tropical, hot, and very wet places at low elevations with little annual temperature variation (tropical and subtropical Asia)

These data were compiled for 11 major HDM species by using distribution data from a database collation of 970 records from 812 named locations across 86 countries, as described by Colloff.<sup>8</sup> For each of the locations, climatic data were recorded for elevation, monthly rainfall, monthly temperature (minimum and maximum), and mean percentage of relative humidity in the morning and afternoon. Monthly values for the Southern Hemisphere were moved by 6 months to create parity for summer and winter data. In the case of missing data for any location, proxy data from nearby localities were used; data for elevation are taken almost entirely from the Northern Hemisphere. The computer program CLIMEX was used to generate data for the distribution of dust mite species correlated with climatic data. The table shows the median values for each variable for each of the major HDM species.

increases quickly after a bed is occupied, which might explain why HDMs are more likely to be found in beds than carpets, with a ratio of 2.7 (range, 0.6-5.9; mean, 1884 mites/g of dust found in beds vs 601 mites/g in carpets).<sup>8</sup> Factors shown to decrease HDM concentrations in the home include use of newer mattresses and carpets,<sup>33</sup> the presence of hard floors as opposed to carpets,<sup>34</sup> choice of mattress type,<sup>35,36</sup> regular mattress replacement,<sup>37</sup> use of central heating,<sup>37</sup> living in a flat as opposed to a house,<sup>37</sup> the presence of an open fireplace,<sup>38</sup> and bedrooms situated on a higher floor.<sup>38</sup> These provide opportunities for intervention at the domestic level that could reduce the HDM concentration.

Domestic cleaning offers a cost-effective universal approach, and evidence that HDM populations are reduced by cleaning is longstanding in the literature. An early study found 1.4 times more HDM allergen in beds where the housekeeping was poor,<sup>39</sup> whereas using chlorine bleach,<sup>40</sup> maintaining good ventilation,<sup>37</sup> and washing textiles regularly with a detergent at higher temperatures<sup>41</sup> appear to remove most HDMs. Focusing on the bed area as a target for allergen reduction, the use of mite-impermeable mattress covers,<sup>14,42</sup> daily vacuuming of mattresses,<sup>43,44</sup> and choice of a more powerful model of vacuum cleaner<sup>38,45</sup> have been shown to reduce HDM concentrations. Although environmental prophylactic interventions designed to reduce allergen exposure are intuitively sensible, their effect on clinical outcomes remains controversial.<sup>46</sup> A recent meta-analysis of randomized studies found no effect of chemical and physical methods to reduce exposure to HDM allergens on asthma symptoms,<sup>47</sup> and a systematic review found that use of HDM-impermeable bedding was unlikely to be effective in reducing rhinitis symptoms; however, use of acaricides and extensive bedroom-based environmental control measures might provide some benefit.<sup>48</sup>

Recent findings challenge the historic assumption that the primary site of HDM exposure is the domestic bedroom, observing that public transport, daily human interaction, or both can also provide opportunities for exposure.<sup>49</sup> However, exposure outside the home is the exception rather than the rule and might explain unusual patterns of allergy development. One example might be the Iceland paradox, in which 9% of the population had positive test results for sensitization to HDM despite domestic tests showing a near absence of the mite.<sup>50</sup> An alternative explanation might be cross-reactivity between allergens from

HDM with those from other species, such as shellfish, shrimp, or both.<sup>51,52</sup> Some mite allergenic proteins are widely cross-reactive among invertebrates, and HDM allergens are suspected to cause or worsen food allergy to snails and crustaceans.<sup>53</sup> There have been reports of symptoms in patients with HDM allergy after consumption of shrimp<sup>52</sup> and snails<sup>54,55</sup> and skin test cross-reactivity between shellfish and HDM.<sup>56</sup> Group 10 allergens (tropomyosins) are believed to be the principal panallergen responsible for cross-reactivity with other invertebrates<sup>53,57</sup>; Der p 10 shows significant homology with the shrimp tropomyosin Pen a 1.<sup>58</sup> HDM allergens that are thought to be responsible for snail cross-reactivity include also Der p 4, Der p 5, Der p 7, and hemocyanin.<sup>53,57</sup>

