

REVIEW

Epidemiology of hymenoptera allergy

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In this article we attempt to summarize available data on hymenoptera allergy as a public health hazard, discuss possible risk factors, and describe the natural history of anaphylactic reactions. In addition to Apidae (honey-bee, bumble bee) and Vespidae (common wasp, poliste, hornet), the hymenoptera order of insects includes Myrmicidae (stinging ants). In this review the Myrmicidae family will not be considered because it is of little practical importance for Europe. Three types of allergic reactions can be observed following hymenoptera, i.e. extensive local swelling (> 10 cm in diameter) lasting at least 24 h, immediate systemic IgE-mediated systemic reactions (urticaria, angioedema, bronchospasm, and anaphylactic shock), and delayed systemic reactions (vasculitis, polyradiculitis, glomerulonephritis, etc). Delayed systemic reactions are uncommon and will not be considered in this review.

Hymenoptera allergy as a public health hazard

Fatal hymenoptera allergy

Table 1 summarizes mortality from insect stings in various countries. Deaths from hymenoptera allergy far outnumber deaths from snake bites. In the USA, hymenoptera allergy causes about 40 deaths a year [1] while in Denmark it causes only 1 [2]. In France, the National Institute of Statistics and Economic Studies reported 16–38 hymenoptera-related deaths a year in the period from 1981 to 1991 [3]. Interestingly in France, the male-to-female ratio was 3 to 1 and deaths occurred mainly in subjects aged 30–75 years.

Post-mortem studies suggest that these data may underestimate fatal hymenoptera allergy. Hoffman *et al.* found IgE antibodies to hymenoptera venoms in half of 10 sera samples collected from adults who had died suddenly and unexpectedly [9]. In a larger study, Schwartz *et al.* [10] reported that 22 out of 94 sera (32%) obtained from 15- to 65-year-old sudden death victims showed elevated IgE antibodies to at least one insect venom. Only 6% of sera from 92 living blood donors contained such specific IgE.

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Prevalence of hymenoptera sensitization and reactions

Sensitization to hymenoptera venoms Sensitization to hymenoptera venoms can be demonstrated by performing skin tests or measuring specific IgE. Published data have consistently shown the rate of sensitization in the general public to range from 15 to 25% (Table 2). Golden *et al.* performed skin tests in a group of 269 subjects with no history of any allergic reactions [11]. Results confirmed sensitization in 15% of the population with positive radioallergosorbent tests (RASTs) for honey-bee venom in 6% and for yellow-jacket venom in 21%. Twenty-four per cent of subjects had a positive RAST to at least one venom. In the Busselton Health Survey [14], RAST was carried out on 2429 sera, positive results being obtained in 16%. At a public health care centre, whilst performing routine check-ups, we observed positive RASTs in 12 of 82 subjects (14.6%) with no history of large local reactions or systemic reactions following a sting [15]. In a group of 80 beekeepers, Bousquet *et al.* [16] detected RAST class 2 or higher in 29 (36%). In another series of 176 beekeepers, the same authors reported positive skin tests in 19 (14.0%) of the 136 non-allergic subjects [17]. Interestingly, there was a negative association between annual number of stings and positive skin-test results. Subjects stung less than 25 times a year were positive for honey-bee venom much more frequently than subjects stung more often.

Large local reactions The prevalence of large local reactions varies widely from study to study: 17% according to Golden [18], 7.4% according to Charpin *et al.* [15], and 3.1% according to Stuckey *et al.* [14]. One problem in evaluating this prevalence with a retrospective questionnaire lies in eliminating non-allergic local reactions which are generally less extensive and do not last as long. According to some studies [18–21], 80–90% of large local reactions in children or adults are associated with positive skin tests. This percentage is similar to the one computed for sting-induced systemic reactions. However, other publications have indicated much lower percentages: 43% RAST class 2 or higher according to Stuckey *et al.* [14] and 26% RAST class 1 or higher according to Charpin *et al.* [15]. The fact that the latter two surveys were carried out in large samples of the

Table 1. Insect sting mortality

Author	Reference	Country Time period	Population (million)	Total number of deaths	Number of deaths/year/ million inhabitants
Parrish	[1]	USA 1950–1959	164	229	0.14
Somerville	[4]	England & Wales 1959–1971	50	61	0.09
Mosbech	[2]	Denmark 1960–1980	5	26	0.25
Nall	[5]	USA 1962–1982	200	677	0.16
Muller	[6]	Switzerland 1961–1963	6	61	0.45
Przybilla	[7]	Germany 1979–1983	60	53	0.18
INSERM	[3]	France 1981–1991	55	263	0.43

According to Müller [8].

general population using a standardized questionnaire could account for these differences.

