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Title

Tabanidae insect (horsefly and deerfly) allergy in humans: a review of the literature

Short title

Allergy to horseflies and deerflies in humans

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Abstract

Allergy to insects of the family Tabanidae (order Diptera), commonly called horseflies or deerflies, is anecdotally common, although the published literature is limited to case reports and small case series. This review summarises the available literature, in which there is enormous variability in clinical detail, identification of species or even genus, and means and thoroughness of assessment of sensitisation. The clinical utility of both *in vivo* and *in vitro* assays remains unclear. Investigation and management of patients reporting anaphylaxis to suspected bites must therefore be pragmatic, by considering other insects (for example Hymenoptera), provision of a written action plan and self-injectable adrenaline if appropriate, and advice on avoidance.

Introduction

Flies from the family Tabanidae (generically called tabanids) are among the most commonly encountered blood-feeding insects. It is a large family within the order Diptera, and contains four subfamilies (Pangoniinae, Chrysopsinae, Tabaninae, and Sepsidinae),¹ (figure 1) of which only the first three are reported to have medical relevance to allergy. There are 144 genera and more than 4500 species and subspecies,² although the genera most clinically relevant to humans and livestock are *Tabanus* (figure 2A), *Haematopota* (figure 2B), and *Chrysops* (figure 2C). Common names vary regionally, but often include horseflies or March flies (typically *Tabanus* spp.), deerflies (typically *Chrysops* spp.), and the more ancient names of gadflies or clegs, both derived from Old Norse.

Tabanids exist worldwide, except for polar regions and some islands. *Tabanus* has a global distribution, and especially common in North America (figure 3A). *Haematopota* is most prevalent in Europe, rare in North America, and absent from South America and Australasia (figure 3B), and *Chrysops* is more variable (figure 3C). Figure 3D shows reports of all insects in the order Diptera, illustrating geographical areas of lower sampling or prevalence; in these areas confident estimation of tabanid prevalence is difficult.

In contrast to Hymenoptera, true flies (Diptera) have relatively large and movable heads, with short antennae, large eyes, and only one pair of wings. They are 6-30 mm long, have large compound eyes with strikingly coloured bands, and are strong flyers. They are usually active in daylight and through the summer months, although the season may be delayed at higher altitudes

and potentially by climate change.³ *Haematopota* spp. are most active in the late afternoon and in rainy weather.⁴

Most species produce a buzz when flying (*Chrysops* spp. more high-pitched and softer than *Tabanus* spp.), fly low, and approach the lower leg in preference to other body areas. In contrast, *Haematopota* spp. fly silently and tend to approach the head and neck (possibly attracted by carbon dioxide).⁵ The reason for this difference is unknown.

The females of many species require blood for oogenesis, and in these species the female mouthparts include two sharp, slender mandibles which penetrate mammalian skin to the superficial dermal vessels. The saliva introduced into the wound contains an array of anticoagulants^{6,7} and other potential allergens but no anaesthetic. After a painful bite the insects use their tongue to lap up 20-600 µL of pooled blood, which is required to complete egg development.¹ Bleeding from the wound is rarely seen with Hymenoptera stings, and may suggest tabanid bites instead. When investigating suspected Hymenoptera allergy 2-5% of patients have negative tests for Hymenoptera sensitisation,⁸ and tabanid allergy may account for some of these cases.

A recent European Academy of Allergy and Clinical Immunology (EAACI) position paper gives a brief overview of hypersensitivity to biting insects including mosquitoes, horseflies, beetles, bugs, caterpillars, lice, and fleas,⁹ but is necessarily broad in its focus. This paper provides a comprehensive review of the allergy to tabanids specifically.

Medical importance

Haematophagous tabanids are most prevalent in areas with plentiful grazing livestock, where they are a serious pest that can result in reduced weight gain and milk production.¹ Tabanids are of significant medical importance because they can transmit a variety of viruses, bacteria, parasites, and protozoa to humans and animals, either biologically (as an intermediate host), or more commonly mechanically, where diseases are transmitted via contaminated blood on the mouthparts of the fly.

The bite usually leaves little more than a transient wheal and flare with minimal bleeding. In some cases there can be prominent erythematous plaques with a central point at the bite site and similar, smaller satellite lesions.¹⁰ Large local reactions are common,¹¹ and systemic allergic reactions following tabanid bites have been reported.