## THE HDM LIFECYCLE: IMPLICATIONS FOR ALLERGEN CONTROL

The 2 key species of HDM in allergy research are *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*. The *Dermatophagoides* genus is probably the most researched of all the HDMs, although species dominance varies geographically, suggesting specialist adaptation.<sup>59</sup> All HDM species reach adulthood within 3 to 4 weeks. Once mature, adult mites have a life expectancy of between 4 and 6 weeks, during which time females can lay between 40 and 80 eggs. With this fast reproductive turnover, mites can colonize a new home within a year.<sup>8</sup>

Dust provides a detrital habitat with 3 key macromolecules derived from organic debris: keratin (human skin scales), cellulose (textile fibers), and chitin (fungal hyphae and mite cuticles). The availability of these substances affects the success of the mite, with keratin, the primary food source, being most important. However, the HDM diet also extends to fibers, bacteria, pollen, fungal mycelia, and the spores of microorganisms. During digestion, disassociated digestive cells from the gut wall bind to ingested food en route through the lumen. These cells contain allergenic digestive enzymes that are excreted in the fecal pellets.<sup>8</sup>

Human and HDM populations are inextricably linked because human skin influences not only diet but also, indirectly, the HDM habitat. Hard surfaces increase the risk of skin desiccation and are less suitable for the mite, whereas insulating fabrics or woven

**TABLE II.** Summary of key HDM allergen groups and action on the human immune systems

Mite allergen group	Identified allergens	Molecular category	Effect on the immune system*	Quantitative allergenicity†
1	Der p 1, Der f 1, Der m 1, Der s 1, Eur m 1, Blo t 1, Pso o 1, Sar s 1	Cysteine protease	<ol style="list-style-type: none"> <li>1. Production of cytokines, chemokines, collagen, pro-T<sub>H</sub>2, and growth factor</li> <li>2. Promotion of T<sub>H</sub>2 polarization and inflammatory cell recruitment</li> <li>3. Increased permeability through disruption of epithelial tight junctions</li> <li>4. Eosinophil and mast cell degranulation</li> <li>5. Fibroblast maturation</li> <li>6. Smooth muscle proliferation</li> <li>7. Downregulation of IDO and T<sub>H</sub>1 polarization</li> <li>8. Airway remodeling</li> <li>9. Cleavage of <math>\alpha_1</math>-antitrypsin and collectins in the airways</li> <li>10. Cleavage of occluding and ZO-1 in airway epithelial cells</li> <li>11. Cleavage of CD40 and DC-SIGN in DCs</li> <li>12. TGF-<math>\beta</math> activation through LAP cleavage</li> <li>13. Unknown cleavage in airway epithelial cells, DCs, eosinophils, basophils, and keratinocytes</li> <li>14. Binding to MR on DCs through group 1 glycosylations</li> </ol>	<p>Dominant (<i>Dermatophagoides</i> species)</p> <p>Unknown (<i>Blomia</i> species)</p> <p>80% IgE binding frequency</p>
2	Der p 2, Der f 2, Der s 2, Eur m 2, Lep d 2, Tyr p 2, Gly d 2, Aca s 2, Pso o 2, Ale o 2, Sui m 2, Blo t 2	MD-2-like lipid-binding protein	<ol style="list-style-type: none"> <li>1. Molecular mimicry of MD-2</li> <li>2. TLR2 and TLR4 activation on DCs, airway epithelium, and airway smooth muscle cells</li> <li>4. Binding to CLR on DCs through group 2 glycosylations</li> <li>5. Cytokine/chemokine production to promote T<sub>H</sub>2 polarization and inflammatory cell recruitment</li> <li>6. Downregulation of IDO</li> <li>7. TNF-<math>\alpha</math> release</li> </ol>	<p>Dominant (<i>Dermatophagoides</i> species)</p> <p>Low (<i>Blomia</i> species)</p> <p>80% IgE binding frequency</p>
3	Der p 3, Der f 3, Der s 3, Eur m 3, Blo t 3, Sar s 3, Gly d 3, Lep d 3	Trypsin-like serine protease	<ol style="list-style-type: none"> <li>1. Production of cytokines, chemokines, collagen, and growth factor</li> <li>2. Increased permeability through disruption of epithelial tight junctions</li> <li>3. Eosinophil and mast cell degranulation</li> <li>4. Fibroblast maturation</li> <li>5. Smooth muscle proliferation</li> <li>6. PAR-2 activation in airway epithelial cells and keratinocytes</li> <li>7. Cleavage of occludin and ZO-1 in airway epithelial cells</li> <li>8. Promotion of T<sub>H</sub>2 polarization and inflammatory cell recruitment</li> <li>9. Airway remodeling and increase in airway inflammation</li> </ol>	<p>16% to 100% IgE binding frequency</p>
4	Der p 4, Der f 4, Eur m 4, Blo t 4	Amylase	Unknown	<p>Midpotency (<i>Dermatophagoides</i> species)</p> <p>Low (<i>Blomia</i> species)</p> <p>40% to 46% IgE binding frequency</p>
5	Der p 5, Blo t 5, Der f 5, Gly d 5, Lep d 5	Lipid-binding protein	<ol style="list-style-type: none"> <li>1. Might bind hydrophobic ligands with the effect of stimulating the innate immune system</li> <li>2. Possible role for TLR activation</li> <li>3. Cytokine/chemokine production to promote T<sub>H</sub>2 polarization and inflammatory cell recruitment</li> </ol>	<p>Midpotency (<i>Dermatophagoides</i> species)</p> <p>Dominant (<i>Blomia</i> species)</p> <p>50% to 70% IgE binding frequency</p>

