

# Long-Term Follow-Up of Children after Venom Immunotherapy: Low Adherence to Anaphylaxis Guidelines

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## Keywords

Adrenaline auto-injector · Anaphylaxis · Children and adolescents · Education programs · Emergency kits · Hymenoptera venom allergy · Long-term protection · Re-sting reactions · Venom immunotherapy

## Abstract

**Background:** Data on the long-term outcome of children after specific venom immunotherapy (VIT) are limited. Therefore, we assessed sting recurrence and anaphylaxis relapse rates as well as adherence to anaphylaxis guidelines with regard to the availability of emergency equipment and education status. **Methods:** For this long-term survey, data of 311 children with a history of anaphylactic reactions to hymenoptera stings were collected by chart review. We included patients who were treated with a 3-year VIT between 1993 and 2009 and had completed a questionnaire. **Results:** Forty of the 311 patients were included. Mean VIT duration was 3.1 years. Of the 40 patients included, 29 children (72.5%) received VIT with vespid venom, 9 with bee venom, and 2 patients with both venoms. During a mean follow-up period of 13 years, 20/40 patients (50%) suffered re-stings. Six of the 20 (30%) patients developed again anaphylactic symptoms (grade 1  $n = 5$ , grade 3  $n = 1$ ); 2 were allergic to vespid and 4

to bee venom. Of the entire cohort, only 5/40 (12.5%) had appropriate emergency kits according to the guidelines of the European Academy of Allergy and Clinical Immunology. Among the patients who had emergency kits available, one third (5/15) felt uncertain about the correct application of the medication. Less than two thirds of our population (25/40) affirmed that they have been educated in emergency management. The vast majority (95%; 38/40) of our patients did not have allergy follow-ups after VIT completion. **Conclusions:** Anaphylactic relapses are not uncommon, and there are considerable deficits in the emergency management of patients. Hence, comprehensive standardized anaphylaxis education programs as well as regular follow-ups of the allergy status are crucial.

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## Introduction

IgE-mediated hymenoptera venom allergy may present with cutaneous, respiratory, cardiovascular, or gastrointestinal symptoms and may lead to life-threatening

C.F., U.M., and F.P. contributed equally to the study.

anaphylaxis. In children, anaphylactic reactions to hymenoptera stings are estimated to occur in 0.4–0.8% [1, 2]. Hymenoptera venom allergy accounts for 20.2% of anaphylactic reactions, which is the second leading cause of anaphylaxis in childhood and adolescence after food allergy [3, 4]. Golden et al. [2, 5] showed that up to one third of children with at least moderate systemic reactions do not outgrow their hypersensitivity and require causal treatment. Specific venom immunotherapy (VIT) is effective and indicated in children with a history of moderate-to-severe allergic reactions [2, 6].

Compared to adults, the clinical benefit of VIT is reported to be higher in children with a recurrence rate of 5–10% [2, 5, 6]. Anaphylaxis guidelines, therefore, recommend that emergency kits should be prescribed even after discontinuing VIT [6, 7]. However, it has been shown that the availability of emergency kits together with knowledge and skills on their correct use are frequently insufficient [8].

To date, there have been few studies investigating the long-term outcome of hymenoptera venom allergy in childhood after VIT completion. Yet, in previous publications, the availability of emergency medication and the training state about the management of anaphylaxis has not been recorded.

This study aimed to examine sting recurrence and relapse rate as well as the equipment with emergency kits and education status of pediatric patients after discontinuing VIT.

## Patients and Methods

### Patient Population

By retrospective chart review, we identified all patients who presented with IgE-mediated allergic reactions to hymenoptera stings between 1990 and 2005 in the University Hospital for Children and Adolescents (University of Leipzig, Germany) ( $n = 311$ ). Details are given in a flowchart (online suppl. Fig. 1; for all online suppl. material, see [www.karger.com/doi/10.1159/000458707](http://www.karger.com/doi/10.1159/000458707)). Inclusion criteria were completion of VIT of at least 3 years and anaphylactic reaction grade 1 with asthma as concomitant risk factor or higher-grade reaction based on the classification of anaphylactic reactions published by Ring and Messmer [9].