Systemic reactions The prevalence of systemic reactions (SR) reported in the literature ranges from 0.15% to 3.3%. Likely reasons for this high variability are differences in the methods of information gathering, the wording of the questionnaire and the setting of the

Table 2. Sensitization to hymenoptera venoms diagnosed either by skin tests or RASTs to venoms

Reference	Population	Test	Positive (%)
[11]	269 non-allergic* company employees	Skin tests	15
		RAST	24
[12]	53 non-allergic subjects	Skin tests	21
[13]	62 non-allergic subjects	Skin tests	22.5
	125 out-patients consulting for respiratory symptoms	Skin tests	24
		RAST	16
[14]	2429 subjects from the general population	RAST	16
[15]	82 non-allergic subjects from the general population	RAST	14.6

* No history of allergy to hymenoptera stings.

survey. Some surveys have been performed in selected groups. Chafee reviewed the records of 3705 out-patients consulting for asthma and/or rhinitis [25] and found a SR prevalence of 0.4%. Using a questionnaire, Golden *et al.* [11] reported a prevalence of 3.3% among 269 employees at Westinghouse Electric Corporation in Baltimore, USA. In a population of 1598 hospital patients interviewed by a physician in an internal medicine department in Switzerland, Müller obtained a prevalence of 1.3% [26].

The earliest surveys were performed in children by Settupane *et al.* in the late 1960s and early 1970s. Parents and physicians of boy scouts and girl scouts enrolled to attend summer camp were asked to fill out an information card. Based on the parents' answers, the prevalence of SR was 0.8% in the 4992 boy scouts recruited [22] and 0.9% in the 2010 girl scouts [23]. In another group of 2964 boy scouts of the same age range studied by the same authors [24], a much higher prevalence (3.9%) was observed. The authors attributed this discrepancy to changes in the wording of the information card. In the girl scout study, the 0.9% prevalence rate dropped to 0.15% when it was determined from the physician's answers.

A few studies have been performed in representative samples of the adult general population (Table 3). In the Busselton health survey, Stuckey *et al.* [14] questioned 3679 subjects and found 2.7% claiming to have experienced SR following a sting. Between 1984 and 1988 we performed three surveys in southeast France, in 18- to 65-

Table 3. Prevalence of systemic reactions to hymenoptera stings

Reference	Population	% SR based on		
		Questionnaire	Physician assessment	Questionnaire + skin test/RAST
[14]	3679 general population	2.7	NA	1.3
[22]	4992 boy scouts	0.8	0.3	NA
[23]	2101 girl scouts	0.9	0.15	NA
[24]	2964 boy scouts	3.9	0.8	NA
[27]	8271 general population	1.9	NA	0.6
	2067 health care centre	0.9	NA	NA
	1415 home computer	3.3	NA	NA

NA. Not available.

year-old adults using the same questionnaire [27]. The first was carried out door-to-door and indicated a prevalence rate of 1.9%. The second was performed in 2067 subjects receiving check-ups at a health care centre. In addition to administration of the questionnaire by a doctor, skin tests to venom were performed in subjects with a history of SR. The prevalence of SR was 0.9% including 0.66% of the population who had both a history of SR and positive skin tests. The third survey was conducted using the country-wide computer network (Minitel) and showed a SR prevalence of 3.3%. Interestingly, the proportion of subjects who had sought medical assistance for SR ranged from 100% in the second survey to 20% in the third. It seems likely that the setting of the study influenced results. The highest rate was obtained in the survey using the computer and the lowest in the one administered by physicians. Physicians may have been more prone to dismiss questionable reactions.

