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Pharmalgen for the treatment of venom allergy

Assessment Report

Produced by: Liverpool Reviews & Implementation Group, University of Liverpool

STRICTLY CONFIDENTIAL

MTA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

The clinical and cost effectiveness of Pharmalgen® for the treatment of bee and wasp venom allergy

This report was commissioned by the NIHR HTA Programme as project number 10/01/01

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UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: The clinical and cost effectiveness of Pharmalgen® for the treatment of bee and wasp venom allergy

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All authors read and commented on draft versions of the evidence review group (ERG) report.

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1 GLOSSARY AND LIST OF ABBREVIATIONS

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader.

Abbreviations:

AAI	Adrenaline auto-injector
A&E	Accident and Emergency
AG	Assessment group
AR	Adverse reactions
CI	Confidence interval
EQ5D	A self-reported preference-based measure of health
FS	Field sting
HDA	High-dose antihistamines
HES	Hospital episode statistics
ICER	Incremental cost-effectiveness ratio
IDT	Intradermal skin testing
IgE	Immunoglobulin E
ITT	Intention to treat
LLR	Large local reaction
LYG	Life years gained
MCMC	Markov Chain Monte Carlo
NICE	National Institute for Health and Clinical Excellence
Non-PhVIT	Venom immunotherapy using non-Pharmalgen® products
PhVIT	Venom immunotherapy using Pharmalgen® products
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life year
QoL	Quality of life
RAST	Radioallergosorbent testing
RCT	Randomised controlled trial
SC	Sting challenge
SCIT	Subcutaneous immunotherapy
SLIT	Sublingual immunotherapy
SPT	Skin prick test
VIT	Venom immunotherapy
WBE	Whole bee extract

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has only been used once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure or table legend.

Definitions of terms

Anaphylaxis	A severe Type 1 hypersensitivity allergic reaction
Aqueous solution	A solution in which water is the solvent
Cost effectiveness	Cost effectiveness has numerous meanings, however for practical purposes it is usually given to mean that the cost per quality adjusted life year gained is below a notional willingness to pay threshold.
Depot	An injection of a pharmacological agent which releases its active compound in a consistent way over a long period of time
Field sting	A sting occurring accidentally
Hymenoptera	A group of stinging insects that include bees, wasps and ants
Immunoglobulin E	Class of antibody that plays an important role in allergy
Local reactions	Reactions mediated by allergic mechanisms but only involve the part of the body in contact with the sting site
Sting challenge	A sting purposefully inflicted in a controlled environment
Systemic allergic reactions	Reactions mediated by allergic mechanisms that spreads to other organs in the body
Venom immunotherapy	A type of allergic desensitisation therapy for people who are highly susceptible to hymenoptera venom

2 EXECUTIVE SUMMARY

2.1 Background

Each year in the UK, there are between two and nine deaths from anaphylaxis caused by bee and wasp venom. Anaphylactic reactions to bee and wasp venom are a medical emergency, necessitating immediate treatment with drugs, oxygen and fluids to decrease the patient's response to the venom and support breathing and circulation.

In venom-sensitive individuals, allergic reactions to bee and wasp venom can occur rapidly following a sting, and vary in severity. Initially mild symptoms can progress to a life-threatening condition within minutes. The most severe systemic (or generalised) allergic reaction is referred to as anaphylaxis, which is characterised by features such as low blood pressure (with fainting or collapse), bronchospasm (asthma-like response) and laryngeal oedema (with constriction of the upper airway).

To avoid further reactions in people with a history of anaphylaxis to bee and wasp venom, the use of desensitisation, through a process known as venom immunotherapy (VIT), has been investigated and is in use in the UK. Venom immunotherapy consists of subcutaneous injections of increasing amounts of purified bee and/or wasp venom extract. Pharmalgen® products have had UK marketing authorisation for VIT (as well as diagnosis) of allergy to bee venom (using Pharmalgen® Bee Venom) and wasp venom (using Pharmalgen® Wasp Venom) since March 1995. These are used by 44 centres in England and Wales.

2.2 Objectives

This review assessed the clinical and cost effectiveness of Pharmalgen® in providing immunotherapy to individuals with a history of type 1 (immunoglobulin E (IgE) mediated) systemic allergic reaction to bee and wasp venom.

2.3 Methods

Three electronic databases were searched for comparative trials and economic evaluations of VIT using Pharmalgen® (PhVIT) in the treatment of venom allergy. Outcomes for clinical effectiveness included systemic reactions, local reactions, mortality, anxiety related to the possibility of future allergic reactions, health related quality of life (QoL) and adverse reactions (ARs) to treatment. Cost effectiveness outcomes included cost per quality adjusted life years (QALYs) gained. Two reviewers independently screened all titles and/or abstracts including economic evaluations, applied inclusion criteria to relevant publications and quality assessed the included studies. Where multiple publications of the same study were identified, data were extracted and reported as a single study. The results of the data extraction and quality assessment are summarised in structured tables and as a narrative description. The manufacturer did not provide an evidence submission to NICE for this appraisal.

2.4 Results

Clinical review

1065 citations were identified, of which 266 full-text papers were obtained. No studies were identified that compared PhVIT with any comparator outlined in the decision problem (adrenaline auto-injector (AAI) prescription and training, high-dose antihistamines (HDA) or advice on the avoidance of bee and wasp stings). The decision problem was widened to include different types of PhVIT (such as subcutaneous vs sublingual) or differing protocols of PhVIT administration. Four RCTs and five quasi-experimental studies were identified for inclusion in the systematic review.

The quality of the included trials was poor, and no studies were carried out in the UK. All trials included in the review were small, with none including more than 65 participants (range 6-65), and all of the studies took place outside of the UK. The authors did not describe the method of randomisation used, and there were imbalances in the rate of drop out between arms in all but one study. There was heterogeneity between studies in the outcomes reported, the timing of re-stings, type and length of treatment and in proportion of people being re-stung. As such, it was not possible to conduct a meta-analysis or multiple treatment comparison (MTC) with the available data.

Eight studies reported re-sting data and the rate of systemic reactions ranged from 0.0% to 36.4%. Adverse reactions to PhVIT were reported in eight studies. Systemic reactions were reported at rates of between 0.0% and 38.1% and none were fatal. Data were supported by non-comparative studies of PhVIT. Seventeen non-comparative studies of PhVIT reported rates of systemic reactions following re-sting which ranged from 0.0% to 32.7%, with 12 studies reporting re-sting data before the completion of VIT. Post-VIT systemic reaction rates ranged from 2.0% to 12.5%.

Health related quality of life was not reported in any of the included studies. However, details of two RCTs that used a combination of PhVIT and non-PhVIT indicate that the QoL of people receiving VIT improved more than those using an EpiPen® (Test for overall effect: $Z = 36.25$ ($P < 0.00001$).

In general, clinical evidence suggests there is a decrease in reactions to stings following PhVIT but there is no direct evidence related to the comparators included in the scope for this project. Venom immunotherapy with Pharmalgen® is associated with ARs, but these are treatable and transient. These ARs are also associated with non-PhVIT and studies have indicated that they may be to some extent balanced by the improvement in the QoL of people.

Economic review

No published economic evidence relevant to the decision problem was identified via the systematic review of cost-effectiveness studies. The manufacturer of PhVIT did not submit any clinical or cost-effectiveness evidence to NICE in support of PhVIT. The assessment group (AG) developed a *de*

novo economic model designed specifically to compare the cost effectiveness of PhVIT with currently available NHS treatments. A questionnaire was designed and sent out to the 44 allergy clinics in the UK which provide PhVIT to elicit data for use in the economic model. PhVIT + HDA +AAI were compared with (i) HDA + AAI and (ii) avoidance advice only.

In the AG base case, the comparison of PhVIT + HDA + AAI vs AAI + HDA, yields an ICER of £18,065,527 per QALY gained; PhVIT + HDA + AAI vs avoidance advice only yields an ICER of £7,627,835 per QALY gained. The results of the sensitivity analyses and scenario analyses showed that the results of the base case economic evaluation were robust for every plausible change in parameter made. Under the base case assumptions, the incremental cost per QALY gained of PhVIT + AAI + HDA compared to an emergency kit of AAI + HDA is never less than £1million per QALY gained under any scenario or any plausible values for parameters within the model. The ICER only falls below £1million when PhVIT + AAI + HDA is compared to avoidance advice when the most optimistic scenario for PhVIT + AAI + HDA is considered, this ICER still exceeds £700,000 per QALY gained.

The AG's results of the "High Risk of Sting Patients" subgroup analysis show that PhVIT + HDA + AAI dominates both AAI + HDA and avoidance advice only (i.e. is less expensive and more effective). The AG's "VIT Anxiety QoL Improvement" subgroup analysis shows that PhVIT + HDA + AAI vs HDA + AAI has an ICER of £23,868 per QALY gained, and PhVIT + HDA + AAI vs avoidance advice only yields an ICER of £25,661 per QALY gained.

Whilst the findings of the economic model are considered robust, there are some key weaknesses in the data used to inform the economic model. The AG has identified key gaps in the available clinical effectiveness literature and notes specifically that there is a paucity of clinical effectiveness data from RCTs of PhVIT vs any other comparator. The AG is also concerned that the number of stings in people who have had PhVIT in the UK and the number of bee and/or wasp stings in the general population is not known. The AG considers that the likelihood of death following sting for individuals who are allergic to bee and/or wasp venom and the size of the improvement in utility due to PhVIT because of a reduction in anxiety due to reduced risk of sting is uncertain.

2.5 Conclusions

The current use of PhVIT in clinical practice in the NHS appears to be based on limited and poor quality clinical effectiveness research.

The AG did not identify any studies of PhVIT that directly addressed the original decision problem set for this appraisal i.e. to compare the use of PhVIT with the alternative treatment options of advice on the avoidance of bee and wasp venom, HDA and/or AAIs.

This lack of evidence and the need to identify data to inform the development of an economic model prompted the AG to broaden the search criteria for the systematic review in order to compare PhVIT with other PhVIT and PhVIT vs non-PhVIT, to consider data from non-comparative studies of PhVIT and to examine studies reporting the clinical effectiveness of non-PhVIT.

In general, research in the area is limited to small scale studies which do not appear to have been carried out using robust methods and none of the studies reported on the use of PhVIT within the UK. There is also heterogeneity in the published evidence related to the methods of PhVIT administration and length of treatment described in the trials. Therefore conclusions regarding the clinical effectiveness of PhVIT to reduce the rate of future systemic reactions in patients with history of bee and/or wasp allergic reaction cannot be drawn with any confidence. Available evidence indicates that sting reactions following the use of PhVIT are low and that the ARs related to treatment are minor and easily treatable.

Anxiety related to the possibility of future stings is an issue for debate and data from studies of VIT indicate a small improvement in QoL due to a decrease in sting-related anxiety after VIT.

No published research on the cost effectiveness of PhVIT or non-PhVIT was identified by the literature searches. The results of the AG's *de novo* base case economic evaluation demonstrate that PhVIT + AAI + HDA compared with AAI + HDA and compared with avoidance advice only yield ICERs in the range of £8-20 million per QALY gained. The results of extensive sensitivity and scenario analyses demonstrate that the base case results are robust. Two subgroups were considered in the economic evaluation and the AG concludes that use of PhVIT + AAI + HDA may be cost effective in both groups. In the subgroup of patients at high risk of future stings (5 stings per year), PhVIT + AAI + HDA dominates the alternatives. In the subgroup of patients whose QoL improves due to PhVIT from reduced anxiety, when PhVIT + AAI + HDA is compared to the alternatives the ICERs are in the range of £25,767 to £27,504 per QALY gained.

2.6 Future research

Use of PhVIT in clinical practice in the UK NHS is common place, it is therefore highly unlikely that placebo controlled studies will ever be carried out. The findings of this review indicate however that it is necessary to identify more clearly the groups of patients most likely to benefit from treatment and ensure that clinical practice is focussed on these groups. Given the paucity of UK data in this area it would be informative if data could be collected routinely when VIT is administered in the NHS (e.g. rates of systemic adverse reactions to VIT, rates of systemic reactions to bee/wasp stings).

3 BACKGROUND

3.1 Clarification of research question and scope

Pharmalgen® products are used for the diagnosis and treatment of immunoglobulin E (IgE)-mediated allergy to bee and wasp venom. The aim of this systematic review was to assess whether use of Pharmalgen® products is of clinical value when providing VIT to individuals with a history of severe reaction to bee and wasp venom, and whether doing so would be considered cost effective compared with alternative treatment options available in the NHS in England and Wales.

3.2 Description of health problem

3.2.1 Aetiology, pathology and prognosis

Apidea (bees), *Vespidae* (wasps and hornets) and *Formicidiae* (ants) form part of the order *Hymenoptera*. Bees and wasps have a modified ovipositor at the terminal end of their abdomen, which gives them the ability to sting other organisms. Bees possess a barbed stinger, which, together with their venom sac, remain in their victim's skin after they sting. This means that bees are able to sting only once, and die soon afterwards. Wasps' stingers are not barbed and they are therefore capable of delivering more than one venom-injecting sting in their lifetime. Bee and wasp stings contain allergenic proteins. In wasps, these are predominantly phospholipase A1,[1] hyaluronidase[1] and antigen 5[2] and, in bees, phospholipase A2 and hyaluronidase.[3] It has been estimated that each bee sting contains 147 μg of venom and each wasp sting contains 17 μg of venom.[4]

The symptoms produced following a sting can be classified into non-allergic and allergic reactions. All envenomated individuals are likely to experience local burning and pain followed by erythema (redness) and a small area of oedema (swelling) at the site of the sting. These are caused by vasoactive components of venom and the mechanism is toxic rather than allergic.[4]

Following an initial sting, some individuals generate an immune response, which produces antibodies of the IgE class. These antibodies sensitise cells, particularly histamine-containing mast cells, so that allergen reintroduced by a subsequent exposure can bind to the preformed IgE molecules, triggering the cells to produce a rapid inflammatory response (this is referred to as a 'type I' or 'immediate-type' hypersensitivity reaction). These allergic reactions in venom-sensitised individuals, can be local or systemic, vary in severity, and are typically of rapid onset.[5,6,7,8] The term 'anaphylaxis' is applied to the most severe reactions. These frequently occur within 15 minutes of a sting; initial symptoms are usually cutaneous (flushing, urticaria, angioedema) followed by hypotension (with light-headedness, fainting or collapse) and/or respiratory symptoms (due to an asthma-like response or laryngeal oedema). Progression to fatal cardio-respiratory arrest can occur within several minutes.[5] Anaphylaxis occurs more commonly in males and in people under 20 years of age,[6] and the species

that cause the most frequent allergic reactions in humans following a sting are the *Apidae* (bees) and the *Vespidae* (wasps and hornets).[7]

In addition to local and systemic allergic reactions, individuals may also experience allergic reactions due to circulating immune complexes or delayed hypersensitivity reaction. This is uncommon, and presents as skin rashes and sickness-like symptoms occurring within 3 days to 2 weeks post-sting.[5]

Severity of systemic reactions to *Hymenoptera* venom can be measured using the Mueller grading system,[8] which is summarised in Table 1. The grading system classifies the reaction to a sting according to the severity of symptoms. Severity ranges from Grade I (symptoms of skin and mucous membranes) to Grade IV (cardiovascular symptoms).

Table 1 Mueller grading system

Grade	Description	Signs and symptoms
I: Slight general reaction	Skin and mucous membrane symptoms	Generalised urticaria or erythema, itching, malaise, or anxiety
II: General reaction	Gastrointestinal symptoms	Any of above, plus two or more of: generalised edema, constriction in chest, wheezing, abdominal pain, nausea and vomiting, dizziness
III: Severe general reaction	Respiratory symptoms	Any of above, plus two or more of: dyspnoea, dysarthria, hoarseness, weakness, confusion, feeling of impending disaster
IV: Shock reaction	Cardiovascular symptoms	Any of above, plus two or more of: loss of consciousness, incontinence of urine or faeces, or cyanosis

3.2.2 Epidemiology

In the UK, insect stings are the second most frequent cause of anaphylaxis outside of medical settings,[9] and *Hymenoptera* venoms are one of the three main causes of fatal anaphylaxis in both the USA and UK.[10] It is estimated that the prevalence of bee and wasp sting allergy is between 0.4% and 3.3%.[11]

The prevalence rates of large local reactions (LLRs) in the general population have been estimated at between 2.4% and 26.4%, and up to 38% in beekeepers.[10] Children are reported to have lower rates of both large local and systemic reactions to *Hymenoptera* stings, at between 11.5% and 19%, and between 0.15% and 0.8% respectively.[5] After an LLR, 5% to 15% of people will go on to develop a systemic reaction when next stung.[12]

The prevalence of systemic reactions to *Hymenoptera* venom is not reliably known, but estimates range from 0.5% to 3.3% in the USA,[12, 13] and between 0.3% and 7.5% in Europe.[10] Differences in rates of systemic allergic reactions in children and adults have been reported; up to 3% of adults, and almost 1% of children have a medical history of severe sting reactions.[11, 13] In people with a mild

systemic reaction, the risk of subsequent systemic reactions is thought to be between 14% and 20%.[12] Within the USA, severe life-threatening reactions occur in 0.4% to 0.8% of children and 3% of adults.[14]

UK data

Between two and nine people in the UK die each year as a result of anaphylaxis due to having experienced reactions to bee and wasp stings.[15] Once an individual has experienced an anaphylactic reaction, the risk of having a recurrent episode has been estimated to be between 60% and 79%.[12] In 2000, the register of fatal anaphylactic reactions in the UK from 1992 to 2000 was reported by Pumphrey and Roberts.[16] Of the 56 post-mortems carried out during this period, 19 deaths (33.9%) were recorded as reactions to *Hymenoptera* venom. A retrospective study in 2004[17] examined all deaths from anaphylaxis in the UK between 1992 and 2001, and estimated 47/212 (22.2%) to have resulted from reactions to *Hymenoptera* venom during this period. This further breaks down into 29/47 (61.7%) from reactions to wasp stings, and 4/47 (8.5%) from reactions to bee stings, the remaining 14/47 being caused by unidentified *Hymenoptera* stings (29.8%).[17]

3.3 Current diagnostic options

Currently, individuals can be tested to determine if they are at risk of systemic reactions to bee and wasp venom. The primary diagnostic method for allergic sensitisation to bee and/or wasp stings is venom skin testing.

Venom skin testing involves skin prick testing (SPT) and/or intradermal skin testing (IDT) by injection with *Hymenoptera* venom protein extracts at concentrations in the range of 0.001 to 1.0 μg/ml. This establishes the minimum concentration giving a positive result. Guidelines produced by the American Academy of Allergy, Asthma and Immunology (AAAAI),[18] the American College of Allergy, Asthma and Immunology (ACAAI), and the European Academy of Allergy and Clinical Immunology (EAACI)[12, 18, 19] recommend that SPT be the first-line of investigation to diagnose *Hymenoptera* venom allergy, and be performed 2 weeks after the sting reaction. Intradermal skin testing should be used when the results of SPT are negative, as IDT is 90% more sensitive than SPT at a concentration of 1 μg/ml.[12] As venom tests show unexplained variability over time,[20] and as negative skin tests can occur following recent anaphylaxis, if an individual displays a history of systemic reactions but their skin tests are negative it is recommended that tests should be repeated 1 to 2 months later, along with serum-specific IgE measurement.[12]

Another method of diagnosis is direct measurement of allergen-specific IgE antibodies in serum (previously, and sometimes still, referred to as radioallergosorbent testing, or RAST, though this is now an anachronistic misnomer). This test is less sensitive than a skin test but is useful when skin tests cannot be done, for example, in people with skin conditions.[21, 22]

3.4 Current treatment options

For treatment of symptoms in the event of being stung, people can be provided with an emergency kit.[23] The contents can be tailored to the perceived risk of a severe reaction but the options include an H1-blocking HDA, a corticosteroid, a bronchodilator and an AAI.

Injected adrenaline (epinephrine, a sympathomimetic drug which acts on both alpha and beta adrenoceptors), administered as part of hospital treatment, is regarded as the emergency treatment of choice for cases of acute anaphylaxis as a result of *Hymenoptera* stings.[24] For adults, the recommended dose is between 0.3 mg and 0.5 mg via intramuscular injection, and 0.01 mg/kg via intramuscular injection for children. Adrenaline auto-injectors available in the UK for carriage by individuals at risk of anaphylactic reactions, and designed for immediate self-administration, include EpiPen® and Anapen®. These AAIs must be prescribed by a clinician. People and their relatives/carers receive training in using the AAI, and are advised to practice regularly using a suitable training device.[25]

In addition to emergency treatments, preventative measures include education (avoidance advice) on how to avoid bee and/or wasp stings. Additionally, education includes advice on recognising the early symptoms of anaphylaxis in order for individuals to summon help quickly and be prepared to use their emergency medication. All those at high risk should consider wearing a device such as a bracelet (e.g. MedicAlert) that provides information about their history of anaphylactic reaction to bee and/or wasp venom.[25]

3.4.1 Venom immunotherapy

In addition to the measures detailed above, people with a history of a systemic allergic reaction to *Hymenoptera* venom can be considered for specific allergen immunotherapy (VIT). It is recommended that VIT is considered 'when positive test results for specific IgE antibodies correlate with suspected triggers and patient exposure'.[26] Venom immunotherapy is intended to prevent or reduce the severity of future systemic allergic reactions and can be administered using a variety of products and according to a variety of protocols. Currently the only products licensed for use in the UK are Pharmalgen® products (Table 2).

Table 2 Venom immunotherapy products

Drug	Manufacturer	Licensed in the UK?
Pharmalgen® bee venom	ALK Abéllo	Yes
Pharmalgen® wasp venom	ALK Abéllo	Yes
Aquagen®	ALK Abéllo	No
Alutard SQ®	ALK Abéllo	No
Alyostal®	Stallergenes	No
VENOMENHAL	HAL Allergy	No
Venomil®	Hollister-Stier Laboratories LLC	No

Venom immunotherapy consists of subcutaneous injections of increasing amounts of venom, and treatment is divided into two periods: the updosing phase and the maintenance phase. Venom immunotherapy is normally discontinued after 3 to 5 years, but adjustments to the treatment regime may be necessary when treating people with intense allergen exposure (such as beekeepers) or those with individual risk factors for severe reactions. There are 44 centres across the UK which provide PhVIT to people for bee and wasp sting allergy.[27] From the findings of the latest UK audit,[14] it is clear that there is no single standard approach to the delivery of PhVIT; different centres appear to follow different dosing and administration protocols and every treatment package is tailored to the requirements of the individual patient.

In 1978, the first RCT[28] assessing the effectiveness of VIT in the treatment of insect venom allergy was published, in which people were randomised to either VIT or placebo. Systemic reactions following re-sting occurred in seven of 12 people receiving placebo, and in one of 18 people receiving VIT. As a direct result of this study, it is now considered unethical to randomise people eligible for VIT to receive placebo treatment.

3.4.2 Assessing the effectiveness of venom immunotherapy

The impact of VIT can be assessed using both clinical and psychological outcomes. Clinical outcomes relate to the effectiveness of VIT in reducing the rate of reaction to subsequent stings and the psychological outcomes relate to QoL and anxiety related to fear of future stings.

The effectiveness of VIT has been assessed using various methods. A method frequently used in clinical trials is that of a hospital sting challenge (SC), where a patient is purposely stung, in a controlled environment, by a living insect of the species they have been desensitised to. Any reaction to the sting is then reported and treated if necessary. Another measure of effectiveness is that of patient reported reactions to accidental field stings (FS). Other methods include the measurement of serum IgE and skin tests similar to those used in the diagnosis of venom allergy. However, there is no completely reliable method of predicting which people will be at risk of further anaphylactic reactions and which will remain anaphylaxis-free in the long term, following VIT.[26]

Local or systemic ARs may occur as a result of VIT. They normally develop within 30 minutes of the injection, but occasionally delayed reactions can occur after several hours. Each patient is monitored closely following each injection to check for ARs. These reactions inform the rate of progression to increased doses during the updosing phase of treatment.

3.4.3 Relevant national guidelines

Emergency treatment

The Resuscitation Council of the UK updated guidelines for the emergency treatment of anaphylactic reactions in 2008.[25] These guidelines detail the diagnosis, treatment, investigation and follow-up of people who have had an anaphylactic reaction, including those reacting to *Hymenoptera* venom. Emergency treatment with 0.5 mg of intramuscular adrenaline (epinephrine) is recommended for people experiencing an anaphylactic reaction. Intravenous adrenaline is recommended only for occasional use by experienced specialists; subcutaneous or inhaled adrenaline is not recommended. Treatment with the highest concentration of oxygen available via a mask, and loading with 500-1000 ml of fluids (for adults) is also recommended, in addition to adrenaline.

High dose antihistamines are recommended as a second-line treatment for anaphylaxis to help counter histamine-mediated vasodilation and bronchoconstriction.[25] For adults, chlorphenamine 10 mg intramuscularly, or intravenously is recommended. People experiencing an anaphylactic reaction should be treated and then observed for at least 6 hours in a clinical area with facilities for treating life-threatening breathing complications.