There are few case reports or series describing systemic allergic reactions to tabanid bites (table 1). Most relate to *Tabanus* spp., with fewer to *Haematopota* spp. and *Chrysops* spp., and some refer only to “horsefly” or “deerfly” with no species given. The earliest reports of anaphylaxis due to tabanid bites are from the United States, where Dr Claude Frazier identified six patients with cutaneous, respiratory, gastrointestinal, and cardiovascular symptoms following “horsefly” bites (likely to be *Tabanus* spp.).¹² A 1992 survey of members of the American College of Allergy, Asthma, and Immunology (ACAAI) and the American Academy of Allergy, Asthma, and Immunology (AAAAI) identified seven patients with systemic reactions to “horsefly” bites (likely *Tabanus* spp.), but many reporting reactions to “deerfly” bites (likely *Chrysops* spp.).¹²

***Tabanus* spp.**

The first report to identify the genus as *Tabanus* was in 1996, and described a 56-year-old male with rapid onset generalised urticaria, presyncope, lip angioedema, and collapse following a *Tabanus americanus* bite on Rhode Island.¹²

In 1990 Solley published a description,¹³ updated in 2004,¹⁴ of 1787 patients with insect allergy presenting to the author’s clinic in Australia. There were 20 with reactions to “March flies” (*Tabanus* is the only genus present in Australia to any great extent); seventeen had anaphylaxis, and two had large local reactions only. One had a reaction classified under “ill-defined responses (ie, serum sickness-like responses or nonallergic responses in patients receiving multiple stings [>40] at one time)”.¹⁴

In 2009 an Italian case was reported of a 51 year old man with rapid onset generalised pruritis and oral paraesthesia followed by syncope after being bitten by an insect which was captured and identified as *Tabanus bovinus*.¹⁵ He had been receiving venom immunotherapy (VIT) for *Vespula* spp. for three years and had tolerated a *Vespula* sting during the course of VIT.

The only mention of serum mast cell tryptase (MCT) in the context of tabanid allergy is from France in 2009, where two cases of allergy to horsefly were included in a series examining the effect of baseline MCT (bMCT) on anaphylaxis to Hymenoptera and Diptera insects.¹⁶ One patient had a normal bMCT, although the features of the allergy aren't described. The other had an elevated bMCT level of 65 ng/mL (ImmunoCAP®, Phadia, Uppsala, Sweden) and reported anaphylaxis with cutaneous, cardiorespiratory, and gastrointestinal symptoms to *Tabanus* sp. and mosquito. The WHO Diagnostic Criteria for diagnosis of systemic mastocytosis were not met in that patient.¹⁷

The largest number of cases is included in a Chinese study of salivary gland allergens from *Tabanus yao*,¹⁸ although unfortunately no clinical details of the 17 children and 20 adults were given. Twenty control sera from individuals with “negative horsefly bite tests” were included, although with no further details.

***Haematopota* spp.**

Reports of reactions to *Haematopota* spp. and *Chrysops* spp. are fewer. A poster was presented at the 1995 European Congress of Allergy and Clinical Immunology that described 8 adult patients with anaphylaxis to “bites from blood-sucking insects” in and around the Netherlands.¹⁹ Reactions ranged from large local reactions with fever and general ill-health to severe anaphylaxis, although individual details of each patient are not described in the abstract. *Haematopota pluvialis* was suspected but not confirmed (presumably partly based on prevalence and partly on description).

A second report describes facial angioedema with generalised urticaria and syncope following a bite by an unidentified insect²⁰ later identified as *H. pluvialis*. Interestingly, like the *T. bovinus* case described above¹⁵ this patient was receiving VIT to *Vespula* spp. after a severe systemic reaction to wasp sting.

The only paediatric case of tabanid anaphylaxis reported is a 6-year-old patient who developed local swelling and generalised pruritis, dyspnoea, nausea and presyncope. After another bite the following day he developed generalised urticaria and dyspnoea, and a number of months later he had anaphylaxis (clinical features not described for this episode) managed with an adrenaline

autoinjector.⁴ Specimens collected the following summer were identified as *H. pluvialis* and *in vivo* tests supported that as the cause.

