

ORIGINAL ARTICLE

Mosquito allergy: Clinical features and natural course

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ABSTRACT

Mosquito bite allergic reactions are due to sensitization to mosquito salivary proteins. The purpose of our study was to assess the clinical features of Thai patients with mosquito allergy, and to define the natural desensitization course. Seventy patients with mosquito allergy were enrolled. Most patients were female. Half of the patients had a personal history of atopy. The average age of onset of mosquito reaction was 5.7 years old (range 2–58). Four patients were in the desensitization phase in which clinical symptoms disappeared within 9.5 years (median). The common cutaneous lesions were erythematous papules (68.6%) and immediate wheals (67.1%). The most common area of involvement was the leg. Forty of 50 patients (80%) had positive skin prick testing to mosquito allergen (*Culex quinquefasciatus*) and 31 of 42 patients (73.8%) had positive immunoglobulin E antibodies against allergens in *C. quinquefasciatus* saliva proteins.

Key words: clinical features, mosquito allergy, natural course.

INTRODUCTION

Mosquito bite allergic reactions are due to sensitization to mosquito salivary proteins.¹ Mosquito saliva-specific immunoglobulin (Ig)E, IgG antibodies and T-cell-mediated delayed type hypersensitivity reaction appear to be involved in the pathogenesis.^{1–3} *Culex quinquefasciatus*, *Aedes aegypti* and *Aedes vexans* are the three most important mosquito species worldwide.⁴ Common cutaneous reactions to mosquito bites include immediate wheals and flares with a peak within 20 min and delayed reaction manifested as itchy indurated erythematous papules with a peak at 24–36 h and then gradually resolving within days or weeks.^{2,5} Other reactions include vesicles, bullae, ecchymosis, Skeeter syndrome (large cellulitis-like local inflammatory reaction and low-grade fever), generalized urticaria, angioedema and anaphylaxis.^{1,6} In severely allergic patients, severe skin lesions may develop into hemorrhagic bulla, necrosis or ulcers healing with residual scarring. Accompanied

systemic symptoms include high fever, generalized malaise, lymphadenopathy, hepatosplenomegaly, hepatic dysfunction and glomerulonephritis.⁷

Even though allergic reactions to mosquito bites are common and impair the quality of life of many people, there are only a few studies concerning the clinical features and natural course of these patients. In our country, *C. quinquefasciatus* is the prevalent human biting species. We previously reported the IgE antibodies against 35.5-, 32.5- and 22.5-kD allergens in *C. quinquefasciatus* saliva proteins in 22 (41%), 15 (28%) and 13 (24%) of 54 patients with a history of mosquito bite allergy.⁸

The purpose of our study was to assess the clinical features of Thai patients with mosquito allergy, and to define the natural desensitization course.

METHODS

This study was approved by the Siriraj Institutional Review Board, Bangkok, Thailand. Cross-sectional

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study was performed by recruiting patients with mosquito allergy aged older than 18 years from the outpatient Department of Dermatology, Siriraj Hospital, Mahidol University, Bangkok, Thailand from January 2004 to December 2008. Patients with underlying lymphoproliferative disorders and those seropositive for HIV were excluded from the study.

Demographic data, a complete past history (onset of the reaction, reaction type, severity, course of mosquito allergy and previous treatment), mosquito allergic reaction at the time of the study, personal and family history of atopy were recorded. Physical examination, morphology and distribution of skin lesions were studied. The skin reaction patterns of the patients at the time of the study have been classified into five stages due to lifetime course of the process of sensitization and desensitization as previously reported:^{9,10} stage 1, the bites do not cause a reaction; stage 2, delayed type of reaction (erythematous papules of >4 mm develop at 3–4 h after bite and with a peak at 24–36 h); stage 3, both delayed and immediate type of reaction (wheal of >4 mm develop a peak ≤20 min after bite); stage 4, only immediate wheals; and stage 5, those with repeated bites eventually lose the reactions.