The Resuscitation Council of the UK[25] also recommends that all people presenting with anaphylaxis should be referred to an allergy clinic to determine the cause of the reactor and to prepare the patient to be able to manage future episodes themselves.

Preventative measures

The AAAAI guidelines for the management and prevention of stinging insect hypersensitivity were first produced in 1999,[29] and were subsequently updated in 2004[30] and 2011.[18] They recommend that people who have experienced a systemic reaction to an insect sting should be referred to an allergist-immunologist for skin testing or in vitro testing for venom-specific IgE antibodies. A positive IDT response to insect venom at a concentration of less than or equal to 1.0 ug/ml demonstrates the presence of specific IgE antibodies, and VIT is recommended. If people have a negative skin test despite a history of anaphylaxis, in vitro testing for IgE antibodies or repeat skin testing is recommended before concluding that VIT is not indicated.

Venom immunotherapy in adults is usually recommended for all individuals who have experienced systemic reactions, but is generally not necessary for individuals who have had only an LLR due to

low risk of a systemic reaction to a subsequent sting. The AAAAI[18] recommends that, once started, VIT should be continued for at least 3 to 5 years. During this time, and in people who did not commence VIT, it is recommended that people carry an AAI at all times.

3.5 The technology

Pharmalgen® products are produced by ALK Abéllo, and have had UK marketing authorisation for the diagnosis (using skin testing/intracutaneous testing) and treatment (using PhVIT) of IgE-mediated allergy to bee venom (Pharmalgen® bee venom) and wasp venom (Pharmalgen® wasp venom) since March 1995 (marketing authorisation number PL 10085/0004).[31] The active ingredient is freeze dried A*pis mellifera* venom in Pharmalgen® bee venom, and partially purified, freeze dried *Vespula spp.* venom in Pharmalgen® wasp venom, each provided with a solvent to prepare for injection.

Before treatment is considered, allergy to bee or wasp venom must be confirmed by case history and diagnostic testing as outlined previously. Treatment with Pharmalgen® bee or wasp venom is performed by subcutaneous injections. The treatment is carried out in two phases: the updosing phase and the maintenance phase.

In the updosing phase, the dose is increased stepwise until the maintenance dose (the maximum tolerable dose before an allergic reaction, or a maximum dose of 100 μg, whichever is the smaller) is achieved. ALK Abéllo recommends the following dosage protocols: 'conventional', 'modified rush' (clustered) and 'rush' updosing. In conventional updosing, the patient receives one injection every 3 to 7 days. In modified rush (clustered) updosing, the patient receives two to four injections once a week. If necessary, this interval may be extended up to 2 weeks. The two to four injections are given with an interval of 30 minutes. In rush updosing, while hospitalised, the patient receives injections at 2-hour intervals and a maximum of four injections per day may be given in the updosing phase.

The updosing phase ends when the individual maintenance dose has been attained and the interval between the injections is increased by 2, 3 or 4 weeks. This is called the maintenance phase, and the maintenance dose is then given every 4 to 6 weeks for at least 3 years.

In the UK, treatment is carried out in hospital, either as an outpatient for conventional updosing, or as an inpatient for rush protocols. Treatment is administered by a specialist, and emergency resuscitation equipment should be available in case it is required to treat any systemic reaction. Venom from ALK Abéllo are used in most clinics in the UK, with 92% of clinics employing the conventional 12 week updosing protocol, and the remainder employing a clustered (7-8 week) updosing protocol.[14]

For bee venom-sensitised people, the relevant PhVIT preparation costs £54.81 during the updosing phase, and then £15.94 per injection during the maintenance phase. For wasp venom-sensitised

people, PhVIT costs £67.20 during the updosing phase, and then £20.51 per injection during the maintenance phase.

Contraindications/warnings

The summary of Pharmalgen® product characteristics (SmPC) [31] lists several contraindications to PhVIT treatment.[31] These are immunological diseases (e.g. immune complex diseases and immune deficiencies), chronic heart/lung diseases, treatment with β-blockers and severe eczema. Side effects include superficial wheal and flare, local swelling (which may be immediate or delayed up to 48 hours), mild general reactions (urticaria, erythema, rhinitis or mild asthma), moderate or severe general reactions (more severe asthma, angioedema or anaphylactic reaction with hypotension and respiratory embarrassment and possible death).[31]

4 DEFINITION OF THE DECISION PROBLEM

4.1 Decision problem

The remit of this review is to assess the clinical and cost effectiveness of PhVIT in providing immunotherapy to individuals with a history of type 1, IgE-mediated, systemic allergic reaction to bee and wasp venom. Table 3 shows the key elements of the decision problem of the appraisal.

Table 3 Key elements of the decision problem

Intervention(s)	Pharmalgen® for the treatment of bee and wasp venom allergy
Population(s)	People with a history of type 1 IgE-mediated systemic allergic reactions to bee venom and/or wasp venom
Comparators	Alternative treatment options available in the NHS, without VIT including: • advice on the avoidance of bee and wasp venom • high-dose antihistamines • adrenaline auto-injector prescription and training *Revised inclusion criteria:* • any VIT
Study design	Randomised controlled trials Systematic reviews Economic evaluations *Revised inclusion criteria:* • comparative studies
Outcomes	Outcome measures to be considered include: • number and severity of type 1 IgE-mediated systemic allergic reactions • mortality • anxiety related to the possibility of future allergic reactions • adverse effects of treatment (i.e. adverse reactions) • health-related quality of life (QoL) • quality adjusted life years (QALYs)
Other considerations	If the evidence allows, considerations will be given to subgroups of people according to their: • risk of future stings (as determined, for example, by occupational exposure) • risk of severe allergic reactions to future stings (as determined by such factors as baseline tryptase levels and co-morbidities) If the evidence allows, the appraisal will consider: • people who have a contraindication to adrenaline separately • children separately

Following completion of the review protocol and preliminary searches, revisions were made to the review protocol so as to include any VIT as a comparator to PhVIT and to include comparative studies in addition to RCTs, systematic reviews and economic evaluations. These are reflected in the revised decision problem set out in Table 3.

This review, for the National Institute of Health and Clinical Excellence (NICE), was limited to Pharmalgen® which is the only licensed venom product for use in VIT in the UK. At the time of writing, a systematic review of all VIT was being undertaken by the Cochrane Skin Group, to be published in 2011.[32] In order to place the current review in the context of the overall literature on the clinical effectiveness of VIT, the AG worked in collaboration with the Cochrane Skin Group to provide the best available summary of the evidence for the use of VIT in the treatment of *Hymenoptera* allergy.

4.2 Overall aims and objectives of assessment

The aim of this review was to assess the clinical and cost effectiveness of Pharmalgen® in providing immunotherapy to individuals with a history of type 1, IgE-mediated, systemic allergic reaction to bee and wasp venom. The review considered the effectiveness of PhVIT when compared to alternative treatment options available in the NHS, including advice on the avoidance of bee and wasp stings, and HDA and AAI prescription and training. The review also examined the existing health economic evidence and identified the key economic issues related to the use of PhVIT in UK clinical practice and developed a *de novo* economic model.

5 ASSESSMENT OF CLINICAL EFFECTIVENESS

5.1 Methods for reviewing effectiveness

The methods used for reviewing both the clinical and cost-effectiveness literature are described in this section.

5.1.1 Search strategy

A comprehensive search strategy using a combination of index terms (e.g. Pharmalgen) and free text words (e.g. allerg$) was developed and used to interrogate the following electronic databases:

- EMBASE (1980 to 2011 Week 04)
- Medline (1948 to February week 3 2011)
- The Cochrane Library (February 2011)

The results were entered into an Endnote X4 library and the references were de-duplicated. Full details of the search strategies and the number of citations returned for each search are presented in Appendix 1.

Inclusion and exclusion criteria

The identified citations were assessed for inclusion through two stages and disagreements were resolved through discussion. In stage 1, two reviewers (JH/GC) independently screened all titles and abstracts and identified the potentially relevant articles to be retrieved. In stage 2, full paper manuscripts of identified studies were assessed independently by two reviewers (JH/GC) for inclusion using the criteria as outlined in the decision problem (Table 3) and described below. Studies that did not meet the criteria were excluded from the review and their bibliographic details are listed alongside reasons for their exclusion in Appendix 2. Bibliographic details of included studies are shown in Appendix 3.

Study design

Any comparative studies were included in the assessment of clinical effectiveness of PhVIT. Full economic evaluations were included in the assessment of cost effectiveness. The ERG also identified and assessed the quality of existing systematic reviews in order to cross check for the identification of additional studies. A summary and critique of relevant systematic reviews is presented in Section 5.4.2.

Intervention

The use of Pharmalgen® within its licensed indication was assessed. Where non-PhVIT was administered and compared to non-VIT interventions, these studies were identified but excluded from the review.

Comparator(s)

All the studies describing the clinical effectiveness of PhVIT compared to any alternative treatment options available in the NHS without VIT i.e. advice on avoidance of bee and wasp venom, HDA or AAIs prescriptions and training, were considered for inclusion. These criteria were later widened to include any comparator to PhVIT, including non-PhVIT and different PhVIT dosing protocols and administration methods. These changes are reflected in the decision problem in Table 3.

Population

To be included studies must have investigated people with a history of type 1 IgE-mediated systemic allergic reactions to bee venom and/or wasp venom determined by a history of a systemic reaction to a sting and a positive skin test and/or positive tests for the detection of serum IgE.

Outcomes

Data on any of the following outcomes were included in the assessment of clinical effectiveness: reaction to subsequent stings (assessed through accidental FS or SC), anxiety related to the possibility of future allergic reactions, reported ARs to treatment and QoL. For the assessment of cost effectiveness, outcomes considered were incremental cost per QALY gained.

5.1.2 Data abstraction strategy

Data relating to both study design and quality were extracted by one reviewer (JH) into a Microsoft Access® database and were cross checked by a second reviewer (GC). Where multiple publications of the same study were identified, data were extracted and reported as a single study.

5.1.3 Critical appraisal strategy

The quality of the included clinical-effectiveness studies was assessed by one reviewer (JH) and checked by a second reviewer (GC) according to criteria based on CRD Report 4.[33] The checklist used to critically appraise the included studies is specific to RCTs; for the non-RCT studies a modified version of this checklist was used. All relevant information was tabulated and summarised within the text of the report. Full details and results of the quality assessment strategy for clinical effectiveness studies are reported in Appendix 4.

5.1.4 Methods of data synthesis

Results of the data extraction are summarised in structured tables and as a narrative description. A standard meta-analysis was planned if sufficient clinically and statistically homogeneous data were available from the included studies. The primary outcomes identified for our evidence synthesis were systemic reaction to FS or SC during treatment and/or adverse reactions to VIT. Secondary outcomes included local reaction to VIT; local reaction to FS or SC; number of stings; deaths.

We planned to extract number of events for each outcome and total number of people in each treatment arm in order to calculate odds ratios (OR) and the correspondent 95% confidence intervals for each study. Studies with no events in both arms would be excluded from analysis. All analyses were planned based on the intention to treat (ITT) population where possible. Where appropriate, the levels of clinical and methodological heterogeneity would be investigated, and statistical heterogeneity would be assessed using Q- and I^2-statistics.[34, 35] Given the small number of trials available, a fixed-effects model was planned using the 'metan' command within STATA Version 9.2[36] where pooling was appropriate.

If the data allowed, a mixed treatment comparison (MTC) of relevant comparators to PhVIT would be considered. An MTC analysis allows for the synthesis of data from direct and indirect comparisons and allows for the ranking of different treatments in order of efficacy and estimation of the relative treatment effect of competing interventions. This approach assumes 'exchangeability' of treatment effect across all included trials, such that the observed treatment effect for any comparison could have been expected to arise if it had been measured in all other included trials. This approach fulfils the objective of providing simultaneous comparison of all the relevant treatment alternatives, and can provide information about the associated decision uncertainty or sufficient information for economic evaluation. Hence, for the purposes of decision-making, a Bayesian MTC framework would be adopted to synthesise information on all technologies simultaneously using Markov Chain Monte-Carlo (MCMC) methods to estimate the posterior distributions for our outcomes of interest. The MCMC simulation begins with an approximate distribution and, if the model is a good fit to the data, the distribution converges to the true distribution. As with all meta-analyses, MTC may be conducted using either fixed or random-effects models. Random-effects models allow for the possibility that the true treatment effect may differ between trials. The model fit will be assessed based on residual deviance and deviance information criteria.

WinBUGS version 1.4 statistical software[37] was planned for use in the MTC.[38] Two chains would be used to ensure that model convergence was met after 50,000 iterations with a burn-in of 100,000. Formal convergence of the models would be assessed using trace plots and the Gelman Rubin approach[39] and through inspection of the history plots.

Data would only be pooled if it was felt that the studies were measuring the same effects and if the studies had the same study design. Where meta-analysis was considered unsuitable for the data that were identified (e.g., due to the heterogeneity of the studies, or no reliable data were presented in the report), a narrative synthesis approach would be employed.

5.2 Results

5.2.1 Quantity and quality of research available

The electronic searches identified 1397 citations which, after de-duplication, included 1065 individual papers, of which 799 were excluded after scanning titles and abstracts in stage 1. The full papers of 266 references were obtained and screened using the previously described inclusion criteria. Of the 266 papers screened at stage 2, 11 papers (9 studies) met the revised inclusion criteria. Of the remaining 255 excluded papers, the majority (161) were not comparative studies of PhVIT; other reasons for exclusion included inappropriate outcomes and irrelevant patient populations.

There were 38 excluded papers that require further mention in this report as they met the majority of the inclusion criteria but were studies of non-PhVIT. These 38 papers included: 16 papers that compared two non-PhVIT treatments and 12 papers which compared non-PhVIT with no VIT (placebo, AAI prescriptions or whole bee extract (WBE)) and are described in the clinical effectiveness section, in Section 5.4.2). Seven papers provided data on QoL, and three were economic papers.

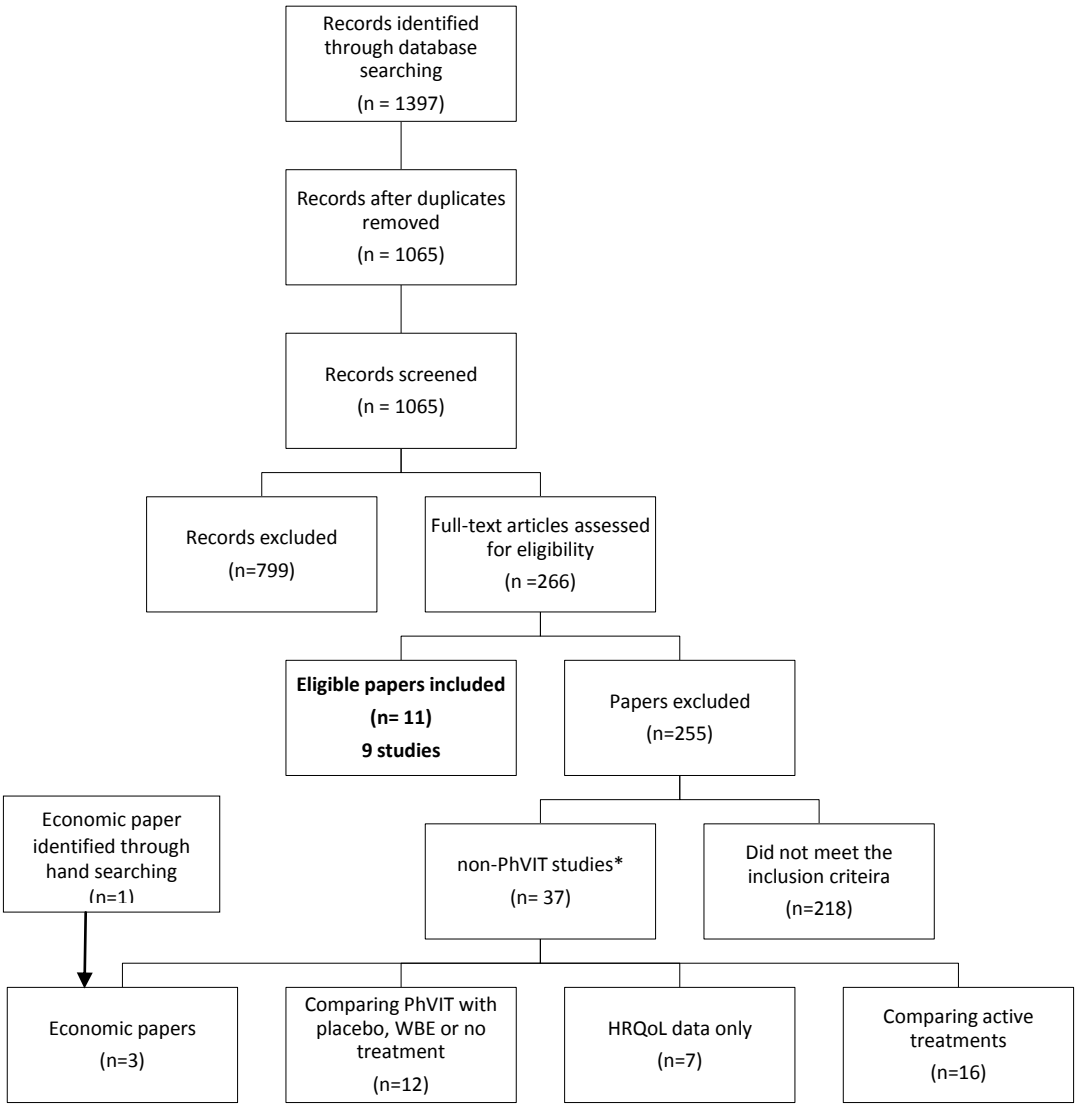

Figure 1 PRISMA flowchart

Nine comparative studies, reported in 11 publications,[40-50] met the inclusion criteria for this review. The reference provided in the text refers to the primary paper and any other publications of the study are listed by study in Appendix 3. A summary of the included studies is shown in Table 4.

Quality assessment

Of the nine studies identified four were randomised controlled trials (RCTs). Studies included small sample sizes at recruitment (range 6-56) and one study[49] did not report on the effectiveness of PhVIT but rather reported ARs only. Six studies used SC to assess the effectiveness of PhVIT and three studies[40, 48, 50] considered a subsequent FS, thereby further decreasing the final number of people assessed in these three studies.

The results of the quality assessment of included trials using CRD Report 4[33] are reported in Appendix 4. None of the RCTs[44, 45, 47, 49] described the randomisation method used, so it was not possible to ascertain whether the method of allocation and its concealment were adequate.

Baseline comparability was achieved in eight studies. One study[45] reported the severity of reaction to initial sting across the groups but otherwise did not comment on the comparability of groups.

All studies reported their eligibility criteria and no co-interventions were identified. Only one[46] of the studies was blinded and though the authors described it as a double-blind study, details of who was blinded were not reported.

All studies reported on the number of withdrawals but only one study[45] reported more than 20% drop out. The rate of dropout differed between the arms and was unadjusted for. Two studies[40, 49] did not report any drop outs and one study[47] reported drop out for the experimental group but not for the historical controls. Where dropouts were reported there was imbalance in the rate of drop out between the arms for all but one study[50] and these imbalances were not explained There was no evidence of more outcomes measured than reported.

Table 4 Summary of included studies

Study ID	Intervention (No. of pts at end of study)	Comparator (No. of pts at end of study)	Design	Outcome data				ARs
				FS/SC	SR	LLR	Other	
RCTs								
Golden 1980[41, 44]	Pharmalgen®: Rush therapy (18)	Pharmalgen® Step therapy (19) Pharmalgen® Slow therapy (19)	RCT	FS/ SC	Yes	No	No	SR, LLR
Mosbech 1986[45]	Pharmalgen®: Aqueous induction and maintenance (3)	Alutard: Depot induction and maintenance (7) Aquagen: Aqueous induction and maintenance (9)	RCT	SC	Yes	No	No	SR, LLR
Müller 1987[46, 47]	Pharmalgen® or Reless: HBV (14)	Modified Pharmalgen®: Monomethoxy polyethylene glycol-coupled HBV (17)	RCT	SC	Yes	Yes	No	SR
Quercia 2001[49]	Pharmalgen®: Cluster (20)	Pharmalgen®: Rush (20) Depot cluster (15)	RCT	NA	No	No	No	SR, LLR
Non RCTs								
Cadario 2004[40]	Pharmalgen®: Aqueous induction and maintenance (18)	Alutard : Depot induction and maintenance (27)	Quasi-experimental: Interventions alternated in consecutive subjects	FS	Yes	No	LR	SR, LR
Golden 1981a[43]	Pharmalgen®: 50ug Maintenance (19)	Pharmalgen®: 100ug maintenance[44] (18) In house venom: 100ug maintenance[28] (19)	Historical control group	SC	Yes	No	No	LLR
Golden 1981b[42]	Pharmalgen®: 6 weekly maintenance (29)	Pharmalgen®: 4 weekly maintenance a (42) Pharmalgen®: 4 weekly maintenance b (56)	Randomly selected pts from larger cohort compared with historical controls (some overlap of people)	SC	Yes	No	No	SR, LLR
Patriarca 2008[48]	Pharmalgen®: Ultra Rush SCIT (20)	Aquagen: Ultra Rush SLIT (17)	Case control: People who declined SCIT were given SLIT	FS	Yes	Yes	No	SR, LLR
Thurnheer 1983[50]	Pharmalgen®: Conventional	Pharmalgen®: Rush	Quasi-experimental: groups determined by season	FS	Yes	No	No	SR, LLR
	Total for both arms (40)							

FS=field sting, SC=sting challenge, NA=not applicable, SR=systemic reaction, LR=local reaction, LLR = large local reaction, NA not applicable

5.2.2 Clinical effectiveness

Trial characteristics

The nine included studies compared PhVIT to an active treatment. Five compared PhVIT with a differing dose or protocol of PhVIT,[42-44, 49, 50] one compared PhVIT with a modified form of PhVIT,[47] three compared PhVIT with non-PhVIT.[40, 45,48] Information on trial characteristics is presented in Table 4.

Four of the studies were RCTs,[44, 45, 47, 49] two compared an intervention group with historical controls[42, 43] and three were quasi-experimental with people allocated to groups by differing means.[40, 48, 50] Cadario et al 2004[40] alternated treatments in consecutive people, Patriarca et al 2008[48] offered sublingual PhVIT to those who had refused subcutaneous PhVIT, and Thurneer et al 1983[50] that administered PhVIT in a rush protocol through the insect flying season and in a conventional protocol out of the insect flying season.

All but one study[49] reported the result of subsequent stings. Five of the studies[42-45, 47] used a SC performed on all people to determine the effectiveness of treatment thereby ensuring that outcome data were available for all people and three studies reported the effects of accidental field stings.[40, 48, 50] Only three studies[40, 47, 48] reported on outcomes other than systemic reaction i.e. LLRs and local reactions (see Table 4). No studies reported on mortality though this is likely due to there being no deaths rather than a failure of reporting. Data on ARs were available from all studies. Eight studies[40, 42-45, 47, 48, 50] reported details of systemic reaction to PhVIT and seven reported data on LLR.[40, 42, 44, 45, 48-50] One study reported data on local reactions.[40]

Details of further trial characteristics are reported in Table 5. None of the studies were conducted in the UK and outcomes were measured at different time points between 4 days and more than 3 years. Sponsorship was not reported in any studies but four studies[40, 45, 47, 49] were co-authored by the manufacturer and three[42-44] stated that the venom was provided by the manufacturer. Two studies[48, 50] reported providing venom and were co-authored by a manufacturer. No studies selected special populations though one[40] stated people selected had to have "significant risks of subsequent exposure whether in terms of actual physical risk of severe reactions or socially relevant impairment of the QoL due to fear of subsequent stings." However in their description of people included in the study they report on people with "low risk".