***Chrysops* spp.**

Finally, there are three reports of anaphylaxis to *Chrysops* spp. The earliest is from Washington DC, presented at the 1975 American Academy of Allergy Annual Meeting.²¹ It describes three patients with systemic reactions to *Chrysops vittatus*. Two of the patients presented with urticaria and wheezing, and the third “suffered anaphylaxis requiring emergency treatment”.

The second was a 59 year old man from Mississippi who had generalised pruritis; hand, foot, and periorbital swelling; and nausea and abdominal cramping following “deerfly” bites (presumed *Chrysops* spp.).²² On each occasion he denied Hymenoptera sting, although the authors pointed out that fly identification was not confirmed.

The final report relating to *Chrysops* spp. was from Italy in 2008, involving a patient on *Vespula* sp. VIT.²⁰ He was bitten on the arm by “a yellow or green insect, very much like a wasp”, and had urticaria and cardiorespiratory compromise, and noted a small drop of blood at the bite site. Six months later he was bitten again with the same symptoms, but captured the insect which was identified as *Chrysops* sp.

The geographical distribution of these reports approximately reflects the ecological prevalence of the different genera. The reports of reactions to *Tabanus* spp. are from different regions including Europe, Australia, US, and China. The reports of *Haematopota* spp. are from Europe, and *Chrysops* spp. cases have been reported in Europe and the USA. The clinical features are all consistent with anaphylaxis with no unusual features to differentiate them from other causes of anaphylaxis, with the possible exception of the drop of blood at the bite site.^{15,20}

***In vivo* testing**

The usual workup of suspected insect hypersensitivity uses *in vivo* testing in the form of skin prick and intradermal testing, and/or *in vitro* testing, usually serum specific IgE. However, the usefulness of such investigations in suspected tabanid allergy is doubtful.⁹

The earliest report found positive skin test results in 3 patients with a 1:100,000 w/v deerfly extract (source not given), although no controls were mentioned. They also used the Prausnitz-Kurstner (P-K) test, which involves passive intradermal sensitisation using autologous serum hours or days prior to intradermal injection of allergen. Increased wheal size indicates sensitisation; the reciprocal of the highest dilution giving a positive result is considered the P-K titre. The patient P-K titres were positive at 90, 270, and 30 although no reference value is provided. The authors also quantified the amount of antigen needed to provoke 50% leukocyte histamine release (HR-50), with results of 60ugP/mL, <50%, and 0.25ugP/mL but again no reference value was given.²¹

Commercially available whole-body extracts of March flies (Commonwealth Serum Laboratories, Melbourne, Australia) and of horsefly (Dome/Hollister-Stier, Sydney, Australia), were used by Solley, and in the absence of negative controls was thought to be useful.^{13,14} However, another study found “scratch testing” using a commercial insect extract (Hollister-Stier Laboratories, USA) to be negative in the patient but positive in 15 of 21 controls (with local reactions to bites only). Intradermal test in the patient was positive, but 11 of 21 controls were also positive. The authors concluded that skin testing was not useful.¹²

Another report used a commercial deerfly whole-body extract from Greer Laboratories, Lenoir, NC, and found positive results in 2 of 3 negative controls.²² Skin testing for Diptera with a commercial mixture of *Aedes communis* (mosquito) and *Tabanidae* whole-body extract (Stallergenes, France) was performed in another case, and was positive with no negative controls reported.^{20,23} Finally, another report found skin testing to be positive but the source of the mixture of *Tabanus* whole-body extract¹⁵ was not given. The remainder of series either did not perform allergy skin testing or did not mention it.

There is one commercial whole-body *Chrysops vittatus* extract currently available (Stallergenes Greer, Cambridge, MA; Catalogue number #B39), although this is different to the Stallergenes product used by Quercia *et al*²⁰ and hasn't been used in any published cases. Home-made extracts risk inadvertent mechanical transmission of disease to subjects undergoing skin testing if the flies used carry pathogens. At present therefore there are no consistently useful skin testing extracts, and results obtained should be interpreted with great caution due to the risk of false positives.

