

# Harmonia axyridis ladybug invasion and allergy

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## ABSTRACT

Beginning in 1916 *Harmonia axyridis*, an orange/red lady beetle with variable black spotting, was imported into the United States from Asia. This agricultural pest-control predator established independent feral populations in North America by 1988. Subsequently, *Harmonia axyridis* has become a pest to homeowners and various horticultural enterprises. Seeking winter hibernation sites, ladybug swarms invade human homes/habitats primarily in the fall. With increased *Harmonia axyridis* exposures, human ladybug allergy was first reported in 1998. Ladybug-specific IgE hypersensitivity has been reported in all ages (1–78 years old) and both sexes. Clinical ladybug allergy manifests variously as rhinoconjunctivitis, asthma, urticaria, and angioedema. A majority, but not all, allergic individuals are primarily exposed at home. Large fall swarms and smaller spring dispersions produce corresponding peaks in ladybug allergy. Ladybug hemolymph is a primary source of allergen. Har a 1 and Har a 2 major ladybug allergens have been characterized. Ladybug allergy prevalence in one endemic area was reported as 10%. Self-report of ladybug pests at home did not predict ladybug allergy, suggesting other exposures are important also. Some individuals have no history of atopy before manifestation of ladybug allergy. Ladybug, cat, cockroach, and house-dust mites are the most likely allergens to present as isolated single positive skin tests in an allergist's office. Ladybug should be a standard skin test allergen for all allergy patients tested in endemic areas. Avoidance of ladybug exposure is paramount to treatment.

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Imagine you are returning to your Midwest home on a cool fall day, when you are enveloped by a swooping swarm of insects obscuring the sunlight. Walking toward your home you are peppered by beating wings and receive a single sharp bite from one of the insects landing on your open skin. You escape indoors only to find the same insects by the hundreds flying through your rooms and crawling on walls, windows, floors, and ceilings. No, these are not Biblical or cinematic swarms of locust or the geographically localized swarms of Great Lakes mayflies (both of which can cause allergic disease<sup>1</sup>). You are being enveloped by the North American continent-wide, escalating invasion of the Asian ladybug, *Harmonia axyridis*.

There are more than 5000 species of ladybugs (class, Insecta; order, Coleoptera; family, Coccinellidae) worldwide, of which >450 species are found in North America. In the last 120 years selected ladybug species have been introduced into North America from other continents (e.g., Australia and Asia) for targeted biological pest control in the citrus and other agricultural endeavors. More than 180 ladybug species have been

imported, of which some 24 have become permanently established in the United States.

Along with species native to North America, imported ladybugs have had an illustrious history of salvaging crops and decorative landscaping from destructive aphids, psyllids, and other soft-bodied insect pests. Ladybugs (known as ladybirds in the United Kingdom) constitute a major component of the predator arm of biological pest control in agriculture and horticulture (other components include natural enemies, pathogens, and parasites). Usual advantages of using predators for pest control include their self-perpetuation, selective choice of prey, and dearth of collateral damage (the predator usually creates no new environmental problems). Exemplifying the truism “for every rule there is an exception,” *H. axyridis* is not selective in its prey and is becoming a severe environmental problem in the Americas, Europe, and other parts of the world.

Initially introduced from Asia into the West Coast of the United States in 1916 and 1964 for biological pest control in the citrus and other agricultural endeavors, additional releases of *H. axyridis* by the United States Department of Agriculture occurred between 1978 and 1982. In its Agriculture Research Service Release Program the United States Department of Agriculture released small numbers of *H. axyridis* into Washington, Louisiana, Mississippi, Georgia, the District of Columbia, Maryland, Ohio, Pennsylvania, Delaware, Connecticut, and Maine. Similar releases were made in

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Canada. Easy to grow in captivity in local communities, entrepreneurs also raised and sold *H. axyridis* for home and agricultural use in the subsequent 20 years. The first feral population of *H. axyridis* was reported in Louisiana in 1988.<sup>2,3</sup>