### Follow-Up

VIT was stopped between 1993 and 2009. Efforts were made to contact the patient or a parent by using the last-known telephone number. The remaining patients were tried to locate by consulting registration offices. A modified German anaphylaxis registry questionnaire [3] was sent to their current address as primary research tool, and patients were requested to complete the form. The questionnaire contained questions about re-stings since discontinuation of VIT, culprit insect, frequency, setting, and symptoms of

re-stings. We inquired about the availability and content of emergency kits, knowledge about correct handling of the medication, participation in anaphylaxis training programs, and regular follow-up appointments (online suppl. Fig. 2).

### Venom-Specific IgE Antibodies

Venom-specific IgE antibody levels were measured before and after VIT (Immuno-CAP; ThermoFisher Scientific/Phadia, Freiburg, Germany). Quantitative levels were assessed in a working range of 0.1–100 kU/L; levels  $>0.35$  kU/L were rated positive.

### Specific VIT

VIT was performed at the University Hospital for Children and Adolescents (Leipzig, Germany) with Venomil® (Bencard, Germany) pure wasp venom (*Vespula* spp.), honeybee venom (*Apis mellifera*), or both types of venom. VIT was started as inpatient treatment over 1 week using a rush protocol until reaching a maintenance dose of 100 µg. Maintenance doses were administered at 4- to 6-week intervals over 3–6 years in an outpatient setting.

### Statistical Methods

A paired *t* test for means was used to compare specific IgE levels before and after treatment and a Welch test for the severity of the initial reaction of honeybee- versus vespid venom-allergic patients. A *p* value  $<0.05$  was considered statistically significant.

## Results

### Patients

A total of 82/311 patients fulfilled our inclusion criteria. We were able to contact 76/82 patients (92.7%), of whom 40/76 (52.6%) completed and returned the questionnaire. Demographic and clinical data are presented in Table 1.

### In vitro Tests

IgE antibody levels before and after VIT were available for 27/40 (67.5%) patients. The mean specific IgE value was 26.51 kU/L prior to VIT and decreased to 5.20 kU/L after VIT ( $p < 0.0001$ ). In patients allergic to vespid venom, the mean specific IgE declined from 25.95 to 5.34 kU/L ( $p = 0.0001$ ) and in patients allergic to honeybees from 34.16 to 4.98 kU/L ( $p = 0.03$ ).

### Severity of Initial Reactions

The severity of initial anaphylactic reactions in our population varied from grade 1 to 4 based on the Ring and Messmer [9] classification, with a slight preponderance for grade 3 (16/40, 40%). There were no remarkable differences in the severity between males and females or between different age groups. The grade of severity differed between patients allergic to bee or vespid venom with 8/9

**Table 1.** Demographic data and characteristics of the 40 study patients receiving venom immunotherapy (VIT)

|                                                        | Total       | VIT          |             |              |
|--------------------------------------------------------|-------------|--------------|-------------|--------------|
|                                                        |             | vespid venom | bee venom   | both venoms  |
| Patients, <i>n</i>                                     | 40 (100%)   | 29 (72.5%)   | 9 (22.5%)   | 2 (5%)       |
| Mean age at VIT initiation, years                      | 9.33 (4–16) | 9.55 (4–16)  | 8.88 (5–13) | 8 (5–11)     |
| Sex, m/f                                               | 20/20       | 16/13        | 3/6         | 1/1          |
| Concomitant diseases                                   | 10/40       | 7/29         | 2/9         | 1/3          |
| Asthma                                                 | 2           | 1            | 1           | –            |
| Atopic eczema                                          | 7           | 5            | 1           | 1            |
| Epilepsy                                               | 1           | 1            | –           | –            |
| Mean duration of VIT, years                            | 3.1 (3–6)   | 3.1 (3–4)    | 3.3 (3–6)   | 3            |
| Mean follow-up after VIT completion, years             | 13 (5–21)   | 13 (7–18)    | 12.2 (5–21) | 16.5 (14–19) |
| Severity of the initial reaction, <i>n</i> of patients |             |              |             |              |
| Grade I                                                | 13          | 11           | 1           | 1            |
| Grade II                                               | 10          | 8            | 2           | –            |
| Grade III                                              | 16          | 10           | 5           | 1            |
| Grade IV                                               | 1           | –            | 1           | –            |