***In vitro* testing**

The earliest reports of tabanid allergy used *in vitro* radioallergosorbent testing (RAST) to detect sensitisation, but like skin testing extracts this was susceptible to false positivities.¹² A fluorescence enzyme immunoassay with allergen coating solid-phase cellulose (Phadia ImmunoCAP, Uppsala, Sweden) is now the most common assay to measure specific IgE against Tabanidae. In the literature this has been positive in two cases involving *Tabanus* spp.,^{15,16} two involving *Chrysops* spp.,^{20,22} and one where the species wasn't identified.²³ It was negative in one case of "horsefly" reaction (genus not identified).²⁴ Pharmacia (which became Phadia) created bespoke ImmunoCAPs using collected *Haematopota pluvialis* specimens for one report, and it produced positive results in 5/8 subjects.¹⁹ Finally, in-house assays have been used,^{4,18} one of which included a normal control sample which showed no reactivity.⁴

The commercial Phadia ImmunoCAP allergen (code i204) is derived from whole-body extract prepared in-house from *Tabanus* spp., and while Phadia cites some data suggesting cross-reactivity with *Chrysops* spp.²⁴ they were unwilling to disclose the clinical characteristics of the samples used to validate the assay (personal communication), so the clinical sensitivity and specificity of the assay remains unknown.

The other currently commercially-available assay uses enzyme-enhanced chemiluminescent immunoassay with liquid-phase kinetics in a bead format (Siemens Immulite 2000 3gAllergy Specific IgE I204, Siemens Healthcare Diagnostics Inc., Erlangen, Germany). This also uses *Tabanus* spp. only, but according to the manufacturer "should cross-react with insects in the same genus". Its validation was performed against an enzyme-labeled immunoassay using biotin-labeled allergen extracts that bind in the fluid phase to specific IgE (AlaSTAT™, Diagnostic Products Corp., Los Angeles, CA, USA), using 70 samples with limited clinical background (personal communication) and the clinical sensitivity and specificity of the assay therefore also remains unknown.

Even though tabanid salivary molecular allergen components have been described, immunoassays for purified or recombinant preparations are not yet commercially available. It is therefore

reasonable to measure commercial specific IgE testing when investigating tabanid allergy, although the potential for false positives and false negatives must be considered.

Tabanid salivary allergens

The salivary allergens of tabanids are not well characterised partly because of the difficulty obtaining sufficient salivary gland extract. A 69kD protein from *Chrysops* spp. was identified more than twenty years ago²⁴ without complete characterisation, but the most comprehensive study is Chinese from 2011, in which 60,000 *Tabanus yao* horseflies weighing 10kg in total were collected to create reagents.¹⁸ They performed IgE immunoblot using sera from 37 adults and children with allergy to horsefly bites, and 20 control subjects with “negative horsefly bite tests”. They described the only three allergens characterised so far:^{18,25} Tab y 1, an apyrase anticoagulant similar to Aed a 1 in mosquitoes; Tab y 2, a hyaluronidase with some homology to that found in *Vespula vulgaris* (Ves v 2) and *Vespula magnifica* (Vesp ma 2); and Tab y 5, an antigen-5-related protein similar to Ves v 5 and Vesp ma 5. Unfortunately the terminology in the original manuscript was incorrect (a correction was added after online publication); the authors called the Ag 5 protein Tab a 1, when in fact in the WHO and International Union of Immunological Societies (WHO/IUIS) systematic allergen nomenclature²⁶ and their subsequent publication in 2012²⁵ they correctly named it Tab y 5. Similarly, they used Tab a 2 instead of the WHO/IUIS nomenclature Tab y 2.

Systematic studies of cross-reactivity between different genera of Tabanidae have not been performed. Interestingly however, there is some similarity between tabanids and insects from the order Hymenoptera. For example, there is some structural homology between *Vespa magnifica* wasp venom and *Tabanus yao* horsefly salivary components, with the hyaluronidases Tab y 2 and Ves ma 2 having 41% sequence homology, and the Ag 5-like proteins Tab y 5 and Ves ma 5 having 27% sequence homology.²⁵ The same study demonstrated some cross-inhibition by ELISA and cross-reactivity on skin prick testing with purified components, although whether this translates to commercially-available specific IgE platforms and skin prick testing solutions has not been studied. There has been some clinical support for a “wasp-horsefly” syndrome,^{15,20} with Hymenoptera sensitisation demonstrated in one case of anaphylaxis to *Haematopota pluvialis*,²⁰ one *Tabanus bovinus*,¹⁵ a third *Tabanus americanus*,¹² and two *Chrysops* sp.,^{20,22} indicating either that the sequence homology is more extensive among the Tabanidae genera, or that co-

sensitisation is common perhaps because individuals who spend time outdoors are more likely to have been stung by both types of insects. Importantly, many tabanids may resemble wasps to untrained observers, and this must be considered when evaluating patients with anaphylaxis due to unidentified flying insects.