Since the early 1990s, public interest in these imported beetles has risen dramatically as their populations have expanded outside their intended agricultural and horticultural confines into human habitat in North America. Unlike other imported (exotic) or native ladybug species, *H. axyridis* is omnivorous, consuming a wide variety of insects and able to transition to alternate nutritional sources. They out-compete other exotic and native ladybugs for available resources, displacing other species as they proliferate in a nonnative environment lacking effective natural predators. *H. axyridis* has transformed itself from an asset in biological pest control to a notorious global pest. By the 1990s in North America and Europe, its expansive populations escaped territorial and human control, making it an invasive species. As of 2006, feral populations of *H. axyridis* had been reported in every state of the United States except for Arizona, Montana, and Wyoming and in the contiguous Canadian provinces except Saskatchewan. Independent colonies of this ladybug also have been reported in many cities of Mexico. There have been reports of allergic reactions to ladybug since the 1990s, coming primarily from the East Coast, Northeast, and Midwestern United States, where feral populations of ladybugs have rapidly proliferated in the last 10 years.<sup>3</sup>

In summer ladybugs forage individually for food; aphids and other soft-bodied insects are preferred if available. If necessary, *H. axyridis* will dine on almost any insect, fruit, grain, pollen, or other available food. Through summer, two or three generations may cycle through a metamorphosis from egg, to larva, to pupa, and, finally, to adult ladybug. Individual ladybugs may survive for 2–3 years. Adults in North America are primarily colored orange and red with from 0 to 19 black spots. A black “W” on an ivory-colored pronotum is characteristic (Fig. 1). Worldwide, *H. axyridis* is known for its wide variety of >200 color/spot patterns,<sup>4</sup> which vary by ecosystem, earning it pseudonyms such as Halloween lady beetle, harlequin lady beetle, multicolored Asian lady beetle, and multivariate lady beetle.

As days shorten and cool in late fall, individual beetles are drawn together to swarm in search of hibernation sites. Being a semiariboreal species, *H. axyridis* swarms are more commonly seen in agricultural and forested areas. Adjacent urban areas also are prime hunting ground for these adaptable ladybug swarms seeking winter hibernation sites. In their Asian ancestral homes, *H. axyridis* hibernate in cliffs. Across North America, *H. axyridis* choose human homes and build-



**Figure 1.** Variations of *H. axyridis* colors and markings. The black “W” markings on the pronotum (arrows) are typical variations. Lower left: *H. axyridis* leaving a horizontal surface to climb a vertical wall. (Source: Photographed on window sills and a plant leaf by the author in his West Virginia allergy office, spring dispersion 2007.)

ings as a primary substitute for cliff dwelling. Their swarms prefer light-colored buildings and will preferentially alight on the warm sunny side of the home in search of entry through small cracks into the walls and attic spaces where they will hibernate through winter. There they wait for warmer and longer days of spring when surviving adults will leave hibernation. Tear open a wall in a heavily infested home and you may remove ladybugs by the liter or gallon.

Not surprisingly, in fall (and to a lesser degree again in spring) humans may come into close contact with fall swarming (spring dispersing) *H. axyridis*. An individual’s exposure varies, because your home may attract ladybugs in the fall, while your close neighbor is passed over by the beetles. You may find them at your work, school, or in public buildings. Once inside a building, some ladybugs seem to become trapped in the indoor human habitat, thereby increasing close contact with humans. Flying through rooms and crawling over walls, ceilings, and floors, they leave a faint yellowish dust, which in part is a product of their “reflex bleeding” from tibiofemoral joints. Reflex bleeding brings hemolymph (arthropod blood equivalent) and its allergens to the beetle surface where it can be dispersed by rapidly beating wings in flight, or sloughed during ambulation over surfaces. This externalization of hemolymph seems to serve more than one purpose: in low quantities for chemical communication among like-kind beetles, and in high quantity for defense when the beetle is alarmed.<sup>5</sup> Of concern to you and other humans, externalized hemolymph also contains major allergens of *H. axyridis*. Encounter a lady-

bug that alights on your skin or flies around your head, and your skin and mucous membranes are exposed to a potpourri of potent potential allergens. Squash a ladybug and you will further produce a noxious odor, leave a stain on organic surfaces, and disperse ladybug antigens.