(Continued)

TABLE II. (Continued)

Mite allergen group	Identified allergens	Molecular category	Effect on the immune system*	Quantitative allergenicity†
6	Der p 6, Der f 6, Blo t 6	Chymotrypsin-like serine protease	<ol style="list-style-type: none"> <li>1. Production of cytokines, chemokines, collagen, and growth factor</li> <li>2. T<sub>H</sub>2 polarization and inflammatory cell recruitment</li> <li>3. Increased permeability through disruption of epithelial tight junctions</li> <li>4. Eosinophil and mast cell degranulation</li> <li>5. Fibroblast maturation</li> <li>6. Smooth muscle proliferation</li> <li>7. PAR-2 activation in keratinocytes</li> <li>8. Cleavage of occludin and ZO-1 in airway epithelial cells</li> </ol>	40% IgE binding frequency
7	Der p 7, Der f 7, Lep d 7, Gly d 7, Blo t 7	Lipid-binding protein	<ol style="list-style-type: none"> <li>1. Might be involved in activation of TLRs</li> <li>2. Might be involved in polarization of T<sub>H</sub>2 cells</li> <li>3. Might act as a ligand for other bacterial ligands; structural similarity to LPS-binding protein</li> <li>4. Might interact with the innate immune system</li> </ol>	Midpotency ( <i>Dermatophagoides</i> species) Uncertain ( <i>Blomia</i> species) 50% IgE binding frequency
8	Der p 8, Pso o 8, Sar s 8, Gly d 8, Lep d 8, Blo t 8	Glutathione-S-transferase	Unknown	20% to 40% IgE binding frequency
9	Der p 9, Der f 9, Blo t 9	Collagenolytic-like serine protease	<ol style="list-style-type: none"> <li>1. Increased permeability through disruption of epithelial tight junctions</li> <li>2. Production of cytokines, chemokines, collagen, and growth factor</li> <li>3. Smooth muscle proliferation</li> <li>4. Eosinophil and mast cell degranulation</li> <li>5. Airway remodeling</li> <li>6. T<sub>H</sub>2 polarization and inflammatory cell recruitment</li> <li>7. PAR-2 activation in airways epithelial cells and keratinocytes</li> <li>8. Cleavage of occludin and ZO-1 in epithelial cells</li> </ol>	90% IgE binding frequency
10	Der p 10, Der f 10, Blo t 10, Lep d 10, Pso o 10, Tyr p 10, Gly d 10, Der g 10	Tropomyosin	Unknown	Low ( <i>Dermatophagoides</i> species) Low ( <i>Blomia</i> species) 50% to 95% IgE binding frequency
11	Der p 11, Der f 11, Blo t 11, Pso o 11, Sar s 11	Paramyosin	Unknown	80% IgE binding frequency
12	Der p 12, Blo t 12, Lep d 12	Chitinase	Unknown	50% IgE binding frequency
13	Der f 13, Blo t 13, Lep d 13, Aca s 13, Try p 13, Gly d 13	Lipocalin	Might be involved in the activation of TLRs, polarization of T <sub>H</sub> 2 cells, or both	10% to 20% IgE binding frequency