Investigations were performed in patients who gave permission and included skin prick testing (SPT) using mosquito allergen (*C. quinquefasciatus*) and another 28 allergens (13 aeroallergens and 15 food allergens: Alk-Abello; Lincoln Diagnostics, Dallas, TX, USA), sera tested for *C. quinquefasciatus* saliva-specific IgE antibodies using enhanced chemiluminescence immunoblot technique.⁸

The diagnosis of mosquito allergy was defined by bite reactions (immediate wheals and flares with a peak ≤20 min and delayed reaction manifested as itchy indurated erythematous papules with a peak at 24–36 h and then gradually resolving within days or weeks; other reactions include vesicles, bullae, ecchymosis, generalized urticaria and angioedema), or, in severe cases, anaphylaxis and systemic symptoms, developing after a witnessed mosquito bite. In cases with no confirmed witnessed mosquito bite, diagnosis was made by positive SPT to mosquito allergen and/or positive serum *C. quinquefasciatus* saliva-specific IgE. Written informed consents were obtained from all individuals.

SPT

The SPT was performed by placing a drop of antigen extract on the skin then using a hypodermic needle to gently tent the skin and puncture it in order to introduce the allergen. In addition, 0.9% saline and histamine 10 mg/mL were included as negative and positive controls, respectively. In all patients, skin reactivity was tested on the volar surface of the forearm by the same trained and experienced person. The results were read at 15 min. A positive result yielded a wheal at least 3 mm in diameter larger than the negative control. Besides mosquito allergen, the studied allergens included 16 food allergens (i.e. egg white, egg yolk, cow's milk, wheat, banana prawn, giant tiger prawn, giant freshwater prawn, undulated surf clam, green mussel, blue swimming crab, sea crab, snapper, cuttlefish, butterflyfish, mackerel, yeast) and 12 aeroallergens composed of molds (*Aspergillus*, *Penicillium*, *Cladosporium*), pollens (para grass, bermuda grass, careless weed), house dust, mites (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*), cat hair, dog epithelium and cockroach.

Mosquito extracts

Mosquito saliva extracts were collected from *C. quinquefasciatus* following the method of Boorman with some modification.¹¹ Briefly, living female mosquitoes were captured by anesthesia. Their proboscis was inserted into the capillary tubes which were filled with 20 µL of distilled water. Stimulating salivation was achieved by applying 0.5% (v/v) malathion to their thoraxes. Then, the content in the capillary tubes was collected, pooled and lyophilized sequentially. Protein content of the extracts was determined by Bradford's method.¹²

C. quinquefasciatus saliva-specific IgE detection by an enhanced chemiluminescence immunoblot

Specific IgE was detected by an enhanced chemiluminescence immunoblot technique (ECL-immunoblot). Saliva extracts prepared from *C. quinquefasciatus* were separated by sodium dodecylsulfate polyacrylamide gel electrophoresis (SDS-PAGE) and transferred onto a nitrocellulose membrane (NC). The blotted NC was blocked in a solution of Tris-buffered saline Tween (TBS-T) with 5% non-fat dry powdered milk (w/v) for at least 1 h

at room temperature. Then, patients' sera as well as positive and negative controls were added to the blocked NC at the dilution of 1:2 and incubated for 1 h at room temperature. The NC was then washed three times for 5 min each time in TBS-T followed by applying the horseradish peroxidase (HRP)-conjugated secondary antibodies at the dilution of 1:1000 and incubated for 1 h at room temperature. The NC was again washed with TBS-T as previously. The developing solution (ECL substrates) was prepared by mixing equal parts of stable peroxide solution and luminol solution (5 mL of each) in a square Petri dish. The washed NC was incubated with developing solution, swirling constantly. The NC was rinsed with TBS. Then, the NC was placed face down on a piece of saran wrap, and the edges folded under to seal the NC which was then placed into an X-ray film cassette with the edged tapes. The developed NC was exposed to the film and was processed.

Statistical analysis

Descriptive statistics (e.g. mean, median, minimum, maximum and percentages) were used to describe demographic data and positivity of SPT and specific IgE to mosquito. All statistical data analyses were performed using SPSS for Windows ver. 10.0.

RESULTS

Seventy patients were enrolled with a mean age of 31.3 years (standard deviation 11.4; range 18–63) (Table 1). Sixty-one (87%) were women. Median age of onset of mosquito reaction was 5.7 years (range 2–58). Half of the patients had a personal history of atopy, mostly allergic rhinitis. Forty-four percent of the patients had a family history of atopy. One-quarter of the patients had a family history of mosquito allergy. Twenty-two patients (31.4%) had both personal and family histories of atopy.