Several alkaloid toxins in the *H. axyridis* hemolymph are integral to its defense and communication functions and produce the noxious, pungent odor accompanying reflex bleeding. Chief among these alkaloids is 2-isopropyl-3-methoxypyrazine. This alkaloid is found in a number of other insects, but in smaller quantities than in *H. axyridis*. It also is found in several foods where it contributes to the distinctive odors of bell pepper, cheddar cheese, and coffee, to which it provides a roasted or earthy aroma.

Despite some entomologists' claims that their mandibles are too small, ladybugs bite humans with a limited frequency. Some experts have attributed the sharp several-second pain to the beetle using its legs to "pinch" the skin. Regardless of which maneuver produces the bite, many individuals who are allergic to *H. axyridis* report that the bite will produce a wheal and flare response, much as in a skin-prick test. The placement of *H. axyridis* hemolymph allergens on the surface of the beetle during reflex bleeding makes either of these mechanisms plausible in a ladybug allergic individual.

### ***H. axyridis* Allergic Disease and Allergens**

*H. axyridis* exposure to a sensitized individual can trigger a full range of allergic responses including allergic rhinoconjunctivitis, asthma, pruritus, urticaria, angioedema, and anaphylaxis. Yarbough *et al.*<sup>6</sup> in 1999 were first to report ladybug allergy in two adults in Georgia and Virginia (Table 1). Davis *et al.*<sup>7</sup> described 4- and 5-year-old boys who developed rhinitis and facial angioedema when playing with ladybugs. In both reports, whole-body extracts of ladybugs produced positive skin-prick test responses in patients and negative responses in controls. Ray and Pence<sup>8</sup> reported a Kentucky woman with ladybug asthma and allergic rhinitis and reviewed nine published and abstract cases before 2004. They speculated that ladybug allergen was contained in the hemolymph or other surface emissions/waste because a washing of ladybugs was an effective skin test material, giving the same results as a whole-body extract in their patient. Albright *et al.*<sup>9</sup> described eight women with ladybug rhinoconjunctivitis, asthma, urticaria, and angioedema, all of whom were positive to skin testing with a whole-body ladybug extract. Nakazawa *et al.*<sup>10</sup> selected 20 clinically ladybug allergic individuals of whom all 10 skin tested with a whole-body extract were positive. Allergy symptoms correlated with infestations or ex-

posures to *H. axyridis* in these clinical reports in Table 1.

The closer the physical contact with ladybugs, the fewer ladybugs are required to induce clinical symptoms. Removing exposure generally results in a prompt decline in allergic symptoms. When reported, the initial exposure to *H. axyridis* usually precedes clinical allergy symptoms by 1 or 2 years. Although most patients have preexisting atopic disease, for some individuals ladybug allergy is their first expression of atopy.

Looking at ladybug pests from an extreme perspective, Shama *et al.*<sup>11</sup> surveyed 167 Kentucky homes with a history of the heaviest infestation by *H. axyridis*. Seasonal in-home observations of ladybugs in 99 responses were highest in fall (80%), followed by winter (67%), spring (60%), and summer (32%). Allergic disease was self-reported in 77% of homes. Of reporting individuals, 50% identified ladybugs as a trigger of their allergy and 19% reported contact allergy to ladybugs manifested by rash and conjunctivitis. Both the high rates of ladybug clinical allergy and the summer persistence of ladybug presence in homes were atypical and depicted the extremes of home infestation.

Rather than describing a group of self-reported ladybug allergic individuals, this author<sup>12</sup> performed two retrospective surveys within an allergy clinic population in northern West Virginia. Patients had been routinely skin tested for *H. axyridis* hypersensitivity since 2001. The whole-body *H. axyridis* extract was prepared locally.<sup>12</sup> In the first survey, all skin test panels performed from 2001 through 2004 were analyzed. The usual panel contained 58 allergens. Of the 1839 skin tests, 24% were all-negative panels. Ladybug was positive on 21% of panels and exceeded in frequency only by cat (24%), cockroach (27%), house-dust mites (40%), and a few pollens (Hickory, Maple, and grass). Single-positive panels made up 12% of all skin tests. Of the single-positive tests, 8% were ladybug, 8% were cat, 12% were cockroach, and 31% were house dust mite with any other antigen making up <3%. Ladybug and cockroach skin tests were highly concordant. Only ladybug showed a greater skin test prevalence in rural versus urban homes. The second survey reviewed 400 randomly chosen allergy clinic charts and focused on ladybug exposures and allergy symptoms (Table 1). Although overall allergy was equally prevalent across home demographics, ladybug home infestation was reported almost twice as often in rural homes compared with urban homes, ladybug-positive skin tests were 32% more frequent in rural versus urban homes, and ladybug allergy prevalence in rural homes was twice that in urban homes. Although frequency of ladybug home infestation showed prevalence trends similar to skin test results and ladybug allergy by home demographics, the report of infestation by ladybugs