Severity of reactions is graded based on the classification of Ring and Messmer [9]. Ranges are given in parentheses.

(88.9%) honeybee-allergic subjects compared to 19/29 (65.5%,  $p = 0.03$ ) vespid venom-allergic subjects showing respiratory or cardiovascular symptoms.

#### Follow-Up

Twenty of the 40 patients (50%) of our study cohort had been re-stung by the insect they were allergic to since VIT completion. Re-stings were caused by wasps in 14/20 (70%) and by honeybees in 6/20 patients (30%). The mean time interval between VIT and the most recent sting was 7.2 years (range 1–21 years). The majority of the re-stung patients (14/20, 70%) did not show any allergic reactions. Six of the 20 patients (30%) developed repetitive anaphylactic symptoms: 2 were allergic to vespid and 4 to bee venom (Table 2). One patient took emergency medication immediately after the sting and remained asymptomatic. In 3/20 re-stung patients, exercise was identified as augmenting factor.

Among those with repetitive anaphylactic reactions, a majority (5/6) showed mild symptoms limited to the skin (grade 1). Only 1 patient developed a severe anaphylactic reaction with involvement of the respiratory and cardiovascular system. This individual was the only patient in our cohort with more than 1 field sting and received an increased allergen dose by 10 re-stings after discontinuing VIT. No patient developed more severe symptoms than the initial reaction.

**Table 2.** Re-stings and anaphylaxis recurrence rate in the 40 study patients

|                               | Total   | Vespid venom | Bee venom |
|-------------------------------|---------|--------------|-----------|
| Re-stung                      | 20 (50) | 14 (35)      | 6 (15)    |
| Systemic reactions            | 6 (30)  | 2 (14.3)     | 4 (66.7)  |
| Severity of relapse reactions |         |              |           |
| Grade I                       | 5       | 2            | 3         |
| Grade II                      | –       | –            | –         |
| Grade III                     | 1       | –            | 1         |
| Grade IV                      | –       | –            | –         |
| Severity of initial reactions |         |              |           |
| Grade I                       | 2       | 1            | 1         |
| Grade II                      | –       | –            | –         |
| Grade III                     | 4       | 1            | 3         |
| Grade IV                      | –       | –            | –         |

Numbers of patients (%) are shown. Severity of sting reactions (relapse and corresponding initial reaction) of patients with repeated anaphylaxis is based on the classification of Ring and Messmer [9].

#### Emergency Kits and Handling

Of the 40 patients, 15 (37.5%) were still carrying emergency kits but in only 5/15 (33.3%) cases all components recommended by the European Academy of Allergy and Clinical Immunology were included [6]. Nine of the 15 cases (66.6%) were holders of an adrenaline auto-injector,