14	Der p 14, Der f 14, Eur m 14, Sar s 14, Blo t 14, Pso o 14	Vitellogenin/apolipoprotein-like	Might be involved in the activation of TLRs, polarization of T <sub>H</sub> 2 cells or both Might be involved in production of IL-4 and IL-13	90% IgE binding frequency
15	Der p 15, Der f 15	Chitinase	Unknown but might be involved in the polarization of T <sub>H</sub> 2 cells	70% IgE binding frequency
16	Der f 16	Gelsolin	Unknown	50% IgE binding frequency
17	Der f 17	EF-hand Ca <sup>2+</sup> -binding protein	Unknown	35% IgE binding frequency
18	Der p 18, Der f 18, Blo t 19	Chitinase	Unknown but might be involved in the polarization of T <sub>H</sub> 2 cells	55% IgE binding frequency
19	Blo t 19	Antimicrobial peptide	Unknown	10% IgE binding frequency
20	Der p 20	Arginine kinase	Unknown	—
21	Der p 21, Blo t 21	Lipid-binding protein	Unknown but might be involved in the activation of TLRs	Midpotency ( <i>Dermatophagoides</i> species) Dominant ( <i>Blomia</i> species)
22	Der f 22	Lipid-binding protein	Unknown	—

(Continued)

TABLE II. (Continued)

Mite allergen group	Identified allergens	Molecular category	Effect on the immune system*	Quantitative allergenicity†
23	Der p 23	Chitin-binding protein	Unknown but homology observed with peritrophin-A domain	—
24	Der f 24	Ubiquinol-cytochrome C reductase-binding protein homolog	Unknown	—

The data have been compiled from several references<sup>8,61,62,65-68</sup> and [www.allergen.org](http://www.allergen.org) (accessed December 12, 2013). Allergen nomenclature is presented based on International Union of Immunological Societies allergen standard consensus by which the species genus is abbreviated to 3 letters followed by the first letter of the species name and the number corresponding to a group of allergens sharing similar molecular features. The *Identified allergens* column was created by using a composite of all the published references and [www.allergome.org](http://www.allergome.org); allergens from the published references were not all found in [allergome.org](http://allergome.org), which predominantly reports *Dermatophagoides* species allergens.

*CLR*, C type lectin receptors; *DC*, dendritic cell; *DC-SIGN*, dendritic cell-specific intercellular adhesion molecule 1-grabbing nonintegrin; *IDO*, indoleamine-2,3,-dioxygenase; *LAP*, latency-associated peptide; *MR*, mannose receptor; *PAR-2*, protease-activated receptor 2; *TLR*, Toll-like receptor; *ZO-1*, zonula occludens 1.