Table 1 Demographics and symptoms in published cases of individuals with ladybug allergic disease

	Ray and Pence Review 2004 <sup>8</sup>	Davis <i>et al.</i> 2006 <sup>7</sup>	Albright <i>et al.</i> 2006 <sup>9</sup>	Nakazawa <i>et al.</i> 2007 <sup>10</sup>	Goetz 2007 <sup>12</sup>
Male/female	4/5	2/0	0/8	3/17	15/16
Age (yr)	22–67	4–5	10–50	18–78	1–76
No prior atopy	2/9	1/2	1/8	NR	NR
Home					
Georgia	×				
Virginia	×			×	
Kentucky	×				
Missouri	×	×			
Wisconsin	×				
Indiana			×		
Illinois			×		
West Virginia					×
Ladybug sIgE–positive skin test	9/9*	2/2*	7/8*	10/10*	31/31#
Ladybug sIgE–positive <i>in vitro</i>				15/20*	
Ladybug symptoms					
Rhinoconjunctivitis	9/9	2/2	8/8	12/20	30/31
Asthma	5/9		5/8	11/20	6/31
Urticaria/Angioedema	1/9	2/2	3/8	1/20	3/31
Anaphylaxis			1/8		
Primary ladybug Exposure					
Home	7/9	1/2	8/8	20/20	15/31
Work/other	2/9	1/2			16/31

\*Chosen by self-identification, by ladybug allergy symptoms, among an allergy clinic population before testing.

#Chosen by positive ladybug skin test, from a random sample of 400 allergy clinic patients. Among the 305 skin-tested and 60 ladybug skin test–positive individuals, 31 also had documented symptoms with ladybug exposure. Among 4 years of skin tests 299/1400 were skin test positive for ladybug.<sup>12</sup>

NR: not reported.

was not predictive of an individual's ladybug hypersensitivity (positive predictive value was equal to chance). This supports the conclusions that exposures outside the home are important for some individual's ladybug sensitization. It was concluded that skin testing in endemic areas must be universal.

Beginning with Yarbrough *et al.*,<sup>6</sup> human IgE immunoblots have been used by authors to identify ladybug allergens in whole-body extracts by molecular weight. Albright *et al.*<sup>9</sup> used immunohistochemical staining of *H. axyridis* sections and identified the anatomic binding of human IgE binding in the hemolymph, including that being released by reflex bleeding around the abdominal-femoral leg joints. Then, in 2007, Nakazawa *et al.*<sup>10</sup> isolated and named the first two major allergens of *H. axyridis*: Har a 1 (10 kDa with unique N-terminal sequence) and Har a 2 (55 kDa and homology with aldehyde dehydrogenase of the red flour beetle). Har a 1 was incorporated into an immunoassay that could identify *H. axyridis* allergen in air samples and

house-dust samples. Using an inhibition assay, ladybug-cockroach cross-reactivity was assessed at 5–10%. A third incompletely characterized *H. axyridis* 30-kDa protein was provisionally identified as an allergen cross-reactive with cockroach. Their group of 20 *H. axyridis* hypersensitive individuals is described in Table 1. Of note, 5 of the 20 individuals were sensitive only to *H. axyridis* by the ladybug specific-IgE CAP assay developed in the study.

#### Mitigation and Treatment of *H. axyridis* Allergy

Although ladybug allergy commonly is associated with home infestations, ladybug exposure at sites other than home can be both sensitizing and a trigger for symptoms (Table 2). Some reported cases of ladybug allergy have involved exposures limited to the work or other settings (Table 1). Mitigation of ladybug allergy focuses on avoidance of exposure and treatment of allergic disease when it develops.