Table 5 Trial characteristics

Study ID	Setting	Country	Design	Duration of trial	Sponsorship	Special population
RCTs						
Golden 1980[41, 44]	NR	US	RCT	20 weeks	Provided venom	No
Mosbech 1986[45]	2 allergy clinics	Denmark	RCT	2.5-3 years	One author from Alllergologisk Laboratorium A/S (Producers of ALK Aquagen)	No
Müller 1987[46, 47]	NR	Switzerland and South Africa	RCT	14 weeks	One author from ALK Abello	No
Quercia 2001[49]	NR	Italy	RCT	4 days-6 weeks	One author from ALK Abello	No
Non RCTs						
Cadario 2004[40]	8 medical care units, outpatient	Italy	Interventions alternated in consecutive subjects	≥3 years	One author from ALK Abello	No*
Golden 1981a[43]	NR	US	Historical control group	20 weeks	Provided venom	No
Golden 1981b[42]	NR	US	Randomly selected pts from larger cohort compared with historical controls (some overlap of people)	2.5-2.75 years	Provided venom	No
Patriarca 2008[48]	Allergy department	Italy	People who declined SCIT were given SLIT	2 years	Provided venom and one author from ALK Abello	No
Thurnheer 1983[50]	Hospital with maintenance at family doctor	Switzerland	Quasi-experimental: groups determined by season	3 years	Provided venom and one author from Pharmacia	No

*Significant risks of subsequent exposure whether in terms of actual physical risk of severe reactions or socially relevant impairment of the QoL due to fear of subsequent stings. Patient table also includes people with low risk, NR=not reported

Inclusion/exclusion criteria

All studies recruited people who were shown to be allergic to *Hymenoptera* venom determined through skin tests and seven confirmed this diagnosis with IgE testing (the majority using RAST). No studies used a SC as a diagnostic tool or selected people on the duration of their allergy or particular demographics such as age or sex. Five studies[40, 42-44, 50] did not select people on species of venom allergy, two[45, 48] selected only wasp venom allergic people and two[47, 49] included bee venom allergic patient only. Severity of reaction was an inclusion criteria for three studies.[40, 49, 50] Two studies[40, 49] only included people with a Grade 2 or higher reaction as determined by an adapted Mueller grading system.[51] One study[44] stated that people with a sting related anaphylaxis had been included (Table 6). Only two studies reported any exclusion criteria, these being β-blocker therapy, cardiovascular, renal or respiratory disease or pregnancy in one study[48] and no previous VIT in the other study.[45]

Table 6 Inclusion and exclusion criteria

Study ID	Inclusion criteria							Exclusion criteria		
	Skin testing	**IgE**	**Diagnostic SC**	**Severity of condition**	**Duration of condition**	**Demographics**	**Species**	**Other/recent treatments**	**Other illness**	**Other criteria**
RCTs										
Golden 1980[41, 44]	Intradermal	RAST	No	Sting related anaphylaxis	No	No	*Hymenoptera*	No	No	No
Mosbech 1986[45]	Skin prick test	RAST	No	None	No	No	Yellow jacket (Wasp)	No	No	No VIT previously
Müller 1987[46, 47]	Intradermal	Yes	No	None	No	No	Honey bee	No	No	No
Quercia 2001[49]	Prick test and intracutaneous	RAST	No	≥ Grade 2 Mueller[8]	NR	No	*Apis mellifera* (honey bee)	No	No	No
Non RCTs										
Cadario 2004[40]	Prick and intradermal	RAST	No	≥Grade 2 Mueller [8] (revised by Wuthrich)[52]	No	No	*Hymenoptera*	No	No	No
Golden 1981a[43]	Intradermal	No	No	None	No	No	*Hymenoptera*	No	No	No
Golden 1981b[42]	Intradermal	No	No	None	No	No	*Hymenoptera*	No	No	No
Patriarca 2008[48]	Skin prick and intradermal	Uni CAP	No	None	No	No	*Vespula* (wasp)	β-blocker therapy	Cardiovascular, renal or respiratory disease	Pregnancy
Thurnheer 1983[50]	Intradermal	RAST	No	Grade 1-4 Mueller[51] with modifications by Huber[53]	No	No	*Hymenoptera*	No	No	No

RAST= Radioallergosorbent testing, UniCAP= an allergic Immunoanalyser,

Intervention characteristics

Details of the dosing protocols for each of the studies are described in Table 7. As many of the studies were looking at different regimens, the updosing protocols differed between the studies with PhVIT given in between six to 35 doses over 3 hours to 16 weeks. The maintenance dosing protocols were more similar across the studies with most studies reporting a maintenance dose of 100 ug every month/4 weekly. The exceptions to this were by Golden 1981a[43] which compared a monthly 100 ug maintenance dose with a monthly maintenance dose of 50 ug, Golden 1981b[42] which compared a 6 weekly 100 ug maintenance protocol with two historical groups who received a 100 ug maintenance dose every 4 weeks and Müller 1987[47] who compared a monthly maintenance dose of 200 ug with one of 100 ug. Outcomes were measured at between 2 weeks and 5 years of maintenance therapy. No trial reported pre-treatment with a HDA; two studies stated that no pre-treatment was used.

Table 7 Intervention characteristics

Study ID	Intervention	Updosing: frequency, dose(s) received on initial visit	Maintenance: dose and frequency	Duration of maintenance at time of reporting	Supplier/ trade name	Pre-treatment
RCTs						
Golden 1980[41, 44]	Slow therapy	**14 doses in 14 visits (weekly). Total 14 weeks** Week 1: 0.01 ug	Week 17: 100 ug Week 20: 100 ug	6 weeks	Pharmalgen® Pharmacia	NR
	Step therapy	**10 doses in 8 visits. Total 11 weeks** Initial: 1 ug, 5 ug, 10 ug (every 30 mins)	Week 13: 100 ug Week 15: 100 ug Week 18: 100 ug	9 weeks	Pharmalgen® Pharmacia	NR
	Rush therapy	**6 doses in 4 visits (2 weeks). Total 6 weeks** Initial: 1 ug, 5 ug, 10 ug (every 30 mins)	100 ug every 4 weeks	14 weeks	Pharmalgen® Pharmacia	NR
Müller 1987[46, 47]	HBV	**9 doses in 7 visits (weekly). Total 6 weeks.** Week 0: 0.1, 1.0, 3.0 ug	100 ug week 7, 9, 12, 16 then monthly	NR	Pharmalgen® or Reless	NR
	Monomethoxy polyethylene glycol-coupled HBV	**7 doses in 5 visits (weekly). Total 4 weeks.** Week 0: 0.5, 5.0, 10.0 ug	200 ug week 7, 8, 9, 11 then monthly	NR	Pharmalgen® Pharmacia	NR
Mosbech 1986[45]	Pharmalgen®	**26 doses in 13 visits (twice weekly). Total 13 weeks.(**>1 injection per visit initially until local swelling exceeded 5 cm in diameter.) Initial dose Vol 0.2 0.001 ug/ml concentration	100 ug or the dose four times giving local swelling >5 cm, 4+-1 weeks	2.5 to 3 years	Pharmalgen® Pharmacia	NR
	Alutard®	**19 doses in 19 visits (weekly). Total 19 weeks.** Initial dose 0.02, ug	100 ug or the dose four times giving local swelling >8 cm, 6+-2 weeks	2.5 to 3 years	Alutard® ALK Abello	NR
	Aquagen®	**26 doses in 13 visits (twice weekly). Total 13 weeks** (>1 injection per visit initially until local swelling exceeded 5 cm in diameter.) Initial dose Vol 0.2ug/ml concentration	100 ug or the dose four times giving local swelling >5 cm, 4+-1 weeks	2.5 to 3 years	Aquagen® ALK Abello	NR

Study ID	Intervention	Updosing: frequency, dose(s) received on initial visit	Maintenance: dose and frequency	Duration of maintenance at time of reporting	Supplier/ trade name	Pre-treatment
Quercia 2001[49]	Pharmalgen® cluster	**12 doses in 6 visits (every week). Total 6 weeks.** Week 1: 5 doses 0.01, 0.1, 1.0, 3.0, 6.0 (hourly)	100 ug per visit for weeks 2, 3 and 4 then every 4 weeks	5 years	Pharmalgen® ALK Abello	No
	Pharmalgen® Rush	**13 doses in 4 visits (every day). Total 4 days.** Day 1: 4 doses, 0.01, 0.1, 1.0, 2.0 (hourly)	100 ug per visit at weeks, 2, 3 and 4 then every 4 weeks	5 years	Pharmalgen® ALK Abello	No
	Depot cluster	**12 doses in 5 visits (weekly). Total 5 weeks.** Week 1: 4 doses 0.03, 0.1, 0.3, 1.0 (hourly)	100 ug per visit for weeks 2, 3 and 4 then every 4 weeks	5 years	Alutard® ALK Abello	No
Non RCTs						
Cadario 2004[40]	Aqueous induction and aqueous maintenance	**12 doses in 8 visits (weekly). Total 8 weeks** Week 1, 0.01 ug, 0.1 ug (30 mins between)	100 ug monthly	3 years	Pharmalgen® ALK Abello	No
	Depot induction and depot maintenance	**15 doses in 15 visits (weekly). Total 15 weeks** Week 1, 0.02 ug	100 ug monthly	3 years	Alutard® ALK Abello	No
Golden 1981a[43]	50 ug Maintenance	**6 doses in 6 visits (weekly). Total 6 weeks** 1 ug on first day	50 ug monthly	14 weeks	Pharmalgen® Pharmacia	NR
	100 ug maintenance[2]	**6 doses in 4 visits every 2 weeks. Total 6 weeks**	100 ug monthly	14 weeks	Pharmalgen® Pharmacia	NR
	100 ug maintenance[28]	**12 doses in 9 visits. Total 4 weeks.**	100 ug monthly	2 weeks	In house venom	NR
Golden 1981b[42]	4 weekly maintenance a	NA	100 ug every 4 weeks	2 years	Pharmalgen® Pharmacia	NR
	6 weekly maintenance	NA	100 ug every 4 weeks for 2 years then 100 ug every 6 weeks	2 years + 25-36 weeks	Pharmalgen® Pharmacia	NR

Study ID	Intervention	Updosing: frequency, dose(s) received on initial visit	Maintenance: dose and frequency	Duration of maintenance at time of reporting	Supplier/ trade name	Pre-treatment
	4 weekly maintenance b	NA	100 ug every 4 weeks	1 year	Pharmalgen® Pharmacia	NR
Patriarca 2008[48]	Ultra Rush SCIT	**6 doses in 1 visit (every 30 mins). Total 3 hours.** Day 1: 0.1ug	100 ug monthly	2 years	Pharmalgen® ALK Abello	NR
	Ultra Rush SLIT	**10 doses in 1 visits (every 20 mins). Total 3 hours.** Initial dose dilution1:10,000, 1 drop,	10 drops of pure extract given three times a week	2 years	Aquagen® ALK Abello	NR
Thurnheer 1983[50]	Conventional	**24 doses in 10 visits (weekly). Total 10 weeks** Day 1: 0.1 ml, (10-7 g/l) 0.1 ml (10-6 g/l), 0.1 ml (10-5 g/l),	1.0 ml, twice/week for 4 weeks 1.0 ml, weekly for 4 weeks 1.0 ml, every 2 weeks for 8weeks, 1.0ml monthly	3 years	Pharmalgen® ALK Abello	NR
	Rush	**35 doses in 10 visits (daily). Total 10 days** Day 1: 0.1 ml, 0.2 ml, 0.4 ml, 0.8 ml (10-7 g/l)	1.0 ml, twice/week for 4 weeks, 1.0 ml, weekly for 4 weeks, 1.0 ml, every 2 weeks for 8 weeks, 1.0 ml, monthly	3 years	Pharmalgen® ALK Abello	NR

Patient characteristics

The number of people recruited to each study ranged between 30 and 65 and the number included in the final analyses ranged between 19 and 56. The average age of participants was similar across studies and ranged between 35 and 49 years. All studies reported a higher percentage of males than females (between 57% and 88%). The severity of systemic reaction to the initial sting was reported in terms of Mueller grades[51] in four studies[49, 40, 48,50] and not at all by one study.[42] The remaining studies[35, 37-41] reported severity by clinical symptoms.

Table 8 Patient characteristics

Study ID	Name of intervention	N	Age (range) years	Male N (%)	Severity	Loss to follow up			
						Reason	Total N (%)	Final N	ITT
RCTs									
Golden 1980[41, 44]	Slow therapy	22	NR	NR	Cutaneous signs only=7/64 (10.9%) Urticaria=44/64 (68.8%) Dizziness or hypotension=43/64 (67.2%) Throat swelling or hoarseness=32/64 (50.0%) Dyspnoea=31/64 (48.4%) Loss of consciousness=19/64 (29.7%) Wheezing=5/64 (7.8%)	2 no SC not reached maintenance due to SR and LR reactions to VIT 1 no SC not reached maintenance as 2 month interruption in therapy	3 (13.6%)	19	No
	Step therapy	20				1 no SC due to cardiac status	1 (5.0%)	19	No
	Rush therapy	22				2 no SC due to illness or cardiac status 1 no SC only treated with polistes wasp venom 1 no SC whose anti-venom IgE was in doubt at the time	4 (18.2%)	18	No
Mosbech 1986[45]	Pharmalgen®	10	46 (21-62)	NR	Urticaria/angioedema=8/10 (80%) Respiratory symptoms=6/10 (60%) CNS symptoms = 5/10 (50%)	1 Immunotherapy with bee venom 1 Local and systemic side effects 1 other disease 1 lack of time 3 no SC reason unclear	7 (70.0%)	3	No
	Alutard®	12	41 (29-79)	NR	Urticaria/angioedema=11/12 (91.7%) Respiratory symptoms=7/12 (58.3%) CNS symptoms = 9/12 (75%)	1 Psychic reactions 1 Other disease 1 Unknown 1 Emigration 1 no SC reason unclear	5 (41.7%)	7	No
	Aquagen®	10	40 (24-60)	NR	Urticaria/angioedema=7/10 (70%) Respiratory symptoms=3/10 (30%) CNS symptoms = 7/10 (70%)	1 no SC reason unclear	1 (10.0%)	9	No
Müller 1987[46, 47]	HBV	17	34.5 (17-57)	15 (88.2%)	Urticaria/angioedema=3/17 (17.6%) Respiratory=10/17 (58.8%) Shock=4/17 (23.5%)	2 side effects 1 went abroad	3 (17.6%)	14	No
	Monomethoxy polyethylene glycol-coupled HBV	17	34.6 (17-70)	13 (76.5%)	Urticaria/angioedema=5/17 (29.4%) Respiratory=9/17 (52.9%) Shock=3/17 (17.6%)	None	0 (0%)	17	No

Study ID	Name of intervention	N	Age (range) years	Male N (%)	Severity	Loss to follow up			
						Reason	Total N (%)	Final N	ITT
Quercia 2001[49]	Pharmalgen® cluster	20	46.35 (28-76)	16/20 (84%)	Grade 1: 0 (0.0%) Grade 2: 10 (50.0%) Grade 3: 5 (25.0%) Grade 4: 5 (25.0%)	NA	0 (0%)	20	NA
	Pharmalgen® Rush	20	48.5 (18-73)	16/20 (84%)	Grade 1: 1 (5.0%) Grade 2: 5 (25.0%) Grade 3: 11 (55.0%) Grade 4: 3 (15.0%)	NA	0 (0.0%)	20	NA
	Depot cluster	15	41.47 (18-68)	13/15 (86.7%)	Grade 1: 1 (7.7%) Grade 2: 4 (30.8%) Grade 3: 6 (46.2%) Grade 4: 4 (30.8%)	NA	0 (0.0%)	15	NA
Non RCTs									
Cadario 2004[40]	Aqueous induction and aqueous maintenance	18	42.6 (19-69)	15 (83.3%)	Grade 2 =9 (50.0%) Grade 3 = 0 (0.0%) Grade 4 =9 (50.0%)		0 (0.0%)	18	NA
	Depot induction and depot maintenance	27	39.0 (15-68)	19 (70.4%)	Grade 2 =5 (18.5%) Grade 3 =9 (33.3%) Grade 4 =13 (48.1%)		0 (0.0%)	27	NA
Golden 1981a[43]	50 ug Maintenance	23	NR	14 (60.9%)	Cutaneous signs only=10/65 (15.4%) Urticaria=50/65 (77%) Dizziness or hypotension=41/65 (63.1%) Throat swelling or hoarseness=26/65 (40%) Dyspnoea/wheezing=27/65 (41.5%) Loss of consciousness=22/65 (33.8%)	4 not available for SC	4 (17.4%)	19	No
	100 ug maintenance[44]	22		13 (59.1%)		2 no SC: illness or cardiac status 1 no SC: only treated with polistes wasp venom 1 no SC: anti-venom IgG was in doubt at the time	4 (18.2%)	18	No
	100 ug maintenance[28]	20		13 (65.0%)		1 no SC: could not tolerate maintenance dose	1 (5.0%)	19	No
Golden 1981b[42]	4 weekly maintenance a		NR	NR	NR	1 not available for SC None others stated	NR	42	No
	6 weekly maintenance	30	NR	NR	NR	1 not available for SC	1	29	No
	4 weekly maintenance b		NR	NR	NR	1 not available for SC None others stated	NR	56	No

Study ID	Name of intervention	N	Age (range) years	Male N (%)	Severity	Loss to follow up			
						Reason	Total N (%)	Final N	ITT
Patriarca 2008[48]	Ultra Rush SCIT	20	35 (+-14)	16/20 (80%)	Grade I=1 (5%) Grade II =9 (45%) Grade III=4 (20%) Grade IV = 6 (30%)		0/20 (0.0%)	20	No
	Ultra Rush SLIT	21	38 (+-16)	15/21 (71.4%)	Grade I=3 (14.3%) Grade II =11 (52.4%) Grade III= 3 (14.3%) Grade IV =4 (19.0%)	2 lack of compliance 2 continued but did not have other outcomes measured	4/21 (19.0%)	17	No
Thurnheer 1983[50]	Conventional	21	36.3 (+-15.4) (6-69)	12/21 (57.1%)	Grade I=2 (9.5%) Grade II=3 (14.3%) Grade III=11 (52.4%) Grade IV=5 (23.8%)	1 pregnancy 1 treatment failure	2/42 (4.8%)	40	No
	Rush	21	36.1 (+-19.3) (11-70)	13/21 (61.9%)	Grade I=1 (4.8%) Grade II=5 (23.8%) Grade III=9 (42.9%) Grade IV=6 (28.6%)				

NA =not applicable, NR=Not reported

Outcomes

Although it was not their primary outcome, all but one study[49] reported clinical effectiveness outcomes; the study not reporting on clinical effectiveness only reported on ARs. The other eight studies reported the number of systemic reaction to re-stings and two reported the number of LLRs. For three studies[40, 48, 50] re-stings were FS and therefore not all people had been re-stung. The percentage of people re-stung in these studies were: Cadario[40] 24%, Patriarca[48] 35%, and Thurneer[50] 60%, the remaining studies used SC; the time-point of any re-sting (FS or SC) varied between studies but all occurred during treatment.

The incidence of systemic reaction to re-sting ranged from 0.0%[40, 44, 45] to 36.4%[50] (Table 9). Two studies[42, 43] compared the rate of systemic reaction across the arms of the studies and neither reported a significant difference between the arms.

Large local reactions were reported in two studies (Table 10). The frequency of LLRs was similar in the two arms of the Müller study[47] (35.7% and 41.2%) and differed between PhVIT administered subcutaneously and PhVIT administered sublingually in the Patriarca study[48] (88.9% and 50.0% respectively).

Table 9 Number of people re-stung and the number of systemic reactions reported

Study ID	Name of intervention	FS or SC	Time point	Final N	Re-stung n (%)	Systemic reaction n (%)	p*
RCTs							
Golden 1980[41, 44]	Slow therapy	FS (4), SC (52)	18-20 wks of VIT	19	19 (100%)	0 (0.0%)	NR
	Step therapy			19	19 (100%)		
	Rush therapy			18	18 (100%)		
Mosbech 1986[45]	Pharmalgen®	SC	2.5-3 yrs	3	3 (100%)	0 (0.0%)	NR
	Alutard®			7	7 (100%)	0 (0.0%)	
	Aquagen®			9	9 (100%)	0 (0.0%)	
Müller 1987[46, 47]	HBV	SC	~14 wks	14	14 (100%)	2 (14.3%) (angioedema)	NR
	Monomethoxy polyethylene glycol-coupled HBV	SC	~14 wks	17	17 (100%)	4 (23.5%), (Urticaria 1 (5.9%), Respiratory 3 (17.6%), Shock 2 (11.8%), Gastrointestinal =2 (11.8%))	
Non RCTs							
Cadario 2004[40]	Aqueous induction and aqueous maintenance	FS	3 yrs	18	5 (27.8%)	0 (0.0%)	NR
	Depot induction and depot maintenance	FS	3 yrs	27	6 (22.2%)	0 (0.0%)	
Golden 1981a[43]	50 ug maintenance	SC	20 wks of VIT	19	19 (100%)	4 (21.1%)	p=0.0587
	100 ug maintenance a[44]	SC	20 wks of VIT	18	18 (100%)	0 (0.0%)	
	100 ug maintenance b[28]	SC	6 wks of VIT	19	19 (100%)	NR	NR
Golden 1981b[42]	4 weekly maintenance a	SC	2 yrs	42	42 (100%)	1 (2.4%)	p >0.05
	6 weekly maintenance	SC	2 yrs+6-9 mths	29	29 (100%)	1 (3.4%)	
	4 weekly maintenance b	SC	1 yr	56	56 (100%)	1(1.8%)	
Patriarca 2008[48]	Ultra Rush SCIT	FS	During treatment	20	9 (45%)	1 (11.1%) (dizziness)	NR
	Ultra Rush SLIT	FS	During treatment	17	4 (23.5%)	1 (25.0%) (2/6 (33.3%) stings at 12 and 24 mths (throat constriction))	
Thurnheer 1983[50]	Conventional	FS (22), SC (2)	NR	40	24 (60%)†	4 (36.4%) (3 (27.3%) pts diminished SR (mild symptoms) 1 (9.1%) pts same SR) †	NR
	Rush		NR			3 (23.1%) pts (diminished SR (mild symptoms)) †	NR

NB Quercia 2001[49] does not report any outcome data. Data are for no. of people unless otherwise stated, * difference between arms of having a systemic reaction
† 24/40 pts were re-stung. 11 people in each arm were able to identify the insect and systemic reaction rates are reported for them

Table 10 Number of people re-stung and the number of large local reactions reported

Study ID	Name of intervention	SC or FS	Time point	Final N	Pts re-stung N (%)	N (%)
Müller 1987[46, 47]	HBV	SC	~14 weeks	14	14 (100%)	5 (35.7%)
	Monomethoxy polyethylene glycol-coupled HBV	SC	~14 weeks	17	17 (100%)	7 (41.2%)
Patriarca 2008[48]	Ultra Rush SCIT	FS	During treatment	20	9 (45.0%)	8 (88.9%)
	Ultra Rush SLIT	FS	During treatment	17	4 (23.5%)	2 (50.0%) (2/6 (33.3%) stings at 1 and 12 mths

Data are for number of people unless otherwise stated

Adverse reactions

Details of ARs during treatment were reported by eight studies: one study during induction only,[40] five during treatment (induction and maintenance) [44, 47-50] and two studies during maintenance only.[42, 45]

Systemic reactions during induction were reported in two studies. Cadario 2004[40] reported no difference in the frequency of systemic reactions in the aqueous and depot arms (11.1% and 7.4% respectively). Mosbech 1986[45] reported no systemic reactions in the PhVIT and non-PhVIT (ALK Aquagen®) arms and 3/10 people in the non-PhVIT (Alutard®) arm experienced systemic reactions during the induction phase (Table 11). Five studies[44, 47-50] reporting the frequency of systemic reactions during the whole treatment period reported frequencies of between 0.0% and 38.1%. The statistical difference between arms was calculated in two of these studies[44, 48] and no statistically significant difference was found. A third study reported the same rates in each arm (Table 11). [50]

Two studies[3742, 45] reported the rates of systemic reactions during maintenance therapy. In one[37] no reaxctions were reported and in Mosbech et al 1986[45] study 3/10 people experienced a systemic reaction (Table 11).

Cadario et al 2004[40] reported general local reactions during induction and showed a significantly higher rate of local reactions in the aqueous treatment arm (7/18 (38.9%) pts, 13/216 (6.0%) doses) than in the depot arm (4/27 (14.8%) pts, 5/405 (1.2%) doses) (p=0.0328 (pts), p=0.0004 (doses)) (Table 12).

The four studies[44, 48-50] reporting LLRs during treatment reported frequencies of LLR from subcutaneous PhVIT of between 6.7% and 60.0%. People receiving sublingual PhVIT (SLIT)[48] reported no LLRs. The difference in LLRs between arms was reported in one study[41, 44] with no difference in rates between the arms reported. Of the two studies[42, 45] reporting LLRs during the

maintenance phase of treatment, one[42] reported LLRs on average of six per 100 injections for the 4 weekly maintenance programme and two per 100 injections for the 6 weekly maintenance programme. The second study[45] reported that no LLRs occurred in any of the treatment arms (Table 12).