\**Dermatophagoides* species allergens are described on the basis of the current literature. However, the extent of molecular and functional parity of a specific allergen molecule in different species is not known.

†IgE binding frequency is expressed as the percentage of patients in different studies.

textiles provide a matrix for skin scales that can minimize the effect of changes in temperature and humidity on mites.<sup>8</sup> A relative humidity of less than 50% critically reduces HDM prevalence. Adaptations, such as the ability to capitalize on brief periods of humidity to compensate for arid periods, might explain their success across habitats, making humidity alone a poor predictor of mite survival.<sup>60</sup> It might be that the ability to respond rapidly to changes plays a role, with some research suggesting that strong fluctuations in humidity constrain population growth.<sup>61</sup>

## HDM ALLERGENS AND THEIR ROLE IN THE HUMAN IMMUNE RESPONSE

Allergic effects in HDM allergy are thought to be orchestrated through 2 main routes: through the CD4<sup>+</sup> T<sub>H</sub>2 cells that induce and drive the IgE-dependent allergic response and through the innate immune system.<sup>6,62</sup> It is the combined effect of the adaptive and innate immune reactions that makes HDM allergens so powerful.<sup>63</sup> Components that can activate the immune system include not only proteases and immunogenic epitopes but also the structural polysaccharide chitin from the exoskeleton, microbial adjuvant compounds, and ligands originating from mite-associated compounds.<sup>62,63</sup>

Molecules from different mite-related products vary in size, affecting the likelihood of inhalation and how the allergen penetrates into the lung. Smaller particles (1.1-4.7 μm) might be inhaled less frequently than larger particles (>4.7 μm) but can penetrate deeper into the lung.<sup>64</sup> Large molecules might induce a more substantial early-phase response than smaller ones, provoking symptoms at lower quantities.<sup>23</sup> Group 1 molecules (Table II)<sup>8,61,62,65-68</sup> in particular have the capacity to activate multiple routes to distort the immune response, characterizing the virulent effect of HDM allergens on the immune system. In addition to their powerful direct effects, group 1 molecules can also activate the innate immune response and are thought to be recognized by protease-activated receptors and Toll-like receptors and to mimic pathogen-associated molecular pattern activation.<sup>6</sup> They can also cause direct damage to the respiratory epithelial cells, activating mast cells independently of IgE.<sup>69</sup> Indirect effects are also relevant: synchronous exposure to enzymatic allergens, such as Der p 1, might facilitate an allergic response to nonenzymatic allergens.<sup>70</sup> The combined effect of

these processes might explain why therapeutic targeting of individual elements of the immune system has not yet translated into clinical efficacy.<sup>63</sup>