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Table 2 *H. axyridis* ladybug facts

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1. *H. axyridis* carries no known human diseases.
  2. *H. axyridis* is the only ladybug species known to invade homes.
  3. The native distribution of *H. axyridis* extends from the Altai Mountains in central Asia in the West to the Pacific Coast in the East, and from southern Siberia in the north to southern China in the South.
  4. Larger ladybug populations follow cool, wet summers that produce higher populations of prey.
  5. Metamorphosis life cycle of *H. axyridis* is egg (3–5 days), larva (12–14 days), pupa (5–6 days), adult (1–3 yr).
  6. In spring and summer, *H. axyridis* feed solitarily, mate, and reproduce through two to three generations.
  7. *H. axyridis* is omnivorous, not only consuming aphids, scale insects, psyllids, and other soft-bodied insects—pest and nonpest alike—but also fruit, grain, pollen, and other available fare.
  8. Unlike other ladybug species it is invasive, displacing other species and spreading into new territories. Enemies are few but include birds, wasps, ants, moths, and larger ladybugs (cannibalism).
  9. *H. axyridis* coloring and spotting is affected by diet and environmental conditions.
  10. *H. axyridis* can fly when temperatures reach above 50° F.
  11. The *H. axyridis* sesquiterpene, (–)-*b*-caryophyllene, is found only in the female species. It also is found in oil of cloves and several fruits.
  12. *H. axyridis* larvae may consume 600–1200 aphids in its stage, while adults may consume 90–270 aphids a day.
  13. Other names for *H. axyridis* include Asian lady beetle, Japanese lady beetle, multicolored Asian lady beetle, multivariate lady beetle, southern lady beetle, Halloween lady beetle, and harlequin lady beetle.
  14. Vineyards infested by *Harmonia axyridis* may bear heavy losses due to tainting of wines made from grapes containing *Harmonia axyridis* adult beetles. These wines have normal physical characteristics but contain significant levels of 2-isopropyl-3-methoxypyrazine. Resultant wines have higher scores for peanut, bell pepper, and asparagus aromas while being lower in fruit attributes.<sup>13</sup>
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Escaping the allergic consequences of ladybug exposure appears to be somewhat easier than escaping animal danders and dust-mite allergen, which persist in human environments, and in the case of animal danders may be carried from habitat to habitat (e.g., home to school). When ladybugs are swarming and an individual is exposed to multiple ladybugs inside or outside a building, ladybug-induced allergic reactions may occur in sensitized individuals, and in the most severe cases may result in hospitalization. When ladybugs are not physically present in the home/building, allergic individuals usually are able to return to daily living/working there with minimal or no persistent ladybug allergy symptoms until the beetle's next appearance. This suggests that once-visible dead ladybug debris is cleaned away, the *H. axyridis* allergens have a short half-life in common environments where humans are exposed. An exception may occur in some homes/buildings where permeable walls filled with dead ladybugs may provide continued ladybug allergen exposure throughout the year.

Primary prevention of ladybug allergy focuses on your living in an ecosystem in which *H. axyridis* does not invade human habitat. The omnivorous tastes of *H. axyridis* makes it difficult to identify geographic areas not likely to be coinhabited by the ladybug now or in the future. Even South America is now being invaded by *H. axyridis* after its successful infiltration of North America and Europe.<sup>3</sup> The semi-arboreal nature of *H. axyridis* has been suggested as somewhat slowing or limiting its expansion into high mountainous and plains areas with limited forestation. Once you have chosen your continent, country, and local community, further primary prevention of ladybug allergy may be exercised locally by choosing a home far from woods and agriculture, with an outside finish in dark colors.

Secondary prevention involves thwarting swarming *H. axyridis* from entering your home. Seal external cracks and openings that would allow the beetles entry into the home. The external surfaces of the home also may be treated with deterrents to entry. Pyrethroid insecticides often are used professionally, including  $\lambda$ -cyhalothrin, deltamethrin, bifenthrin, cyfluthrin, cypermethrin, and tralomethrin.<sup>14</sup> Suggested but unproven alternative noninsecticide deterrents include lemon-scented household sprays or lemon-containing home mixes sprayed around windows, doors, and other potential sites of beetle entry.