Management of tabanid allergy

Avoidance of geographical areas where tabanids exist is ideal but not always possible. Tabanids are attracted to horizontally polarised light, and tend to prefer darker hosts to lighter²⁷ and avoid striped and spotted patterns. The combination of these (light coloured spots/stripes on clothing or body paint) may therefore be a useful strategy for deterring bites. Interestingly, white-striped body painting used by indigenous African and Australian people may serve to deter horseflies.²⁸ Barrier protection including a hat, long sleeves, and trousers can be useful, and standard insect repellents are generally only marginally effective. When flies are swarming, swatting them or running is not efficient and may attract more flies.²⁹

Allergic symptoms following a tabanid bite should be managed according to general guidelines. A written action plan should be provided, with prescription of self-injectable adrenaline if indicated. Serial serum MCT should be taken acutely if possible, and at baseline. Consideration must be given to other biting or stinging insects, as this would change investigation and management. A potentially useful feature is a drop of blood at the bite site, which seems to be more common with tabanids than with Hymenoptera stings,^{15,20} although this is neither universal nor pathognomonic. Oral H₁ antihistamines may be effective in reducing local reactions, but topical administration of these is not effective. Topical or systemic corticosteroids can be used to treat severe delayed reactions.⁹

Allergen immunotherapy from various sources has been used in some reports. Wilbur *et al*²¹ used an aqueous *Chrysops vittatus* extract (source not stated) and found a reduction in P-K titre in all three patients and a reduction in HR-50 in two. Two of the three individuals sustained bites some months after starting immunotherapy with less severe reactions. Solley¹³ reported that three patients were undergoing a trial of immunotherapy, although gives no further detail regarding extract, regimen, or outcome.

Hrabak *et al*²² used deerfly whole-body 1:20 wt/vol preparation (Greer Laboratories, Lenoir, NC) for immunotherapy, and the patient subsequently tolerated multiple deerfly bites with no systemic symptoms. The regimen was typical: 0.05mL of 1:200,000 wt/vol increased over 3 months to a maintenance dose of 0.5mL of 1:200 wt/vol.

A commercial whole-body *Chrysops vittatus* immunotherapy extract (Stallergenes Greer, Cambridge, MA; Catalogue number #B39) is still available in some countries. However, the evidence for immunotherapy is weak, especially when considering other genera. Currently, no standardized allergen immunotherapy against other biting insects is available.

Conclusion

Allergy to the Tabanidae family of insects is anecdotally common, although the literature is limited. Reports are confounded by enormous variability in description of clinical features, confidence in identification of species or even genus, means and thoroughness of assessment of sensitisation, and use of negative control samples. Even the largest manufacturers of *in vitro* assays cannot be confident in the sensitivity and specificity of their assays. Investigation and management of patients reporting suspected tabanid anaphylaxis must therefore be pragmatic, considering other insects (e.g. bees, wasps) that might be amenable to VIT, measurement of MCT, and provision of a written action plan and adrenaline autoinjector if appropriate. Specific IgE testing may be requested, but a negative result cannot exclude sensitisation. In some reports positive skin testing and specific IgE results have been seen in controls, and therefore – whatever the result of testing – the emphasis needs to be on the clinical history. Allergen immunotherapy is available for one species (*Chrysops vittatus*), but further work in this field prospectively is needed to improve our understanding of tabanid allergy, diagnosis, and treatment.

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Figure legends:

Figure 1: Taxonomic classification of tabanids.

Figure 2: (A) *Chrysops lateralis* (CDC/Dr Gary Alpert, public domain); (B) *Tabanus stygius* (CDC/Dr Gary Alpert, public domain); (C) *Haematopota pluvialis* (photo (c) Entomart, <https://www.entomart.be>, unrestricted copyright).

