Allergen immunotherapy for insect venom allergy: a systematic review and meta-analysis

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Allergen immunotherapy for insect venom allergy: a systematic review and meta-analysis

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Abbreviations

Allergen immunotherapy (AIT)

Controlled before-and-after studies (CBA)

Controlled clinical trial (CCT)

Confidence interval (CI)

Effective Practice and Organisation of Care (EPOC)

European Academy of Allergy and Clinical Immunology (EAACI)

Incremental cost-effectiveness ratio (ICER)

Interrupted time series (ITS)

National Health Service (NHS)

National Institute for Health and Care Excellence (NICE)

Non-randomized controlled clinical trial (CCT)

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

International Prospective Register of Systematic Reviews (PROSPERO)

Odds ratio (OR)

Quality adjusted life year (QALY)

Randomized controlled trials (RCT)

Risk ratio (RR)

Venom immunotherapy (VIT)

Whole body extract immunotherapy (WBE)

Abstract

Background: The European Academy of Allergy and Clinical Immunology (EAACI) is in the process of developing the EAACI Guidelines on Allergen Immunotherapy (AIT) for the management of insect venom allergy. To inform this process, we sought to assess the effectiveness, cost-effectiveness and safety of AIT in the management of insect venom allergy.

Methods: We undertook a systematic review, which involved searching 15 international biomedical databases for published and unpublished evidence. Studies were independently screened and critically appraised using established instruments. Data were descriptively summarized and, where possible meta-analysed.

Results: Our searches identified a total of 16,917 potentially eligible studies of which 17 satisfied our inclusion criteria. The available evidence was limited both in volume and quality, but suggested that venom immunotherapy (VIT) could substantially reduce the risk of subsequent severe systemic sting reactions (OR=0.08, 95% CI 0.03 to 0.26); meta-analysis showed that it also improved disease specific quality of life (risk difference=1.41, 95% CI 1.04 to 1.79). Adverse effects were experienced in both the build-up and maintenance phases, but most were mild with no fatalities being reported. The very limited evidence found on modeling cost-effectiveness suggested that VIT was likely to be cost-effective in those at high risk of repeated systemic sting reactions and/or impaired quality of life.

Conclusions: The limited available evidence suggested that VIT is effective in reducing severe subsequent systemic sting reactions and in improving disease specific quality of life. VIT proved to be safe and no fatalities were recorded in the studies included in this review. The cost-effectiveness of VIT needs to be established.

Keywords: Allergy, anaphylaxis, hymenoptera venom allergy, insect sting, insect venom allergy, systemic sting reaction.

Introduction

Hymenoptera venom allergy is a potentially life-threatening allergic reaction following a bee, wasp (i.e. paper wasp, yellow jacket or hornet) or ant (i.e. fire ants) sting. The risk of anaphylaxis to hymenoptera stings is greater in adults compared to children due to increased sting exposure, co-morbidities and concomitant medication use. Systemic reactions have been reported in up to 3% of adults, but in less than 1% of children.[1 2]

Symptoms range from large local reactions at the sting site to mild, moderate and severe systemic reactions. Mild systemic reactions usually manifest as generalized skin symptoms including flush, urticaria and angioedema. Typically, dizziness, dyspnea and nausea are examples of moderate reactions, while shock and loss of consciousness, or even cardiac or respiratory arrest all define a severe sting reaction. Seemingly mild reactions can progress into more severe reactions with little warning. The fear of future severe systemic reactions usually greatly impairs quality of life. Around a quarter of fatalities from anaphylaxis are caused by venom allergy.[3 4 5]

Patients are advised to carry an emergency kit comprising of adrenaline (epinephrine), H_1-antihistamines, and corticosteroids depending on the severity of their previous sting reaction(s).[6] The only treatment that can potentially prevent further systemic sting reactions is venom immunotherapy (VIT). This may result in long-term clinical benefits and improved quality of life.[7] [8] However, despite these possible advantages, VIT is still not commonly used by physicians across all European countries.[9] This is likely to reflect uncertainty about the clinical benefits and risks associated with use of VIT, uncertainties about the ethics of mounting further formal experimental studies when VIT is established practice in some countries, as well as the practical and economic implications associated with this treatment.

The European Academy of Allergy and Clinical Immunology (EAACI) is in the process of developing guidelines for AIT. This systematic review is one of five inter-linked evidence syntheses that were undertaken in order to provide a state-of-the-art synopsis of the current evidence base in relation to evaluating AIT for the treatment of insect venom allergy, allergic rhinoconjunctivitis, food allergy, allergic asthma, and allergy prevention.[10] [11] [12] [13] [14] These reviews will be used to contribute to and inform the formulation of key clinical recommendations for subsequent clinical practice guidelines.

AIMS

We assessed the effectiveness, safety and cost-effectiveness of VIT for the treatment of insect venom allergy.

METHODS

The detailed methods for this review have already been described in our published protocol. [10] Here, we provide a more succinct account of the methods employed.

Search strategy

A highly sensitive search strategy was developed, and validated study design filters were applied to retrieve all articles pertaining to the use of VIT for insect venom allergy from electronic bibliographic databases (Appendix 1). We conceptualized the searches to incorporate the four elements below as shown in Figure 1.

To retrieve systematic reviews, we used the systematic review filter developed at McMaster University Health Information Research Unit (HIRU) (http://hiru.mcmaster.ca/hiru/HIRU_Hedges_MEDLINE_Strategies.aspx#Reviews).http://hiru.mcmaster.ca/hiru/HIRU_Hedges_MEDLINE_Strategies.aspx#Reviews). To retrieve randomized controlled trials (RCTs), we applied the Cochrane highly sensitive search strategy for identifying RCTs in MEDLINE.[15] To retrieve non-randomized studies, i.e. controlled clinical trials (CCT), controlled before-and-after (CBA) and interrupted time-series (ITS) studies, we used the Cochrane Effective Practice and Organisation of Care (EPOC) filter Version 2.4, available on request from the EPOC Group.[16] [17] To retrieve case series, we used the filter developed by librarians at Clinical Evidence: http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665076.htmlhttp://clinicalevidence.bmj.com/x/set/static/ebm/learn/665076.html.

We searched the following databases: Cochrane Library including, Cochrane Database of Systematic Reviews (CDSR), Database of Reviews of Effectiveness (DARE), CENTRAL (Trials), Methods Studies, Health Technology Assessments (HTA), Economic Evaluations Database (EED), MEDLINE (OVID), Embase (OVID), CINAHL (Ebscohost), ISI Web of Science (Thomson Web of Knowledge), TRIP Database (www.tripdatabase.com), Clinicaltrials.gov (NIH web), Clinicaltrialsregister.eu, Current controlled trials (www.controlled-trials.com), and the Australian and New Zealand Clinical Trials Registry (http://www.anzctr.org.au).

The search strategy was developed on OVID MEDLINE and then adapted for the other databases (see online supplement). In all cases, the databases were searched from inception to October 31, 2015. Additional references were included through searching the references cited by the identified studies, and unpublished work and research in progress was identified through discussion with experts in the field (see online supplement). We invited a panel of interdisciplinary external experts in the field from different regions to add to the list of included studies by identifying additional published and unpublished papers they are aware of and research in progress (Appendix 2). There were no language restrictions employed; where possible, all relevant literature was translated into English.

Inclusion criteria

Patient characteristics

We were interested in identifying studies conducted on patients of any age with a physician confirmed diagnosis of systemic sting reaction to a venom sting from bees, wasps (i.e. *paper wasp, yellow jacket* or *hornet*) or fire ants.

Interventions of interest

We considered VIT using different products (purified and non-purified, aqueous or depot IT) and different treatment protocols (conventional, cluster, rush and ultra-rush)[18] administered through the subcutaneous (SCIT) or sublingual (SLIT) routes.

Comparators

We were interested in studies comparing VIT with placebo or no treatment (i.e. the natural course of the disease).

Study designs

Systematic reviews of RCTs and RCTs were used to investigate effectiveness; health economic analyses were used to assess cost-effectiveness; and systematic reviews, RCTs and case series, with a minimum of 300 patients, were used to assess safety. We appraised the evidence by looking at higher levels of evidence such as systematic reviews and/or meta-analyses of RCTs, together with individual RCTs. However, as we were expecting to find only a limited number of RCTs, we also searched for and included quasi-RCTs (i.e. non-randomized controlled clinical trials (CCTs), controlled before and after (CBA) studies and interrupted time series (ITS) analyses). Given the high inherent risk of bias in making inferences from quasi-RCTs, our main conclusions in relation to effectiveness have been based on the findings of systematic reviews and RCTs; findings from the quasi-RCTs have only been used to guide suggestions on which areas need to be prioritized in future research.[19]

Our exclusion criteria were: narrative reviews, discussion papers, non-research letters and editorials, animal studies, before-after studies, qualitative studies and case series (involving less than 300 patients).

Outcomes

Primary

- Our primary outcome measure of interest was short- and long-term efficacy assessed by tolerated sting challenge or field sting; long-term was defined as sustained clinical efficacy after discontinuation of VIT.