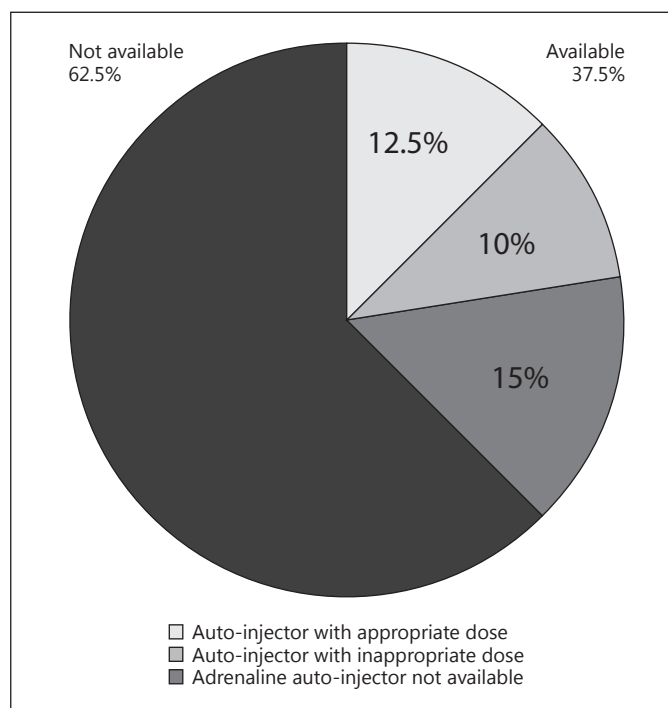


**Fig. 1.** Availability of emergency kits in our cohort ( $n = 40$ ). Among those with emergency kits ( $n = 15/40$ ), percentages of patients carrying adrenaline auto-injectors with appropriate dose ( $n = 5/40$ ), with inappropriate dose ( $n = 4/40$ ), or without any adrenaline auto-injector ( $n = 6/40$ ) are depicted.

but only 5/9 had the appropriate dose (Fig. 1). Regarding the handling of the emergency kit, one third (5/15) felt uncertain about the correct administration of the medication. Less than two thirds (25/40) reported to not have been trained on how to act in case of a new sting reaction and how to apply the emergency drugs. The vast majority of our cohort (38/40, 95%) had not seen an allergist since VIT completion.

Of the patients with repetitive anaphylaxis, only 2/6 still had emergency kits and only 1 carried an auto-injector with an appropriate dose. No patient had applied emergency drugs in the situation of repeated anaphylaxis.

## Discussion

This retrospective study combines the detection of the sting and anaphylaxis recurrence rate with an evaluation of the current allergy care of our patient population. We registered a sting recurrence rate of 50% with a total of 20 re-stings in a mean time of 7.2 years after VIT comple-

tion. These findings are consistent with the results of earlier investigators who reported sting recurrence rates between 39 and 62% [2, 10, 11]. This rate of sting recurrence underlines the need for VIT and provision of detailed instructions about sting avoidance.

In the long-term follow-up after VIT, 95% of the re-stung patients have shown a protection from moderate-to-severe reactions, and 70% have experienced a complete protection from the recurrence of any repeated anaphylactic symptoms. These protection rates are lower than those reported in previous studies in pediatric populations. Golden et al. [2] reported a protection rate of 95% in children with initial moderate-to-severe reactions, but they did not mention the proportion of bee-allergic patients.

More recently conducted surveys presented protection rates of 84.4 and 94.1% in patients allergic to bee and vespid venom, respectively, in a Swiss pediatric population and of 83.4% overall in a Turkish cohort [10, 12].

Our results may be attributable to the small cohort size. Another important factor is the long mean follow-up time of 13 years in our study. Golden et al. [13] reported that up to 15% of patients lost tolerance against hymenoptera venom after VIT over time, which may result in higher relapse rates in longer follow-up intervals after VIT completion. The mean observation periods of the recent studies by Stritzke and Eng [10] and Ertoý Karagol et al. [12] were significantly shorter than in our analysis (7.7 and 5.6 years). Besides, the mean age and proportion of patients allergic to bee venom was lower in the Turkish population. As the recurrence of anaphylaxis increases with the age of children, this may have a minor influence on the protection rate.

The relapse rate in our evaluation was mainly caused by anaphylaxis to bee venom, whose specific immunotherapy is generally less safe and effective than VIT against wasp venom [7, 14–16]. Treatment failure has been shown to be associated with bee venom allergy [17]. Reasons may be the substantially higher amount of venom applied by a bee sting and the fact that main bee venom allergens may be absent or underrepresented in therapeutic VIT preparations [14, 18, 19]. The generally poorer response to bee immunotherapy led to recommendations to continue VIT for at least 5 years and to use elevated doses of bee venom [6, 7, 17]. From the small number of bee venom patients in this study, conclusions on the efficacy of bee VIT cannot be drawn.