Table 11 Systemic reactions

Study ID	Name of intervention	Definition	Timing	N (%)	p
RCTs					
Golden 1980[41, 44]	Slow therapy	SR	During VIT	4/22 (18.2%)pts, 7/450 (1.6%) doses	p>0.05
	Step therapy			2/20 (10.0%) pts, 4/260 (1.5%) doses	
	Rush therapy			4/22 (18.2%) pts, 4/233 (1.7%) doses	
Mosbech 1986[45]	Pharmalgen®	SR	Updosing & Maintenance	0/10 (0.0%) pts, 0/3(0.0%) pts	NR
	Alutard®			3/10 (33.3%) pts, 0/7 (0.0%) pts	
	Aquagen®			0/12 (0.0%) pts, 0/9 (0.0%) pts	
Müller 1987[46, 47]	HBV	Objective SR	During VIT	4/14 pts (28.6%)	NR
	Monomethoxy polyethylene glycol-coupled HBV			2/17 pts (11.8%)	
Non RCTs					
Cadario 2004[40]	Aqueous induction and aqueous maintenance	During Induction SR* † Clinician reported using criteria of Lockey[54] and Mueller[51]	Early= within 60 mins Late = after 60 mins	All 2/18 (11.1%) pts, 9/216 (4.1%) doses, Early = 2/18 (11.1%) pts, 9/216 (4.1%) Late =0/18 (0.0%) pts, 0/216 (0%) doses	All p=0.3205 (pts) p=0.0339 (doses)
	Depot induction and depot maintenance			All = 2/27(7.4%)pts, 7/405(%) doses, Early= 0(0.0%) pts, 0(0.0%), Late= 2/27(7.4%) pts, 7/405(1.7%) doses	
Golden 1981b[42]	4 weekly maintenance a	SR	During maintenance	NR	NR
	6 weekly maintenance			0/30 (0.0%)	
	4 weekly maintenance b		NR	NR	
Patriarca 2008[48]	Ultra Rush SCIT	Mild general side effects (dysphagia, itching, headache and stomach ache	During VIT	1/20 (5%) pts	p>0.05
	Ultra Rush SLIT			2/21 (9.5%) pts	
Quercia 2001[49]	Pharmalgen® cluster	SR Grade 1-4 Mueller	During VIT	1/20 (5.0%) pts	Unclear
	Pharmalgen® rush			7/20 (35.0%)pts	
	Depot cluster			0/15 (0.0%) pts	
Thurnheer 1983[50]	Conventional	All SR grades SR grade 1-2 SR grade 3-4	During 3 year treatment	All = 8/21 (38.1%) pts, Grade 1-2= 7/21 (33.3%) pts, Grade 3-4 = 1/21 (4.8%) pts	NR
	Rush			All = 8/21 (38.1%) pts, Grade 1-2= 5/21 (23.8%) pts, Grade 3-4 = 3/21 (14.3%) pts	

*SRs were all grade 2 and LRs Oedema/erythema apart from 1 late LR which was local pruritus, **SRs were all grade 2 and LRs Oedema/erythema, † one patient also reported a mild SR during the maintenance phase, N.B Golden 1981a did not report on ARs, NR=Not reported

Table 12 Local reactions

Study ID	Name of intervention	Definition	Timing	N (%)	P
Cadario 2004[40]	Aqueous induction and aqueous maintenance	During induction LR* clinician reported using criteria of Lockey[54] and Mueller[51]	Early = Reactions within 60 minutes Late = Reactions after 60 minutes	All 7/18 (38.9%) pts, 13/216 (6.0%) doses Early=1/18 (5.6%) pts, 1/216 (0.5%) doses Late = 6/18 (33.3%) pts, 12/216 (5.6%) doses	All p=0.0328 (pts), p=0.0004 (doses)
	Depot induction and depot maintenance			All 4/27 (14.8%) pts, 5/405 (1.2%) doses Early = 1/27 (3.7%) pts 1/405 (0.2%) doses Late= 3/27 (11.1%) pts, 4/405 (1.0%) doses	
Golden 1980[41, 44]	Slow therapy	LLR	During VIT	9/22 (40.9%)pts, 37/450 (8.2%) doses	p>0.05
	Step therapy			12/20 (60.0%) pts, 31/260 (11.9%) doses	
	Rush therapy			11/22 (50.0%) pts, 22/233 (9.4%) doses	
Golden 1981b[42]	4 weekly maintenance a	LLR	During maintenance	6 per 100 injections	p=>0.05
	6 weekly maintenance	LLR		2 per 100 injections	
	4 weekly maintenance b	LLR	NR	NR	
Mosbech 1986[45]	Pharmalgen®	LLR	During maintenance	1/10(10.0%) pts	NR
	Alutard®			0/12 (0.0%) pts	
	Aquagen®			0/10 (0.0%) pts	
Patriarca 2008[48]	Ultra Rush SCIT	LLR	During VIT	3/20 (15%) pts	NR
	Ultra Rush SLIT			0/21 (0.0%)	
Quercia 2001[49]	Pharmalgen® cluster	LLR (Erythema >10 cm)	During VIT	4 (20.0%) pts	Unclear
	Pharmalgen® rush			4/20 (20.0%) pts	
	Depot cluster			1/15 (6.7%) pts	
Thurnheer 1983[50]	Conventional	LLR	During 3 year treatment	5/21 (23.8%) pts	NR
	Rush			3/21 (14.3%) pts	

N.B Golden 1981a did not report on ARs, NR=Not reported, LLR=large local reaction, LR=local reaction

5.3 Indirect analysis and mixed treatment comparisons

The possibility of conducting a MTC was investigated when no head-to-head studies were identified that compared PhVIT and alternative treatment options available in the NHS without VIT such as: advice on the avoidance of bee and wasp venom; HDA; AAI prescription and training. It was planned that studies that investigated non-VIT against non-PhVIT would be used in the MTC analysis to estimate the indirect treatment effect for PhVIT vs non-VIT. However, given the small number of trials and lack of head-to-head comparisons of PhVIT vs any intervention, pooling of all outcomes using standard meta-analysis was not possible. Any indirect analysis comparing PhVIT with any other intervention (including different doses and administration protocols of PhVIT) would be inappropriate owing to sparse data, heterogeneity in the study designs and in the characteristics of non-PhVIT and non-VIT interventions.

5.4 Additional data

Due to the lack of relevant comparative data on PhVIT, observational non-comparative studies of PhVIT have also been considered as well as comparative studies of non-PhVIT .

5.4.1 Observational studies of Pharmalgen®

In addition to the comparative studies of PhVIT included in this review the searches identified 17 observational studies of PhVIT in the treatment of bee and wasp venom allergy. It is likely that some of these papers are multiple publications from the same studies but in the following description they are assumed to be independent. All 17 studies assessed the rate of systemic reactions to subsequent stings, either FS or SC, after or during PhVIT.

All but one study[55] was conducted in Europe and all studies used a maintenance dose of 100 ug/ml of Pharmalgen®. The number of people receiving treatment ranged between 10 and 562 and the number of re-stings reported in each study ranged between 3 and 290. Three studies[56-58] included only children. Five studies[59-63] split results by insect venom type and a further two[64, 65] only reported outcomes for individuals with a bee venom allergy.

The timing of the sting differed between studies and as such has an important bearing on the rates of systemic reaction reported. Four[55, 61, 65, 66] reported re-sting during maintenance, four[60, 63, 64, 67] during updosing and maintenance, five[58, 62, 68-70] after PhVIT, two[56, 71] during or after PhVIT and two[57, 59] reported details of re-stings during PhVIT and after PhVIT.

The reported rates of systemic reaction ranged between 0.0% and 32.7%. This large range reflects differences in the timing of re-stings with 12 studies reporting data on re-stings before the completion of PhVIT. For the studies reporting systemic reactions after PhVIT three smaller studies[68-70] reported

no systemic reactions, two larger studies[57, 59] reported 4/200 (2.0%) and 8/274 (2.9%) systemic reactions respectively and the remaining two[58, 62]1/29 (3.4%) and 25/200 (12.5%) respectively.

Table 13 Characteristics of non-comparative Pharmalgen® VIT studies

Study ID	Country	Maintenance dose	N	No. of re-stings	No. of systemic reactions	Timing of stings	Type of sting	Comments	Special population
Carballada 2003[71]	Spain	100 ug/ml	241	84	12	During or after treatment	FS	84 stings in 58 pts	
Carballada 2009[56]	Spain	100ug/ml	21	7 pts	0	During maintenance or after	FS		4-16 years old
Carballada 2010[59]	Spain	100 ug/ml	Bee 438, Wasp 124	Bee 130 Wasp 68	Bee 5 Wasp 0	During treatment	FS	6 pts had a maintenance dose of 200ug/ml and 7 people could not tolerate Pharmalgen® and were changed to Aquagen® Do not distinguish between people or re-stings	
				Bee 62 Wasp 14	Bee 3 Wasp 0	After treatment			
Fricker 1997[67]	Switzerland	100 ug/ml	10	9	1	During treatment	3 FS 6 SC	9 stings in 6 pts	Confirmed urticaria pigmentosa
Graft 1987[57]	US	100 ug/ml	66	200	4	During or after treatment	130 FS 60 SC	200 stings in 49 children	4-17 year olds
				68	0	After at least 2 years of treatment			
Haeberli 2003[60]	Switzerland	100 ug/ml	Bee 158 Wasp 101	161	41	During treatment	SC	21 bee venom allergic pts were SC within 6 months of treatment	Some pts heavily exposed to bees/wasps
				Bee 104 (21 early) Wasp 57	Bee 34 Wasp 7				
Haugaard 1991[68]	Denmark	100 ug/ml	25	28	0	After treatment (mean 25.2 months (range 12 to 36 months).	SC	2 pts could only tolerate 60 ug, and 1 only 20ug	
Kalogeromitros 2010[66]	Greece	100 ug/ml	49	59	1	During maintenance	FS	59 stings in 14 pts	
Kochuyt 1994[61]	Belgium	100 ug/ml	217	290	1	During 12 week maintenance (19 mths treatment + bees 25 months (5-76) wasps 31.5 months (3-96)	FS	290 stings in 65 pts	
				Bee 213 Wasp 77	Bee 1 Wasp 0			Bees 213 stings in 17 pts Wasps 77 stings in 48 pts	
Lerch 1998[62]	Switzerland	100 ug/ml	358	200	25	After >=3 yrs	FS		

Study ID	Country	Maintenance dose	N	No. of re-stings	No. of systemic reactions	Timing of stings	Type of sting	Comments	Special population
				Bee 120 Wasp 80	Bee 19 Wasp 6	treatment stopped			
Müller 1989[64]	Switzerland	100 ug/ml	67	67 (29 early, 387 late)	15 (7 early)	During treatment	SC	18 pts had a 200ug/ml maintenance dose 29 pts had a SC in the first year of VIT (mean 4.41+-2.29 months) the remainder had a SC later in VIT treatment (mean 60.6+-21.3 months)	All bee allergic
Müller 1992 [63]	Switzerland	100 ug/ml	Bee 148 Wasp 57	Bee 148 (36 early) Wasp 57	Bee 34 (6 early) Wasp 5	During treatment	SC	31 pts had a maintenance dose of 200ug/ml 36 beekeepers had SC early into maintenance but the rest after at least 3 years of VIT	
Ramirez 1981[55]	US	100 ug/ml	22	12 pts	1 pt	During maintenance	SC	Itchy eyes and ears 20 minutes after sting	
Sanchez-Machin 2010[65]	Spain	100 ug/ml	54	3 pts	0	During maintenance	FS		All bee allergic
Schiavino 2004[69]	Italy	100 ug/ml	57	23 pts	0	After treatment	FS		
Szymanski 1995[70]	Poland	100 ug/ml	21	9 pts	0	After treatment	SC	12 pts did not have SC because contraindications or lack of consent	
Urbanek 1985[58]	Germany	100 ug/ml	66	29 pts	1pt	1 year after treatment	SC	2 yrs after treatment 2/14 mild systemic reaction	4-20 year olds

*number of re-stings unless stated otherwise, Treatment= updosing and maintenance phase, Early= sting performed within 12 months of starting VIT, Late= sting performed 12 months or more after starting VIT, pts=people, FS=field sting, SC=sting challenge,

5.4.2 Comparative studies of VIT other than Pharmalgen®

Whilst the remit of this review was to assess the clinical and cost effectiveness of PhVIT for the treatment of bee and wasp venom allergy, as discussed in Section 3.4.1 there are other VIT products that are available to treat bee and wasp venom allergy. The searches for this review identified one meta-analysis[72] and two systematic reviews[32, 73] reporting on comparative studies of non-PhVIT products in the population of interest, and an overview of the publications are summarised in Table 14.

Table 14 Summary of previous/ongoing systematic reviews/meta analyses

	Ross[72]	Watanabe[73]	Cochrane[32]
Publication year	2000	2010	In press
Databases searched (dates)	Medline (1966-1996)	MedlineLilacs; EMBASE; Scisearch; SciELO; Cochrane database of systemic reviews (All searched from beginning -2008)	CENTRAL (2010 issue 4~); Medline (2005- 2010); EMBASE (2007-2010); Psychinfo (1806-2010); AMED (1985-2010); LILACS (1982-2010); SIGLE Proceedings of the European Academy of Allergy and Clinical Immunology (EAACI) 2008-2010, American Academy of Allergy, Asthma and Immunology (AAAAI) 2008-2011 Plus details of ongoing trials were searched using The metaRegister of Controlled Trials The World Health Organization International Clinical Trials Registry platform The Australian and New Zealand Clinical Trials Registry The U.S. National Institutes of Health Ongoing Trials Register The Ongoing Skin Trials Register
No. of included studies	8	4	8
References of included studies	Graft 1984[74]; Hunt 1978[28]; Müller 1979[75]; Schuberth 1983[76]; Thurneer 1983[50]; Tsicopoulos 1988[77]; Wyss 1993[78]; Yunginger 1979[79]	Brown 2003*[80]; Hunt 1978[28]; Schuberth 1983[76]; Valentine 1990[81]	Brown 2003[80]*; Golden 2009[82]; Hunt 1978[28]; Oude Elberink 2001[83]/Oude Elberink 2002[84]/Oude Elberink 2006[85]; Oude Elberink 2009[86]; Schuberth 1983[76]; Severino 2008a[87]; Valentine 1990[81]
Design of included studies	7 of the 8 were open trials and all were “comparisons of the people’s history with post treatment experience.”	RCTs comparing Hymenoptera VIT with placebo or emergency treatment	RCTs comparing venom immunotherapy with placebo, no treatment, or back-up treatment for prevention of fatal insect sting anaphylaxis such as education and provision of self-administered adrenaline were included.
Other inclusion criteria	Full papers in English in refereed journals. Studies of subcutaneous VIT	None	All participants with a previous systemic reaction or large local reaction to any insect sting and a positive skin test and/or serum specific IgE to insect venom were included in this review, regardless of age, gender, ethnicity, or duration of insect sting allergy. Studies using standardised venom extract in any form of immunotherapy (subcutaneous or sublingual) were included. All appropriate allergens were included at all doses and all durations of treatment. We also planned to include studies that used a mix of different extracts, e.g. bee and wasp together. Placebo, no treatment, or back-up treatment for prevention of fatal insect sting anaphylaxis such as education and provision of self-administered adrenaline. In RCTs comparing more than one treatment arm to control group, only the treatment arm using standard venom extract compared to a control group was included in the analysis.
Exclusion criteria	Studies of oral, sublingual or other routes of administration	Other routes of administration such as sublingual; or oral were excluded	No other exclusion criteria

Reported outcomes	Protection against a major SR Specific IgE IgG tiers ARs	Changes in clinical manifestation after sting challenge or accidental stings Indication for VIT Changes in levels of venom-specific IgE or IgG antibodies	Systemic reaction to field or challenge sting Local reaction to field or challenge sting Quality of life ARs
Conclusions	The findings of this MA support the conclusion that (specific immunotherapy) is effective in the treatment of hymenoptera venom hypersensitivity	Specific immunotherapy should be recommended for adults and children with moderate to severe reactions, but there is no need to prescribe it for children with skin reactions alone, especially if the exposure is very sporadic. On the other hand, the risk-benefit relation should always be assessed in each case	Review in progress

Brown 2003 studies the effectiveness in fire ants which do not occur in the UK and is not treated with Pharmalgen®

The AG assessed the systematic reviews for quality using the database of abstracts of reviews of effect (DARE) quality assessment tool.[88] Both were shown to be of high quality.[32,73] Quality assessment is summarised in Table 15. One of the high quality reviews was a Cochrane review which is ongoing and the AG have worked in collaboration with this group on a number of systematic reviews.

Table 15 Quality assessment of systematic reviews of non-Pharmalgen® VIT studies

	Watanabe[73]	Cochrane[32]
Quality assessment		
Are inclusion/exclusion criteria reported that address the review questions?	Good	Good
Is there evidence of a substantial effort to search for all relevant research literature?	Good	Good
Is the validity of included studies adequately assessed?	Good	Good
Is sufficient detail of the individual studies presented?	Good	Good
Are the primary studies summarised appropriately?	Good	Good

Both of the systematic reviews[32, 73] and the meta-analysis[72] conclude that VIT is effective in preventing future systemic reactions to venom in venom-allergic people.

5.5 Health related quality of life

Whilst some studies have assessed the clinical efficacy of VIT, less research has been conducted on the psychological effects of VIT and *Hymenoptera* venom allergy. Frequency of re-sting in individuals who have undergone VIT is varied, and some individuals may not be stung again post-VIT. However, these individuals may experience anxiety related to the possibility of a future sting, which may impact on their QoL. Quality of life has been assessed in a series of papers by Oude Elberink, [85, 83, 84, 89] and a tool has been developed to specifically measure this: the Vespid Allergy Quality of Life Questionnaire (VQLQ).[85] The VQLQ has been found to have adequate cross-sectional and longitudinal validity.[90]

None of the included studies in our review reported data on the anxiety levels or the QoL of people receiving PhVIT. However in the wider literature there have been several papers published looking at the effect of VIT on people anxiety levels and their QoL. The current Cochrane review of VIT for the prevention of allergic reactions to insect stings[32] is investigating the evidence related to the QoL of VIT and their findings are included here (Table 16).

The Cochrane group searches identified four publications of RCTs reporting QoL data. The relationship between the different publications (Oude Elberink 2001;[83] Oude Elberink 2002;[84] Oude Elberink 2006;[85] Oude Elberink 2009[89]) is not clear and it is possible that one publication reports data on people which are also included in another publication. Therefore, for the purpose of this review it is assumed that the publications of Oude Elberink relate to two separate RCTs, one RCT of VIT for

treatment of adults with a history of anaphylactic reaction to yellow jacket sting (Oude Elberink 2001;[83] Oude Elberink 2002;[84] Oude Elberink 2006[85]) and one RCT of VIT for treatment of adults with a history of cutaneous reaction to yellow jacket sting.[89]

Both trials randomised consenting people to either VIT or an EpiPen®. At the end of the treatment period people who had been randomised to an EpiPen® were given the opportunity to receive VIT. People were asked to complete the Vespid Allergy Quality of Life questionnaire (VQLQ), the State-Trait Anxiety Inventory (STAI), and a burden of treatment (BOT) question (people were asked to weigh the advantages and disadvantages of their treatment on a 7-point scale, ranging from extremely positive (score 1) to extremely negative (score 7)). All measures were taken before treatment and after 1 year of treatment. Oude Elberink 2006[85] also reported results of accidental re-stings after 1 year of treatment.

Table 16 QoL RCTs: trial and patient descriptives

	Trial 1			**Trial 2**
	Oude Elberink 2001;[83]	**Oude Elberink 2002;[84]**	**Oude Elberink 2006;[85]**	**Oude Elberink 2009[89]**
Methods				
Design	Randomized, open label, controlled parallel group trial	Randomized, open label, controlled parallel group trial	Randomized, open label, controlled parallel group trial	Randomized, open label, controlled parallel group trial
Participants				
Country:	The Netherlands	The Netherlands	The Netherlands	The Netherlands
Age range:	Not stated	Adults(18 - 65 years)	Adults(18 - 65 years)	Adults(18 years and older)
Total number	101	74	94	29
Treatment group n Loss to follow up	50 not clear	36(16 males) 2	47 0	15 (9 males) 0
Control group n Loss to follow up	51 not clear	38 (18 males) 3	47 1	14 1
Species of insect venom(s) participants were allergic to:	Yellow jacket.	Yellow jacket.	Yellow jacket.	Yellow jacket.
Inclusion criteria:	History of systemic reaction to yellow jacket sting and 'sensitised to yellow jacket venom'	History of one or more anaphylactic reactions after yellow jacket stings and positive SPT or serum IgE test	History of one or more anaphylactic reactions after yellow jacket stings and positive SPT or serum IgE test	One or more dermal reactions following yellow jacket stings and positive SPT or serum IgE test
Exclusion criteria:	not stated	β-blocker therapy or if there was a need to carry an EpiPen® for other reasons, mastocytosis, or serious medical or surgical illness and pregnancy	β-blocker therapy or if there was a need to carry an EpiPen® for other reasons, mastocytosis, or serious medical or surgical illness and pregnancy	β-blocker therapy or if there was a need to carry an EpiPen® for other reasons, mastocytosis, or serious medical or surgical illness and pregnancy
Interventions				
Treatment:	Subcutaneous injections of VIT	Subcutaneous injections of VIT	Subcutaneous injections of VIT	Subcutaneous injections of VIT
VIT:	Pharmalgen®/Aquagen® ALK Abello	Pharmalgen®/Aquagen® ALK Abello	Pharmalgen®/Aquagen® ALK Abello	Pharmalgen®/Aquagen® ALK Abello
Duration:	One year	One year	One year	One year
Updosing:	Modified semi-rush protocol over approximately 6 week period	Modified semi-rush protocol over approximately 6 week period	Modified semi-rush protocol over approximately 6 weeks	Modified semi-rush protocol over approximately 6 week period
Maintenance dose:	100 µg every 6 weeks	100 µg every 6 weeks	100 µg every 6 weeks	100 µg every 6 weeks
Control:	EpiPen®	EpiPen®	EpiPen®	EpiPen®

	Trial 1			Trial 2
Outcomes		Systematic reaction to accidental insect sting	Systematic reaction to accidental insect sting	
	Quality of life using a 7 point health related quality of life score	Quality of life assessment using "vespid allergy quality of life" questionnaire (VQLQ) at 1 year	Quality of life assessment using "Burden of Treatment" questionnaire at one year	Quality of life assessment using "vespid allergy quality of life" questionnaire (VQLQ) at 1 year
Notes	May be some overlap with people in Oude Elberink 2002 and 2006 publications			

5.6 Additional information

5.6.1 Vespid Allergy Quality of Life questionnaire

In a study of 29 people with a history of LLR to yellow jacket sting Oude Elberink et al[89] reported that 53% had a significant improvement in QoL score (at least 0.5 points increase in VQLQ) at 1 year, in the immunotherapy group compared with 8% in the control group (range from 1-7). Mean VQLQ at the end of treatment was 5.84 in the immunotherapy group and 4.53 in the control group. In an abstract publication[83] the same research group reported a mean difference in QoL score change of 0.96 point improvement on a 1-7 scale after 1 year of yellow jacket immunotherapy in 50 people compared with 0.37 point deterioration in a control group of 51 people, all of whom had a history of systemic allergic reaction. A further publication[84] by the same research group in 69 people with a history of systemic reaction to yellow jacket sting reported 74% had a significant improvement in QoL score (at least 0.5 points increase in VQLQ) at 1 year with immunotherapy compared with 9% in the control group. Mean VQLQ at the end of treatment was 4.35 in the immunotherapy group and 2.90 in the control group. A meta analysis of the two studies for the outcome change in VLQL over time significantly favoured VIT over EpiPen® (Test for overall effect: Z = 36.25 (P < 0.00001).

5.6.2 Acceptability of treatment

The studies of Oude-Elberink[85, 83, 84, 89] reported patient views of the burden of treatment in both venom immunotherapy and control arms using a 7-point scale where a score of 1-3 was classed as a 'positive' view of treatment and a score of 4-7 as negative or neutral view of treatment. In their 2006 study[85] of people with a history of systemic reaction to yellow jacket sting, 44 of 47 immunotherapy treated people had a positive overall assessment of their treatment after 1 year, compared with 22 of 46 people in the control group (P<0.001); in their 2009 study[89] of people with a history of LLR to yellow jacket sting, similarly 93% of immunotherapy treated people and 42% of those in the control group had a positive overall assessment of their treatment at 1 year.

5.7 Summary of clinical evidence

Pharmalgen® VIT studies: comparative

- Nine studies of PhVIT were identified for inclusion in the review; none of the study comparators were non-VIT interventions
- One study compared PhVIT vs non-PhVIT; the others compared PhVIT vs PhVIT
- Four of the included studies were RCTs and five were quasi-experimental studies
- None of the studies were carried out in the UK
- Dosing protocols and administration protocols of PhVIT varied across studies
- Where re-sting data were available, the rate of systemic reactions ranged from 0.0%[40, 44, 45] to 36.4%[50] and timing of re-sting varied across studies
- Systemic reactions were reported at rates of between 0.0% and 38.1% and none were fatal
- None of the included studies reported QoL data

Pharmalgen® VIT studies: non-comparative

- Seventeen non-comparative studies of PhVIT were identified for inclusion in the review
- Reported rates of systemic reactions following re-sting ranged from 0.0% to 32.7%; 12 studies reported re-sting data before completion of VIT
- Post- PhVIT systemic reaction rates ranged from 2.0% to 12.5%
- None of the included studies reported QoL data

Health-related quality of life

- QoL not reported in any PhVIT study
- Two RCTs looked at QoL in people receiving a combination of PhVIT and Alutard® VIT (cross-over trial) vs EpiPen®
- Data showed that QoL of people receiving VIT improved more than those receiving an EpiPen®

Non-Pharmalgen® VIT studies: comparative

- Two systematic reviews and one meta-analysis assessed the clinical effectiveness of VIT vs non-VIT; none included any trials of PhVIT
- All three studies concluded that VIT was effective in reducing systemic reactions to re-stings when compared to non-VIT interventions

5.8 Discussion of clinical results and key issues

The aim of this clinical review was to evaluate the clinical and cost effectiveness of Pharmalgen® (PhVIT) in preventing future systemic reactions to bee and wasp venom in venom-sensitised people. To achieve this, comparisons were sought between the use of PhVIT vs any comparator (i.e. non-PhVIT and other non-VIT such as AAIs, HDAs and advice on the avoidance of bee and wasp stings).