Table 2 shows the relationship between the age of patients, duration of symptoms after the onset and stage of bite reaction at the time of the study. Most patients in this study who were adult, were in stages 3 (42.9%) and 4 (45.7%). Patients of younger age were mainly in stages 2 or 3. Patients of older age were mainly in stages 4 and 5. Mean duration of symptoms after the onset also tended to increase

Table 1. Demographic data of patients studied

Characteristics	No. (%) of patients (<i>n</i> = 70)
Sex	
Male	9 (13)
Female	61 (87)
Age, years; mean (SD)	31.3 (11.4)
Age of onset, years; median (range)	5.8 (2–58)
Patients without symptoms (desensitization)	
No. of patients (%)	4 (5.7)
Duration, years; mean (SD)	9.5 (10.3)
Patients with symptoms	
No. of patients (%)	66 (94.3)
Duration, years; mean (SD)	17.2 (13.7)
Personal history of atopy	41 (58.6)
Atopic rhinitis	34 (48.6)
Atopic dermatitis	11 (15.7)
Asthma	6 (8.6)
Allergic conjunctivitis	5 (7.1)

SD, standard deviation.

Table 2. Relationship between the age of patients, duration of symptoms after onset and stage of bite reaction at time of study (*n* = 70)

Stages of bite reaction [†]	No. of patients (%)	Mean age of patients at time of study; years (SD)	Mean duration of symptoms after onset; years (SD)
1	0 (0)	–	–
2	4 (5.7)	17.8 (6.4)	12.8 (8.6)
3	30 (42.9)	27.8 (9.9)	15.7 (12.1)
4	32 (45.7)	32.7 (12.5)	19.5 (15.2)
5	4 (5.7)	40.0 (9.4)	19.8 (7.9)

[†]Stage 1, the bites do not cause a reaction; stage 2, delayed type of reaction (erythematous papules >4 mm develop at 3–4 h after bite and with a peak at 24–36 h); stage 3, both delayed and immediate type of reaction (wheal >4 mm develop a peak ≤20 min after bite); stage 4, only immediate wheals; and stage 5, those with repeated bites eventually lose the reactions. SD, standard deviation.

with age. Four patients had symptom remission at the mean age of 40 years old.

Table 3 shows clinical manifestation of patients with mosquito allergy. The most common cutaneous lesion was erythematous papule. Immediate wheals were detected in two-thirds of the patients. Angioedema and generalized urticaria were each detected in only 1% of the patients. No patients in this study had systemic symptoms. The most common combination of clinical manifestations detected were immediate wheal and postinflammatory hyperpigmentation (32 cases, 45.7%), followed by immediate wheal

Table 3. Clinical manifestations of patients (*n* = 70)

Clinical manifestations [†]	No. of patients (%)
Primary lesions	
Erythematous papule	48 (68.6)
Immediate wheal	47 (67.1)
Vesicle, bullae	18 (25.7)
Ecchymosis	5 (7.1)
Generalized urticaria without angioedema	1 (1.4)
Angioedema	1 (1.4)
Secondary changes	
Postinflammatory hyperpigmentation	43 (61.4)
Secondary bacterial infection (cellulitis, pustules, abscess)	16 (22.8)
Prurigo simplex-like lesion	8 (11.4)
Atrophic scar	8 (11.4)
Prurigo nodularis	3 (4.3)
Postinflammatory hypopigmentation	5 (7.1)

[†]One patient could have more than one type of clinical manifestation.

together with erythematous papules, and postinflammatory hyperpigmentation (22 cases, 31.4%).

The most common area of involvement was the leg (100%), followed by the forearm (52.9%), neck, thigh and hand (1.4% each). It should be noted here that one patient may have had more than one area of involvement. Underlying diseases among patients studied were breast cancer (CA) (two cases, 2.8%), CA corpus (one case, 1.4%), CA tongue (one case, 1.4%) and others (nine cases, 12.6%).

Forty-two patients had a blood test for mosquito saliva-specific IgE and 50 patients received SPT to mosquito allergen. Twenty-four patients took both tests. Forty of 50 patients (80%) had positive SPT to mosquito allergen. Thirty-one of 40 patients with positive SPT to mosquito allergen (77.5%) also had positive SPT to other allergens. Mite was the most commonly detected allergen (36.5%), followed by insects other than mosquito (34.6%), food allergens and house dust (19.2%). Thirty-one of 42 patients (73.8%) had positive IgE antibodies against allergens in *C. quinquefasciatus* saliva proteins. Nine patients of 24 patients (37.5%) who had taken both tests, were positive to both mosquito saliva-specific IgE and SPT to mosquito allergen. Four of 23 patients (17.3%) gave negative results for both tests. Only one patient was diagnosed by a witnessed mosquito bite without performing mosquito saliva-specific IgE and/or SPT.