Secondary

Our secondary outcome measures of interest were:

- Assessment of disease specific quality of life
- Safety as assessed by local and systemic reactions in accordance with the World Allergy Organization's (WAO) grading system of side-effects[20 21]
- Health economic analysis from the perspective of the health system/payer.

Study selection

All references were uploaded into the systematic review software DistillerSR and de-duplication was undertaken. Study titles were independently checked by two reviewers (SD and HZ) according to the above selection criteria and categorized as included, not included or unsure. For those papers in the unsure category, we retrieved the abstract and re-categorized studies as above. Any discrepancies were resolved through discussion and, when necessary, a third reviewer arbitrated (AS). Full text copies of all potentially relevant studies were obtained and their eligibility for inclusion independently assessed. Studies that did not fulfil all of the inclusion criteria were excluded.

Quality assessment strategy

Quality assessments were independently carried out on each study by two reviewers (SD and HZ) using the relevant version of the Critical Appraisal Skills Programme (CASP) quality assessment tool for systematic reviews and health economic evaluations.[22] We assessed the risk of bias of experimental studies using the criteria suggested by the Cochrane EPOC Group.[23] RCTs, CCTs and CBAs were assessed for generation of allocation sequence, concealment of allocation, baseline outcome measurements, baseline characteristics, incomplete outcome data, blinding of outcome assessor, protection against contamination, selective outcome reporting and other risks of bias using the Cochrane Risk of Bias tool.[24] For ITS designs, we planned to assess the independence of the intervention from

secular trends, the pre-specified shape of the intervention and if the intervention may have had an impact on data collection. These methodological assessments drew on the principles incorporated into the Cochrane EPOC guidelines for assessing intervention studies.[25] We used the quality assessment form produced by the National Institute for Health and Care Excellence (NICE) to critically appraise case series.[26] Any discrepancies were resolved by discussion or, if agreement could not be reached, by arbitration by the third reviewer (AS).

Analysis, data synthesis and reporting

Data were independently extracted onto a customized data extraction sheet in DistillerSR by two reviewers (SD or AK and HZ), and any discrepancies were resolved. To minimize the risk of bias, reviewers were not involved in the quality appraisal of their own studies.

A descriptive summary with data tables was produced to summarize the literature. A narrative synthesis of the data was undertaken. Where possible, and appropriate, meta-analysis was undertaken using random-effects modeling using Stata (version 14).[27]

Sensitivity and subgroup analyses, and assessment for publication bias

We planned to undertake sensitivity analyses by comparing the summary estimates obtained by excluding studies judged to be at high risk of bias, but were unable to do this because of insufficient data.

We planned to perform the following subgroup analyses, but were unable to undertake any of these due to insufficient data:

- Children (5-11 years) versus adolescents (12-17 years) versus adults (≥18 years)
- Conventional versus cluster versus rush versus ultra-rush protocols in SCIT
- Conventional in SLIT versus SCIT

- Three versus five years of treatment
- Different allergen doses (50μg versus 100μg versus 200μg of maintenance VIT)
- Bee versus wasp versus fire ant venom
- Patients with and without co-existent mast cell disorders.[28]

We were unable to assess publication bias through the creation of funnel plots due to the small number of studies but were able to use Begg's rank correlation test.[29]

Registration and reporting

This review has been registered with the International Prospective Register of Systematic Reviews (PROSPERO): http://www.crd.york.ac.uk/prospero/.http://www.crd.york.ac.uk/prospero/. The registration number is CRD42016035374. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used to guide the reporting of the systematic review: http://www.prisma-statement.org/ (Appendix 3; see online supplement)

RESULTS

Overview of results

Our searches identified a total of 16,950 potentially eligible studies of which 17 satisfied our eligibility criteria and were therefore included in this review (see Figure 2). The key characteristics and main findings of all included studies are detailed in Table 1 and the quality assessment of these studies is summarized in Tables 2-4. The main findings are discussed in more detail below.

Of the 17 included articles, five were systematic reviews;[30] [31] [32] [33] [34] two of these systematic reviews undertook meta-analyses.[29] [33] The remaining 12 studies comprised of five RCTs,[35] [36] [37] [38] [39] three CBAs [40] [41] [42] and four case series.[43] [44] [45] [46]

Four of the systematic reviews looked at the effectiveness of VIT,[30 31 32 34] two at safety[30 33] and one at cost-effectiveness.[32] Two of the RCTs looked at disease specific quality of life related issues in adults.[36 37] Two RCTs looked at children;[38 39] one RCT studied both children and adults.[34] One CBA solely focused on the safety of rush VIT protocol in adults,[41] a second CBA looked at the long-term follow-up of children following VIT[40] and the third looked at the effect of VIT on anaphylactic sting reactions.[42] Finally, four case studies investigated safety considerations.[43 44 45 46] All of the primary studies included in this review investigated SCIT.

Effectiveness of VIT as judged by the risk of systemic sting reactions

Twelve studies looked at the effectiveness of VIT. Four of these were systematic reviews, all of which were assessed to be of high quality. [30 31 32 34] The remaining studies were RCTs (n=5) [35 36 37 38 39] and CBAs (n=3). [40 41 42]

Systematic reviews

Boyle *et al.* systematic review included six RCTs and one quasi-RCT.[30] Three of the RCTs studied in this review also satisfied our eligibility criteria and these are therefore considered in detail below.[35 38 39] The others were excluded because they did not meet our inclusion criteria. These included: Brown *et al.* (2003),[47] which looked at the jack jumper ant, which was not an insect of interest in the protocol; Oude Elberink et *al.* (2006),[48] which focussed on the burden of treatment of carriage of an adrenaline (epinephrine) auto-injector compared to VIT, which was not an outcome of interest; and Golden *et al.* (2009) and Severino *et al.* (2008), which both included patients who had experienced large local reactions rather than a systemic reaction to an insect sting.[49 50]

The primary outcome of interest in Boyle *et al.* was systemic reaction rates to a 'field' or a challenge sting in patients during the follow-up period of VIT treatment.[30] The review concluded that VIT was effective in preventing subsequent systemic reactions to insect stings (risk ratio [RR]=0.10, 95% confidence

interval (CI) 0.03 to 0.28). They also found that VIT prevented large local reactions to a sting (RR=0.41, 95% CI 0.24 to 0.69).

The systematic review conducted by Dhami *et al.* on the management of anaphylaxis studied the effectiveness of VIT in preventing venom-triggered anaphylaxis.[31] This review included four systematic reviews (Ross *et al.*, 2010, Watanabe *et al.*, 2010, Boyle *et al.*, 2012 and Hockenhull *et al.*, 2012) and 23 individual studies of varying quality. It concluded that, although much of the evidence is of a low quality, the evidence did consistently suggest that VIT can significantly reduce the risk of systemic reactions in subsequent stings.

The systematic review by Hockenhull *et al.* concluded that VIT reduced the likelihood of future systemic reactions.[32] This review assessed the clinical and cost-effectiveness of a specific brand of VIT: Pharmalgen (ALK-Abelló). The original search strategy was to look at the effectiveness of Pharmalgen (ALK-Abelló) versus other non-VIT treatments, but this had to be modified as no studies were found matching the original objective; they therefore widened the criteria to include other forms of Pharmalgen VIT administration protocols. The quality of trials included in the review were overall judged to be at high risk of bias. The review concluded that although the evidence was poor, it suggested that Pharmalgen VIT reduced the risk of future systemic reactions.

Watanabe *et al.* carried out a high quality systematic review looking at the effectiveness of VIT in patients who presented with a systemic reaction to insect stings.[34] Four studies were included (Hunt *et al.*, 1973, Schuberth *et al.*, 1983, Valentine *et al.*, 1990 and Brown *et al.*, 2003) and a meta-analysis was performed, based on the Schuberth *et al.* and Valentine *et al.* studies, which demonstrated that there was a substantial reduction in the risk of systemic reactions occurring in children treated with VIT following an accidental sting (odds ratio (OR)=0.29 (95% CI $0.10 < OR < 0.87$)). The other two studies were judged to be at low risk of bias, but because of heterogeneity between studies they could not be included in the meta-

analysis. Overall, this systematic review concluded that VIT was effective and should be recommended for adults with systemic reactions and for children with moderate-to-severe reactions, but not for children who only experienced cutaneous manifestations of a systemic reaction.

In summary, the evidence from these four systematic reviews suggests that VIT is effective in reducing subsequent systemic sting reactions in both children and adults; all four reviews have however highlighted the low quality of evidence that this conclusion is based on.