No studies comparing PhVIT with non-VIT interventions were identified. Our search of the clinical-effectiveness literature identified nine trials for inclusion in the review. Five clinical trials compared PhVIT with PhVIT (different doses and administration protocols) and four studies compared PhVIT with non-PhVIT. Several RCTs have been published comparing VIT with non-VIT interventions; however, none of these studies have used PhVIT. The current PhVIT literature is therefore limited to RCTs (n=4) and quasi-experimental studies (n=5) comparing different methods of administering PhVIT, different PhVIT dosing protocols, and other non-PhVIT. Cohort studies reporting adverse reactions to PhVIT and/or the effectiveness of PhVIT in reducing systemic reactions to subsequent re-stings have also been published; 17 non-comparative studies of PhVIT were identified for inclusion in the systematic review.

The results of this review have been limited by the decision problem set by NICE which is focussed on the use of PhVIT. Only studies which include PhVIT as the intervention of interest were therefore included in the systematic review. Not only are there very few published studies of PhVIT but the AG is very much aware that the nine comparative studies included in the systematic review do not accurately reflect, in terms of updosing and/or maintenance programmes, the dosing and administration protocols described in terms of the EU licence and may or may not reflect current UK clinical practice.

The quality of the included clinical trials was poor; all of the trials were small, with none including more than 65 participants (range 6-65), and none were carried out in the UK. The authors of the included studies did not describe the method of randomisation used and there were imbalances in the rate of drop out between arms in all but one study.[50] There was heterogeneity between studies in the outcomes reported, the timing of re-stings, type and length of treatment and in proportion of people being re-stung. Differences were also found between studies in maintenance dosing protocol. Health outcomes were measured at between 2 weeks and 5 years of maintenance therapy, thus precluding accurate comparison of data between studies difficult. The quality of the non-comparative studies was not assessed by the AG.

Venom immunotherapy with Pharmalgen® carries with it a significant risk of systemic allergic reaction, with adverse reactions reported in up to 38% of those treated in studies included in this review. However, these adverse reactions were treatable and transient, and none were fatal.

Fatal sting anaphylaxis is estimated to occur in between two and nine individuals in the UK each year,[15] and due to the rarity of this outcome it is therefore not possible to conclude from either the data presented in the current review or from previous systematic reviews[32, 72, 73] whether PhVIT prevents fatal sting anaphylaxis.

Due to the low occurrence of FS, the clinical effectiveness of VIT is generally assessed via SC i.e. the number of subsequent re-stings in controlled circumstances that lead to systemic adverse reactions Of the eight included studies reporting re-sting rates, three[40, 48, 50] reported FS, with the proportion of people being stung ranging from 24% to 60%. This clinical evidence suggests there may be a degree of protection following PhVIT against systemic reaction to subsequent stings as the systemic reaction rates in these studies following (field) re-sting ranged from 0.0% to 36.4%, which is lower than those reported in 'natural history' studies of untreated people. However, unless all patients are re-stung (FS) true assessment of clinical effectiveness is uncertain.

The non-comparative studies generally support the results of the comparative studies in terms of rates of adverse reactions to PhVIT and reductions in systemic reactions following re-sting.

Only one study[84] was identified which compared a combination of PhVIT/Alutard® with a non-VIT comparator (EpiPen®); the study's main outcome was QoL and limited re-sting data were reported by the authors. It is not therefore possible to directly report on the clinical effectiveness of PhVIT vs EpiPen®.

Two systematic reviews[32, 73] and a meta-analysis[72] have concluded that VIT is effective in preventing future systemic reactions to venom in venom-allergic people. However, these studies included all types of VIT and it may not be possible to generalise the findings of these reviews to PhVIT due to differences in venom extracts and concentrations, and differences in administration methods. The AG notes that venom products for use in VIT are manufactured by several different companies, and some companies produce more than one venom product.

It was not possible for the AG to undertake meta-analyses or a MTC of PhVIT vs non-PhVIT due to the small number of published RCTs and the lack of head-to-head studies available.

The AG is of the opinion that there are limited clinical data to support the use of PhVIT in the treatment of patients with a history of type1 IgE mediated systemic allergic reactions to bee and/or wasp venom. Whether or not the results of the clinical review are generalisable to the UK population

is unknown as current clinical practice in the UK with PhVIT is varied. Clinical experts have advised the AG that PhVIT is always tailored to the needs of the individual as specified in the SmPC[31] which means that it may be inappropriate to focus on a single standardised programme of PhVIT. Interpretation of the clinical effectiveness data assessing PhVIT is problematic due to discrepancies in timing and delivery (FS vs SC) of re-sting.

Other systematic reviews[32, 73] comparing VIT with non-VIT indicate that VIT may be more effective than non-VIT in the treatment of patients with a history of allergic reaction to bee and/or wasp venom.

6 ASSESSMENT OF COST-EFFECTIVENESS

6.1 Systematic review of existing cost-effectiveness evidence

A systematic review of the economic literature was conducted to identify the existing evidence assessing the cost effectiveness of Pharmalgen® for the treatment of bee and wasp venom allergy. The search strategy shown in Section 5 was used to identify the relevant studies for inclusion in the review. Three studies were identified; two were full papers[91, 92] and one was in abstract format.[93] None of the studies compared PhVIT to AAIs, HDAs or avoidance advice, the studies were US based and costs were expressed in US dollars. The AG was unable to apply any systematic review evaluation checklist to the identified studies and therefore brief summaries of each study are reported below.

The study by Bernstein et al (1994)[91] was a 10-year observational study which reported the safety of using rapid VIT compared with modified rush VIT for people with hymenoptera anaphylaxis. In the study, patient mean age was 36.6 years; ten and four people received single honey bee and wasp VIT respectively, and eight people were injected with three different venoms at the same time (honey bee, wasp and mixed vespids). The paper showed that the use of rapid VIT was safe and time-saving for people to reach the dose for maintenance phase compared with modified rush VIT. A cost-analysis was conducted and indicated that rapid VIT is cheaper than modified rush VIT mainly due to reduced inpatient costs.

The study by Shaker[92] in 2007 was a cohort simulation study that evaluated prophylactic self-injectable adrenaline alone for the prevention of fatalities in mild childhood venom anaphylaxis. The cost-effectiveness analysis assumed that the baseline annual risk of venom fatality rate was 0.44 per 100,000 persons, and the estimated ICER was US$469,459 per year of life saved and therefore not cost-effective. Sensitivity analyses were conducted to explore alternative scenarios. When the fatality rate reached 2.2 per 100,000 persons at risk, the ICER was US$97,146 per year of life saved and self-injectable adrenaline appeared to be cost-effective; self-injectable adrenaline was increasingly cost effective with higher fatality rates. Age variation was also explored in the sensitivity analysis; the therapy became more expensive as the cohort aged with the ICER remaining well above the usual thresholds even for a cohort of 3-year olds (US $459,645).

The study by Brown et al (2006)[93] was published in abstract format, and only reported the cost-effectiveness analysis of VIT in children experiencing severe anaphylaxis used as cure and prevention. A Markov model was used taking into account clinical likelihood, QALYs saved, reduced deaths, and costs in US dollars. However, very limited data were available in the abstract. The paper concluded that VIT was cost effective when it was used for risk reduction ($US7876 per life year saved) and cure ($US 2278 per life year saved) in patients with a history of severe venom anaphylaxis at a greater risk of severe reactions.

6.2 Independent economic assessment

The results of the systematic review of cost-effectiveness literature revealed that there were no published economic evaluations relevant to the decision problem set by NICE. The manufacturer of PhVIT did not submit any clinical or cost-effectiveness evidence to NICE. The AG developed a *de novo* economic model designed specifically to compare the cost effectiveness of PhVIT with currently available NHS interventions in people with a history of type 1 IgE mediated systemic allergic reactions to bee and wasp venom.

6.2.1 Overview of Assessment Group model

An overview of the AG's *de novo* economic model is summarised in Table 17.

Table 17 Key characteristics of AG's economic model

Attribute	Economic model developed by the Assessment Group
Decision problem	The model has been structured to match the decision problem defined by NICE
Intervention	PhVIT (Pharmalgen®) (The model assumes that 92% of people receive conventional updosing and 8% use modified rush) The economic model considered PhVIT + HDA + AAI as the technology of interest as PhVIT is typically administered in combination with HDA + AAI
Comparator(s)	Comparators included according to NICE scope: High-dose antihistamine (HDA) Adrenaline auto-injector (AAI) Avoidance advice only The economic model considered (i) HDA + AAI and (ii) avoidance advice only as the two treatment alternatives of interest (based on clinical opinion)
Population	Individuals with prior systemic reactions to bee and/or wasp venom as well as positive test results for specific IgE antibodies Average age of 37 years is applied in the base case, a range of 5 to 55 years is explored in sensitivity analyses; gender is not considered a significant parameter in the economic model due to its lack of impact on clinical effectiveness and cost, this assumption is tested in the sensitivity analysis
Type of model	One year cohort decision tree model which can be extrapolated to have a horizon of multiple years. The only changes are reductions in the size of the cohort at the end of each year due to sting related death or death from other causes
Perspective costs	Costs from NHS Reference Cost 2009/10[94] and PSSRU 2010[95] are used
Drug costs	Drug costs from BNF 61[96] are applied as below: Pharmalgen® bee venom: £54.81 (updosing pack) and £63.76 (maintenance pack) Pharmalgen® was venom: £67.20 (updosing pack) and £82.03 (maintenance pack)
Economic evaluation	Cost-effectiveness analysis
Time horizon	Base case assumes a 10-year horizon while 5, 15, 20 and 25 years are explored in the sensitivity analysis
Outcome measure	Quality adjusted life years
Discount rate	An annual rate of 3.5% is applied to both costs and health effects in base case: 0% and 5% discount rate are applied in scenario analysis
Subgroup analysis	*'High Risk of Sting Patients'* and '*PhVIT Anxiety QoL improvement'* (which assumes PhVIT is not effective at reducing systemic reactions to sting compared to HDA and AAI but does improve QoL) are the only two subgroups considered
Sensitivity analysis	Sensitivity of several model parameters are tested (Table 25)
Scenario analysis	Several model scenarios are explored (Table 26)

6.3 Methods

6.3.1 Economic model

The economic model is constructed as a 1 year cohort decision tree that can be extrapolated to have a horizon of multiple years with the only changes being a reduction in the size of the cohort at the end of each year due to sting related death or death from other causes. The average age of the cohort increases with the time horizon of the model with all cause mortality rates changing as the average age of the cohort increases.[97] Development of a Markov model was not appropriate for disease modelling of the decision problem. To illustrate, with the exception of death, there is no transition into a state that results in changes to the key parameters; for example, being stung does not change the probability of experiencing a systemic reaction from future stings.

The available evidence for the key pathway parameters (likelihood of sting, resulting systemic reaction under different treatment arms and the likelihood of death following systemic reaction) is weak. As such, construction of probability distributions around these parameters was not feasible. Instead, a deterministic model was produced using the best available estimates with sensitivity and scenario analyses employed to test the impact of changing the parameters within plausible ranges.

A schematic of the first year of the model for PhVIT + AAI + HDA is shown in Figure 2. The schematic for subsequent years is identical with the exception that the updosing phase of VIT is no longer present and after PhVIT has stopped the maintenance phase ends. The model then simplifies into the number of stings per patient per year with resulting systemic reactions and the number of deaths from other causes. For the other treatment arms the model is essentially this simplified version of the intervention arm. The cohort is defined as 1000 patients who receive a full course of PhVIT; any extra costs due to non-adherence to treatment are considered implicitly if maintenance continues for 5 years rather than 3 years as described in the sensitivity analysis.

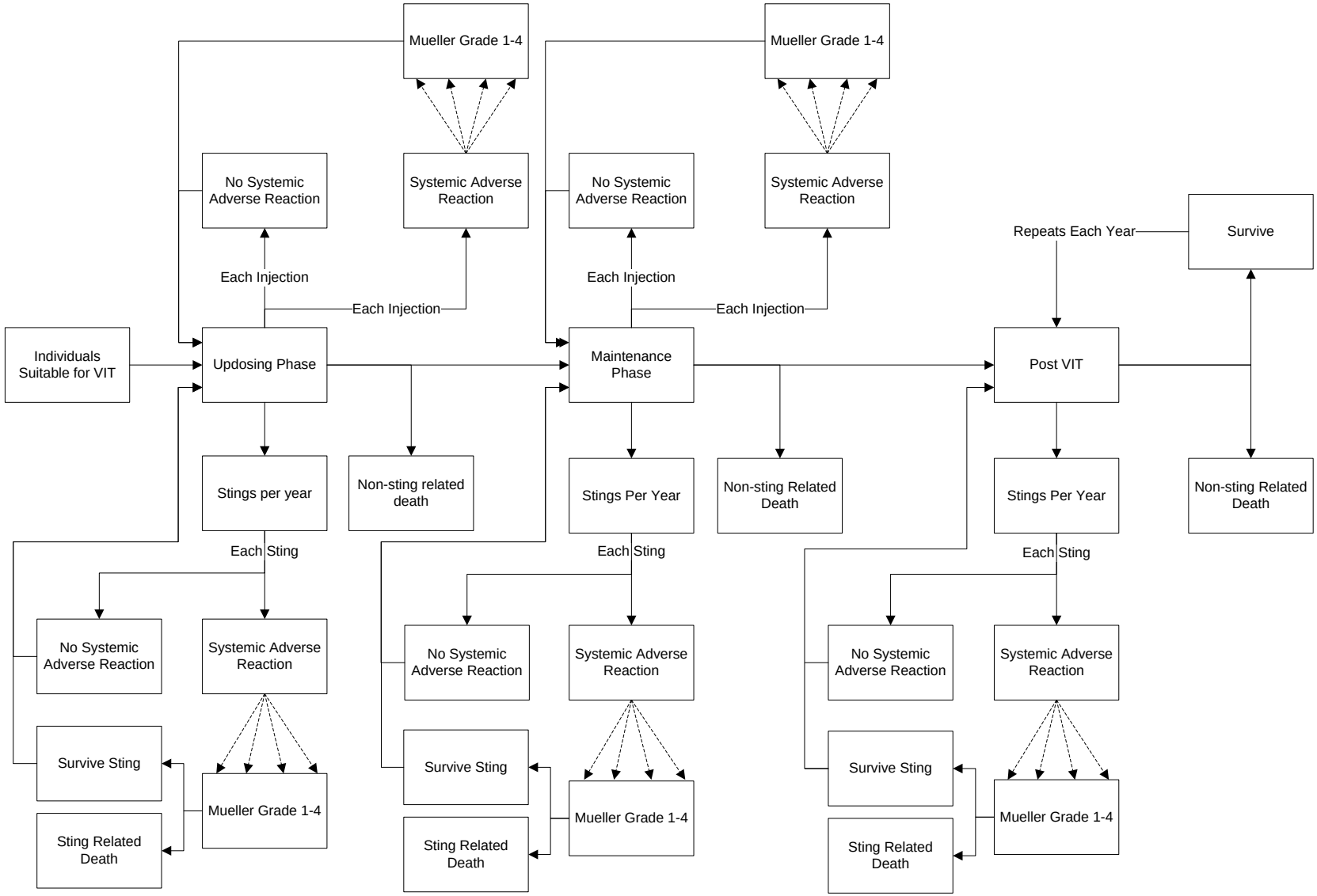

Figure 2 Schematic of the AG's *de novo* economic model in the first year

6.3.2 Treatment options to be evaluated

To provide evidence on treatment pathways we sent out 97 electronic questionnaires to immunology clinicians in allergy clinics in the UK to gather information to inform the economic modelling. The survey and summary results are presented in Appendix 4. This survey identified that approximately 97% (n=200) of people receiving PhVIT in the responding clinics were all provided with an emergency kit which included AAI and sometimes HDA.

The intervention of interest is not considered to be PhVIT in isolation but rather PhVIT in combination with an emergency kit of AAI and HDA. The emergency kit is assumed to be provided to the patient during PhVIT treatment and for the lifetime of the patient after treatment has ended. The comparators of interest are (i) an emergency kit of AAI and HDA **or** (ii) avoidance advice. It is assumed that avoidance advice is provided to all people regardless of receipt of PhVIT or an emergency kit.

Treatment pathways were determined through reviewing the included evidence on effectiveness of PhVIT in Section 5, a published audit of allergy clinics in the UK,[14] published guidelines[98] and our own survey (for results see Appendix 5).

For the PhVIT + AAI + HDA base case, the patient pathway is assumed to start after the individual has been assessed to be suitable for PhVIT. There are two phases to PhVIT – updosing and maintenance. During PhVIT an individual may experience local and systemic adverse reactions. As the cost and QoL considerations for anything but systemic reactions are considered to be zero (discussed below), the pathway and model only consider systemic adverse reactions by Mueller grade[51] (details of Mueller grade can be found in Table 1). The cost of treatment of adverse reactions is assumed to vary by Mueller grade.

The patient pathway assumes that each patient will experience an average number of sting events per year during or after PhVIT. A proportion of these stings results in systemic reactions of one of the four Mueller grades. A proportion of the Grade 4 systemic reactions can result in death. There is also a probability that each year a person can die because of causes unrelated to their sting allergy that is dependent on the age of people.

6.3.3 Patient population

The patient population considered includes people who would be considered for PhVIT as a result of their prior systemic reaction to bee/and or wasp sting and have positive test results for specific IgE antibodies. This reflects both the licensed indication and the study populations described in the available effectiveness evidence.

The average age of people starting PhVIT is taken from our survey of clinicians in UK allergy clinics. The survey was returned by 32 out of 97 clinics (33.0%), of which 16 responded that they used PhVIT. In these clinics approximately 200 people commence PhVIT for wasp and/or bee sting each year.

For simplicity of completion of the survey, an estimate of the percentage of PhVIT people starting in the clinic was requested for three age bands. Assuming people were on average in the middle of each age band (aged 50 in the 40+ band) a simple average age across responding clinics was estimated to be 37. This age is comparable to the average age reported in the trials included in the effectiveness review shown in Table 8. Sensitivity analysis was used to explore how the age of the individual when starting PhVIT influenced results, with a range between 5 and 55 years being explored.

Evidence from published studies suggests the majority of people undertaking PhVIT are male. In the base case 80% of people are assumed to be male. As effectiveness and cost are not linked to gender, and age-related QoL norms vary only marginally by gender, it was not anticipated that this would have a significant bearing on results. To test this assumption, two scenarios were created; one where all people were male ("100% male") and one where all people were female ("100% female").

6.3.4 Model parameters

The choice of parameters and their values used in the model is based on the available published literature, discussion with UK clinicians and the results of the short economics survey of UK allergy clinics (Appendix 4).

Annual number of stings for people in receipt of Pharmalgen® venom immunotherapy

The model requires an estimate of the annual number of times an individual receiving PhVIT will be stung. No data were available from the UK but six studies[40, 48, 50, 84, 99, 100] identified in the literature search did contain data on FS during/following treatment with VIT. These studies provided detailed information on the number of FS events over a specified time period and included more than ten people in each study. Other studies, notably observational studies, did provide information on FS but were either too small (10 or fewer people) or did not provide a specific length of follow up over which the FS occurred. Findings from the six included studies are summarised in Table 18.

Table 18 Field sting data during/following treatment with VIT

Study	Country	Number of people	Number people with re-stings	Number of years	Stings per year per person
Haye 2005[99]	Norway	315	201	5	0.128
Roesch 2008[100]	Germany	146	65	6.5	0.068
Oude Elbrink 2002[84]	Netherlands	148	2	1	0.014
Cadario 2004[40]	Italy	45	11	3	0.081
Patriarca 2008[48]	Italy	41	13	2	0.159
Thurnheer 1983[50]	Switzerland	40	22	3	0.183
Total	-	735	314	4.09 (weighted average)	0.095

None of the studies listed above is significantly methodologically stronger than the others and as such a simple pooling of the studies through a weighted average was used to generate an average number of stings per year (0.095); this rate compares favourably to the rates of FS reported by Cadario[40] (Section 5.5.2). In the base case this value (0.095) is used. Sensitivity analysis varies the annual number of stings between lowest and highest published rates (0.014 to 0.183). The lower value addresses the issue that bee and wasp stings are not separated in the above data and no evidence was found in the review detailing how people with wasp allergy react with bee sting and vice versa. If people allergic to one of the venoms are no more likely to have an allergic reaction to another venom from a different insect, then the reference rate of sting used in the base case in the economic model may overestimate the actual rate and so the number of stings to which PhVIT people could have an allergic reaction could be lower than the base case.

Findings from these studies and from the observational studies indicated that there were people that experienced multiple stings. For example, whilst Kochuyt 1994[61] did not provide detailed information on length of follow up, as this varied, the study found that 17 people suffered 213 bee stings during follow up whereas 18 people had no FS during follow up. This could be explained by differential follow up periods, but could also suggest that there are some people undergoing VIT who are at significantly higher risk of sting than others. This is supported by the fact that one of the factors in considering suitability for PhVIT is that an individual has an occupation or lifestyle that substantially increases their risk of sting.

A subgroup analysis ("High Risk of Sting People") was used to explore how people with substantially increased rates of sting affected the model findings. This subgroup has a base number of five stings per year with sensitivity analysis exploring the impact of one to ten stings per year.

Systemic adverse reactions due to Pharmalgen® venom immunotherapy

Systemic adverse reactions due to PhVIT are included in the model as the likelihood of systemic adverse reaction following each PhVIT injection. Non-systemic adverse reactions are not included in the base case as evidence from the effectiveness review suggests that local reactions, even if large, are short lived and, based on discussion with clinical experts, do not incur any cost beyond the occasional use of topical or oral antihistamines. In a scenario analysis ("PhVIT Local Adverse Reactions"), we explored the impact of ignoring local reactions by assuming 25%, 50%, 75% and 100% of post-injection adverse reactions results in local reactions that require the administration of an antihistamine cream.

Evidence from studies described in Section 5 states that the rate of systemic adverse reaction per patient due to PhVIT is between 0% and 38.1% during treatment. However, only two papers provided the dose risk of systemic reaction. During the updosing phase, Golden 1980b[44] suggests a dose risk of systemic adverse reaction of 1.6% and a rate of 2.6% is taken from Cadario 2004.[40] A pooled estimate across people within these trials suggests a dose risk of systemic adverse reaction during updosing of 2.0% and this is used in the base case. Sensitivity analysis explores rates between 0% and 2.6%; the model has therefore explored what happens with higher or lower plausible values for systemic adverse reactions no matter the reason for the increase/decrease (e.g. if there are more/fewer systemic adverse reactions with bee PhVIT compared with wasp PhVIT).

No studies were found that reported any dose risk leading to systemic adverse reaction during the maintenance phase. However, Haye 2005[7] in a cohort study of 315 people receiving VIT found 138 people had a systemic adverse reaction during updosing phase and 59 during maintenance phase. Insufficient detail was provided to calculate the number of injections this related to. However, our base case assumes that over 3 years with a 4 week interval at maintenance and 12 injection updosing phase (conventional protocol) there are approximately three times as many injections during maintenance as updosing. If the same updosing: maintenance injection ratio is applied in the model as described in the Haye 2005[7] study, 7.8 systemic adverse reactions would occur during updosing for every one during maintenance. Applying this ratio to our base case dose risk of systemic adverse reaction during updosing suggests a dose risk during maintenance of 0.26% and this is used in the model base case.

A scenario analysis assumes a dose risk in maintenance that is equal to that in updosing ("Equal AE risk Updosing/Maintenance") and sensitivity analysis explores dose risk values in maintenance of 0 to 1%.

Thurnheer 1983[50] is the only study that provides information on the grade of systemic adverse reaction. This study reported 75% of systemic adverse reactions are Grade 1-2 and 25% Grade 3-4. Data on sting systemic reaction in people without VIT (Table 19) suggests that only a very small

percentage of systemic reactions are Grade 4 (1.1%). As such we assumed that Grade 1-2 reactions are split evenly between grades so in the base case Grade 1 and Grade 2 are 37.5% of the total.

Scenario analysis explored if 100% of reactions are Grade 1 ("ARs all Grade 1") and all the Grade 3/4 reactions are Grade 4 ("25% ARs Grade 4").

Death due to PhVIT was not reported in any published study we identified and was assumed to be zero in the base case and was not varied in either sensitivity analysis or scenario analysis.

Systemic reactions due to stings

The model requires estimates of systemic reaction due to a sting for the three treatment arms: PhVIT + HAD + AAI vs HAD + AAI vs avoidance advice only.

For avoidance advice only, whilst the risk of sting may be reduced (which is accounted for by looking at the rate of sting in people who have received PhVIT – all of whom are assumed to have been given vespid sting avoidance advice) the rate of systemic reaction following sting is assumed to be equal to that of allergic people suitable for PhVIT but with no treatment.