Figure 3: Distribution shown by occurrences between 1975-2020 in the Global Biodiversity Information Facility of (A) *Tabanus* spp.^(reference 30) (B) *Haematopota* spp.^(reference 31) (C) *Chrysops* spp.^(reference 32) (D) Occurrences of all insects in the order Diptera^(reference 33) from 2010-2020, illustrating geographical areas of lower sampling or prevalence (central Africa, parts of Central Asia, Russia, and Greenland); confidence in estimation of tabanid prevalence in these areas is difficult.

Table 1: Summary of reports of tabanid allergy

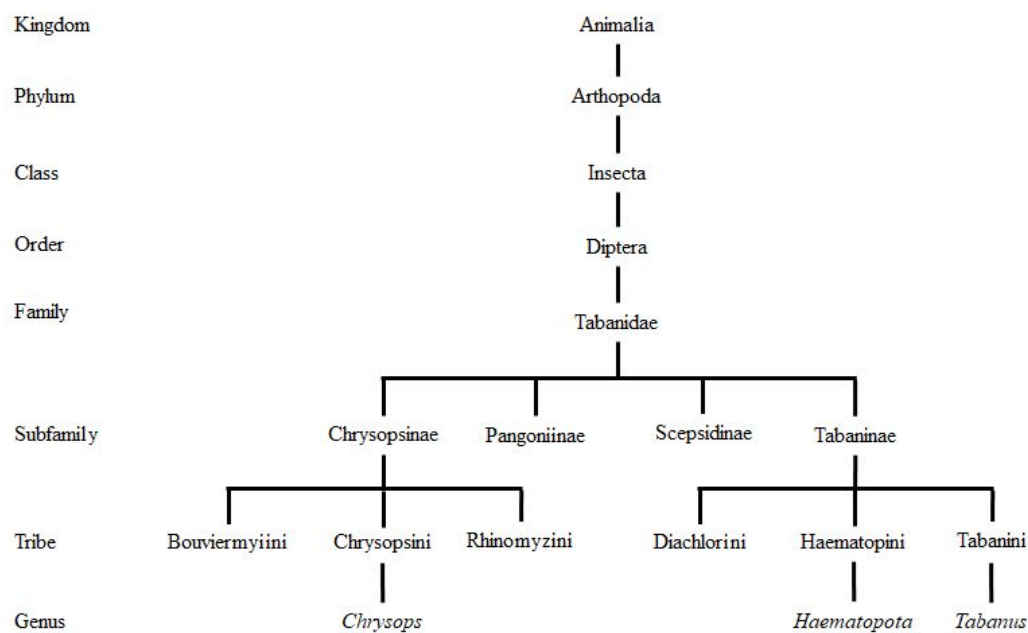
	Year	Location	Insect	Number of cases	<i>In vivo</i> testing	<i>In vitro</i> testing	Comments	Reference
Tabanus	2017	Bolivia	T. bovinus	7	ND	ND	Large, flattened, erythematous plaques	Veraldi and Esposito ¹⁰
	1996	United States	T. americanus	1	Commercial IDT +ve	+ve (RAST)	"Scratch test" is reported as +ve in the text, but -ve in the table. 15/21 controls also +ve on scratch test, and 11/21 +ve on IDT	Freye and Litwin ¹²
	2004	Australia	Tabanus sp	20	Commercial SPT +ve	ND		Solley 1990 ¹³ , 2004 ¹⁴
	2009	France	Tabanus sp	2	ND	+ve (Phadia)	One patient had elevated MCT	Potier <i>et al</i> ¹⁶
	2009	Italy	T. bovinus	1	+ve (source not given)	+ve (Phadia)	On Vespula VIT	Quercia <i>et al</i> ¹⁵
	2011	China	T. yao	37	?	IgE immunoblot +ve for Tab y 1 and Tab y 5	No clinical details	Ma <i>et al</i> ¹⁸
Haematopota	1995	Netherlands	H. pluvialis	8	ND	+ve in 5/8 patients (bespoke Phadia assay)	2/5 with +ve and 1/3 with -ve results had sIgE against Vespula spp	de Maat-Bleeker and van Bronswijk ¹⁹
	2006	Netherlands	H. pluvialis	1	ND	+ve (Phadia), also +ve in-house assay	Paediatric case	de Groot ⁴
	2008	Italy	H. pluvialis	1	Commercial SPT +ve		On Vespula VIT	Quercia <i>et al</i> ²⁰
Chrysops	1975	United States	C. vittatus	3	+ve (P-K test)	2/3 +ve (HR-50)	Immunotherapy used - decrease in P-K titre in all and HR-50 in 2/3	Wilbur and Evans ²¹
	2003	United States	Chrysops sp	1	Commercial SPT -ve, IDT +ve	"Equivocal" (RAST), +ve (Phadia)	Immunotherapy used. 2/3 controls had stronger IDT +ve than subject	Hrabak and Dice ²²
	2008	Italy	Chrysops sp	1	Commercial SPT +ve	+ve (Phadia)	On Vespula VIT	Quercia <i>et al</i> ¹⁵