RCTs

Five RCTs (Hunt *et al.*, Oude Elberink *et al.* 2002 and 2009, Schuberth *et al.* and Valentine *et al.*) also focussed on the effectiveness of VIT. [35 36 37 38 39]

Hunt *et al.* was a single blind RCT of 59 patients aged 15-69 years investigating VIT versus whole body extract (WBE) immunotherapy versus placebo; it was judged to be at high risk of bias.[35] After 6-10 weeks of treatment, patients were randomly selected for a sting challenge. Of the 19 patients receiving VIT, 18 were stung with only one (5%) systemic reaction. The WBE and placebo groups each had 20 patients from which 11 (64%) and 12 (58%) patients were stung, respectively. In both groups, there were seven systemic sting reactions (35%). There were significantly more systemic reactions to the sting challenge in the WBE and placebo groups when compared with the VIT group ($P<0.01$). There was no difference in effectiveness between the WBE and placebo group ($P=1.0$). The authors concluded that VIT was superior to both WBE and placebo in preventing further systemic sting reactions and recommended the use of VIT to prevent life-threatening systemic sting reactions.

The two Oude Elberink *et al.* RCTs, which primarily looked at quality of life, also reported on re-sting rates. In both studies, they randomized patients to VIT or adrenaline auto-injector. In the 2002 study, two

patients experienced a re-sting, one patient from the randomized control arm experienced a sting and developed a systemic reaction (1/38) which required use of an adrenaline auto-injector; one patient in the VIT group had a re-sting, but did not develop a systemic reaction. This patient was in the randomized VIT group.[36] In the 2009 study, of 29 patients whose index sting reaction was confined to systemic cutaneous reactions, five patients experienced a field sting: three in the VIT group and two in the adrenaline auto-injector group. None of these five patients experienced a systemic sting reaction.[37]

Schuberth *et al.* and Valentine *et al.* both looked at children with non-life-threatening sting reactions.[38 39] Both of these trials were judged to be at moderate risk of bias. They randomized children to VIT or no VIT and studied systemic sting reactions to bees and wasps in those experiencing accidental stings. Schuberth *et al*, who looked at 181 children with systemic sting reactions limited to cutaneous manifestations found no statistical difference in the number of systemic sting reactions following an accidental sting in the VIT and no treatment group.[36] They further found that no subsequent reaction was more severe than the original and in the no-VIT group of eight systemic reactions only one was as serious as the original. This led to their conclusion that children with primarily cutaneous manifestation to a sting were unlikely to experience a further systemic reaction following a re-sting. A total of 242 children were included in the Valentine *et al.* study. Of 45 children who experienced 55 stings, only one child in the VIT group experienced a systemic reaction to a field sting (1.8% systemic reactions/sting) compared to seven systemic reactions from 68 stings in 61 children who did not receive VIT (10.3% systemic reactions/sting) over a period of four years (RR=0.21, 95% CI 0.03 to 1.66, P=0.14).[37] Both studies concluded that VIT is not indicated in children with cutaneous manifestations only.

CBAs

The CBAs by Golden, Pasaoglu and Reisman *et al.* were all judged to be at moderate risk of bias.[40 41 42] Golden *et al* assessed the long-term effectiveness of VIT compared to no VIT in preventing systemic sting reactions in 512 children (aged 10-20) after an average of 3.5 years of VIT treatment. They found a

prolonged benefit in the treatment group as the VIT group experienced less systemic sting reactions (2 of 64 patients, or 3%) than the untreated patients (19 of 111 patients, or 17%; P=0.007).[40] This study suggested VIT was effective in children with moderate-to-severe reactions, but that VIT was not recommended in children who experienced mild reactions.

In contrast, the CBA by Pasaoglu *et al.* looked at the effectiveness of a seven day rush protocol of VIT in 18 patients.[41] Seven received bee VIT, seven yellow jacket VIT and four were controls. Of the 14 patients who received VIT, two experienced accidental stings (including a bee keeper who had multiple stings). No systemic sting reactions occurred. They concluded that a seven day rush protocol is effective.

The CBA by Reisman *et al.* looked at children and adults with anaphylaxis to stings from honeybee or yellow jacket or bald-faced hornets or paper wasps.[42] They looked at three groups and their subsequent reactions to accidental stings over a seven year period: those who had VIT, those who started VIT, but stopped prematurely and those without VIT. The group which took VIT for the recommended duration (mean 34 months) had 87 re-stings with only two systemic reactions (1%). The group which stopped VIT prematurely (duration of VIT one month to 6.5 years) experienced 61 re-stings with 11 systemic reactions (17%). The group with no-VIT experienced 40 re-stings with 14 systemic reactions (35%). They concluded that VIT was almost 100% protective against subsequent sting triggered anaphylaxis.

Meta-analysis of the Reisman and Golden *et al.* studies demonstrated an overall substantial protective effect of VIT against subsequent systemic reactions (OR=0.08, 95% CI 0.03 to 0.26) (see Figure 3).

Impact on disease specific quality of life

Systematic reviews

The systematic review by Boyle *et al.* drew on two RCTs by Oude Elberink *et al.* 2006[48] and 2009,[36] the latter of which is also included in this review and discussed below. This systematic review found that VIT was associated with a significant improvement in disease specific quality of life after one year of VIT (RR=7.11, 95% CI 3.02 to 16.71).[30]

RCTs

Two RCTs (Oude Elberink *et al.*, 2002 and Oude Elberink *et al.*, 2009) assessed the impact of VIT on disease specific quality of life measured using the Vespid allergy Quality of Life Questionnaire (VQLQ).[36] [37] Both of these studies looked at patients allergic to yellow jackets. The Oude Elberink *et al.* (2009) RCT study looked at the impact on disease specific quality of life in patients who had experienced only cutaneous manifestations of a systemic reaction; patients were randomized to VIT or an adrenaline auto-injector. The VQLQ score of patients in the VIT arm improved significantly (mean change 0.83 (SD 0.87); P<0.01), in contrast to patients randomized to an adrenaline auto-injector whose scores deteriorated (mean change -0.42 (SD 0.64)), resulting in an overall risk difference of 1.25 (95% CI 0.63 to 1.87). The study suggested that all adults, including those who only had dermal reactions as a systemic allergic reaction to yellow jacket stings, should be considered for VIT and sole treatment with an adrenaline auto-injector should be avoided.[37]

A similar earlier RCT (2002) by the same research team looked at disease specific quality of life in patients who had experienced a systemic reaction after a yellow jacket sting that was not solely confined to the skin.[36] The findings of this study were confirmed in their 2009 study, whereby there was a clinically relevant improvement in disease specific quality of life in patients treated with VIT. The mean change in VQLQ score in the group randomized to VIT was 1.07 (95% CI, 0.68 to 1.46), and this improvement was also statistically significant (P <0.0001) compared with that seen in the group randomized to the adrenaline auto-injector, in which this change was –0.43 (95% CI, –0.71 to –0.16) with a mean difference

between the two groups of 1.51 (95% CI, 1.04 to 1.98). Of every three patients treated with VIT, two patients experienced a clinically relevant important improvement in their disease specific quality of life. Overall, it was found that 72% of patients benefited from VIT, this corresponding to a number needed to treat (NNT) of 1.4. Meta-analysis of these studies demonstrated an improvement in disease specific quality of life (1.41, 95% CI 1.04 to 1.79) (see Figure 4). The Begg test (P=0.317) showed no evidence of publication bias.

Safety

Systematic reviews

The review by Boyle *et al.* assessed the safety of VIT, six trials reported on this outcome. They concluded that VIT carries a small but significant risk of systemic reactions (RR=8.16; 95% CI 1.53 to 43.46).[30] They further looked at 11 observational studies for safety and found that systemic adverse events occurred in 14.2% of participants treated with bee venom VIT and 2.8% of those treated with wasp venom VIT.

The systematic review by Park *et al.*, which was assessed as of a low quality, looked at identifying the frequency and types of adverse events associated with different types of bee venom therapy; in doing so they included VIT, but also acupuncture.[32] It included 145 studies consisting of 20 RCTs, 79 audits and cohort studies, 33 single case studies and 13 case series. Two RCTs on VIT were included (Oude Elberink *et al.* 2002 and 2006), one of which we have included in this review (2002), and 63 case series/cohort studies. From 46 VIT case series/cohort studies, the median incidence of adverse events was 28.9%. Of these, 50.4% had systemic reactions and 10.0% large local reactions. 35.8% showed just local reactions and 3.9% had "other" reactions.