Moreover, the response rate of the questionnaires may bias the results in our investigation. Severe events may be reported preferentially. Similar participation rates, how-

ever, were also recorded in previous long-term surveys [2, 13].

Another important factor affecting the recurrence rate is the grade of the initial reaction as severe anaphylaxis constitutes a risk factor for the recurrence of serious reactions [2, 7, 20]. In our cohort, 88.9% of the patients allergic to bee venom and 67.5% in total had initially moderate-to-severe reactions.

As in our study, the venom-specific IgE antibody level usually decreases during treatment. In our study, even all patients with anaphylactic reactions after re-sting had a significant reduction in specific IgE. However, previous trials failed to show a predictive value of specific IgE antibody levels for the subsequent clinical course [11, 16]. Recently, osteopontin has been suggested as a surrogate marker for successful VIT albeit further evaluation is required [21].

In accordance with earlier studies, there were considerable deficits regarding the equipment and education within our cohort even though individual training was part of our primary clinical management [8, 22–25]. Initially, all patients had been prescribed a complete emergency kit including self-injectable adrenaline as first-line treatment. Our data show that the auto-injectors have not been replaced over the years in the majority of patients, which is associated with the low rate of follow-ups at allergists. Besides, a previous investigation demonstrated that the main reason for not having an auto-injector was the feeling that it was no longer necessary [8]. Consequently, the risk of relapse is relevant, especially in patients with honeybee allergy, and should be addressed during regular follow-ups. Carrying adrenaline auto-injectors seems indicated even after completion of VIT [1, 6].

The appropriate use of an emergency kit is often hampered by educational deficits or psychological barriers

[22–24]. One third of our included patients felt unsure about the correct drug administration. None of our patients with re-sting reactions used the emergency kit. Earlier studies verified that despite training programs only a minority of patients were competent in the practical use of the auto-injector. An improvement is associated with regular allergist follow-ups [8, 23].

Most patients in our study have been treated before the widespread introduction of structured anaphylaxis education programs, which is why future surveys might show a different picture.

The major weakness of this study is the small cohort size, which reduces the significance of the results overall and limits the possibility for further subgroup analyses. Especially the results in the bee venom group may be biased by the small number. Owing to the retrospective survey, we had to rely on the memory and statements of the patients. This may have resulted in misjudgments of the severity of reactions. None of our patients received a sting challenge test.