No patients had leukocytosis or eosinophilia. Concerning the natural histories of the patients at the time of the study, four of 70 (5.7%) were in the stage of desensitization. These patients had no clinical symptoms within a median of 9.5 years (range 2–20) after onset of clinical symptoms. Ninety-four percent (66 of 70 patients) had unremitting symptoms. Nine patients (12.9%) were deteriorating after a mean duration of 6.5 years. Twenty-eight patients (40%) had unchanged symptoms. Clinical improvement was observed in 29 patients (41.4%). Eleven of 70 patients (15.7%) had clinical improvement of 50–75% with a median duration of 12 years (range 3–54). Eight patients (11.4%) had clinical improvement more than 75% with a median duration of 17 years (range 3–26). The remaining patients had little clinical improvement.

More than half of the patients received their treatment from physicians. Most of them were satisfied with the use of topical steroids as well as oral antihistamines to relieve their symptoms. Some of the patients used self-treatment by using balm. For mosquito bite protection, nearly half of the patients used mosquito wire screens and insect repellents. A few patients wore long-sleeve clothes and long pants. A minority of patients avoided outdoor activities.

DISCUSSION

Oka *et al.*¹⁰ studied the relationship between age and bite reaction. Mosquito bite reactions in humans exposed continuously are known to change from stage 1 to stage 5. The younger age groups (group 1, 1–6 years; group 2, 7–10 years; group 3, 11–20 years) were mainly in stages 2 or 3. The older age groups (group 4, 21–50 years; group 5, 51–68 years) were mainly in stages 3 and 4. Similarly, most of our patients, who were all adults (18–63 years), were in stages 3 (42.9%) and 4 (45.7%).

In our study, women were more commonly found to be allergic to mosquito bites. Mosquitoes are attracted to humans through the CO₂, odor and estrogen that surround human skin.¹³ Floral fragrances from perfumes and body care products may also attract mosquitoes.¹⁴ These reasons may support findings in our study that women are more frequently bitten by mosquitoes. However, Gilbert *et al.*¹⁵ reported that men are bitten more readily than

women, perhaps due to having larger bodies and greater relative heat or CO₂ output.¹⁶

More than half of the patients in this study had a personal history of atopy, mostly allergic rhinitis. In 2001, Vichyanond *et al.*¹⁷ reported the prevalence of allergic rhinitis and asthma in Thai university students as 26.3% and 8.8%, respectively. This data implied the increased prevalence of atopy in our patients with mosquito allergy.

In this study, we aimed to study the cutaneous allergic reactions to mosquito bite in real life. The most common cutaneous lesion was erythematous papule. Immediate wheals were detected in two-thirds of the patients. The common combination of clinical manifestations detected were immediate wheal and postinflammatory hyperpigmentation, followed by immediate wheal together with erythematous papules and postinflammatory hyperpigmentation.

Exaggerated reactions to mosquito bites were reported in lymphoproliferative disorders such as chronic lymphocytic leukemia (CLL) and natural killer (NK) cell leukemia/lymphoma related to chronic Epstein-Barr (EBV) infection.^{18,19} Tokura *et al.*¹⁸ reported that “the triad of hypersensitivity to mosquito bites, chronic EBV infection and NK cell leukemia/lymphoma is a clinical entity seen mostly in Asians”. Davis *et al.*¹⁹ studied eight patients with CLL (aged 51–69 years), and one patient had exaggerated arthropod-bite lesions 10 years prior to the diagnosis of CLL. Seven patients had CLL before developing skin lesions. Ohshima *et al.*²⁰ demonstrated that EBV-carrying NK cells in patients with hypersensitivity to mosquito bites (HMB) overexpressed Fas ligand or soluble Fas ligand. These suggested that enhanced Fas ligand might be related to tissue damage. Asada *et al.*²¹ reported that CD4⁺ T cells in these patients could induce reactivation of latent EBV infection in NK cells that might be involved in the pathogenesis of HMB. Because it was questionable whether these lesions might be caused by vasculopathy mediated by Arthus type immune reactions to mosquito saliva or other mechanisms (not by IgE-mediated skin reaction), we decided to exclude patients with lymphoproliferative disorders from this study.