Bilo et al 2005[12] report repeat anaphylactic risk rates following sting, assuming an episode in the past, as between 60% and 79%. This appears to be a lifetime risk rather than a per sting risk. Reismann 1992[101] reported the results of a survey of 220 people who had not received VIT but who had had a systemic reaction to sting in the past and had received a second sting since the first event. There were 124 of these people who had a systemic reaction on second sting. This suggests that the probability of systemic reaction in people with previous history of systemic reaction following sting but without PhVIT is 56.4% per sting and this is used as the base value for the avoidance advice arm.

The grade of systemic reaction following sting without VIT is taken from a survey by Roesch 2008[100] in Germany of people' reaction to sting before VIT. This is provided in Table 19 below.

Table 19 Percentage of people with different grades of systemic reaction

Grade	People with systemic reaction following a sting without VIT (%)	People with systemic reaction following a sting with VIT (%)
Grade 1	6.5%	38.5%
Grade 2	80.3%	54.0%
Grade 3	12.1%	7.5%
Grade 4	1.1%	0%

The risk of systemic reaction following PhVIT was calculated by pooling the sting data from the available trial data described in Section 5. The pooled data suggest that of 337 people stung following PhVIT there were 22 systemic reactions, a rate of 6.5% per sting; from the data available it was not possible to estimate a more accurate systemic reaction rate per sting as the systemic reaction rates are

reported at different times in PhVIT studies. This rate is supported by the evidence from the observational trial studies included in Section 5.4.1. In sensitivity analysis the rate of systemic reaction explored with PhVIT ranges from 5% to 15%.

Whilst some authors report effectiveness of 100%, these studies are small and, given other studies have found systemic reactions with PhVIT, the balance of evidence does not support suggesting 100% effectiveness for PhVIT in stopping systemic reactions. Evidence that effectiveness declines over time is mixed so in the base case it is assumed that there is no decline in effectiveness over time. A scenario analysis assumes that effectiveness declines smoothly from 5% at the end of therapy year 1 to 15% at 10 years following the end of therapy ("Declining VIT Effectiveness").

Evidence on effectiveness of PhVIT suggests that the severity of systemic reaction following sting is reduced with PhVIT but trials that actually reported the grade of systemic reaction were too small to establish the actual impact on grade of systemic reaction.

The survey by Roesch 2008[100] that provided grade of systemic reaction to sting for people before VIT also provided the grade of systemic reaction for the same people following sting after having received VIT. Whilst these are observational rather than trial data, in the absence of more robust data, it is the best evidence available for use in the model. The rate of systemic reaction following sting with VIT is also shown in Table 19 Percentage of people with different grades of systemic reaction

High dose antihistamine (HDA) is given as an emergency treatment following a sting to reduce the possibility and severity of systemic reaction. The results of our survey found that clinicians advise the use of AAI following a sting only if symptoms of systemic reaction occur. Therefore AAI can only reduce the severity of systemic reaction. However, for both HDA and AAI there is no published evidence to support the use of these interventions in the treatment of systemic allergic reactions.[102, 103] Effectiveness therefore has to be assumed. For simplicity, in the base case, HDA is assumed to be 25% as effective as VIT at reducing the likelihood of systemic reaction meaning the risk of systemic reaction is 43.9% with no reduction in severity of reaction. Adrenaline auto-injector is assumed to reduce the number of Grade 3 and Grade 4 systemic reactions by half of the reduction with VIT with these reactions evenly distributed between Grade 1 and Grade 2 reactions but AAI does not reduce the possibility of systemic reaction.

The addition of AAI and HDA to PhVIT is assumed not to alter the effectiveness of stopping or reducing the severity of systemic reaction compared to PhVIT alone.

As these assumptions are without an evidence base, it is important that scenario analysis is used to explore how important these assumptions are to model findings. Therefore a scenario is used where AAI + HDA is assumed to be no more effective than avoidance advice only i.e. they make no

difference to the likelihood or severity of systemic reaction following sting ("AAI + HDA No Systemic Reaction Effectiveness"). A separate scenario analysis assumes that AAI + HDA is as effective at reducing the likelihood and severity of systemic reaction as PhVIT, although an increase in QoL through reduced sting anxiety with PhVIT is introduced. This is discussed further in the section discussing QoL in the model.

Local reactions to sting are assumed to be trivial in terms of both cost and QoL impact and so are excluded from the model.

Deaths following sting

Deaths following sting are rare in the UK (and the rest of the world) so making an estimate of the death rate following sting is difficult. Whilst deaths due to sting are recorded, it is not known how many of these people received VIT or how many sting events this relates to.

To provide an estimate of sting death rate an indirect approach was taken based upon the findings from Pumphrey 2004.[104] The survey reported an average of 20 deaths due to allergic anaphylaxis (all causes) per year in the UK. Hospital episode statistics (HES)[105] data suggest that there are approximately 1600 inpatient episodes due to anaphylaxis each year. Combining these facts suggests a death rate following anaphylaxis (which we assume in the model to be a Mueller Grade 4 reaction) of 1.25%. This rate is used in the model in the base case by assuming that death from allergic anaphylaxis is independent of the allergen.

As the probability of Grade 4 reaction with PhVIT is assumed to be 0% then, by default, the death rate with PhVIT due to bee/wasps sting is assumed to be zero.

With no published range of fatality rates following sting, sensitivity analysis undertaken around this parameter explores the effect of the value being 50% higher and lower than the base case.

Quality of life

The model estimates the number of deaths and life years under each treatment arm over the time horizon chosen. The life years are adjusted to calculate QALYs by using age dependent EQ-5D Weighted Heath Status Index population norms published by the University of York.[106]

Evidence[84, 89] presented in Section 5 shows that fear of sting in some people not receiving VIT reduces QoL and this is at least partly negated by PhVIT. However, no evidence is available to support this finding using a validated utility measure such as EQ-5D.[106] As such, in the base case no change in utility due to anxiety is assumed. Having a systemic reaction could potentially impact on QoL and different severities of reaction could impact on QoL differently. Unfortunately there is no evidence on utility levels during a systemic reaction and as such the QoL differences resulting from the number of

systemic sting reactions in different treatment arms are not included in the model. This means that any health benefits from VIT are entirely due to its effectiveness in reducing systemic reactions from sting and resulting deaths.

A separate subgroup analysis assumes that anxiety of sting does affect the utility of some people and that VIT reduces this anxiety and so negates this loss in QoL ("VIT Anxiety QoL Improvement"). The survey of EQ-5D norms[106] by the University of York suggested that a Level 2 "anxiety/depression" health state health induces a detriment to utility of 0.07 per year. A Level 2 "usual activities" health state induces a utility decrement of 0.036. The actual reduction would not make a significant difference to the findings of the economic model, but provides an indication of the likely scale of the positive benefit from PhVIT.

The actual reduction in utility per person per year is unlikely to exceed 0.16 in total if the fear of sting causes both a reduction in utility due to anxiety and interferes with usual activities. As a cautious estimate we assume that the actual reduction in utility due to fear of sting is 25% of the potential 0.16 per person per year maximum and that this is alleviated by PhVIT by 25%. This means that having PhVIT increases utility by 0.01 per person per year.

This can be interpreted as a cautious estimate of the impact of PhVIT on utility. Sensitivity analysis explores increases in utility from PhVIT between 0.004 and 0.04 (10% to 100% of assumed decrease in utility due to anxiety) per person per year.

As stated previously, a separate scenario analysis explores the cost effectiveness of PhVIT assuming it is not effective at reducing systemic reaction to sting compared to AAI + HDA but does improve utility ("PhVIT Anxiety QoL Improvement Only"). The improvement in utility from PhVIT is assumed to be the same as the base case but sensitivity analysis explores HDA + AAI with the same increase in QoL with PhVIT.

Cost of treatment and health states

The model requires estimates of the costs of treatment in the different intervention arms as well as healthcare costs in different health states, specifically from systemic adverse reactions to PhVIT and systemic reactions to sting.

To produce these estimates a range of unit costs is applied to resource use. The resources considered in the model and the unit costs are provided in Table 20.

Table 20 Resources and unit costs used in the model

Resource	Unit		Unit Cost	Source
A&E attendance	Per attendance		£103	NHS Reference Costs 2009/10[94] (code: TAandEMSNA)
Inpatient stay	Per day		£350	NHS Reference Costs 2009/10[94] (code: WA16Y)
AAI (EpiPen®)	Per injector		£28.77	BNF 61[96]
Ampoule of adrenaline	Per 1 ml ampoule		£0.57	BNF 61[96]
Syringe and needle	Per syringe/needle		£0.10	Assumed
HDA	Per dose		£0.14	BNF 61[96] (average of 4 most commonly used HDAs)
Allergy clinic nurse specialist	Per minute		£1.07	PSSRU 2010[95]
Pharmalgen® bee venom	Per kit	Initial pack	£54.81	BNF 61[96]
		Maintenance pack	£63.76	BNF 61[96]
Pharmalgen® wasp venom	Per kit	Initial pack	£67.20	BNF 61[96]
		Maintenance pack	£82.03	BNF 61[96]

Cost of drugs and drug administration

Following published clinical guidelines,[98] administration of PhVIT was assumed to include the use of a syringe, a prophylactic HDA, time involved in a pre-injection health check, venom injection preparation and post-injection observation (this has been defined as individuals staying in the consulting room with specialists to be seen if any immediate reactions manifest). No published information was available on the actual resource usage of these individual elements so values were assumed by the AG and then verified by a consultant in an allergy clinic.

The model assumes that bee, wasp and bee plus wasp PhVIT are equally effective. However, the cost of Pharmalgen® for these treatments varies. Our survey of UK allergy clinic clinicians suggested that approximately 23% of people are bee allergic, 70% of people are wasp allergic, and 7% both. These proportions are used in our base case but scenario analysis explores the difference in findings if people are 100% bee allergic, 100% wasp allergic or 100% both.

According to the manufacturer's SmPC,[31] conventional updosing is done weekly for 12 weeks with one injection per visit. A modified rush protocol is made up of 16 injections over a period of 7 weeks. The published allergy clinic survey suggests that 92% of people receive conventional updosing and 8% use modified rush. These values are used in the model and scenario analysis is used to explore the importance of the type of protocol on results ("100% Conventional" and "100% Modified Rush").

In the base case the maintenance phase is assumed to be 3 years following updosing. This is varied in the sensitivity analysis between 3 and 5 years. The interval between injections during maintenance

phase is 4 weeks as per available guidelines but sensitivity analysis explores the impact of intervals of between 5 and 8 weeks.

The resources used and costs associated with PhVIT administration are shown in Table 21below.

Table 21 Resource use and cost of administering PhVIT

Resource	Unit	Usage (sensitivity analysis)	Cost
Prophylactic high dose antihistamine	Per visit	1 dose	£0.14
Pre injection health check (Nurse specialist time)	Per visit	15 minutes (10-20 minutes)	£16 (£10.67 to £21.33)
Venom injection preparation (Nurse specialist time)	Per dose	5 minutes (3-7 minutes)	£5.33 (£3.20 to £7.47)
Post injection observation (Nurse specialist time)	Per dose	3 minutes (2-4 minutes)	£3.20 (£2.13 to £4.27)
PhVIT costs updosing	Updosing phase	1 kit	£68.19*
PhVIT costs maintenance	Per injection	Quarter of a kit	£20.57

*cost differs slightly from costs in Table 20 because a mix of bee and wasp venom is assumed

The emergency kit is assumed to comprise a HDA and AAI. The AAI is assumed to be EpiPen® and have a shelf life of 18 months after which a new one is issued. The HDA in the emergency kit is assumed to be replaced annually. Avoidance advice is assumed to constitute a 60 minute consultation with a nurse specialist at a cost of £64 from PSSRU 2010.[95] As these costs are added equally to all three intervention arms the actual cost incurred should make no difference to the results of the incremental analysis and so no sensitivity analysis was performed around these values.

Treatment of systemic adverse reactions to PhVIT

For local adverse reactions to PhVIT the costs of treatment are considered to be trivial involving the administration of an antihistamine cream or ice pack. The model focuses on systemic reactions.

No data were available describing the resources used to treat systemic adverse reactions; therefore assumptions were made and then checked with an allergy clinic clinician. In the base case we assume that in all cases of systemic adverse reaction to PhVIT a HDA would be given and an ampoule of adrenaline drawn and administered by a nurse. The clinician suggested that in all cases of systemic adverse reaction people would be observed closely for at least 30 minutes following emergency treatment. It is assumed that all Grade 4 systemic reactions result in close observation by a nurse for 60 minutes and 50% of people require a hospital inpatient stay for overnight observation. The resource use associated with systemic adverse reactions is provided in Table 22. Scenario analysis explores the cost of systemic reaction that is 50% higher ("50% Higher Systemic AR Cost") and 50% lower ("50% Lower Systemic AR Cost") than the total cost and a scenario analysis also explores the impact of no Grade 4 systemic reactions resulting in an inpatient stay ("No Admissions Due to Systemic Adverse Reactions").

Table 22 Resource use and costs due to systemic adverse reaction to PhVIT

	Grade 1-3		Grade 4	
	Resource use	**Cost**	**Resource use**	**Cost**
Antihistamines	1 dose	£0.14	1 dose	£0.14
Adrenaline	1 ampoule	£0.57	1 ampoule	£0.57
Needle/syringe for adrenaline	1	£0.10	1	£0.10
Observation time in unit (Nurse specialist time)	30 minutes	£32.00	60 minutes	£64.00
Inpatient stay (1 day)	0% of people	£0.00	50% of people	£175.00
Total cost		£32.81		£239.81

Treatment of systemic reactions to sting

Resource use and costs related to systemic reactions to sting are displayed in Table 23 and Table 24.

Table 23 Resource use and costs due to systemic reactions to sting for patients in PhVIT + AAI + HDA and AAI + HDA arms

	Grade 1		**Grade 2**		**Grade 3**		**Grade 4**	
	Resource use	**Cost**	**Resource use**	**Cost**	**Resource use**	**Cost**	**Resource use**	**Cost**
A & E visit	100% of patients	£103	100% of patients	£103	100% of patients	£103	100% of patients	£103
Inpatient stay	0% of patients	£350	10% of patients	£350	30% of patients	£350	50% of patients	£350
Anti-histamine	1 dose	£0.14	1 dose	£0.14	1 dose	£0.14	1 dose	£0.14
EpiPen®	1	£28.77	1	£28.77	1	£28.77	1	£28.77

Table 24 Resource use and costs due to systemic reactions to sting for patients in avoidance advice only arm

	Grade 1		**Grade 2**		**Grade 3**		**Grade 4**	
	Resource use	**Cost**	**Resource use**	**Cost**	**Resource use**	**Cost**	**Resource use**	**Cost**
A & E visit	100% of patients	£103	100% of patients	£103	100% of patients	£103	100% of patients	£103
Inpatient stay	0% of patients	£350	10% of patients	£350	30% of patients	£350	50% of patients	£350
Anti-histamine	1 dose	£0.14	1 dose	£0.14	1 dose	£0.14	1 dose	£0.14
Adrenaline	1 ampoule	£0.67	1 ampoule	£0.67	1 ampoule	£0.67	1 ampoule	£0.67

It was considered that all individuals experiencing a systemic sting reaction visit the Accident and Emergency (A&E) department regardless of treatment arm. This is confirmed by our survey where we asked for avoidance advice given to people by clinicians should they be stung and all said that those experiencing a systemic reaction to sting are told to attend A&E. We assume that all people are able to attend A&E without the need for ambulatory care which we accept potentially acts as a deflator to the actual cost of treating systemic reactions. However, no data were available on the number of people being stung and requiring paramedic assistance.

For people with an emergency kit, the model assumes all people with a systemic reaction would use the AAI and HDA. For people receiving avoidance advice only, adrenaline is administered via ampoule in the A&E department.

There is a risk of delayed anaphylactic shock with sting and we assume that a proportion of people with systemic reactions would be observed overnight in hospital as an inpatient. We have no data on the likelihood of an inpatient stay so we asked for clinician advice on likely values for this parameter. In the base case the model assumes that 50% of those with a Grade 4 systemic reaction would be held overnight for observation; it is also assumed that 30% of those with a Grade 3 reaction, 10% with a Grade 2 systemic reaction and no-one with a Grade 1 systemic reaction would be held overnight for observation.

Scenario analysis explores the cost of systemic reaction that is 50% higher ("50% Higher Systemic Sting Treatment Cost") and 50% lower ("50% Lower Systemic Sting Treatment Cost"). Scenario analysis is also used to explore the impact of no inpatient stays regardless of grade of systemic reaction ("No Systemic Reaction Inpatient Stay") and 100% stay for those with a Grade 4 systemic reaction ("100% Grade 4 Systemic Reaction Inpatient Stay").

Time horizon

In the base case the time horizon is 10 years. This was chosen as there is evidence that PhVIT is still effective up to 10 years after maintenance but no studies could be found that had looked at periods beyond this. Results over 5, 15, 20 and 25 years are also estimated based upon the assumption that PhVIT is equally effective over all these periods.

Discount rate

Discount rates of 3.5% per annum are applied to both costs and benefits in the base case. Scenario analysis is used to explore the impact of no discount rate for costs and benefits and a discount rate of 5% per annum.

Other model assumptions

There are several assumptions made in order to make the model tractable that have not previously been mentioned.

The efficacy of bee and wasp PhVIT is assumed to be the same in terms of reducing the probability and severity of systemic reaction following sting.

Adverse reactions per dose and efficacy of PhVIT are assumed to be independent of the type of updosing phase used or length of maintenance phase (provided the maintenance phase is at least three years as suggested by the available evidence).

In the clinical effectiveness literature identified via the systematic review, there was no mention of adverse reactions related to AAI and HDA, therefore adverse reactions are assumed to be zero. If there are significant adverse reactions to either AAI or HDA then the costs of systemic reaction to

sting are likely to be higher than we have suggested in the model. This is explored in sensitivity analysis by raising costs of systemic reactions to sting by 50%.

6.3.5 Model validation

Internal validation of Assessment Group model

During model construction the algorithms within the model were checked using extreme value analysis for parameters to ensure that results generated were within acceptable bounds. To verify the accuracy of the model, key algorithms within the model were checked by an independent statistician. On completion, the model was assessed and validated by a team of external economists and statisticians.

External validation of Assessment Group model

The model was also cross checked by an external consultant. The economic model was checked for functionality, clarity, accuracy, consistency and validity. Validation of calculated parameters within the model was carried out where possible against observational studies. However given that this is *de novo* economic model, it was not possible for the external consultant to conduct validation regarding final results.

6.3.6 Model parameters and values used in the base case, sensitivity analysis and scenario analysis

Table 25 summarises the parameters that can vary within the model, the values applied in the base case and varied in sensitivity analysis.

Table 25 Base case and sensitivity analysis model values

Parameter	Base case values (sensitivity analysis)
Number of stings per year for PhVIT people	0.095 (0.014 to 0.183)
Subgroup "High Risk of Sting People" (number of stings per year)	*5 (1-10)*
Pre injection health check (Nurse specialist time)	15 (10-20)
Venom injection preparation (Nurse specialist time)	5 (3-7)
Post injection observation (Nurse specialist time)	3 (2-4)
Proportion of PhVIT doses leading to adverse systemic reaction	Updosing: 0.02 (0 to 0.026) Maintenance: 0.0026 (0 to 0.01)
Grade of adverse systemic reaction due to VIT dose	Grade 1 37.5%, Grade 2 37.5%, Grade 3 21.9%, Grade 4 3.1%
Proportion of stings that lead to systemic reaction (advice only)	0.56
Grade of systemic reaction following sting (advice only)	Grade 1 6.5%, Grade 2 80.3%, Grade 3 12.1%, Grade 4 1.1%
Proportion of stings that lead to systemic reaction (PhVIT +AAI+HDA)	0.065 (0.05 to 0.15)
Grade of systemic reaction following sting (PhVIT +AAI+HDA)	Grade 1 38.5%, Grade 2 54.0%, Grade 3 7.5%, Grade 4 0.0%
Proportion of stings that lead to systemic reaction (AAI+HDA)	0.439
Grade of systemic reaction following sting (AAI+HDA)	Grade 1 9.8%, Grade 2 83.6%, Grade 3 6.05%, Grade 4 0.55%
Probability of death following Grade 4 systemic reaction to sting	0.0125 (0.00625 to 0.01875)
Percentage of people using conventional updosing	92%
Length of maintenance phase	3 (3-5)
Length of intervals between doses during maintenance	4 (4-12)
Percentage of systemic sting reactions with inpatient stay	
Grade 1	0%
Grade 2	10%
Grade 3	30%
Grade 4	50%
QoL decrement due to anxiety of sting and impact on normal activities	0
Subgroup "PhVIT Anxiety QoL Improvement" (QoL decrement)	*Reduction of QoL due to fear of sting 0.04 per annum*
QoL increment due to reduction in anxiety with VIT	0
Subgroup "PhVIT Anxiety QoL Improvement" (QoL increment)	*Increase in QoL due to VIT 0.01 per annum (0.004 to 0.04)*
Age starting VIT	37 (5 to 55)
Discount rate (costs and benefits)	0.035 (0 to 0.05)

Several scenario analyses were undertaken (Table 26) and these are summarised in terms of the difference in parameters from the base case.

Table 26 Model values in scenario analysis

Scenario	Parameters changed	Value taken (sensitivity analysis)
5, 15, 20, 25 year time horizon	Time horizon	5, 15, 20, 25 years
100% male	Gender	Male 100%
100% female	Gender	Male 0%
100% bee	Percentage people receiving bee PhVIT only	100%
100% wasp	Percentage people receiving wasp PhVIT only	100%
100% bee/wasp	Percentage people receiving both bee and wasp PhVIT	100%
100% conventional updosing	% of people on conventional updosing protocol	100%
PhVIT local adverse reactions	Inclusion of costs for local adverse reactions to PhVIT	Add £0.84 to the cost per PhVIT injection in both phases
Equal AR risk updosing/maintenance	Dose risk of systemic reaction during maintenance phase	Risk of systemic adverse reaction in maintenance phase 2.0%
ARs all Grade 1	Mueller Grade of adverse systemic reactions	Grade 1 systemic adverse reactions 100%
25% ARs all Grade 4	Mueller Grade of adverse systemic reactions	Grade 4 systemic adverse reactions 25%
50% higher systemic AR cost	Cost of all grades of adverse systemic reactions to PhVIT	Cost of all grades of adverse systemic reactions to PhVIT + 50%
50% lower systemic AR cost	Cost of all grades of adverse systemic reactions to PhVIT	Cost of all grades of systemic adverse reactions to PhVIT -50%
50% higher systemic sting treatment cost	Cost of all grades of systemic reactions to sting	Cost of all grades of systemic reactions to sting + 50%
50% lower systemic sting treatment cost	Cost of all grades of systemic reactions to sting	Cost of all grades of systemic reactions to sting - 50%
No admissions due to systemic adverse reactions to PhVIT	Percentage of Grade 4 adverse systemic reactions resulting in admission	0%
Declining PhVIT effectiveness	Risk of systemic reaction from sting with PhVIT	5% at year one following the end of maintenance increasing by 1% per annum to 15% after 10 years following maintenance
No systemic reaction inpatient stay	Proportion of people requiring an inpatient stay after systemic sting reaction	0%
100% Grade 4 systemic reaction inpatient stay	Proportion of people requiring an inpatient stay after a Grade 4 systemic sting reaction	100%
AAI+HDA no systemic reaction effectiveness	Risk and severity of systemic reaction	Same as “Advice” intervention
PhVIT anxiety QoL improvement only	QoL age related norms, sting systemic reactions with AAI + HDA	Reduction of QoL due to fear of sting 0.04 per annum, increase in QoL due to PhVIT 0.01 per annum (0.004-0.04). Risk and severity of systemic reaction following sting with AAI + HDA equal to PhVIT + AAI + HDA
Best case	All parameters varied in base case sensitivity analysis	Values chosen that make PhVIT the most cost effective (lowest cost/QALY)
Worst case	All parameters varied in base case sensitivity analysis	Values chosen that make PhVIT the least cost effective (lowest cost/QALY)

6.3.7 Results

For the hypothetical cohort of 1000 patients, the total number of systemic adverse reactions to PhVIT, number of stings, severity of systemic reactions to sting, sting related death, total life years and QALYs over 10 years for each treatment arm for the base case and the two subgroups (*"High Risk of Sting Patients*" and "*PhVIT Anxiety QoL Improvement"*) are shown in Table 27.