RCTs

Of the RCTs included in this review two reported very limited information on safety considerations of VIT and this is included in Table 2.[35 37]

CBAs

The CBA conducted by Pasaoglu *et al.* evaluated the safety of a rush VIT protocol lasting on average seven days and monitored for local and systemic reactions during both the induction and maintenance phases of VIT treatment over a one year period. The study concluded that rush VIT was safe and associated with a low risk of systemic reactions (four systemic reactions from a total of 469 injections, this equating to a 0.85% risk per total number of injections) and that this treatment approach could therefore be considered for patients requiring rapid protection such as those with a high risk of subsequent stings (e.g. bee keepers and their families). The risk of systemic reaction to VIT was related to the type of venom used with vespid venom being better tolerated than bee venom.[41]

Case series

Four large case series (i.e. Brehler, Mosbech, Ruëff and Stoevesandt *et al.*) met our eligibility criteria. The Brehler *et al.* study looked at the safety implication of shortening the 7-9 day rush protocol to two days as well as increasing the initial dose of venom administered. No anaphylactic reactions were seen in 1055 VIT treatments in 966 patients; most adverse events were mild and none needed treatment with adrenaline. Overall, they concluded the two day rush protocol is safe and the risk of systemic reactions is rare when the number of injections administered is reduced from 20 subcutaneous injections to nine.[43]

The Mosbech *et al.* case series included 840 patients, was conducted in 10 European countries and assessed the safety of VIT in both the build-up and maintenance phases in patients allergic to honey bees, wasps and paper wasps.[46] Treatment protocols were not standardised across centres and conventional, rush and cluster protocols were used. 782 patients received VIT with one venom and 58 with two venoms respectively. A total of 26,601 injections were administered and 299 systemic side-effects occurred (1.2% of injections). Most of these reactions were mild with only one-third needing treatment. One patient required adrenaline. Adverse events were more frequent during the dose-increase phase than the maintenance phase (mean: 1.9% vs. 0.5% of all injections). Other factors were identified that resulted

in an increase in adverse events. These included female gender, rapid dose-increase regimens, and VIT with bee-venom extract. They concluded that systemic side-effects may occur in up to 20% of patients, but are usually mild.

The Ruëff *et al.* case series looked at measuring the severity of reactions according to the Ring and Meßmer[51] tool during the build-up phase of VIT, which required emergency intervention. They evaluated conventional, rush and ultra-rush protocols for bee and vespid immunotherapy. The study identified a number of risk factors that led to a higher frequency of adverse events requiring emergency intervention during VIT; these included bee venom immunotherapy and using rush and ultra-rush protocols. The authors concluded that patients receiving bee VIT warrant closer monitoring than those patients receiving VIT to other insects.[44]

Stoevesandt *et al.* looked at the incidence of systemic reactions during 818 build-up cycles (rush five day or ultra-rush three day inpatient treatment protocol) and the severity of VIT related anaphylaxis was graded according to the WAO classification system.[20] The data from this study indicated that rush protocols were safe with very low numbers of patients suffering from moderate-to-severe systemic anaphylaxis based on the WAO classification system (i.e. 673 (82.3%) of 818 documented build-up cycles were tolerated without complications). However, the authors acknowledged that due to low numbers of moderate-to-severe anaphylaxis reactions (0.8% of patients in the total cohort), robust statistical conclusions could not be drawn.[45]

Health economic analysis

We found only one study, the review by Hockenhull *et al.*, that looked at the economic evaluation of VIT – a modeling study looking at the cost-effectiveness of VIT for the treatment of bee and wasp venom allergy.[32] The study compared VIT with Pharmalgen plus high dose H_1-antihistamines plus adrenaline

auto-injectors versus high dose H1-antihistamines plus adrenaline auto-injectors and avoidance advice only. It found that VIT was not cost-effective in the general population (incremental cost-effectiveness ratio (ICERs) of £18 million and £7.6 million per quality adjusted life year (QALY) against high dose H1-antihistamines plus AAI and avoidance advice only, respectively), but more effective than other treatment options and cost saving in patients likely to be stung more than five times per year such as bee keepers. This one study, despite the fact that it was based largely on expert opinion and plausible assumptions, resulted in the suggestion that VIT for bee and wasp venom allergy is only cost-effective from a UK National Health Service (NHS) perspective for very high risk groups likely to be exposed to multiple exposures to venom per year such as bee keepers. The modelling analysis suggests plausible ranges of exposure to such events to qualify a patient as a member of a high risk group and explores a wide range of sensitivity and scenario analyses to demonstrate the robustness of its findings.

We were unable to find any primary studies assessing the cost-effectiveness of VIT for venom allergy.

DISCUSSION

Statement of principal findings

This systematic review has found a modest body of evidence of moderate quality which suggests that VIT is effective in reducing subsequent severe systemic sting reactions in both children and adults and that this treatment modality can have a significant beneficial impact on disease specific quality of life when compared with carrying an adrenaline auto-injector The available data on the safety of VIT suggests that although adverse events occurred during both the build-up and maintenance phases, the vast majority were relatively mild with adrenaline only being needed very infrequently and – importantly – no fatalities being recorded. We found no primary evidence on the cost-effectiveness of VIT; the one modelling study found that VIT would be cost-effective in high risk groups or if disease specific quality of life was taken into consideration.

Strengths and limitations

There are a number of strengths to this systematic review. In particular, we searched a broad array of databases for published and in progress research, and also consulted with a panel of international experts in an attempt to identify unpublished evidence. Furthermore, our systematic review was conducted according to a pre-defined, published protocol with no deviations from this.[10]

The limitations of this review also need to be considered. Key here were the limited number of studies identified, despite the fact that we also included CBAs. The review is further limited by the low quality of the primary studies. Furthermore, two of the RCTs included in this systematic review (i.e. Valentine and Schuberth) excluded patients who had life-threatening systemic reactions to the initial sting – the group of patients who would be most likely to benefit from VIT.[37 38] Furthermore, it should be noted that in both of these studies, the definitive identification of the culprit insect responsible for the accidental sting was not possible. Thus, whether the child was stung by the insect responsible for the index sting which resulted in a systemic reaction was unknown. This is in contrast to the Hunt trial in which patients were sting challenged by the insect they were known to be allergic to.[36] As this review did not include the jack jumper species of ants the double-blind placebo controlled RCT by Brown *et al.* (2003) could not be included in this review.[46] This study concluded that VIT significantly reduces the risk of serious subsequent sting reactions from the jack jumper ant ($P<0.0001$). Only one study assessed the cost-effectiveness of VIT and this was limited to looking only at one product and based on an economic modeling analysis.[31] Finally, as with any systematic review there is the possibility that we missed some studies.

Interpreting the results of this review in the context of the wider literature

In undertaking this systematic review, we sought to identify all relevant previous systematic reviews. Our findings are broadly in accordance with these previous reviews, namely that VIT is beneficial, but that this judgement is limited by the paucity and quality of the relevant evidence base. Guidelines for the long term management of allergic reactions to venom advocate the use of VIT in patients who have experienced

moderate to severe systemic reactions.[52 53] In agreement with our findings, VIT is not recommended in children whose index reaction was confined to cutaneous manifestations. SLIT remains an experimental treatment in VIT; no SLIT studies satisfied our eligibility criteria.

Implications for policy, practice and research

The results of our review indicate that people who experience moderate-to-severe systemic reactions to venom are likely to benefit from treatment with VIT. This benefit consists of a reduction in the frequency and severity of subsequent systemic reactions following future stings and/or a clinically relevant improvement in disease specific quality of life. We found very limited evidence on the cost-effectiveness of VIT for venom allergy which thus needs to be interpreted cautiously; the available evidence, from a single economic modeling study, indicated that VIT is likely to be cost-effective in patients at high risk of future sting reactions and/or if quality of life is impaired.

Given the paucity of high quality evidence uncovered, consideration needs to be given to undertaking high quality studies investigating the effectiveness and cost-effectiveness of VIT. RCTs in both adults and children would be of interest, but due to the risk of life-threatening reactions in untreated patients, RCTs may not be considered ethical by some clinicians and furthermore they may not be approved by some ethics committees. It seems unlikely therefore that there will be further placebo controlled trials of VIT preparations in the foreseeable future. As for VIT regimens, at present many protocols for VIT are used discretionally at treatment centers with varying build-up and maintenance doses with no defined duration of treatment. These protocols vary from conventional (12 weeks) to one day ultra-rush protocols during the build-up phase. Time taken to reach the maintenance dose will be dependent on the build-up phase and varies across centers. Trials should therefore be considered comparing different VIT regimens, doses and durations of VIT. Whether trials of SLIT for venom allergy are indicated is debated.[48 54] More standard reporting of VIT associated adverse events is needed in order to allow comparison across studies. Primary studies of cost-effectiveness are also needed

Conclusions

The limited available evidence suggests that VIT is effective in reducing subsequent severe systemic sting reactions and in improving disease specific quality of life. VIT proved to be safe and no fatalities were recorded in the studies included in this review. The cost-effectiveness of VIT needs to be established.