Penneys *et al.*²² studied seven patients with AIDS, five of whom had chronic non-specific-appearing skin eruption that could not be explained by defin-

able cause and could be suggestive of insect bite reaction, had increased antibody titers to mosquito-salivary glands of *Aedes taeniorhynchus*, a mosquito commonly found in southern Florida, USA. Resneck *et al.*²³ studied 102 patients with pruritic papular eruption in HIV infection (PPE), and 84% had biopsy findings characteristic of arthropod bites. These patients had significantly higher peripheral eosinophil counts and their CD4 cell counts were generally low. Because of the inconclusive pathogenesis of PPE, we also excluded patients with PPE from this study.

The limitation of this study was that we did not perform serum saliva-specific IgE to *A. aegypti* and *A. vexans*. In Thailand, *C. quinquefasciatus* and *A. aegypti* are commonly found. *A. aegypti* commonly causes acute hemorrhagic fever but it may cause allergic reaction as well. However, only one patient was diagnosed with mosquito allergy by a witnessed mosquito bite without performing mosquito saliva-specific IgE and/or SPT. The others had positive results of mosquito saliva-specific IgE or SPT to *C. quinquefasciatus* or both.

Wongkamchai *et al.* studied the serum from Thai patients who were allergic to mosquitoes bites; the specific IgE antibodies were not only bound to saliva allergens of the three human biting species, but also bound to the allergens of *Anopheles minimus*, which is a zoophilic strain, suggesting that sensitization of allergic subjects by mosquito bites from one species can confer reactivity against another species. The 35.5-kDa allergen was found in *C. quinquefasciatus* and *A. aegypti*. The 32.5-kDa allergen was found in *C. quinquefasciatus* and *A. minimus*. The 22.5-kDa allergen was found in *C. quinquefasciatus*, *Aedes albopictus* and *A. minimus*. This result indicates that the saliva of *C. quinquefasciatus* may contain shared allergens with other mosquito species (Dr Sirichit Wongkamchai, unpubl. data, 2008)

Sensitization and desensitization to salivary allergens after mosquito bites has been classified into five stages of reactivity.^{9,10} In one who has never been bitten by mosquito, the initial bite causes no reaction (stage 1). Subsequent bites cause a delayed cutaneous reaction (stage 2). After repeated bites, immediate whealing reactions develop (stage 3). With further exposure, delayed reactions disappear with only immediate wheals detected (stage 4). With long-term

exposure, patients eventually lose all reactions (stage 5). In the prospective experimental study, an individual receiving mosquito bites developed delayed and immediate skin reactions at week 3, which peaked at weeks 5–19. Reactions disappeared by week 26. However, in real life, natural desensitization may be different from the experimental study. Peng *et al.*²⁴ studied 401 infants, children and adolescents and reported that both saliva-specific IgE and IgG declined with age. They suggested that “natural desensitization probably occurs during childhood and adolescence”. In our study, four patients had symptom remissions. These occurred at a median of 9.5 years after onset of the reaction (range 2–20 years) and these patients had symptom remission at the mean age of 40 years. The duration of symptom remission seemed to be longer than in the *in vitro* study reported by Peng *et al.* However, we had only a small number of patients who were in the desensitization stage.

Concerning patients’ behaviors for mosquito bite prevention in this study, most patients used mosquito wire screens and insect repellents. Only a few patients used long-sleeve clothes and long pants, probably due to the hot climate in our country.

In summary, most patients with mosquito allergy had limited cutaneous symptoms. Natural desensitized duration was longer than the time previously reported in the laboratory test.