Table 27 Health related outcomes for the base case and two subgroups

Treatment effect	Treatment arm	Base case	High risk of sting people	VIT anxiety QoL improvement
Systemic adverse reaction to VIT	VIT + AAI + HDA	450	450	450
Grade 1		169	169	169
Grade 2		169	169	169
Grade 3		99	99	99
Grade 4		14	14	14
Stings	VIT + AAI + HDA	943	49639	943
	AAI + HDA	943	49606	943
	Advice only	943	49554	943
Systemic reaction to sting	VIT + AAI + HDA	61	3223	61
	AAI + HDA	414	21777	414
	Advice only	528	27750	528
Grade 1	VIT + AAI + HDA	24	1239	24
	AAI + HDA	41	2134	41
	Advice only	34	1804	34
Grade 2	VIT + AAI + HDA	33	1742	33
	AAI + HDA	346	18206	346
	Advice only	424	22283	424
Grade 3	VIT + AAI + HDA	5	242	5
	AAI + HDA	25	1318	25
	Advice only	64	3358	64
Grade 4	VIT + AAI + HDA	0	0	0
	AAI + HDA	2	120	2
	Advice only	6	305	6
Sting related deaths	VIT + AAI + HDA	0.00	0.00	0.00
	AAI + HDA	0.03	1.50	0.03
	Advice only	0.07	3.82	0.07
Total life years	VIT + AAI + HDA	9908.0	9908.0	9908.0
	AAI + HDA	9907.8	9899.8	9907.8
	Advice only	9907.6	9887.1	9907.6
Total QALYs	VIT + AAI + HDA	7626.6	7626.6	7371.9
	AAI + HDA	7626.5	7620.7	7286.9
	Advice only	7626.3	7611.5	7286.7

The total costs for the hypothetical 1000 patient cohort in terms of intervention costs, treatment costs for adverse reactions to PhVIT and treatment costs for systemic reactions following sting in the base case and two subgroups is provided in Table 28 below:

Table 28 Costs of intervention and systemic reactions to sting for 1000 patients in the base case and subgroups for the different treatment arms

Cost Element	Treatment arm	Base case	High risk of sting patients	PhVIT anxiety QoL improvement
Treatment costs	PhVIT + AAI + HDA	£2,299,327	£2,299,223	£2,299,327
	AAI + HDA	£228,330	£228,228	£228,330
	Advice only	£64,000	£64,000	£64,000
Systemic adverse reaction	PhVIT + AAI + HDA	£17,637	£17,637	£17,637
Systemic reaction to sting	PhVIT + AAI + HDA	£9,764	£513,919	£9,764
	AAI + HDA	£69,591	£3,660,233	£69,591
	Advice only	£77,285	£4,060,750	£77,285
Total costs	PhVIT + AAI + HDA	£2,326,729	£2,830,778	£2,326,729
	AAI + HDA	£297,921	£3,888,461	£297,921
	Advice only	£141,285	£4,124,750	£141,285

The incremental cost between the three treatment arms, incremental QALYs and cost per QALY of PhVIT + AAI + HDA compared to the two treatment alternatives for the base case and two subgroups for a 1000 patient cohort is shown in Table 29, Table 30 and Table 31 below.

Table 29 Incremental costs, QALYs and ICERs for PhVIT +AAI+HDA under the base case

	AAI + HDA	Avoidance advice only
Incremental cost	£2,028,808	£2,185,444
Incremental QALYs	0.11	0.29
Cost per QALY (ICER)	£18,065,527	£7,627,835

Table 30 Incremental costs, QALYs and ICERs for PhVIT +AA +HDA for the "*High Risk of Sting Patients"* subgroup

	AAI + HDA	Avoidance advice only
Incremental cost	-£1,057,682	-£1,293,972
Incremental QALYs	5.91	15.06
Cost per QALY (ICER)	-£179,020	-£85,903

Table 31 Incremental costs, QALYs and ICERs for PhVIT +AAI+HDA for the *"VIT Anxiety QoL Improvement"* subgroup

	AAI + HDA	Avoidance advice only
Incremental cost	£2,028,808	£2,185,444
Incremental QALYs	85.00	85.17
Cost per QALY (ICER)	£23,868	£25,661

Under the base case assumptions over 10 years PhVIT + AAI + HDA generates an additional 0.00011 and 0.00029 QALYs per patient compared to AAI + HDA and avoidance advice respectively. This is at an additional cost of £2,029 and £2,185 per patient compared to AAI + HDA and avoidance advice respectively. The ICER of PhVIT + AAI + HDA is therefore £18,065,527 per QALY gained compared to AAI + HDA and £7,627,835 per QALY gained compared to avoidance advice.

For the "*High Risk of Sting Patient*" subgroup, at five stings per year, the reduction in costs from systemic reactions to sting over 10 years because of PhVIT outweigh the VIT treatment costs. As PhVIT also generates additional QALYs by reducing sting deaths for this subgroup PhVIT + AAI + HDA dominates the alternatives.

The subgroup analysis which allows for QoL changes due to sting anxiety and the use of PhVIT, estimates that PhVIT + AAI + HDA generates an additional 0.0850 and 0.0852 QALYs per patient compared to AAI + HDA. The incremental cost per patient is the same as the base case. The ICER for the subgroup with sting anxiety that is partially alleviated with PhVIT + AAI + HDA is therefore £23,868 per QALY gained compared to AAI + HDA and £25,661 per QALY gained compared to avoidance advice only.

6.3.8 Sensitivity analysis

The results of the sensitivity analysis for the base case and two subgroups are presented in Table 32, Table 33 and Table 34 and show the impact on the ICER when parameters are varied; PhVIT + AAI + HDA is compared with the two treatment alternatives.

Table 32 Impact of sensitivity analysis on the ICER of PhVIT + AAI +HDA against different treatment arms in the base case

Parameter	Cost/QALY vs AAI+HDA	Cost/QALY vs advice only
Number of stings per year	£9,122,183 to £125,668,803	£3,846,558 to £53,122,895
Pre injection health check (Nurse specialist time)	£15,724,577 to £20,406,478	£6,710,254 to £8,545,415
Venom injection preparation (Nurse specialist time)	£17,115,470 to £19,015,585	£7,255,442 to £8,000,228
Post injection observation (Nurse specialist time)	£17,590,498 to £18,540,556	£7,441,638 to £7,814,031
Proportion of PhVIT doses leading to adverse systemic reaction (Updosing phase)	£17,979,460 to £19,098,328	£7,594,099 to £8,032,661
Proportion of PhVIT doses leading to adverse systemic reaction (Maintenance phase)	£17,994,545 to £18,267,553	£7,600,012 to £7,707,023
Proportion of stings that lead to systemic reaction (PhVIT + AA I+HDA)	£18,045,462 to £18,179,228	£7,619,970 to £7,672,402
Probability of death following Grade 4 systemic reaction to a sting	£36,130,899 to £12,043,736	£15,255,509 to £5,085,277
Length of maintenance phase	£18,065,527 to £27,331,818	£7,627,835 to £11,259,936
Length of intervals between injections during maintenance phase	£18,065,527 to £7,903,259	£7,627,835 to £3,644,538
Age starting PhVIT	£16,924,162 to £21,390,991	£7,148,354 to £9,015,238
Discount rate (costs and benefits)	£15,129,011 to £19487889	£6,452,674 to £8,196,637

Table 33 Impact of sensitivity analysis on the ICER of PhVIT +AA I+ HDA against different treatment arms in the *"High Risk of Sting Patients"* subgroup

Parameter	**Cost/QALY vs AAI + HDA**	**Cost/QALY vs avoidance advice only**
Number of stings per year (1to10)	£1,234,283 to -£355,512	£511,546 to -£160,398
Pre injection health check (Nurse specialist time)	Dominates	Dominates
Venom injection preparation (Nurse specialist time)	Dominates	Dominates
Post injection observation (Nurse specialist time)	Dominates	Dominates
Proportion of PhVIT doses leading to adverse systemic reaction (Updosing phase)	Dominates	Dominates
Proportion of PhVIT doses leading to adverse systemic reaction (Maintenance phase)	Dominates	Dominates
Proportion of stings that lead to systemic reaction (PhVIT + AAI + HDA)	Dominates	Dominates
Probability of death following Grade 4 systemic reaction to a sting	Dominates	Dominates
Length of maintenance phase	Dominates	Dominates
Length of intervals between injections during maintenance phase	Dominates	Dominates
Age starting PhVIT	Dominates	Dominates
Discount rate (costs and benefits)	Dominates	Dominates

Table 34 Impact of sensitivity analysis on the ICER of PhVIT +AA I+ HDA against different treatment arms in the *"PhVIT Anxiety QoL Improvement"* subgroup

Parameter	**Cost/QALY vs AAI + HDA**	**Cost/QALY vs avoidance advice only**
Number of stings per year	£23,189 to £24,495	£24,853 to £26,409
Pre injection health check (Nurse specialist time)	£20,775 to £26,961	£22,574 to £28,748
Venom injection preparation (Nurse specialist time)	£22,613 to £25,124	£24,408 to £26,914
Post injection observation (Nurse specialist time)	£23,241 to £24,496	£25,035 to £26,287
Proportion of VIT doses leading to adverse systemic reaction (Updosing phase)	£23,755 to £25,233	£25,547 to £27,023
Proportion of PhVIT doses leading to adverse systemic reaction (Maintenance phase)	£23,775 to £24,135	£25,567 to £25,927
Proportion of stings that lead to systemic reaction (PhVIT + AAI + HDA)	£23,842 to £24,019	£25,634 to £25,811
Probability of death following Grade 4 systemic reaction to sting	£23,883 to £23,853	£25,702 to £25,620
Length of maintenance phase	£23,868 to £36,111	£25,661 to £37,880
Length of intervals between injections during maintenance phase	£23,868 to £10,442	£25,661 to £12,261
Age starting PhVIT	£23,711 to £24,697	£25,497 to £26,510
Discount rate (costs and benefits)	£21,065 to £25,140	£22,875 to £26,925
Age related QoL norm (decreases by 0.04) QoL norm with PhVIT (increases by 0.004 to 0.04)	£5,973 to £59,558	£6,431 to £63,845

6.3.9 Scenario analysis

The impact of changes on the ICERs for PhVIT + AAI + HDA, under the different scenarios presented, compared to the alternative treatments is provided in Table 35, Table 36 and Table 37 for the base case *"High Risk of Sting Patients"* subgroup and *"PhVIT Anxiety QoL Improvement"* subgroup respectively.

Table 35 ICER of PhVIT + AAI + HDA against different treatment arms under various scenarios for the base case

Scenario	Cost/QALY vs AA I+ HDA*	Cost/QALY vs avoidance advice only*
5 year time horizon	£58,112,401 (+321.68%)	£23,728,992 (+311.08%)
15 year time horizon	£9,475,380 (-47.55%)	£4,112,030 (-46.09%)
20 year time horizon	£6,158,390 (-65.91%)	£2,733,478 (-64.16%)
25 year time horizon	£4,549,884 (-74.81%)	£2,056,752 (-73.04%
100% male	£18,094,419 (+0.16%)	£7,639,773 (+0.16%)
100% female	£17,950,948 (-0.63%)	£7,580,491 (-0.62%)
100% bee	£16,391,486 (-9.27%)	£6,971,662 (-8.60%)
100% wasp	£18,034,830 (-0.17%)	£7,615,802 (-0.16%)
100% bee/wasp	£23,872,923 (+32.15%)	£9,904,156 (+29.84%)
100% conventional updosing protocol	£18,095,990 (+0.17%)	£7,639,775 (+0.16%)
100% modified rush updosing protocol	£17,715,201 (-1.94%)	£7,490,518 (-1.80%)
PhVIT local adverse reactions	£18,439,612 (+2.07%)	£7,774,465 (+1.92%)
Equal AR risk updosing/maintenance	£18,540,562 (+2.63%)	£7,814,034 (+2.44%)
ARs all Grade 1	£18,039,836 (-0.14%)	£7,617,765 (-0.13%)
25% ARs Grade 4	£18,247,022 (+1.00%)	£7,698,975 (+0.93%)
50% higher systemic AR cost	£18,144,052 (+0.43%)	£7,658,614 (+0.40%)
50% lower systemic AR cost	£17,987,003 (-0.43%)	£7,597,056 (-0.40%)
50% higher systemic sting treatment cost	£17,799,166 (-1.47%)	£7,510,002 (-1.54%)
50% lower systemic sting treatment cost	£18,331,888 (+1.47%)	£7,745,668 (+1.54%)
No admissions due to systemic adverse reactions	£18,043,808 (-0.12%)	£7,619,321 (-0.11%)
Declining PhVIT effectiveness	£18,087,837 (+0.12%)	£7,636,580 (+0.11%)
No systemic reaction inpatient stay	£18,185,034 (+0.66%)	£7,700,600 (+0.95%)
100% Grade 4 systemic reaction inpatient stay	£18,062,700 (-0.02%)	£7,624,569 (-0.04%)
AAI + HDA no systemic reaction effectiveness	£7,002,582 (-61.24%)	N/A
Best case scenario	£1,449,007 (-91.98%)	£731,302 (-90.41%)
Worst case scenario	£570,668,032 (+3058.88%)	£232,820,521 (+2952.25%)

* % difference from base case in brackets

Table 36 ICER of PhVIT +AAI+HDA against different treatment arms under various scenarios for the *"High Risk of Sting Patients"* subgroup

Scenario	**Cost/QALY vs AAI+HDA***	**Cost/QALY vs avoidance advice only***
5 year time horizon	£274,556	£84,006
15 year time horizon	Dominates	Dominates
20 year time horizon	Dominates	Dominates
25 year time horizon	Dominates	Dominates
100% male	Dominates	Dominates
100% female	Dominates	Dominates
100% bee	Dominates	Dominates
100% wasp	Dominates	Dominates
100% bee/wasp	Dominates	Dominates
100% conventional updosing protocol	Dominates	Dominates
100% modified rush updosing protocol	Dominates	Dominates
PhVIT local adverse reactions	Dominates	Dominates
Equal AR risk updosing/maintenance	Dominates	Dominates
ARs all Grade 1	Dominates	Dominates
25% ARs Grade 4	Dominates	Dominates
50% higher systemic AR cost	Dominates	Dominates
50% lower systemic AR cost	Dominates	Dominates
50% higher systemic sting treatment cost	Dominates	Dominates
50% lower systemic sting treatment cost	£87,248	£31,829
No admissions due to systemic adverse reactions	Dominates	Dominates
Declining PhVIT effectiveness	Dominates	Dominates
No systemic reaction inpatient stay	Dominates	Dominates
100% Grade 4 systemic reaction inpatient stay	Dominates	Dominates
AAI + HDA no systemic reaction effectiveness	Dominates	N/A
Best case scenario (Fixed at 5 stings per annum)	Dominates	Dominates
Worst case scenario (Fixed at 5 stings per annum)	£547,263	£172,930

*Values shown when ICER becomes positive

Table 37 ICER of PhVIT +AAI + HDA against different treatment arms under various scenarios in the *"PhVIT Anxiety QoL Improvement"* subgroup

Scenario	**Cost/QALY vs AAI + HDA***	**Cost/QALY vs advice only***
5 year time horizon	£44,328 (+85.72%)	£46,126 (+79.75%)
15 year time horizon	£17,128 (-28.24%)	£18,912 (-26.30%)
20 year time horizon	£13,806 (-42.16%)	£15,582 (-39.28%)
25 year time horizon	£11,879 (-50.23%)	£13,647 (-53.18%)
100% male	£23,884 (+0.07%)	£25,677 (+0.06%)
100% female	£23,807 (-0.26%)	£25,598 (-0.25%)
100% bee	£21,657 (-9.27%)	£23,453 (-8.60%)
100% wasp	£23,828 (-0.17%)	£25,620 (-0.16%)
100% bee/wasp	£31,541 (+32.15%)	£33,319 (+29.84%)
100% conventional updosing protocol	£23,909 (+0.17%)	£25,701 (+0.16%)
100% modified rush updosing protocol	£23,406 (-1.94%)	£25,199 (-1.80%)
PhVIT local adverse reactions	£24,363 (+2.07%)	£26,154 (+1.92%)
Equal AR risk updosing/maintenance	£24,496 (+2.63%)	£26,287 (+2.44%)
ARs all Grade 1	£23,834 (-0.14%)	£25,627 (-0.13%)
25% ARs Grade 4	£24,108 (+1.01%)	£25,900 (+0.93%)
50% higher systemic AR cost	£23,972 (+0.44%)	£25,764 (+0.40%)
50% lower systemic AR cost	£23,765 (-0.43%)	£25,557 (-0.40%)
50% higher systemic sting treatment cost	£23,516 (-1.47%)	£25,265 (-1.55%)
50% lower systemic sting treatment cost	£24,220 (+1.48%)	£26,057 (+1.54%)
No admissions due to systemic adverse reactions	£23.840 (-0.12%)	£25,632 (-0.11%)
Declining PhVIT effectiveness	£23,898 (+0.12%)	£25,690 (+0.11%)
No systemic reaction inpatient stay	£24,026 (+0.66%)	£25,906 (+0.95%)
100% Grade 4 systemic reaction inpatient stay	£23,865 (-0.01%)	£25,650 (-0.04%)
AAI + HDA no systemic reaction effectiveness	£23,557 (-1.30%)	N/A
PhVIT anxiety QoL improvement only	£24,605 (+3.09%)	N/A
Best case scenario (Fixed at 0.01 per annum PhVIT QoL Improvement)	£6,179 (-74.11%)	£7,906 (-69.19%)
Worst case scenario (Fixed at 0.01 per annum PhVIT Qol Improvement)	£47,390 (+98.55%)	£49,320 (+92.20%)

* % difference from base case in brackets

6.3.10 Summary of economics evidence

- No published economic evaluations relevant to the decision problem were identified by the systematic review of cost-effectiveness studies

- The manufacturer of PhVIT did not submit any supporting clinical or cost effectiveness evidence to NICE

- The AG developed a *de novo* economic model to compare PhVIT with currently available NHS treatments in patients with a history of type 1 IgE mediated systemic allergic reaction to bee and/or wasp venom

- In the AG's base case, VIT+HDA+AAI reached an ICER of £18,065,527 per QALY gained compared with AAI+HDA

- In the AG's base case, VIT+HDA+AAI reached an ICER of £7,627,835 per QALY gained compared with avoidance advice only

- In the AG's base case the results of the sensitivity analyses and scenario analyses showed that the results of the economic evaluation were robust for every plausible change in parameter made

- The AG's *"High Risk of Sting Patients"* subgroup analysis showed that the ICER of VIT+HDA+AAI dominates both AAI+HDA and avoidance advice only

- The AG's *"VIT Anxiety QoL Improvement"* subgroup analysis showed that VIT+HDA+AAI vs HDA + AAI had an ICER of £23,868 per QALY gained

- The AG's *"VIT Anxiety QoL Improvement"* subgroup analysis showed that VIT+HDA+AAI vs avoidance advice only had an ICER of £25,661 per QALY gained

6.4 Discussion of economics results and key issues

No relevant economic evaluations of PhVIT vs any comparator were identified from the systematic review of cost-effectiveness literature. The manufacturer did not submit any clinical or cost-effectiveness evidence to NICE which means that the AG did not have any additional data from the manufacturer. The AG developed a *de novo* economic model to answer the decision problem set by NICE.

Under the base case the incremental cost per QALY gained of PhVIT + AAI + HDA compared to an emergency kit of AAI + HDA is never less than £1million per QALY gained under any scenario or any plausible values for parameters within the model. The ICER only falls below £1million when PhVIT + AAI + HDA is compared to avoidance advice when the most optimistic scenario for PhVIT + AAI + HDA is considered; this ICER still exceeds £700,000 per QALY gained.

As scenario analysis explored extreme values where assumptions had to be made – such as in the costs associated with treating a systemic reaction following sting – this finding can be considered robust and unlikely to change if additional information were available to provide more accurate values for these assumptions. The underlying driver for this ICER is that, whilst PhVIT can achieve savings through reduced systemic reaction treatment costs and generate QALYs through saving lives, the likelihood of being stung and then dying from that sting is very low – even for individuals allergic to sting. The ability of PhVIT to generate QALY gains and reduce demand on NHS resources is therefore low.

The findings are considerably different for the two subgroups that are considered in our analysis.

Firstly, considering allergic individuals at high risk of sting, subgroup analysis suggests that under all other base case values, at a rate of five stings per year, PhVIT + AAI + HDA reduces the number of systemic reactions to stings, and therefore total costs of systemic sting reaction, to a point that it actually costs less than the other treatment arms. Whilst even at this level of sting the number of deaths averted and therefore QALYs generated are low with PhVIT + AAI + HDA, as it still generates some QALYs compared to the other treatment arms, its lower cost means that it dominates the other arms as a treatment option. This finding is invariant to the changes made to almost all parameters in scenario analysis and sensitivity analysis. The exceptions are if a time horizon of only 5 years is considered, treatment costs for systemic reaction are 50% lower than the base case or the most pessimistic plausible values for all parameters in the model are chosen.

Our survey found that allergy clinics advise all people that, if stung and having signs of systemic reaction, they should attend A&E. It is therefore not plausible that this cost should be lower than we have considered. The only other cost of treatment considered that could significantly inflate the cost

of treatment is inpatient care. Under the scenario of no inpatient care following sting, PhVIT + AAI + HDA still dominated.

Assuming all other parameters for the base case hold, the number of stings at which PhVIT + AAI + HDA would no longer dominate and incremental costs per QALY be generated, would be 3.3 stings per year compared to AAI + HDA and 3.2 stings per year compared to avoidance advice only. The number of stings per year where PhVIT + AAI + HDA would generate an ICER of £30,000 per QALY gained is 3.1 compared to AAI + HDA and 2.8 compared to avoidance advice only. We considered a third subgroup that would combine an improvement in utility from reduction in anxiety in a population with a high risk of sting. As PhVIT + AAI + HDA dominates, assuming no improvement in QoL from receiving PhVIT, this subgroup analysis was considered unnecessary.

For people with the base case risk of sting or lower risk[1] of sting, then the cost effectiveness of PhVIT improves substantially if QALYs are not only generated by stopping sting deaths but also through reductions in sting anxiety. The evidence on improvement in QoL is limited but suggests that PhVIT does effectively reduce sting anxiety. Whilst the actual effect of this on utility as measured by a recognised survey is absent, the research by the University of York previously discussed suggests that QoL can be substantially influenced by both the individual's inability to undertake usual activities and also because of anxiety.

Our analysis explored how cost effectiveness of PhVIT varies if fear of sting only has a small negative impact on QoL compared to that due to the potential impact identified by the University of York research. It also assumed that PhVIT + AAI + HDA has only a small impact in negating this loss in utility. If fear of sting reduces utility by 0.04 of a QALY per annum and PhVIT improves utility by 25% of this value (0.01 of a QALY per annum) the ICERs for PhVIT + AAI + HDA are less than £30,000 per QALY gained compared to AAI + HDA and avoidance advice only if all other base case values hold. This result holds across a range of scenarios and potential plausible parameter values, even if PhVIT is assumed to be no more effective than an emergency kit of AAI + HDA at stopping and alleviating systemic reactions to sting.

The finding is somewhat sensitive to PhVIT treatment costs, most notably the length of the maintenance phase. With a maintenance phase of 5 years the ICER rises to just under £40,000 per QALY gained compared to the alternative treatments. For people requiring both bee and wasp PhVIT the ICER also rises to between £33,440 per QALY gained and £35,163 per QALY gained compared to AAI + HDA and avoidance advice only respectively.

[1] Keeping in mind the base case risk will potentially include people at significantly higher risk of sting than others and that the sting risk is a combined wasp and bee sting risk and people may not have an allergic response to both

If the reduction in utility from sting anxiety is 0.04 per annum then for PhVIT + AAI + HDA to generate an ICER of £30,000 per QALY gained it has to negate this reduction by 0.008 per annum compared to AAI + HDA and 0.009 compared to avoidance advice only. For people receiving both bee and wasp PhVIT, the incremental increase in QoL per annum has to rise from 0.01 to 0.011 to achieve an ICER of £30,000 per QALY gained compared to both AAI + HDA and avoidance advice only.

As the treatment costs are all incurred within the first 5 years of the analysis but benefits continue to accrue past this point, the ICERs at 5 years are higher than the base case ICERs at 10 years and continue to fall up to 25 years. As the available evidence suggests that PhVIT continues to be effective up to at least 10 years but is limited beyond this, the choice of a 10 year time horizon is in our opinion justified.

Whilst we consider the findings robust, there are some key weaknesses of our analysis:

- the lack of data on effectiveness of PhVIT from RCTs
- the lack of any published evidence on PhVIT + AAI + HDA vs AAI + HDA or avoidance advice only
- the absence of direct data on the number of stings in PhVIT people in the UK and the number of stings that are from bees or wasps
- there are no direct data on the likelihood of death following sting for sting allergic people
- there are no robust data on the improvement in utility because of sting anxiety in allergic people

To counter this lack of evidence and potential criticism of simplifying assumptions, substantial sensitivity and scenario analyses were used to highlight those parameters that are key to the cost-effectiveness analysis and explore the impact on the cost-effectiveness results of the intervention in question across ranges of plausible values. The final weakness is shown to be irrelevant if increases in utility from reduced sting anxiety arise through PhVIT as the findings hold even if PhVIT has no effectiveness on systemic reactions to sting.

7 CONCLUSIONS

The current use of PhVIT in clinical practice in the NHS appears to be based on limited and poor quality clinical effectiveness research.

The AG did not identify any studies of PhVIT that directly addressed the original decision problem set for this appraisal i.e. to compare the use of PhVIT with the alternative treatment options of advice on the avoidance of bee and wasp venom, HDA and/or AAIs.