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Figure 1: Conceptualization of systematic review of allergen immunotherapy for insect venom allergy (10)

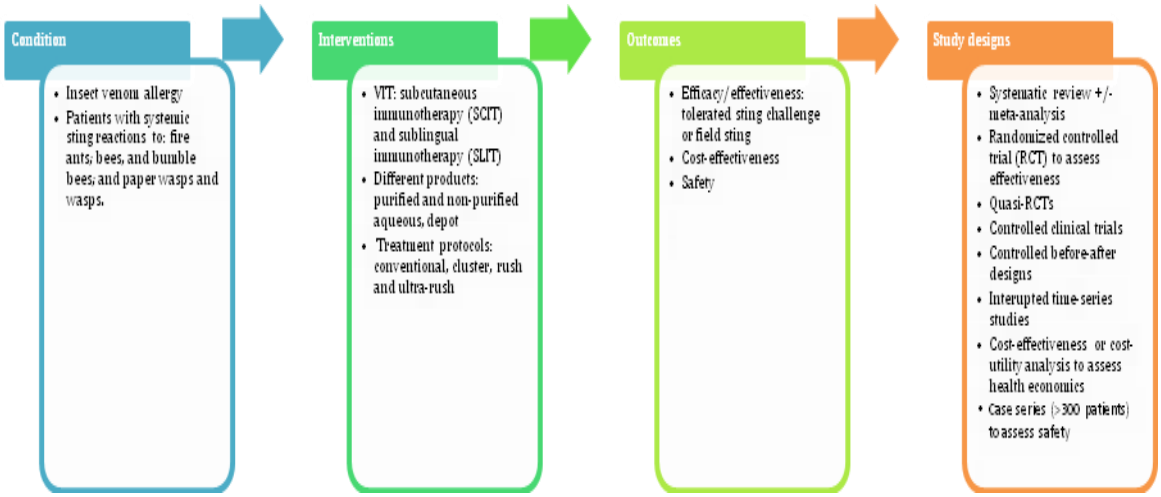


Figure 2: PRISMA diagram: allergen immunotherapy for insect venom allergy

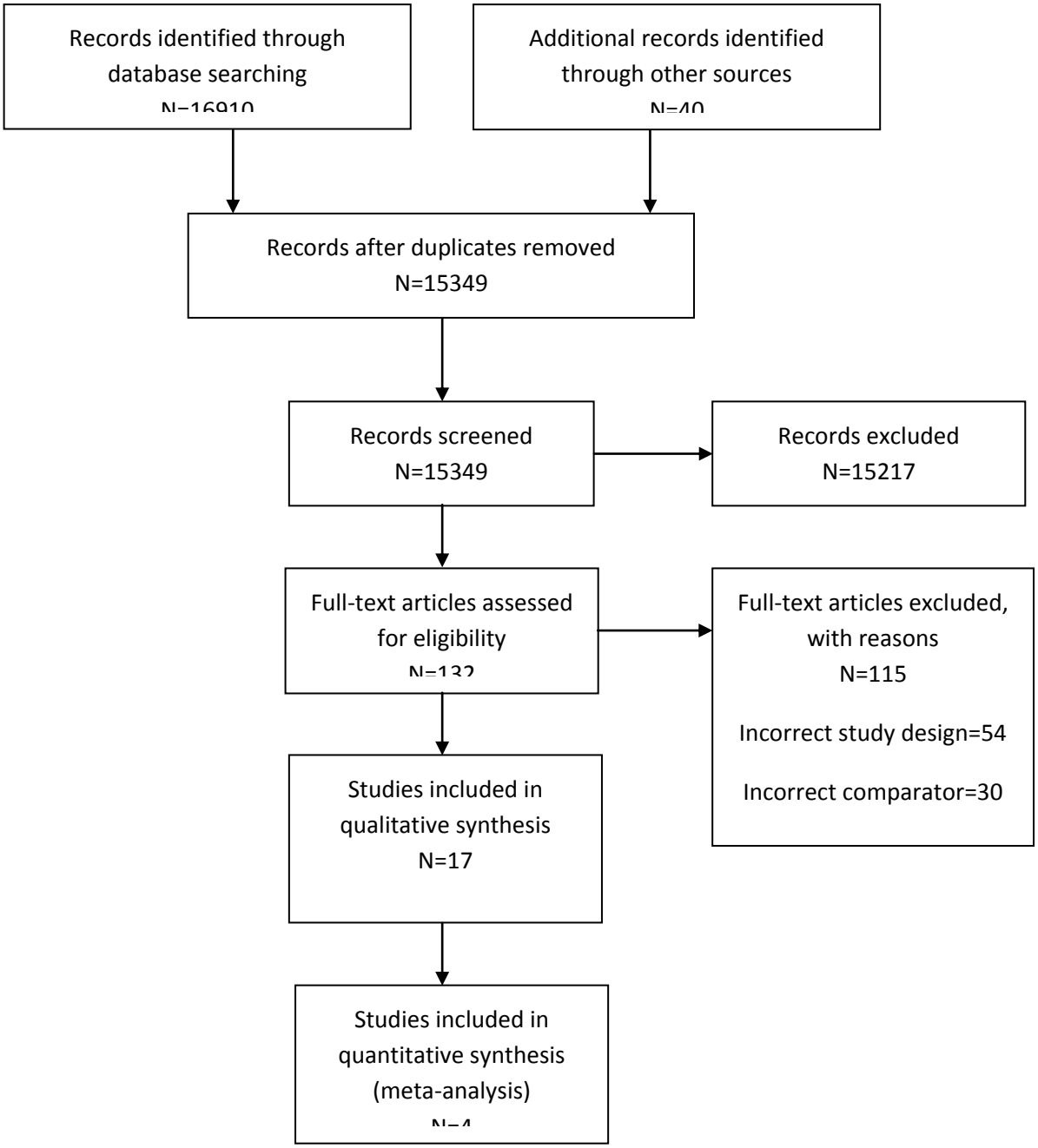


Table 1: Characteristics of included studies

Author/ year/Article title/ Country	Study design	Number of studies(N)/subjects included(n)/age	Participants - physician confirmed diagnosis of systemic sting reaction to a venom sting from	Outcome of interest	Comparators (intervention/controls)/route of administration	VIT using different products	Quality	Main outcome	Comment
Primary outcome: Efficacy of VIT									
Boyle *et al,* 2012 Venom immunotherapy for preventing allergic reactions to insect stings: A Cochrane systematic review Worldwide	SR of RCT's and quasi-RCT's	All ages eligible N=7 n=392	Physician confirmed diagnosis of systemic reaction to bees, wasps or fire ants	Primary: Systemic reaction to a 'field' insect sting or a sting challenge during treatment. Fatal SR due to a field or challenge insect sting over the same period. Secondary: Large local reactions to a field sting or sting challenge	Standardized venom extract vs placebo, no treatment or back-up treatment	SLIT 1 trial SCIT 6 trials	High	6 RCT's and 1 quasi-RCT included Included ant, bee, and wasp immunotherapy in children and adults with previous systemic or large local reactions to a sting, using sublingual (one trial) or subcutaneous (six trials) VIT VIT is effective in preventing systemic allergic reaction to an insect sting. Fewer patients treated with VIT	Undertook additional analysis of 11 observational studies to estimate risk of adverse events

				during treatment or during the 10 years following treatment. Quality of life or anxiety score, assessed using a published scale				had a severe systemic reaction to a subsequent sting compared with untreated patients risk ratio [RR] 0.10 (95%CI 0.03, 0.28). Unable to confirm whether VIT prevents fatal reactions to insect stings Increased risk of systemic adverse reactions to treatment: RR=8.16 (95%CI 1.53, 43.46)	
Dhami *et al,* 2013 Management of anaphylaxis: a systematic review Worldwide	SR RCTs, quasi-RCTs, CBAs, ITS and case series	N=55; but only 16 relevant to VIT	Patients with an anaphylaxis reaction to venom	Long term management of venom anaphylaxis by use of VIT			High	VIT reduces the risk of subsequent systemic reactions to venom stings	
Golden *et al* 2004, Outcomes of allergy to insect	CBA	n=1033	Allergy to bees or paper wasps	Outcome of allergic reactions to stings 10 to 20 years after VIT or no VIT in children	VIT versus no VIT	SCIT	Low	Between 1978-85, 1033 of children, 356 received VIT. 1997-2000 postal and telephone surveys were used to assess the long term outcome.512	

stings in children, with and without venom immunotherapy. USA								(50%) patients replied. VIT results in significantly lower sting reactions. This prolonged benefit seen is children 10 to 20 years after Rx is greater than that seen in adults	
Hunt *et al,*1978. A controlled trial of immunotherapy in insect hypersensitivity . USA	RCT Single blind	n=59 Age= 15-59 years	Physician confirmed diagnosis of systemic sting reaction to a venom sting from Honey bee or, yellow jacket. Patients with a history of a generalized allergic reaction to a sting included, some had a previous anaphylactic reaction to a sting.	Tolerance to a challenge sting of the insect they were most sensitive to if they tolerated a venom dose greater than that found in a sting.	Standardized venom extract vs placebo or whole body extract. Three matched groups were given placebo, whole-body extract or venom immunotherapy.	SCIT; semi-rush protocol	Low	Venom group after receiving a dose of 100mcg were sting challenged. 18 stung, one had mild urticaria. 1 patient was not challenged as failed to tolerate treatment Whole-body extract group, of 11 patients 7 were stung, 64% had systemic symptoms to the challenge. Placebo group, of 12 patients 7 were challenged and 58% had systemic symptoms to the sting. Last two groups no statistical difference but	Of 59 patients 5 successfully achieved desensitization with venom immunotherapy Advocate use of Venom immunotherapy over whole-body extract for the prevention of life-threatening reactions to

								significantly greater than the venom treated group, P<0.01. Control arm of study was aborted when second patients experienced a severe systemic reaction 14 patients who were treatment failures from the placebo and whole-body extract group and a further 17 patients who were not challenged were then given venom and stung. Of these 1 patient had urticaria following sting challenge.	insect stings.
Park *et al,* 2015. Risk associated with bee venom therapy: a systematic review and meta-analysis.	SR	N=145 20 RCTs, 79 audits and cohort studies, 33 single case-studies, 13 case -series	Any user of bee venom therapy	Frequency and type of adverse event to bee venom therapy	Safety considerations, all study types included	Bee venom acupuncture, bee sting acupuncture, conventional VIT, cluster VIT, rush VIT, ultra-rush VIT, SIT, rush specific immunotherapy .	Low	2 RCTs included which look at VIT, Oude Elberink 2002 and 2006, no systemic AEs are reported. 63 case series/cohort studies looked at VIT and showed prevalence of AEs ranged from 0.0%	Most of the studies in this SI do not meet our inclusion criteri and did not look at VIT.