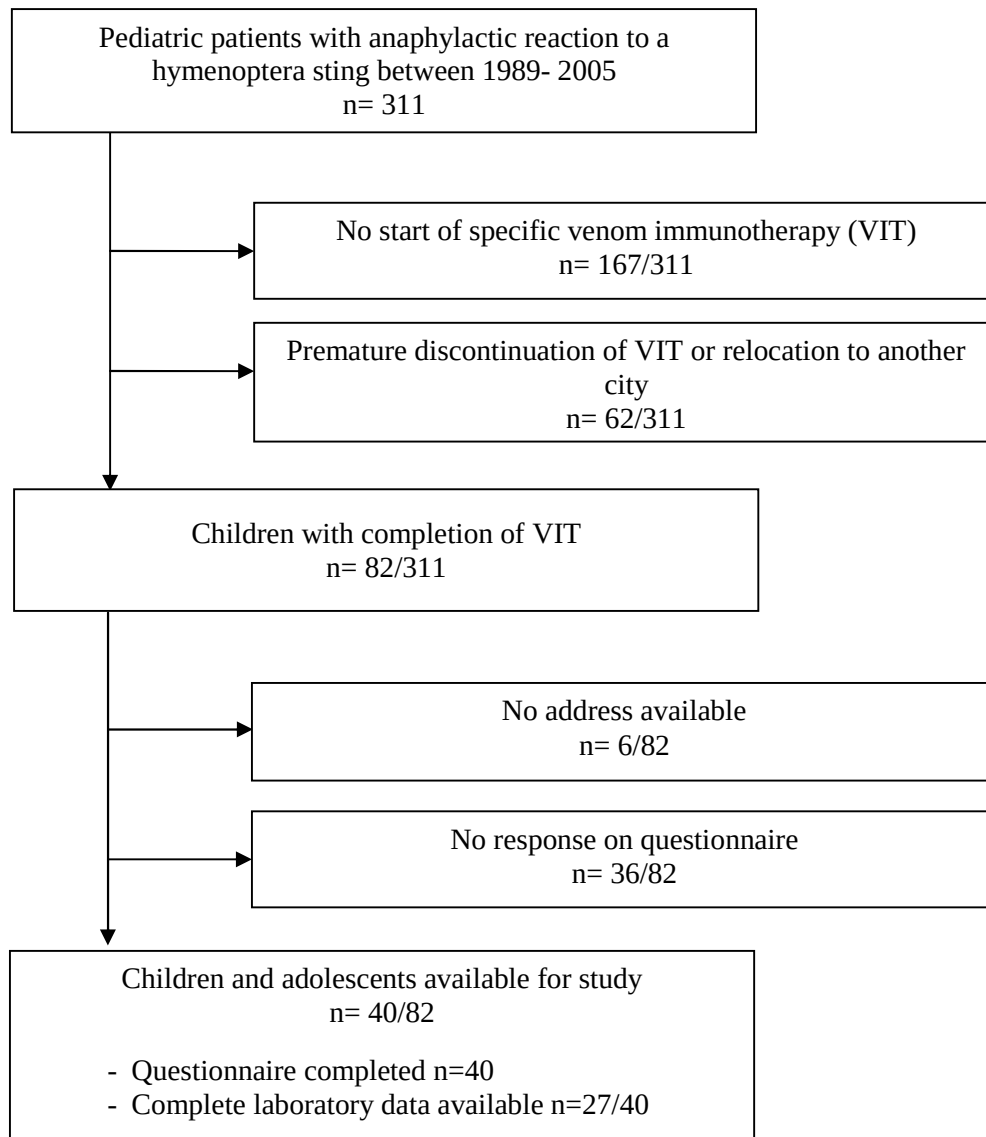
The strength of this study is the combined evaluation of sting recurrence and relapse rate and the detailed allergy care situation of patients with a long mean follow-up. The presentation of the individual severity grades gives a detailed overview of the anaphylactic reactions.

In conclusion, re-stings occurred frequently in our study group. Children seem to benefit from VIT in the long-term as the minority of our cohort suffered anaphylactic reactions on re-stings. In those with repeated anaphylactic symptoms, the reactions were considerably milder than before VIT. Emergency kits are required beyond the completion of therapy, but in reality they are available only in a small number of patients. Alarming deficits are revealed in patients' competence to use emergency medication. These aspects seem to be related to a very low rate of regular follow-ups with allergists.

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Flow-chart on Patient population

## Questionnaire for long-term evaluation of hymenoptera venom allergy after completed hyposensitization

1. Which allergic symptoms were developed on insect stings before initiation of hyposensitization? (multiple responses allowed)

- Skin/mucous membrane:

- Circumscript redness around the puncture site ☐
- Generalized/extensive redness of the skin ☐
- Hives ☐
- Itching ☐
- Conjunctival redness/ red eyes ☐

-Gastrointestinal tract:

- Stomach pains/ cramps ☐
- Diarrhea ☐
- Nausea/ vomiting ☐

- Airways:

- Wheezing ☐
- Tightness in the chest ☐
- Coughing ☐
- Dyspnea ☐
- Respiratory arrest ☐

- Cardiovascular system:

- Dizziness ☐
- Drop in blood pressure/collapse ☐
- Palpitations/ cardiac arrhythmia ☐
- Unconsciousness ☐
- Cardiac arrest ☐

2. What is your/ your child's current bodyweight?

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3. In which year has the allergy immunotherapy been completed?