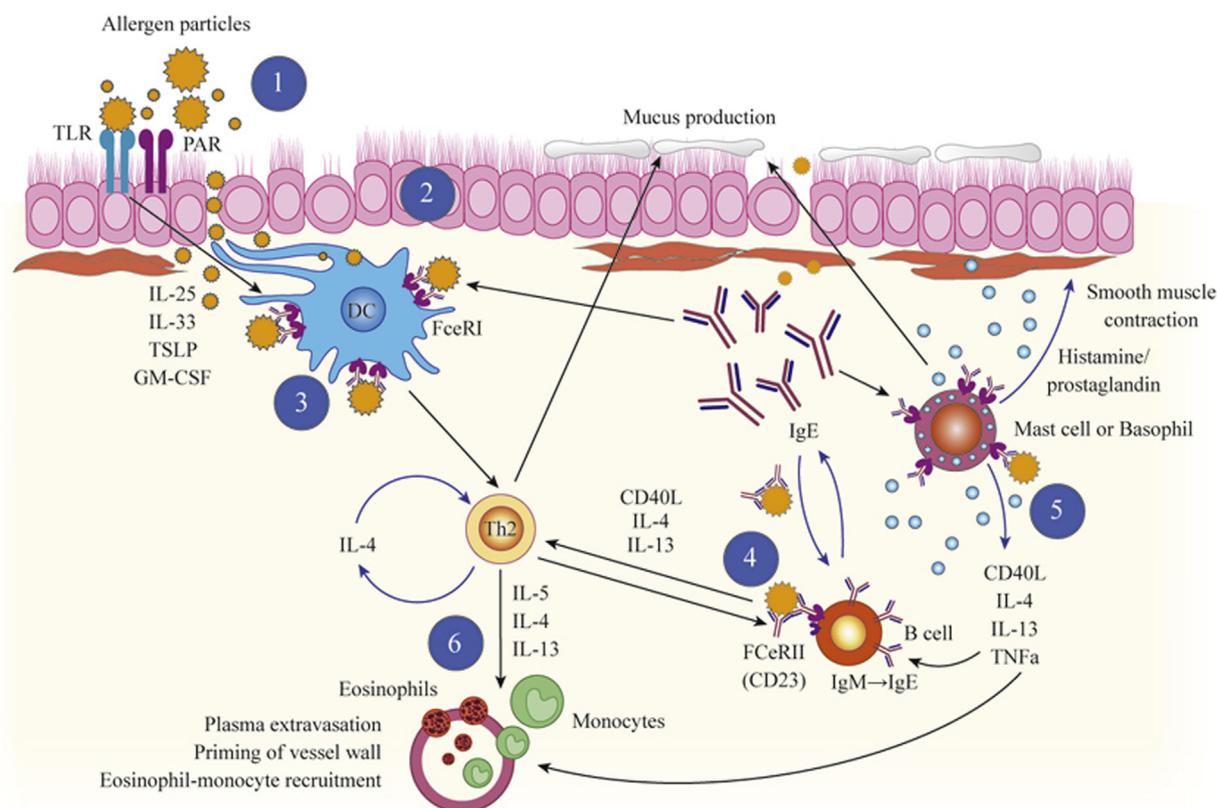
Fig 1<sup>65</sup> shows the immune response to HDM allergens and the potential enhancement by HDM proteases both in the IgE-mediated immediate response and the inflammatory late-phase response. Although the clinical relevance of these proteolytic effects is still largely unknown, they might play important roles in contributing to the high allergenicity of HDMs. The inhaled aeroallergens penetrate the airway epithelium, which, in subjects predisposed to allergy, stimulates the migration of dendritic cells to the lymph nodes.<sup>71</sup> Inflammation in the airways is then orchestrated by dendritic cells and stimulation of T<sub>H</sub>2 cell-mediated immunity. The perpetuation of this immune response is critical and known to be increased in patients with HDM allergy.<sup>72</sup>

Although Fig 1 shows the core model for HDM allergy, HDM allergens manifest different pathways depending on their molecular structure. Table II summarizes the currently identified HDM allergens grouped by molecular profile and likely activity. The 2 most significant groups (groups 1 and 2) have very different effects; the protease activities of group 1 allergens potentially destroy the epithelial tight junctions, whereas group 2 allergens might induce mimicry of the Toll-like receptor 4 coreceptor MD-2.<sup>62</sup> Der p 1 and Der p 2 are the most frequently recognized clinically relevant HDM allergens. It is increasingly recognized that the dominant causative allergen in a population might differ regionally<sup>59</sup> and could also vary between patients.

The primary HDM allergens (ie, group 1 and 2 allergens) are not species specific because of considerable sequence and structural homology. However, individual HDM-specific IgE repertoires can only occasionally distinguish between Der p 1 and Der f 1 or even less frequently between Der p 2 or Der f 2.<sup>73</sup> Although Der p 1 and Der p 2 are commercially available for testing, new allergens are being discovered: Der p 23 has recently been described and has been found to react with IgE antibodies in 74% of patients with HDM allergy studied.<sup>74</sup>

## UPPER AND LOWER AIRWAYS: THE RELATIONSHIP IN HDM ALLERGY

The strong correlation between allergic asthma and allergic rhinitis as comorbidities is often interpreted as evidence of an