Worldwide								to 90.63%. In the 46 VIT studies the median AEs was 28.7%, these include SRs (50.37%), LR (35.8%), LLR (9.99%)	
Pasaoglu *et al,* 2006. Rush Hymenoptera venom immunotherapy is efficacious and safe. Turkey	CBA	n=18 Age 18-53 7 treated with vespula venom 7 treated with honey bee venom 4 control group	Physician confirmed diagnosis of a systemic sting reaction to yellow jacket or honeybee	Side-effects of Rush VIT Clinical response	VIT versus control group	SCIT; rush	Low	7 day rush VIT protocol followed as inpatients.14 patients received 469 injections in 1 year, 240 for bee venom, 229 for yellow jacket. 4 systemic reactions occurred(0.85%) in 1 patient to bee venom during the build-up phase. Reactions treated with adrenaline corticosteroids, antihistamines, bronchodilators.1 1 late local reactions occurred (2.34%) during the maintenance period, 8 to bee venom 3 to yellow jacket. No Rx was needed or dose reduction. No fatal or life threatening reactions. Rush VIT is safe	2 patients experienced fiel stings, one patient a bee keeper experienced multiple stings, no systemic reactions occurr

								and effective	
Reisman *et al*, 1985. Stinging insect allergy: Natural history and modification with venom immunotherapy. USA	CBA	n= 271 Age= 4 -83	Sting anaphylaxis to honeybee, yellow jacket, bald-faced hornet and Polistes venoms	The natural history of sting anaphylaxis and its modification with VIT	VIT or no VIT or premature discontinuation of VIT	SCIT conventional of rush		127 patients received VIT for 6 months to 9 years. 39 (31%) honeybee venom, 51(40%) yellow jacket venom, 26 (20%) honeybee and yellow jacket venoms, 7 (5%) multiple vespid venoms, 2 received multiple vespid and honeybee venoms, 1 hornet venom, and 1 Polistes venom. Most received 50ug maintenance dose at 4-6weeks. 87 re-stings in 48 patients, 2 SRs. No VIT group (n=56), 2 months to 12 years after index sting, 40 re-stings in 28 patients, 14 SRs. 88 patients discontinued VIT prematurely, after 1 month to 6.5 years. 61 re-stings in 41 patients, 11 SRs 1 month to 6	Maintenance dose 50ug Not sure of identity of insects in re-stings as accidental

								years after stopping VIT. Conclusion: VIT almost completely protective of a subsequent anaphylactic reaction. Re-sting SR, 1% in VIT group, 35% in no VIT group, 17% in premature discontinued VIT group.	
Schuberth *et al* , 1983. Epidemiologic study of insect allergy in II. Effect of accidental stings in allergic children. USA	Comprehensive cohort design includes an RCT	n=181 Age=3-1 6	Non–life threatening systemic reactions to: Bees, wasps, yellow jackets, yellow and white faced hornets	Blood samples for antibody titres, yearly skin tests and toxicity studies, skin tests, antibody measurements and accidental stings	VIT or no treatment	SCIT	Moderate	Children were randomised to VIT or no VIT, ratio of 1:1.5. Those who didn't want to be randomised chose their own Rx. The results for randomised and non- randomised are not presented separately. Accidental field stings in 2 years: 28 in 17 VIT patients and 74 in 47 no VIT patients. SRs were low in both groups and no statistical difference shown. No reaction was	Children only included with non-life threatening systemic reactions. Those with respiratory or cardiovascula symptoms were given VIT. Accidental sting not sure if stung by insect they

								more serious than the index reaction. 7 of 9SRs resolved without epinephrine. Results indicate that most children with cutaneous manifestations after a sting reaction will not get a re-sting so VIT is not indicated.	were allergic to
Valentine *et al,* 1990. The value of immunotherapy with venom in children with allergy to insect stings. USA	Comprehensive cohort design includes an RCT	n=242 Children age 2-16 68 VIT, 174 did not About half were randomized others parent/patient chose treatment	Physician confirmed diagnosis of a systemic sting reaction to bees or wasps	Accidental stings during 4 years were evaluated	VIT versus no VIT	SCIT	Moderate/Low	Randomisation ratio of 1.5 to 1.Group1a no VIT=61, 1ba VIT=45. Non randomised: 2a no VIT=113, 2b VIT=23. VIT group of 45 there were 55 stings in 45 patients, 1SR. NRVIT of 23 there were 29 stings in 12 patients, no SRs. Rno VIT of 61 there were 68 stings in 21 patients, 7SRs. NR no VIT group of 113, there were128 stings in 59 patients, 11	Systemic reactio confined to the skin Only 18.6% of children who were not treate went on to have subsequent systemic sting reactions.

								SRs. Conclude that using VIT for children with mild systemic reactions is not justified but should be used in those with life threatening reactions	
Watanabe *et al*, 2010. Specific immunotherapy using Hymenoptera venom: systematic review. Brazil	SR	N=4, n=2273 Children and adults	Anaphylaxis to sting reaction plus positive skin test to any hymenoptera insects	Change in clinical reaction following sting or field challenge	Venom immunotherapy vs. placebo or no treatment		High	Risk of systemic reactions after specific immunotherapy was evaluated using odds ratios plus their 95% confidence intervals. It was appropriate to do meta-analysis of 2 trials in children which showed OR=0.29 (95%CI 0.10,0.87) for systemic reactions after further accidental stings in VIT treated children. No indication for VIT in children who have only had a cutaneous reaction following a sting. Conclude that	Lack of allocatio concealment an the act that the trials were not double-blind ma have contribute to over-estimati of the treatment effect

								specific VIT should be recommended for children with previous moderate-severe reactions and adults with previous systemic reactions.	
Secondary outcome: Disease specific quality of life									
Oude Elberink *et al*, 2002. Venom immunotherapy improves health-related quality of life in patients allergic to yellow jacket venom. Netherlands	Comprehensive cohort design includes an RCT	n=74 randomised; N=74 non-randomised Age:18-65	Yellow jacket wasps	Health related quality of life	Comparison of HRQL outcomes measured with a disease specific quality of life instrument. Vespid Allergy Quality of life questionnaire in patients allergic to yellow jacket treated with VIT or adrenaline auto-injector	Semi-rush protocol	Moderate	VQLQ score calculated from mean of 14 items, range of 1, severe impairment of HRQL to 7, no impairment. Mean change in VQLQ score was calculated. Randomised group, pre-treatment scores were similar, results from 34 VIT group and 35 adrenaline auto-injector group. Mean VQLQ score improved more in the VIT group, from 3.28 to 4.35 (P<.0001) compared to the adrenaline auto-injector group, score decreased	Half of patients refused randomisation and 80% wanted to start VIT Patients choosing VIT had greater improvement in scores. Patients randomised to treatment with

								from 3.34 to 2.9, (P<.003). Mean change in VIT group is 1.07(95% CI 0.68 to 1.46), mean change in adrenaline auto-injector group is _0.43 (95% CI -0.71 to -0.16), mean difference between the 2 groups is 1.51 (95%CI 1.04-1.98) Non-randomised group: pre-treatment VQLQ scores similar. After 1 year VIT group, VQLQ score improved from 2.84 to 4.29, (P< .0001) and no significant change in the adrenaline auto-injector group. Expectation of outcome: mean pre-treatment scores similar, after 1 year R-VIT group (P<.0001), improved from 5.66 to 2.88 and NR-VIT group from 5.45 to 2.88. In the adrenaline auto-injector	an adrenaline auto-injector had a deterioration in score