The prevalence of SR to bee-stings in beekeepers has been evaluated at up to 42% [16] and down to 3.3% [29]. Bousquet's study [17] demonstrated an inverse correlation between the annual number of stings received and prevalence of SR to stings. Yunginger *et al.* [30] studied some beekeeper's family members and showed a higher rate of SR among those who had had the least contact. Haymund [29] demonstrated a 9.5% rate of SR in family members.

Awareness of hymenoptera allergy in the general population

A large gap exists between the prevalence of SR to hymenoptera allergy and the number of patients consulting for that reason. This gap may be related to a lack of awareness on the part of patients and/or physicians.

None of the subjects in Golden's study [11] sought medical attention for SR. In our surveys, only a third of the 8127 individuals from the general population was aware of the possibility of SR following hymenoptera stings [31]. In our survey using a computer network [27], we observed that only a third of subjects with a history of SR had consulted an allergy specialist.

Risk factors for hymenoptera allergy

Risk factors for fatal allergic reactions

As shown in Table 4, multiple stings account for less than 5% of all hymenoptera sting deaths. Most deaths occur after a single sting. As we previously mentioned, the typical victim is middle-aged. Based on his review of the literature, Müller computed that 71% of deaths occurred in subjects of 40 years or more [8] although the risk of being stung was highest in children. A probable explanation for this discrepancy is the presence of arteriosclerosis, coronary artery disease and/or chronic obstructive pulmonary disease in older patients [33]. There was a 3:1 male:female ratio. According to the same review [8], death was inflicted by vespids in 36% of cases, polistes in 16% and honey-bees in 43%. In the published series, only 9–25% of bee-sting fatalities had a previous history of hymenoptera allergy. A probable explanation for this low incidence is that anamnesis in retrospective studies is often incomplete. Indeed in a series including 25 deaths Harvey [32] noted previous SR in four out of seven cases in which a full history was obtained. Most fatal stings occurred on the head, neck and throat. When the site was the throat, the cause of death was sometimes a large local reaction rather than a SR.

Table 4. Deaths after hymenoptera stings in function of number of stings received

Author	Reference	Total number of deaths	Deaths (%) [*] after		
			1 sting	2–50 stings	> 50 stings
Lecomte	28	241	188(78)*	43(20)	4(2)
Somerville	4	61	48(79)	12(20)	1(2)
Mosbech	2	26	22(84)	3(12)	1(4)
Nall	5	641	410(64)	231 (36)	

*According to Müller [8].

Risk factors for hymenoptera allergy

Sensitization to hymenoptera venom Allergic sensitization is more frequent when stings are repeated at close intervals of time. Zora *et al.* [13] demonstrated positive skin tests to venom in 41% of subjects stung within the previous 12 months as opposed to only equal to 6% in those stung more than 3 years previously. Jarish *et al.* observed specific IgE sensitization to honey-bee venom in 14% of his population after one injection and in 31% after two injections [34]. Golden *et al.* [11] documented an association between atopy (defined as positive skin tests to common aeroallergens) and positive skin tests to venoms. In 125 out-patients visiting our allergy department for asthma and/or rhinitis, the percentage of positive skin tests to venoms was 29% in atopic subjects vs 19% in non-atopic subjects (non-significant). The corresponding percentages of positive RAST were 22% and 9.4% ($P < 0.05$; unpublished observations). In a group of non-allergic beekeepers, Yunginger *et al.* demonstrated higher specific IgE to honey bee venom in atopic than non-atopic subjects [30].

Systemic reactions Data concerning SR are scarce. The incidence is lower in children than adults. In adults the male : female sex ratio was 2 : 1 according to Golden [18], and Birnbaum *et al.* [35]. The role of atopy is controversial. Large studies performed in boy scouts [23] or in patients consulting for hymenoptera allergy [36–38] showed no association with atopy. Similarly in a recent case-control study including a group of 33 patients with a history of SR to hymenoptera stings, we found no difference between atopic and non-atopic subjects with regard to positive skin tests to common allergens [39]. In contrast atopy seems to be a risk factor in beekeepers [16,40].

Severe systemic reactions Lantner and Reisman [37] studied a group of 158 patients who had severe anaphy-

lactic reactions characterized by loss of consciousness, throat/laryngeal oedema and/or marked respiratory distress. Unlike mortality, severe SR was not more common in older subjects. The sting site was more often on the head than the arms. There was no relationship between the number of stings and the severity of the reaction. Severe reactions were more frequent in subjects with a history of cardiac disease and beta-blocker use. No correlation was found between the severity of reaction and the lapse of time since the last sting or the reaction thereto. Only 20% of patients had previous sting-induced SR.