This lack of evidence and the need to identify data to inform the development of an economic model prompted the AG to broaden the search criteria for the systematic review in order to compare PhVIT with other PhVIT and PhVIT vs non-PhVIT, to consider data from non-comparative studies of PhVIT and to examine studies reporting the clinical effectiveness of non-PhVIT.

In general research in the area is limited to small scale studies which do not appear to have been carried out using robust methods and none of the studies reported on the use of PhVIT within the UK. There is also heterogeneity in the published evidence related to the methods of PhVIT administration and length of treatment described in the trials. Therefore conclusions regarding the clinical effectiveness of PhVIT to reduce the rate of future systemic reactions in patients with history of bee and/or wasp allergic reaction cannot be drawn with any confidence. Available evidence indicates that sting reactions following the use of PhVIT are low and that the ARs related to treatment are minor and easily treatable.

Anxiety related to the possibility of future stings is an issue for debate and data from studies of VIT indicate a small improvement in QoL due to a decrease in sting-related anxiety after VIT.

No published research on the cost effectiveness of PhVIT or non-PhVIT was identified by the literature searches. The results of the AG's *de novo* base case economic evaluation demonstrate that PhVIT + AAI + HDA compared with AAI + HDA and compared with avoidance advice only yield ICERs in the range of £8-18 million per QALY gained. The results of extensive sensitivity and scenario analyses demonstrate that the base case results are robust. Two subgroups were considered in the economic evaluation and the AG concludes that use of PhVIT + AAI + HDA may be cost effective in both groups. In the subgroup of patients at high risk of future stings (5 stings per year), PhVIT + AAI + HDA dominates the alternatives. In the subgroup of patients whose QoL improves due to PhVIT from reduced anxiety, when PhVIT + AAI + HDA is compared to the alternatives the ICERs are in the range of £23,868 to £25,661 per QALY gained.

7.1 Future research

Use of PhVIT in clinical practice in the UK NHS is common place, it is therefore highly unlikely that placebo controlled studies will ever be carried out. The findings of this review indicate however that it is necessary to identify more clearly the groups of patients most likely to benefit from treatment and ensure that clinical practice is focussed on these groups. Given the paucity of UK data in this area it would be informative if data could be collected routinely when VIT is administered in the NHS (e.g. rates of systemic adverse reactions to VIT, rates of systemic reactions to bee/wasp stings).

8 REFERENCES

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9 APPENDICES

Appendix 1: Literature search strategies

Table 38 Search strategy for EMBASE 1980 to 2011 Week 04

	Searches	Results
1	exp wasp/ or exp bee/ or exp hymenoptera/ or exp bumblebee/ or exp honeybee/ or exp orchid bee/ or exp stingless bee/	13498
2	(wasp$ or bees or honeybee$ or bumblebee$ or orchid bee$ or yellow hornet$ or yellow jacket$ or white hornet$ or poliste$).tw.	9959
3	exp hymenoptera venom/ or exp bee sting/ or exp bee venom/ or exp wasp venom/	3382
4	((wasp$ or bees) adj (venom$ or sting$ or hypersensitivit$ or allerg$ or anaphyla$ or systemic reaction$)).tw.	818
5	(pharmalgen or venom immunotherapy).af.	692
6	exp pharmalgen/	84
7	or/1-4	19103
8	or/5-6	692
9	7 and 8	518
10	limit 9 to english language	**435**

Table 39 Search strategy for Ovid MEDLINE(R) 1948 to February week 3 2011

	Searches	Results
1	exp Wasps/ or exp Bees/ or exp Hymenoptera/	12580
2	(wasp$ or bees or honeybee$ or bumblebee$ or orchid bee$ or yellow hornet$ or yellow jacket$ or white hornet$ or poliste$).tw.	8437
3	exp Wasp Venoms/ or exp Bee Venoms/	5214
4	((wasp$ or bees) adj (venom$ or sting$ or hypersensitivit$ or allerg$ or anaphyla$ or systemic reaction$)).tw.	662
5	exp "Insect Bites and Stings"/	4448
6	or/1-5	22197
7	(pharmalgen or immunotherapy).af.	52392
8	exp Desensitization, Immunologic/ or *Immunotherapy/ or Anaphylaxis/th	19439
9	7 or 8	57963
10	6 and 9	1130
11	limit 10 to english language	**906**

Table 40 Search strategy for Cochrane February 2011

	Searches	Results
1	MeSH descriptor **Wasps** explode all trees	7
2	MeSH descriptor **Bees** explode all trees	13
3	MeSH descriptor **Wasp Venoms** explode all trees	11
4	MeSH descriptor **Bee Venoms** explode all trees	28
5	wasp* or bees	231
6	(#1 OR #2 OR #3 OR #4 OR #5)	231

Appendix 2: Excluded studies

Table 41 Table of excluded studies with rationale

Comparing active treatments, none of which were Pharmalgen®
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Quercia, O., F. Emiliani, S. Pecora, S. E. Burastero and G. F. Stefanini (2006). "Efficacy, safety, and modulation of immunologic markers by immunotherapy with honeybee venom: Comparison of standardized quality depot versus aqueous extract." Allergy and Asthma Proceedings 27(2): 151-158.[118]
Reisman, R. E. and R. Lantner (1989). "Further observations of stopping venom immunotherapy: comparison of people stopped because of a fall in serum venom-specific IgE to insignificant levels with people stopped prematurely by self-choice." Journal of Allergy & Clinical Immunology 83(6): 1049-54.[119]
Reisman, R. E., D. J. Dvorin, C. C. Randolph and J. W. Georgitis (1985). "Stinging insect allergy: Natural history and modification with venom immunotherapy." Journal of Allergy and Clinical Immunology 75(6): 735-740.[120]
Rerinck, H. C., B. Przybilla and F. Ruff (2009). "Venom Immunotherapy (VIT) in people with Systemic Mastocytosis (SM) and Hymenoptera Venom Anaphylaxis (HVA): Safety and efficacy of different maintenance doses." Journal of Allergy and Clinical Immunology 1): S242.[121]
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Comparing VIT with placebo, WBE or no treatment but not Pharmalgen®
Golden, D. B., A. Kagey-Sobotka, P. S. Norman, R. G. Hamilton and L. M. Lichtenstein (2004). "Outcomes of allergy to insect stings in children, with and without venom immunotherapy." New England Journal of Medicine 351(7): 668-74.[123]
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Müller, U., U. Thurnheer, R. Patrizzi, J. Spiess and R. Hoigne (1979). "Immunotherapy in bee sting hypersensitivity. Bee venom versus wholebody extract." Allergy 34(6): 369-78.[75]
Oude Elberink, H. O., J. D. Monchy, G. Guyatt and A. Dubois (2001) Venom immunotherapy (VIT) improves health-related quality of life (HROL) in people with allergic reactions following yellow-jacket stings - extended observations. Journal of Allergy and Clinical Immunology 107, S22[83]

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Valentine, M. D., K. C. Schuberth, A. Kagey-Sobotka, D. F. Graft, K. A. Kwiterovich, M. Szklo, et al. (1990) The value of immunotherapy with venom in children with allergy to insect stings. The New England journal of medicine 1601-3[81]
Economic papers but not Pharmalgen®
Bernstein, J. A., S. L. Kagen, D. I. Bernstein and I. L. Bernstein (1994). "Rapid venom immunotherapy is safe for routine use in the treatment of people with Hymenoptera anaphylaxis." Annals of Allergy 73(5): 423-428.[91]
Brown KF, Shaker MS, Jenkins PC, Verdi MS. A Cost-Effectiveness Analysis of Venom Desensitization in Children Treated for Cure and Risk-Reduction. The Journal of allergy and clinical immunology. 2006; 117(2):S309[93].
Shaker, M. S. (2007) An economic evaluation of prophylactic self-injectable epinephrine to prevent fatalities in children with mild venom anaphylaxis (Structured abstract). Annals of Allergy, Asthma and Immunology 424-428[92]
Details of QoL but not RCTs
Cichocka-Jarosz, E., B. Tobiasz-Adamczyk, P. Brzyski, G. Lis, U. Jedynak, J. Pietrzyk, et al. (2009). "Health related quality of life (HRQoL) in polish children treated with specific Venom immunotherapy (VIT): A multicenter study." Allergy: European Journal of Allergy and Clinical Immunology 64: 343.[127]
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Kahan, E., R. Ben-Moshe, E. Derazne and R. Tamir (1997). "The impact of Hymenoptera venom allergy on occupational activities." Occupational Medicine 47(5): 273-6.[130]
Koutsostathis, N., V. Vovolis, G. Poulios, E. Sifnaios, S. Keratsas and N. Mikos (2009). "Factors associated to proper technique and carrying compliance with self-injectable adrenaline in insect venom allergic people and its effect on people' quality of life." Allergy: European Journal of Allergy and Clinical Immunology 64: 34-35.[131]
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Appendix 3: Included studies

RCTs	
1	Golden, D. B. K., M. D. Valentine, A. Kagey-Sobotka and L. M. Lichtenstein (1980). "Regimens of hymenoptera venom immunotherapy." Annals of Internal Medicine 92(5): 620-624.[44]
2	Golden, D., M. D. Valentine, A. K. Sobotka and L. M. Lichtenstein (1979). "Regimens of hymenoptera venom immunotherapy." Journal of Allergy and Clinical Immunology 63(3): No. 156.[41]
3	Mosbech H, Malling HJ, Biering I. Immunotherapy with yellow jacket venom. A comparative study including three different extracts, one adsorbed to aluminium hydroxide and two unmodified. Allergy: European Journal of Allergy and Clinical Immunology. 1986; 41(2):95-103.[45]
4	Müller U, Rabson AR, Bischof M, Lomnitzer R, Dreborg S, Lanner A. A double-blind study comparing monomethoxy polyethylene glycol-modified honeybee venom and unmodified honeybee venom for immunotherapy. I. Clinical results. Journal of allergy and clinical immunology. 1987; (3 Pt 1):252-61.[47]
5	Müller U, Lanner A, Schmid P, Bischof M, Dreborg S, Hoigné R. A double blind study on immunotherapy with chemically modified honey bee venom: monomethoxy polyethylene glycol-coupled versus crude honey bee venom. International archives of allergy and applied immunology. 1985; (1-2):201-3.[46]
6	Quercia, O., S. Rafanelli, P. Puccinelli and G. F. Stefanini (2001). "The safety of cluster immunotherapy with aluminium hydroxide-adsorbed honey bee venom extract." Journal of Investigational Allergology and Clinical Immunology 11(1): 27-33.[49]
Non RCTs	
7	Cadario G, Marengo F, Ranghino E, Rossi R, Gatti B, Cantone R, et al. Higher frequency of early local side effects with aqueous versus depot immunotherapy for Hymenoptera venom allergy. Journal of Investigational Allergology and Clinical Immunology. 2004; 14(2):127-33.[40]
8	Golden, D. B. K., A. Kagey-Sobotka, M. D. Valentine and L. M. Lichtenstein (1981). "Prolonged maintenance interval in hymenoptera venom immunotherapy." Journal of Allergy and Clinical Immunology 67(6): 482-484.[42]
9	Golden, D. B. K., A. Kagey-Sobotka, M. D. Valentine and L. M. Lichtenstein (1981). "Dose dependence of hymenoptera venom immunotherapy." Journal of Allergy and Clinical Immunology 67(5): 370-374.[43]
10	Patriarca, G., E. Nucera, C. Roncallo, A. Aruanno, C. Lombardo, M. Decinti, et al. (2008). "Sublingual desensitization in people with wasp venom allergy: Preliminary results." International Journal of Immunopathology and Pharmacology 21(3): 669-677.[48]
11	Thurnheer U, Müller U, Stoller R. Venom immunotherapy in hymenoptera sting allergy. Comparison of rush and conventional hyposensitization and observations during long-term treatment. Allergy: European Journal of Allergy and Clinical Immunology. 1983; 38(7):465-75.[50]

Appendix 4: Quality assessment

Table 42 Data quality assessment

Checklist item	Cadario 1983[40]	Golden 1980[44]	Golden 1981 a[43]	Golden 1981 b[42]	Mosbech 1986[45]	Müller 1987[47]	Patriarca 2008[48]	Quercia 2001[49]	Thurnheer 1983[50]
Randomisation									
Was the randomisation method adequate?	NA	NS	NA	NA	NS	NS	NA	NS	NA
Was the allocation of treatment adequately concealed?	NA	NS	NA	NA	NS	NS	NA	NS	NA
Was the number of participants randomized stated?	NA	✓	NA	NA	✓	✓	NA	✓	NA
Baseline comparability									
Were details of baseline comparability presented?*	✓	✓	✓	✓	✓	✓	✓	✓	✓
Were the groups similar for prognostic factors?	✓	✓	✓	✓	×	✓	✓	✓	✓
Eligibility criteria and co-interventions									
Were the eligibility criteria for study entry specified?	✓	✓	✓	✓	✓	✓	✓	✓	✓
Were any co-interventions identified?	×	×	×	×	×	×	×	×	×
Blinding									
Were outcome assessors blinded to treatment allocation?	×	×	×	×	×	NS*	×	×	×
Were administrators blinded to the treatment allocation?	×	×	×	×	×	NS*	×	×	×
Were people blinded to the treatment allocation?	×	×	×	×	×	NS*	×	×	×
Was the blinding procedure assessed?	×	×	×	×	×	×	×	×	×
Withdrawals									
Any unexpected imbalances in drop-outs between groups? Were they explained or adjusted for?	× NA	✓ ×	✓ ×	NS NS	✓ ×	✓ ×	✓ ×	× NA	× NA
Were ≥80% people included in the final analysis?	✓	✓	✓	✓	×	✓	✓	✓	✓
Were reasons for withdrawals stated?	NA	✓	✓	×/✓	✓	✓	✓	NA	✓
Was an intention to treat analysis included? Was this appropriate? Were appropriate methods used to account for missing data?	NA	×	×	×	×	×	×	NA	×
Outcomes									
Evidence of more outcomes measured than reported?	×	×	×	×	×	×	×	×	×

×✓ NA=not applicable, NS=not stated/unclear

*Double blind trial but no details

Appendix 5 Economic survey results

Table 43 Summary of the economic survey responses

Questions	Response
Type of clinical unit	14 from a unit in an acute hospital One from a unit in a community hospital One unit in a specialist hospital, no acute service
Type of individual receiving VIT in unit	12 units provide VIT only to adults Two units only with children Two units with children and adults
Number of new venom allergic individuals in a typical year	Wasp venom: 9.37 Bee Venum: 3 Both wasp and bee venom: 0.87 Note that these are simple averages from 15 responses, one clinician did not fill in this question; No weighting was taken into account because we did not ask for the total number of individuals in each clinical unit. One provided a range of 5 to 0, and the median 7.5 was used for the average calculation
Age proportions of new individuals with severe systemic reaction to bee/wasp venom in a typical year	Under 20 years: 15% 20-39 years: 30% 40 plus; 54% These are simple averages without weighting
Proportions of treatment option prescribed to new patients with severe bee/wasp bee venom allergy	The majority of clinics provided VIT + HDA + AAI; four clinics provided VIT + AAI and one clinic used VIT monotherapy only. For individuals not able to receive VIT,. 10 cliinics used HDA + AAI as an alternative treatment option. Very small numbers of clinics prescribed either HDA only or AAI only
Antihistamines prescribed (dosage)	Acrivastine (16mg), acrivastine (8mg), cetirizine (10-20mg), fexofenadine (180mg), piriton, loratadine (10-20mg), chlorphenamine (8mg)
VIT for individuals with both bee and wasp allergy	Five clinics provided VIT for the more severe allergy Three clinics provided VIT for both bee and wasp allergy
Advice given to people undergoing VIT should the experience re-sting	Three clinics advised use of HDA followed by AAI (if systemic reaction occurs). Also advise visit to A & E. Four clinics advised use of HDA and administration of AAI if individual has difficulty breathing or feels faint One clinic advised use of HDA, steroid and AAI if systemic reaction occurs One clinic advised HDA only One clinic advised removal of sting, use of HDA and AAI
Most common ARs during VIT	Local reactions (mainly swelling and itching) stated by all 15 clinics. Other common ARs included urticaria and fatigue. Less common reactions included pain, wheezing, local redness, Arthus-type reaction, anxiety tachycardia, headache, anaphylaxis and reduction in peak expiratory flow rate

Appendix 6: Data abstraction tables

Table 44: Dosing protocols

Study ID	Intervention	Updosing: doses and frequency
Cadario 2004[40]	Aqueous induction and aqueous maintenance	**12 doses in 8 visits (weekly). Total 8 weeks** Week 1, 0.01 ug, 0.1 ug (30 mins between) Week 2, 1 ug, 2 ug (30 mins between) Week 3, 4 ug, 8 ug (60 mins between) Week 4, 10 ug, 20 ug (60 mins between) Week 5, 40 ug Week 6, 60 ug Week 7, 80 ug Week 8, 100 ug
	Depot induction and depot maintenance	**15 doses in 15 visits (weekly). Total 15 weeks** Week 1, 0.02 ug Week 2, 0.04 ug Week 3, 0.08 ug Week 4, 0.2 ug Week 5, 0.4 ug Week 6, 0.8 ug Week 7, 2 ug Week 8, 4 ug Week 9, 8 ug Week 10, 10 ug Week 11, 20 ug Week 12, 40 ug Week 13, 60 ug Week 14, 80 ug Week 15, 100ug
Golden 1980[41, 44]	Slow therapy	**14 doses in 14 visits (weekly). Total 14 weeks** Week 1: 0.01 ug Week 2: 0.03 ug Week 3: 0.1 ug Week 4: 0.25 ug Week 5: 1.0 ug Week 6: 2.5 ug Week 7: 5.0 ug Week 8: 10.0 ug Week 9: 20.0 ug Week 10: 30.0 ug Week 11: 40.0 ug Week 12: 60.0 ug Week 13: 80.0 ug Week 14: 100.0 ug
	Step therapy	**10 doses in 8 visits. Total 11 weeks** Initial: 1 ug, 5 ug, 10 ug (every 30 mins) Week 1: 25 ug Week 3: 25 ug Week 5: 25 ug Week 6: 50 ug Week 8: 50 ug Week 10: 50 ug Week 11: 100 ug
	Rush therapy	**6 doses in 4 visits (2 weeks). Total 6 weeks** Initial: 1 ug, 5 ug, 10 ug (every 30 mins) Week 2: 30 ug Week 4: 60 ug Week 6: 100 ug
Golden 1981a[43]	50 ug Maintenance	**6 doses in 6 visits (weekly). Total 6 weeks** 1 ug on first day and achieving 50 ug dose after 6 weeks
	100 ug maintenance[2]	**6 doses in 4 visits every 2 weeks. Total 6 weeks** Designed to achieve 100 ug dose within 6 weeks
	100 ug maintenance[28]	**12? doses in 9? visits. Total 4 weeks.** Designed to achieve 100 ug dose within 4 weeks
Golden 1981b[42]	4 weekly maintenance a	NA
	6 weekly maintenance	NA
	4 weekly maintenance b	NA

Study ID	Intervention	Updosing: doses and frequency
Müller 1987[46, 47]	HBV	**9 doses in 7 visits (weekly). Total 6 weeks.** Week 0: 0.1, 1.0, 3.0 ug Week 1: 5 ug Week 2: 10 ug Week 3: 20 ug Week 4: 40 ug Week 5: 65 ug Week 6: 100 ug
	Monomethoxy polyethylene glycol-coupled HBV	**7 doses in 5 visits (weekly). Total 4 weeks.** Week 0: 0.5, 5.0, 10.0 ug Week 1: 30 ug Week 2: 60 ug Week 3: 100 ug Week 4: 200 ug
Mosbech 1986[45]	Pharmalgen	**26 doses in 13 visits (twice weekly). Total 13 weeks.** >1 injection per visit initially until local swelling exceeded 5 cm in diameter. Vol 0.2, 0.4, 0.8 ml at 0.001 ug/ml concentration, Vol 0.2, 0.4, 0.8 ml at 0.01 ug/ml concentration, Vol 0.2, 0.4, 0.8 ml at 0.1 ug/ml concentration, Vol 0.2, 0.4, 0.8 ml at 1 ug/ml concentration, Vol 0.2, 0.3, 0.4, 0.6, 0.8, ml at 10 ug/ml concentration Vol 0.1, 0.15, 0.2, 0.3, 0.4, 0.6, 0.8, 1 ml at 100ug/ml
	Alutard	**19 doses in 19 visits (weekly). Total 19 weeks.** Once a week 0.02, 0.04, 0.08, 0.2, 0.4, 0.8, 2.0, 3.0, 4.0, 6.0, 8, 10, 15, 20, 30, 40, 60, 80, 100 ug
	ALK aquagen	**26 doses in 13 visits (twice weekly). Total 13 weeks.** >1 injection per visit initially until local swelling exceeded 5 cm in diameter. Vol 0.2, 0.4, 0.8 ml at 0.001 ug/ml concentration, Vol 0.2, 0.4, 0.8 ml at 0.01 ug/ml concentration, Vol 0.2, 0.4, 0.8 ml at 0.1 ug/ml concentration, Vol 0.2, 0.4, 0.8 ml at 1 ug/ml concentration, Vol 0.2, 0.3, 0.4, 0.6, 0.8, ml at 10 ug/ml concentration Vol 0.1, 0.15, 0.2, 0.3, 0.4, 0.6, 0.8, 1 ml at 100ug/ml
Patriarca 2008[48]	Ultra Rush SCIT	**6 doses in 1 visits (every 30 mins). Total 3 hours.** Day 1: 0.1, 1, 10, 20 ,30, 40 ug
	Ultra Rush SLIT	**10 doses in 1 visits (every 20 mins). Total 3 hours.** Dilution1:10,000, 1 drop, Dilution1:1000, 1 drop, Dilution1:100, 1 drop, Dilution1:10, 1 drop, Pure, 1 drop Pure, 2 drop Pure, 4 drop Pure, 6 drop Pure, 7 drop Pure, 10 drop
Quercia 2001[49]	Pharmalgen cluster	**12 doses in 6 visits (every week). Total 6 weeks.** Week 1: 5 doses 0.01, 0.1, 1.0, 3.0, 6.0 (hourly) Week 2: 1 dose 20.0 Week 3: 1 dose 40.0 Week 4: 1 dose 60.0 Week 5: 2 doses 40.0, 40.0 Week 6: 2 doses 50.0, 50.0
	Pharmalgen Rush	**13 doses in 4 visits (every day). Total 4 days.** Day 1: 4 doses, 0.01, 0.1, 1.0, 2.0 (hourly) Day 2: 4 doses, 4.0, 6.0, 10.0, 20 (hourly then 4th 30 mins) Day 3: 2 doses 40.0, 40.0 (hourly) Day 4: 3 doses 60.0, 50.0, 50.0 (hourly)

Study ID	Intervention	Updosing: doses and frequency
	Depot cluster	**12 doses in 5 visits (weekly). Total 5 weeks.** Week 1: 4 doses 0.03, 0.1, 0.3, 1.0 (hourly) Week 2: 2 doses 2.0, 4.0 (hourly) Week 3: 2 doses 10.0, 20.0 (hourly) Week 4: 2 doses 40.0, 40.0 (hourly) Week 5: 2 doses 50.0, 50.0 (hourly)
Thurnheer 1983	Conventional	**24 doses in 10 visits (weekly). Total 10 weeks** Day 1: 0.1 ml, (10-7 g/l) 0.1 ml (10-6 g/l), 0.1 ml (10-5 g/l), Day 8: 0.1 ml (10-4 g/l), 0.1 ml (10-3 g/l), 0.2 ml (10-3 g/l) Day 15: 0.4 ml (10-3 g/l), 0.8 ml (10-3 g/l) Day 22: 0.1 ml (10-2 g/l), 0.2 ml (10-2 g/l), 0.4 ml (10-2 g/l), 0.8 ml (10-2 g/l) Day 29: 0.4 ml (10-2 g/l), 0.8 ml (10-2 g/l) Day 36: 0.1 ml (10-1 g/l), 0.2 ml (10-1 g/l) Day 43: 0.3 ml, 0.4 ml Day 50: 0.5 ml, 0.6 ml Day 57: 0.7 ml, 0.8 ml Day 64: 0.9 ml, 1.0 ml
	Rush	**35 doses in 10 visits (daily). Total 10 days** Day 1: 0.1 ml, 0.2 ml, 0.4 ml, 0.8 ml (10-7 g/l) Day 2: 0.1 ml, 0.2 ml, 0.4 ml, 0.8 ml (10-6 g/l) Day 3: 0.1 ml, 0.2 ml, 0.4 ml, 0.8 ml (10-5 g/l) Day 4: 0.1 ml, 0.2 ml, 0.4 ml, 0.8 ml (10-4 g/l) Day 5: 0.1 ml, 0.2 ml, 0.4 ml, 0.8 ml (10-3 g/l) Day 6: 0.1 ml, 0.2 ml, 0.4 ml, 0.8 ml (10-2 g/l) Day 7: 0.1 ml, 0.2 ml, 0.4 ml, 0.8 ml (10-1 g/l) Day 8: 0.4 ml, 0.5 ml, 0.6 ml Day 9: 0.7 ml, 0.8 ml Day 10: 0.9 ml, 1.0 ml