								groups there was no change NNT=1.4 VIT results in clinically significant HRQL improvement, after 1 year of Rx, in males and females, anxious patients and not, those stung recently and more than a year before 2 patients from the VIT groups dropped out due to side-effects	
Oude Elberink *et al*, 2009. Immunotherapy improves health-related quality of life of adult patients with dermal reactions following yellow jacket stings. Netherlands	Comprehensive cohort design includes an RCT	Randomised n=29, VIT=15, adrenaline auto-injector =14 Non-randomised n=26, VIT=11, adrenaline auto-injector =15	Yellow jacket wasps	Health related quality of life	Comparison of HRQL outcomes measured with a disease-specific quality of life instrument- Vespid Allergy Quality of life questionnaire (VQLQ) in patients allergic to yellow jacket venom treated with VIT or with an adrenaline auto-injector in an open label RCT.	Semi-rush protocol	Moderate	HRQL was measured using the Vespid allergy Quality of Life Questionnaire (VQLQ) Anxiety was measured using the Spielberg State Trait Anxiety Inventory (STAI) All patients were given an adrenaline auto-injector on diagnosis, those who agreed were randomised to VIT	Systemic reaction confined to the skin Patients with mastocytosis excluded

								or adrenaline auto-injector and the adrenaline auto-injector in the VIT group was relinquished on reaching the maintenance dose. Those who did not want to be randomised chose VIT or adrenaline auto-injector. After 1 year of Rx the measures were retaken. VQLQ score at beginning 4.89 Responses from R-VIT=15, R-Epi=13, VIT VQLQ score improved from 5 to 5.84 (.002), R-Epi scores went from 4.95 to 4.53 (P=0.045). Mean change in VQLQ score in R-VIT 0.83 (SD 0.87, P=0.000). R-Epi mean difference 0.42 (SD 0.64) Overall difference 1,25 (95% CI 0.63-1.87) NR-VIT=10, NR-VIT=8. VQLQ in NR-VIT improved	

								from 4.6 to 5.52 (P=0.008) and did not change significantly in the NR -Epi group (4.88 and 4.86) HRQL improves significantly with VIT compared to adrenaline auto-injector, whose HRQL deteriorated.	
Secondary outcome: Safety									
Brehler *et al*, 2000. Safety of a two-day ultra-rush insect venom immunotherapy protocol in comparison with protocols of longer duration and involving a larger number of injections. Germany	Case series	N=966 Bee VIT=122 Wasp VIT=933 Age = 2 to 84	Bee or wasp allergy	Does shortening the 7 to 9 day rush protocol to 2 days and increasing the initial administered dose increase the incidence and severity of side-effects	Safety	SCIT Rush	Low	Cohort 1 : n=317, 20 injections over 7-9 days Cohort 2: n= 335, 72.2% had 10, 11, 12 or 14 injections, mainly 3 to 5 days Cohort 3: n=403, 9 injections over 2 day protocol, No statistical difference between the cohorts at the beginning No life threatening anaphylactic	

								reactions occurred 224 (21.2%) patients had an adverse reaction; 124 (11.8%)-generalised skin reactions; 160 (15.2%) systemic reactions: 7 (0.7%) had a drop in BP of less than 20% but did not need epinephrine Overall demonstrates the safety of a 2 day VIT protocol	
Mosbech *et al*, 2000. Side-effects of insect venom immunotherapy: results from an EAACI multicenter study. Europe	Case series Multi-centre	N=840 457 males and 383 females Vespula-venom 71 Honey bee venom 27% mean age 41 years (range: 5±77 years)	Honey bee, wasp or paper wasp allergy	Analyze the character and frequency of side effects and risk factors of VIT	Safety	SCIT Conventional, rush and cluster protocols. Protocols were not harmonised across centres		417 males and 365 females, were treated with one venom extract. Fifty-eight patients had two venom-extract treatments concomitantly. A total of 26,601 injections were given, 23 602 to patients receiving treatment with only one extract A total of 299 systemic side-effects were reported; of	When analyzed separately, female sex, rapid dose-increase regimens, and treatment with bee-venom extract seemed to increase the risk of side-effects. Patients with pre-existing allergic rhinitis

								these, 280 occurred in patients treated with one venom. 20% of the patients had at least one systemic reaction and 1.2% of injections elicited reactions. The majority of systemic symptoms were mild, one-third required treatment. Oral antihistamine was the drug most frequently used. A drop in BP in 9 cases, but only one patient received adrenaline. This patient and one other patient suffered fainting/collapse. The frequency of reactions was higher during the dose-increase phase than the maintenance phase (mean: 1.9% vs 0.5% of all injections).	more often had side effects (29% vs 19%, P<0.05).The following factors did not influence the risk of systemic side-effects in either separate analyses or logistic regression: age, pre-existing asthma or urticaria, severity of original insect sting symptoms, time interval between sting and symptoms, number of systemic sting reactions, progression in sting reactions, type of extract (with or without aluminium hydroxide), and number of

									venom extracts used for treatment (one or two).
Ruëff *et al*, 2010. Predictors of side effects during the build up phase of venom immunotherapy for Hymenoptera venom allergy: The importance of baseline serum tryptase. Europe	Case series	N=680	Honeybee or vespid allergy	Emergency intervention during the build-up phase of VIT	Safety	Conventional, rush and ultra-rush	Low	27.5% had a Grade III or IV index field sting. 24.9% had prophylactic anti-allergy Rx before VIT. Conventional 10,3%; rush 55%; ultra-rush 34.7%. Emergency intervention required in 8.4%. Emergency Rx more likely with bee venom; those with positive IgE to venom; rush and ultra-rush.	Patients undergoing VIT to bee venom need closer observation
Stoevesandt *et al*, 2014. Risk stratification of systemic allergic reactions during Hymenoptera	Case series	n=818 Age 7-84 Honeybee=160(19.6%) Vespula=658 (80.4%)	Physician confirmed diagnosis of a systemic sting reaction to honey bees or wasps	Systematically evaluate the time course and clinical symptoms of VIT related systemic reaction	Safety	Rush	Low	In patient rush protocol. 220 (22.5%) 5 day protocol, 592(72.45%) 3 day protocol. 673 (82.3%)of 812 injections were well tolerated	Severity of SR correlates with severity of index reaction according to Ring classification. 23 Grade I;3 Grade II; 2

venom immunotherapy build up phase. Germany								35(4.3%) LLR Rx with oral anti-histamines 71(8.7%) subjective symptoms, 31 of whom Rx with oral or iv anti-histamines 28 had objective anaphylaxis, 23 Grade I; 3 Grade 2: 2 Grade 4. Confirmation of safety of rush protocols. 3.4% rate of objective VIT-related anaphylaxis is low if we include subjective cases then 12.1% more in line with other studies	Grade III Isolated urticarial often developed 8 hours after the last injection, a case for hospitalisation during up-dosing.
Secondary outcome: Health economic analysis									
Hockenhull *et al*, 2012. A systematic review of the clinical effectiveness and cost-	SR RCTs Quasi-RCTs Health economic modelling	N=9 n=1065	Bee or wasp venom allergy	A systematic review of the clinical effectiveness and cost effectiveness of Pharmalgen for the treatment of bee and wasp			High	Evidence available poor but indicates reduction of future stings following the use of Pharmalgen VIT	

effectiveness of Pharmalgen(R) for the treatment of bee and wasp venom allergy. Worldwide				venom allergy					

Table 2: Quality assessment of systematic reviews

Author, year	Focused question	Inclusion of appropriate studies	Inclusion of eligible studies	Quality assessment of studies	Appropriateness of synthesis	Overall results of review	Applicability to local populations	Considering all relevant outcomes	Benefits vs. harms/costs	Overall quality assessment
Boyle, 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Dhami 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Hockenhull, 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Park, 2015	No	No	Yes	Yes	Yes	Unclear	No	Yes	Yes	Low
Watanabe,2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High

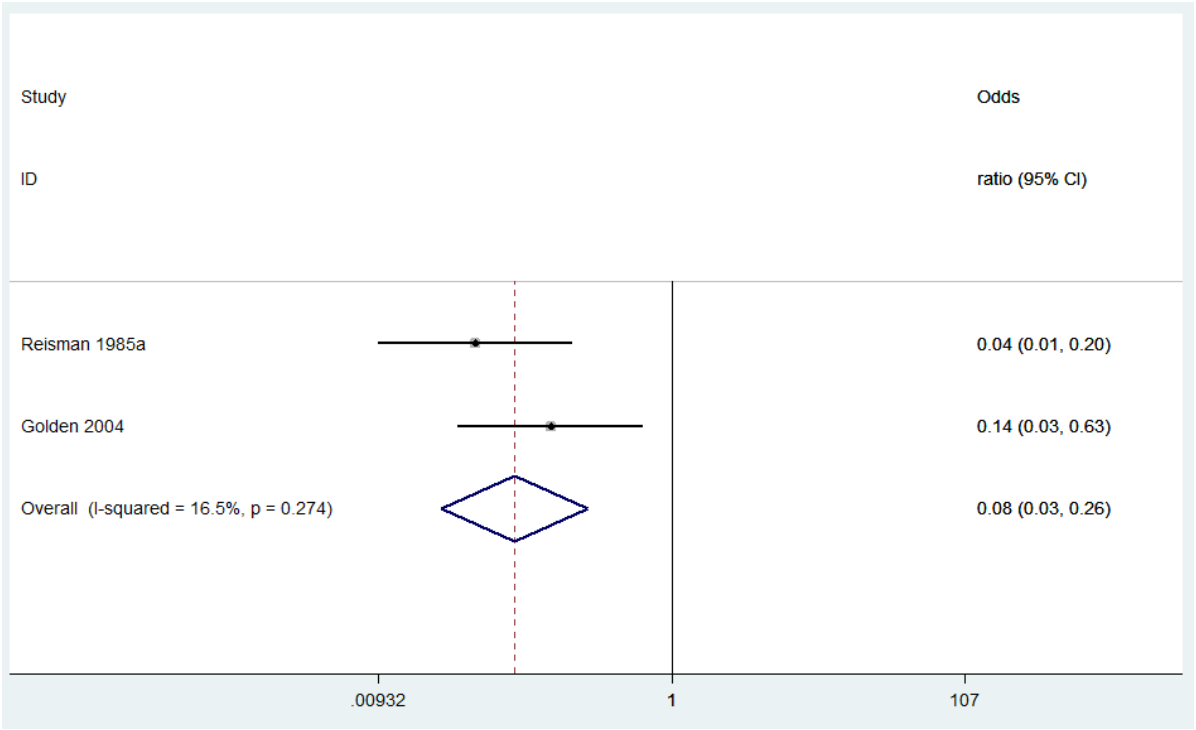
Table 3: Quality assessment of RCTs and CBA original studies