Tertiary prevention of ladybug allergy involves careful cleanup of beetles that have invaded your home. Use of indoor insecticides is not recommended both because of potential toxicity to humans and because, rather than leaving in the spring, dead *H. axyridis* will

contaminate walls, attics, and other spaces. Care should be taken not to crush the beetles and thereby avoid staining furnishings and flooring, while minimizing the unpleasant odors of released hemolymph. Vacuum removal of ladybugs in human spaces is recommended. Homemade ladybug traps made from nylon stockings or similar materials can be inserted between hose and wand to limit contamination of vacuum cleaners by ladybugs, which would otherwise be crushed while passing through the vacuum cleaner and its mechanics.<sup>14</sup>

Beyond avoidance measures, symptomatic treatment of allergic individuals exposed to *H. axyridis* is tailored to the patient's allergic disease, whether rhinoconjunctivitis, asthma, urticaria, angioedema, anaphylaxis, or more unusual allergic responses. Diagnosis of ladybug allergy and specific IgE is hampered by the lack of a commercial *H. axyridis* skin testing extract. Unfortunately, this deficiency likely will never be corrected, because no cost-effective commercial skin test and allergen vaccine therapy (immunotherapy) extract can be produced in the United States due to the extreme expense of obtaining the necessary Food and Drug Administration approval. Neither *H. axyridis* nor any other new routine antigen extract can readily reach commercial viability. This is a particularly acute clinical deficiency, because allergy and specific IgE to *H. axyridis* is as highly prevalent in endemic areas as animal danders and cockroaches and much more prevalent than the majority of allergens on current allergen skin test panels. Every patient seen and skin tested for environmental allergens in endemic areas should be tested for *H. axyridis*-specific IgE. The only current means to accomplish this mandate is with locally produced extracts of either whole-body *H. axyridis* or surface washings of *H. axyridis*. A commercial *in vitro* *H. axyridis*-specific IgE assay may be available in the near future and provide an alternate means of testing; however, *in vivo* testing and vaccine therapy for *H. axyridis* still will require either an Food and Drug Administration approved or locally prepared extract. In the author's practice since 1999, a locally prepared whole-body extract (1:20 w/v in 25% glycerine) has been used both for testing and for ladybug allergen vaccine treatment.<sup>12</sup> Since 2001 the standard skin test panel has included *H. axyridis*.

In the author's allergy practice, if patients were not skin tested routinely to cats, 1 in 100 would have been misclassified as nonatopic. If patients were not skin tested routinely for ladybugs, 1 in 75 would have been misclassified, with cockroaches 1 in 50 and mites 1 in 25. Clinical correlation of symptom history and skin testing to ladybug was present 50% of the time. By history and skin testing, *H. axyridis* ladybug rhinitis was diagnosed in 10% of those skin tested, ladybug

asthma in 2% of those tested, and urticaria/angioedema in 1% of those tested. These results highlight the strong prevalence of ladybug allergy in endemic areas and the need for routine testing for specific IgE to *H. axyridis*.

In the author's practice<sup>12</sup> between 2001 and 2004, allergen vaccine therapy for 481 patients was prepared, of which 18% included *H. axyridis* in the treatment mixture based on patient correlation of allergy symptoms with ladybug exposures and positive skin tests to ladybug. Although anecdotal, the clinical improvement seen with ladybug immunotherapy was comparable or greater than that seen for cats (usually highly successful). There were no adverse reactions. No individuals reaching and maintaining maintenance immunotherapy reported failure. All could tolerate greater ladybug exposures with fewer allergy symptoms. Several individuals with extreme allergic reactions were able to return home to live rather than live elsewhere when ladybugs were resident. Asthmatic patients who were hospitalized regularly in the fall when ladybugs swarmed did not require hospitalization after initiating allergen vaccine therapy for *H. axyridis*. Confirmation of this high rate of successful allergen vaccine therapy for *H. axyridis* awaits controlled trials.

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