- ① Airway mucosa: Perennial occurrence of HDM leads to continuous exposure to HDM allergens. Particles carrying the allergens are inhaled and extracted on the airway mucosa, where allergens come into contact with the immune system. HDM faecal particles are small and reach deep down into the lungs.
- ② Epithelium: The allergens are taken up by dendritic cells and transported to draining lymph nodes. Allergen specific IgE facilitates allergen uptake by antigen presenting cells. HDM allergens with proteolytic activity degrade epithelial tight junctions and further facilitate uptake. Other HDM allergens activate co-stimulatory receptors, such as PAR and TLR, thereby enhancing the allergic Th2 response.
- ③ Antigen presentation: In the lymph nodes, dendritic cells interact with allergen specific T cells. Partly degraded allergen fragments are presented to the T cell in complex with HLA tissue type antigen. In atopic individuals the dendritic cells are skewed to promote Th2 differentiation in T cells, and proteolytic cleavage of soluble low affinity IgE receptor by HDM-derived proteases may further enhance Th2 differentiation.
- ④ IgE production: Allergen-specific Th2 cells produce IL-4, IL-5 and IL-13. These cytokines induce class switching in B cells and IgE production in activated B cells. Continuous exposure to HDM allergens lead to continuous production of HDM specific IgE as well as continuous maintenance of allergic inflammation in the airways.
- ⑤ Immediate allergic reaction: Soluble IgE secreted from activated B cells binds to specific high affinity receptors on basophils and mast cells. These cells are armed with potent enzymes and chemicals, e.g. histamine, which can be released immediately upon repeated encounter with allergen. Direct actions of HDM proteases on basophils and mast cells may further increase degranulation and add to this response. HDM proteases may also act on smooth muscle cells and increase contraction.
- ⑥ Sustained inflammatory responses are maintained by continuous exposure to HDM allergen. IL-5 produced by allergen-specific Th2 cells activates and recruits eosinophil granulocytes. Eosinophils produce potent enzymes and chemicals driving airway remodelling and asthma progression. The sustained Th2 environment may be further enhanced through the various proteolytic actions exerted by HDM allergens.

**FIG 1.** Potential enhancement of the allergic response by HDM allergens. Uptake of HDM allergen particles, immediate allergic reaction, and sustained inflammatory response are shown.<sup>65</sup>

underlying sensitization.<sup>75,76</sup> The term “respiratory allergic disease” recognizes a unifying allergic mechanism for the pathogenesis of allergic subtypes within asthma and rhinitis. In practice, patients present to physicians with specific symptoms from one or both conditions, with the causal allergen less of a focus. Identification and treatment of HDM allergy is a worthwhile investment in future patient outcomes, regardless of whether the condition exists independently or concurrently with other allergies.

HDM allergens might be highly prevalent, but only a minority of persons exposed to them have clinical symptoms. Observed familial trends suggest that genetic predisposition renders some

patients more vulnerable to sensitization than others.<sup>15</sup> By using nasal brushings from children with HDM allergy and allergic rhinitis, *in vitro* exposure to IL-4, IL-13, IFN- $\alpha$ , IFN- $\beta$ , and IFN- $\gamma$  was used to generate a subgroup cluster analysis of gene expression. Genetic signatures relevant to the Th2-driven immune response had a 91% success rate in predicting allergic rhinitis, suggesting an underlying genetic effect.<sup>77</sup> Similar *in vitro* cluster analyses for asthma associated with HDM allergy identified genetic effects of 2 functional single nucleotide polymorphisms mediating thymic stromal lymphopoietin, indicating that aberrant innate immunity might be linked to certain polymorphisms.<sup>78</sup>

Epigenetic effects involved in lung and airway remodeling in response to challenge from HDM allergens are of particular interest: animal models suggest that aberrant methylated genes might be involved in airway hyperresponsiveness.<sup>79</sup> It is likely that many such effects exist, and at the time of writing, a systematic search of the Online Mendelian Inheritance in Man (2014) database found 231 records associated with HDM allergy.