-----

4. For how many years was the allergy immunotherapy continued?

☐ 3 years

☐ 4 years

☐ 5 years

☐ other

5. Do you/ your child suffer from pre-existing medical conditions?

☐ yes

☐ no

If so, what illnesses have occurred:

Cardiovascular disease ☐

Thyroid disease ☐

Asthma ☐

Neurodermatitis ☐

Malignant disease ☐

Other \_\_\_\_\_

6. Are you equipped with an emergency kit for an allergic reaction on a sting?

☐ yes

☐ no → continue question 7

If so...:

a) Which drugs are available? (multiple responses allowed)

- Adrenaline autoinjector: ☐ dose: 150µg ☐  
300µg ☐  
I don't know ☐

- Cortisone preparation as: tablets ☐ dose: \_\_\_\_\_  
liquid ☐ dose: \_\_\_\_\_  
suppositories ☐ dose: \_\_\_\_\_

- Antihistamine  
(e.g.: Cetirizin, Fenistil) as: tablets ☐ dose: \_\_\_\_\_  
liquid ☐ dose: \_\_\_\_\_  
drops ☐ dose: \_\_\_\_\_

- Salbutamol metered-dose inhaler: ☐ dose: \_\_\_\_\_

b) Are you familiar with the correct handling of the drugs contained in your emergency kit?

☐ yes

☐ no

☐ uncertain

7. Have you/ your child suffered another insect sting since discontinuation of therapy?

☐ yes

☐ no → continue question 8

If so...:

a) Which was the culprit insect?

☐ Bee

☐ Wasp

☐ Other

b) In which year did the re-sting occur?

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c) Where did the re-sting take place?

- Kindergarten ☐
- School ☐
- At home, garden ☐
- City ☐
- Forest ☐

d) Did you/ your child suffer a renewed allergic reaction on the re-sting?

☐ yes

☐ no → continue question 8

e) Which symptoms did occur? (multiple answers allowed)

- Skin/mucous membrane:
  - Circumscribed redness around the puncture mark ☐
  - Generalized/extensive redness of the skin ☐
  - Hives ☐
  - Itching ☐
  - Conjunctival redness/ red eyes ☐
- Gastrointestinal tract:
  - Stomach pains/ cramps ☐
  - Diarrhea ☐
  - Nausea/ vomiting ☐
- Airways:
  - Wheezing ☐
  - Tightness in the chest ☐
  - Coughing ☐
  - Dyspnea ☐
  - Respiratory arrest ☐
- Cardiovascular system:
  - Dizziness ☐
  - Drop in blood pressure/collapse ☐
  - Palpitations/ cardiac arrhythmia ☐
  - Unconsciousness ☐
  - Cardiac arrest ☐

f) Did you make use of the emergency kit?

☐ yes

☐ no

Is so, which drug/s did you apply?

- Adrenaline ☐
- Cortisone ☐
- Antihistamine ☐
- Salbutamol ☐
- other: \_\_\_\_\_

If not, why not?

- spontaneous improvement ☐
- never been prescribed an emergency kit ☐
- emergency kit not to hand at the moment of allergic reaction ☐
- correct utilisation unclear ☐
- required drug not available in emergency kit ☐
- Other: \_\_\_\_\_ ☐

g) Were there any accompanying circumstances (see below) at the moment of re-sting, which might have promoted or enhanced the allergic reaction?

☐ yes

☐ no

If so, which: (multiple responses allowed)

- Exercise/physical activity ☐
- Psychological strain ☐
- Infection ☐
- Alcohol consumption ☐
- Medication intake (such as: drugs for treating high blood pressure, thyroid medication, antipyretics, pain reliever...) ☐

8. Have you/ your child ever been educated how to deal with the allergy or to recognize and rapidly react to an allergic emergency?

☐ yes

☐ no

9. Do you/your child participate in regular follow-up appointments with an allergist?

☐ yes

☐ no