Author, year	Design	Adequate sequence generation	Allocation concealment	Blinding / patient-related outcomes	Incomplete outcome data addressed	Free of selecting reporting	Free of other bias *	Overall quality assessment
Golden, 2004	CBA	No	No	No	Yes	Yes	No	Low
Hunt, 1978	RCT	Yes	Unclear	No	Yes	Unclear	No	Low
Oude Elberink, 2002	Comprehensive cohort design includes an RCT	Yes	Yes	No	Yes	Yes	No	Moderate
Oude Elberink, 2009	Comprehensive cohort design includes an RCT	Yes	Yes	No	Yes	Yes	No	Moderate
Pasaoglu, 2006	CBA	No	No	No	Yes	Yes	No	Low
Reisman, 1984	CBA	No	No	No	Yes	Yes	No	Low
Schuberth, 1983	Comprehensive cohort design includes an RCT	Yes	Yes	No	Yes	Yes	No	Moderate
Valentine, 1990	Comprehensive cohort design includes an RCT	Yes	Unclear	No	Yes	Yes	No	Moderate/low

Table 4: Quality assessment of case series studies

Author /year	Collected in more than one centre	Objective of the study clear	Clear reporting of inclusion /exclusion criteria	Clear definition of outcomes reported	Data prospectively collected	Were patients recruited consecutively	Clear description of main study findings	Are outcomes stratified	Score out of 8 / Quality
Brehler, 2000	No	Yes	Yes	Yes	No	No	Yes	Yes	5/Low
Mosbech, 2000	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/Low
Ruëff, 2010	Yes	Yes	No	Yes	Yes	No	Yes	Yes	6/Low
Stoevesandt, 2014	No	Yes	No	Yes	No	No	Yes	Yes	4/Low

Figure 3: Meta-analysis of CBA studies investigating the effectiveness of VIT on risk of systemic sting reactions (random effects)



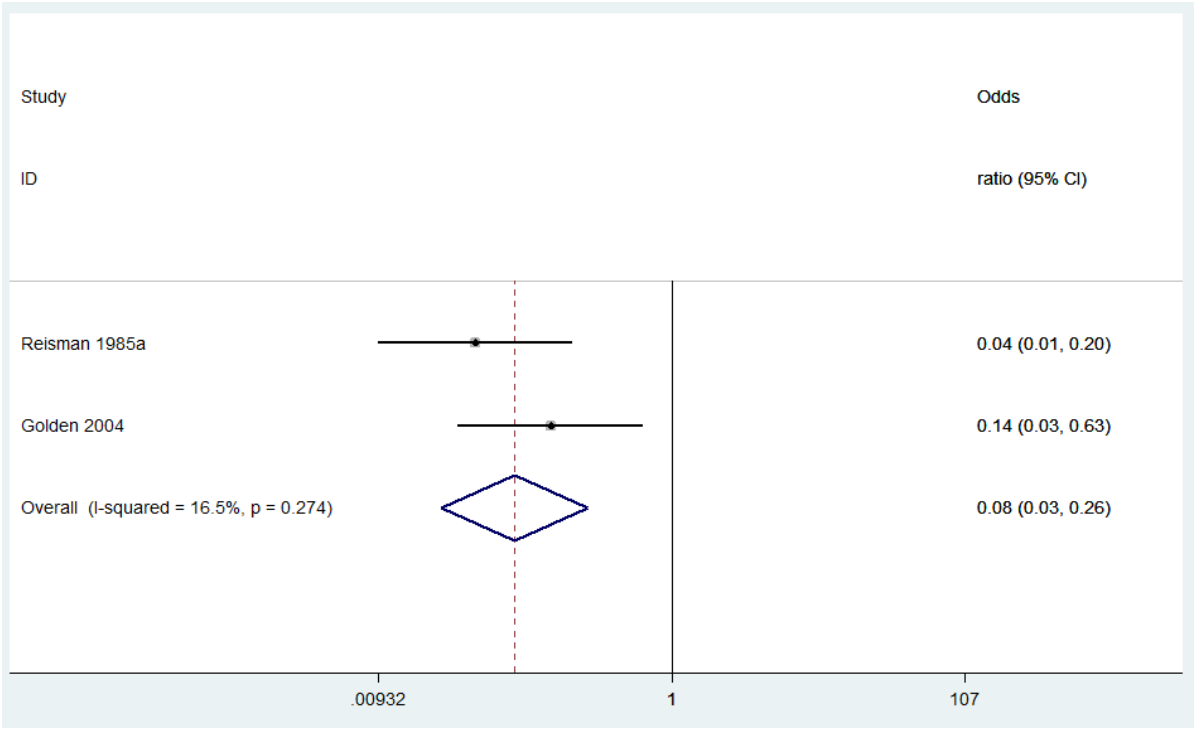
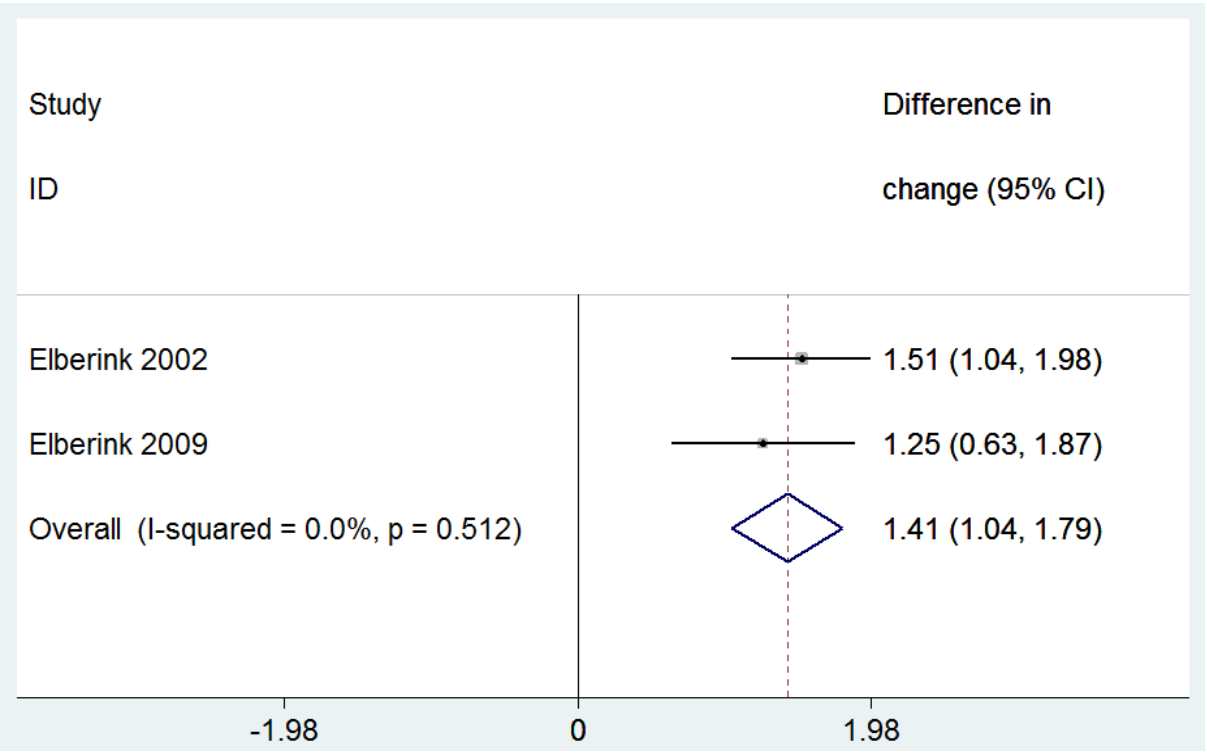


Figure 4: Meta-analysis of RCTs investigating the effectiveness of VIT on VQLQ (random effects)



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