Other	1969	United States	"Horsefly"	6	ND	ND	Survey conducted by Dr Claude Frazier	Freye and Litwin ¹²
	1992	United States	"Horsefly"/"Deerfly"		ND	ND	Survey of ACAAI/AAAAI - 7 cases to horsefly, "many" to deerfly	Freye and Litwin ¹²
	1995	Italy	"Horsefly"	1	Commercial SPT +ve	+ve (Phadia)		Pucci <i>et al</i> ²³
	1998	Germany	"Horsefly"	1	ND	-ve (Pharmacia)	IgE immunoblot +ve to Chrysops spp extract	Hemmer <i>et al</i> ²⁴

ND: Not done or not reported. IDT: Intradermal skin test. SPT: Skin prick test. RAST: Radioallergosorbent test. Phadia: Manufacturer of ImmunoCAP specific IgE analyser. MCT: Mast cell tryptase.

VIT: Venom Immunotherapy. sIgE: specific IgE. P-K test: Prausnitz-Kurstner test. HR-50: leucocyte histamine release assay. ACAAI/AAAAI: American College of Allergy and Clinical

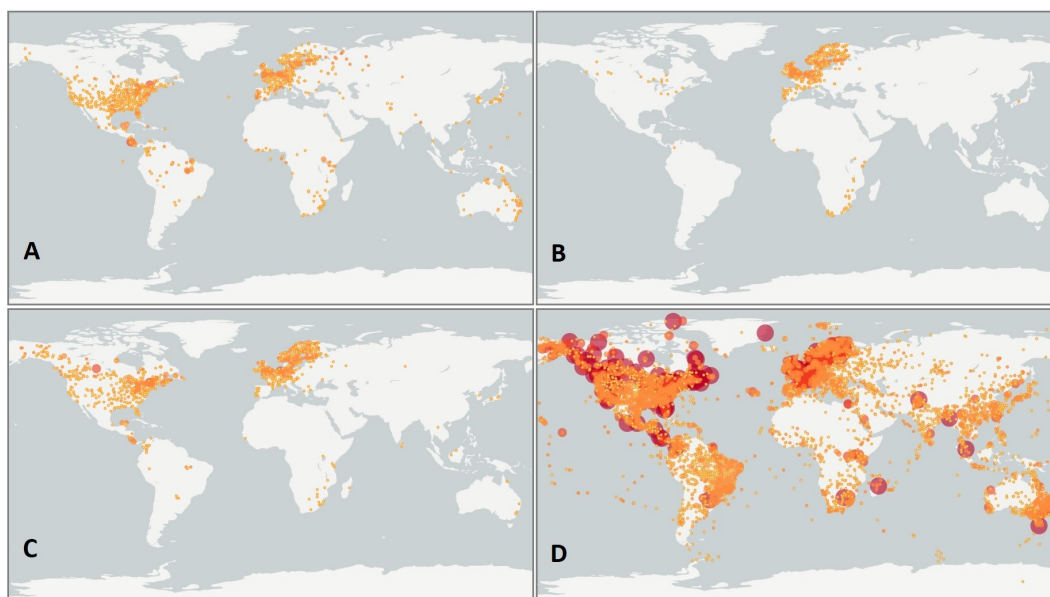
Immunology; American Academy of Allergy, Asthma, and Immunology. Pharmacia: became Phadia in 2006.



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