Is there a genetic predisposition to hymenoptera allergy?

Evidence concerning a putative genetic predisposition to hymenoptera allergy is contradictory. In a Swiss study, 10.5% of patients acknowledged a family history of hymenoptera allergy [41]. Conversely, Kuhn *et al.* [42] analysed HLA-types in families with a purported predisposition and found no correlation with a particular HLA phenotype. The high incidence of SR to hymenoptera allergy in certain families could be the coincidental result of a shared life-style that exposes members to repeated stings.

Natural history of hymenoptera allergy

Are positive skin tests or RAST predictive of systemic reaction?

Sensitization to hymenoptera venom, demonstrated either by skin tests or detection of specific IgE is obviously far more common than a history of hymenoptera allergy. As was the case for a third of the 269 subjects studied by Golden *et al.* [11], stings often trigger IgE responses. In most cases, however, this response is transient and sensitivity is lost before another sting occurs [43,44]. The question of the predictive value of positive tests in subjects with no history of reactions to stings is moot since outside the framework of

epidemiological studies there is no rationale for such testing in asymptomatic individuals.

Is a large local reaction predictive of systemic reaction?

In a small series of patients [20], Hoffman demonstrated that the proportion of positive RASTs was the same in patients with large local reactions as in those with a history of SR. The same author also reported that a significant number of patients experience both reactions. These findings were brought into question by Mauriello *et al.* [21] who conducted a 9-year prospective study of 79 patients with large local reactions. Patients with large local reactions tended to continue to have large reactions regardless of their IgE status. Other prospective studies [18,21] indicate that 5–10% of adults and 2% of children presenting sting-induced large local reactions have SR following a subsequent sting. These findings suggest that neither skin tests nor immunotherapy is necessary in these patients.

How great is the risk of systemic reaction in subjects with a history of sting-induced systemic reaction?

Retrospective studies designed to evaluate the risk of systemic reaction in subjects with a history of sting induced systemic reaction are biased because subjects with a previous SR who did not develop another reaction when re-stung were excluded. As a result, the only reliable data is provided by prospective studies involving accidental field stings. Based on his review of 285 cases from the literature, Muller [8] evaluated the risk of systemic reaction upon 're-sting' at 29%. Four factors appear to influence this risk. The first is the severity of the previous reaction. In a retrospective study of 400 patients, Woermann [45] demonstrated that the severity of subsequent reactions were usually the same. Reisman [46] confirmed these findings in a prospective study of 220 patients who presented venom anaphylaxis and did not receive venom immunotherapy. Out of the 150 patients who had a SR when re-stung, 62% exhibited the same grade of severity. The second factor influencing the risk of SR is age. Schubert *et al.* [47] showed that only 16% of children with mild SR demonstrate another SR when re-stung. More recently, Valentine *et al.* [48] studied 174 children between the ages of 2 and 16 years with a history of mild sting-induced SR and found that subsequent stings led to reactions of similar or lesser severity. These authors concluded that immunotherapy was unnecessary in this group. The third factor is the hymenoptera species. Generally speaking, bee stings involve a greater dose of venom than vespid stings [49]. Blaauw and Smithuis [50] showed that the risk of SR upon re-sting was 24% for

patients allergic to yellow-jacket venom as compared with 50% for patients allergic to bee venom. The fourth factor is the lapse of time between two successive stings. Settupane and Chafee [36] showed that stings occurring within 2–3 weeks of each other (refractory period) or after at several years of interval had the best prognosis. However, this conclusion was challenged by Reisman [44] who observed SR in 81% of patients stung at intervals of 10 years or more.

On the basis of the preceding data, a number of recommendations concerning the use of specific venom immunotherapy have been made [51]. Immunotherapy should not be used for large local reactions. On the other hand it can be undertaken for mild systemic reactions occurring not only in children but also in adults presenting anxiety, increasingly severe reactions, cardiovascular disease, or high exposure (e.g. beekeeper family). Immunotherapy is mandatory in patients with a history of severe SR.

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