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REFERENCES

- Peng Z, Simons FE. Mosquito allergy: immune mechanisms and recombinant salivary allergens. *Int Arch Allergy Immunol* 2004; **133**: 198–209.
- Peng Z, Yang M, Simons FE. Immunologic mechanisms in mosquito allergy: correlation of skin reactions with specific IgE and IgG antibodies and lymphocyte proliferation response to mosquito antigens. *Ann Allergy Asthma Immunol* 1996; **77**: 238–244.
- Oka K. Correlation of *Aedes albopictus* bite reaction with IgE antibody assay and lymphocyte transformation test to mosquito salivary antigens. *J Dermatol* 1989; **16**: 341–347.
- Peng Z, Li H, Simons FE. Immunoblot analysis of salivary allergens in 10 mosquito species with worldwide distribution and the human IgE responses to these allergens. *J Allergy Clin Immunol* 1998; **101**: 498–505.
- Peng Z, Simons FE. A prospective study of naturally acquired sensitization and subsequent desensitization to mosquito bites and concurrent antibody responses. *J Allergy Clin Immunol* 1998; **101**: 284–286.
- Simons FE, Peng Z. Skeeter syndrome. *J Allergy Clin Immunol* 1999; **104**: 705–707.
- Tokura Y, Tamura Y, Takigawa M *et al.* Severe hypersensitivity to mosquito bites associated with natural killer cell lymphocytosis. *Arch Dermatol* 1990; **126**: 362–368.
- Wongkamchai S, Techasintana P, Wisuthsarewong W, Kulthanan K, Suthipinittharm P, Eakpo P. Analysis of IgE-binding allergens in *Culex quinquefasciatus* saliva protein in mosquito bite allergic patients. *Ann Allergy Asthma Immunol* 2007; **98**: 200–201.
- Mellanby K. Man’s reaction to mosquito bites. *Nature* 1946; **158**: 554.
- Oka K, Ohtaki N. Clinical observations of mosquito bite reactions in man: a survey of the relationship between age and bite reaction. *J Dermatol* 1989; **16**: 212–219.
- Boorman J. Induction of salivation in biting midges and mosquitoes, and demonstration of virus in the saliva of infected insects. *Med Vet Entomol* 1987; **1**: 211–214.
- Bradford M. A rapid and sensitive method for quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. *Anal Biochem* 1976; **72**: 248–254.
- Brown AWA. The attraction of mosquitoes to hosts. *JAMA* 1966; **196**: 249–252.
- Foster WA, Hancock RG. Nectar-related olfactory and visual attractants for mosquitoes. *J Am Mosq Control Assoc* 1994; **10**: 288–296.
- Gilbert IH, Gouck HK, Smith N. Attractiveness of men and women to *Aedes aegypti* and relative protection time obtained with DEET. *Entomol* 1966; **49**: 53–66.
- Port GR, Boreham PFL. The relationship of host size to feeding by mosquitoes of the *Anopheles gambiae* Giles complex (Diptera: Culicidae). *Bull Entomol Res* 1980; **70**: 133–144.
- Vichyanond P, Sunthornchart S, Singhirannusorn V, Ruangrat S, Kaewsomboon S, Visitsunthorn N. Prevalence of asthma, allergic rhinitis and eczema among university students in Bangkok. *Respir Med* 2002; **96**: 34–38.
- Tokura Y, Ishihara S, Tagawa S, Seo N, Ohshima K, Takigawa M. Hypersensitivity to mosquito bites as the primary clinical manifestation of a juvenile type of Epstein-Barr virus-associated natural killer cell leukemia/lymphoma. *J Am Acad Dermatol* 2001; **45**: 569–578.

- 19 Davis M, Perniciaro C, Dahl PR, Randle HW, McEvoy MT, Leiferman KM. Exaggerated arthropod-bite lesions in patients with chronic lymphocytic leukemia: a clinical, histopathologic, and immunopathologic study of eight patients. *J Am Acad Dermatol* 1998; **39**: 27–35.
- 20 Ohshima S, Ishii M, Asada H *et al*. A possible mechanism of NK-cell lineage granular lymphocyte proliferative disorder (NK-GLDP) in a patient with chronic active Epstein-Barr virus infection (CAEBV) and severe hypersensitivity to mosquito bites (SHMB). *Intern Med* 2002; **41**: 651–656.
- 21 Asada H, Miyagawa S, Sumikawa Y *et al*. CD4⁺ T-lymphocyte-induced Epstein-Barr virus reactivation in a patient with severe hypersensitivity to mosquito bites and Epstein-Barr virus-infected NK cell lymphocytosis. *Arch Dermatol* 2003; **139**: 1601–1607.
- 22 Penneys NS, Nayar JK, Berstein H, Knight JW. Chronic pruritic eruption in patients with acquired immunodeficiency syndrome associated with increased antibody titers to mosquito salivary gland antigens. *J Am Acad Dermatol* 1989; **21**: 421–425.
- 23 Resneck JS, BeeK MV, Furmanski L *et al*. Etiology of pruritic papular eruption with HIV infected in Uganda. *JAMA* 2004; **292**: 2614–2621.
- 24 Peng Z, Ho MK, Li C, Simons FE. Evidence for natural desensitization to mosquito salivary allergens: mosquito saliva specific IgE and IgG levels in children. *Ann Allergy Asthma Immunol* 2004; **93**: 553–556.