Current thinking suggests a multifactorial model for allergy, in which an initial trigger (viral or environmental) stimulates the innate immune response to effect prolonged chronic inflammation, which might, in those with a genetic susceptibility, interact with exposure to 1 or more allergens facilitating allergy.<sup>80</sup> The German Multicentre Allergy Study comparing atopic and nonatopic children with wheeze and impaired lung function found that children in the nonatopic group had no symptoms at school age (90%) and had normal lung function in puberty.<sup>3</sup> Those sensitized to perennial allergens in the first 3 years of life experienced poor lung function, particularly when combined with high exposure to the sensitizing allergen. These children had a forced expiratory volume/forced vital capacity of 87.4 (SD, 7.4) compared with non-sensitized children 92.6 (SD, 6.0). The authors suggest that the first 3 years of life are critical in the formation of future allergy<sup>3</sup> because children might be particularly vulnerable to allergen exposure during organogenesis. The concept of a “2-hit” model in which combined factors elicit long-term damage is increasingly accepted as an explanation for the development of allergy.<sup>80</sup>

The idea of a critical window is supported by results from several pediatric cohort studies, which suggest that sensitization to HDM in children less than 5 years of age is a significant risk factor for asthma later in childhood.<sup>81,82</sup> The Manchester Asthma and Allergy Study followed children from birth by using unsupervised cluster analyses to identify multiple atopic phenotypes. At age 8 years, sensitization to HDM, both independently and as part of multiple sensitizations, increased the risk of respiratory disease in 87% of the original cohort.<sup>83</sup>

The translation from silent sensitization to symptomatic allergic disease after exposure to HDM is incompletely characterized and understood and is complicated by interacting strata of the immune response. The clinical reaction to an allergen challenge might be immediate or delayed, broadly corresponding to a reactive sensitization and chronic inflammation; both states can occur sequentially, independently, or synchronously. A study collating data from asthmatic patients found that after allergen exposure, the late response was more frequent after exposure to HDM than to cat or grass pollen.<sup>84</sup>

Although nonrespiratory allergic symptoms are beyond the scope of this review, it is worth noting that sensitization can be both systemic and localized. Inhalation of HDM aeroallergens can elicit eczematous lesions,<sup>85,86</sup> and patients with nonsteroidal anti-inflammatory drug-induced urticaria/angioedema show a high prevalence of HDM sensitization.<sup>87</sup> This suggests that deposition of an allergen in one organ (the respiratory tract) causes symptom flare-ups in another organ. Local allergen-dependent mechanisms can theoretically cause concomitant reactions elsewhere in the body, with the most severe form being a systemic anaphylactic reaction.

## Conclusions

HDM allergy is highly prevalent and can manifest in the respiratory system as allergic rhinitis, allergic asthma, or both but

should be thought of as one common condition affecting the whole respiratory tract. Although mite populations are constrained by humidity, the adaptive spread of the HDM, overlapping as it does with human habitation, suggests that it thrives in preferred human living conditions. Therefore controlling exposure is challenging. Studies indicate that HDM allergen levels should be maintained at less than 2  $\mu\text{g/g}$  to decrease the likelihood of sensitization; however, measures to decrease HDM exposure have shown little or no benefit on symptoms in sensitized subjects.

HDM allergens are unusually potent and able to activate both the adaptive and innate immune systems. The exact pathways vary according to allergen group, and elucidating these offers could be an exciting new avenue of future research for understanding HDM allergy in human subjects. However, the interactions between allergen, immune response, sensitization, and airways disease are highly complex and still incompletely understood. The best outcomes for patients might be achieved by focusing directly on the HDM and its allergens, and identifying HDM allergy as the underlying cause of respiratory allergic disease is an important step in managing clinical control of symptoms, as well as potentially preventing disease progression.

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