

Early life risk factors for atopic dermatitis in Ethiopian children

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Background: Atopic dermatitis (AD) has increased in prevalence in many countries in recent decades, but the risk factors for AD in developing countries are unknown.

Helminthic parasites may play a role in protecting against allergic disease, but few studies have investigated the association of AD with parasitic infection.

Objective: To establish the independent effects of parasitic infection and other early life factors on the risk of AD in Ethiopia.

Methods: We conducted a cross-sectional survey and nested case-control study of children age 1 to 5 years in Jimma and surrounding rural areas in southwest Ethiopia. Cases were defined according to the International Study of Asthma and Allergies in Childhood criteria for AD and confirmed by clinical examination. Information on lifestyle and other potential risk factors was collected by parental questionnaire, and stool samples were analyzed for parasites.

Results: Complete data were obtained on 306 AD cases defined by International Study of Asthma and Allergies in Childhood criteria (prevalence, 4.4%) and 426 controls. There was no reduction in the risk of AD in relation to intestinal parasite infection; in fact, AD was increased in subjects with *Trichuris* (1.61; 95% CI, 1.14-2.26). The risk of AD was also unrelated to family size, crowding in the home, or breast-feeding, but was related to previously unrecognized factors including malaria and access to piped drinking water. Similar findings were apparent in cases and controls confirmed by clinical examination.

Conclusion: Neither intestinal parasite infection nor other proposed risk factors for AD appear to be related to the presence of the condition in young children in Ethiopia, suggesting that other factors may be more important in this population. (*J Allergy Clin Immunol* 2005;115:370-6.)

Key words: Atopic dermatitis, Ethiopia, helminthic parasites, etiology

Atopic dermatitis (AD), also known as *atopic eczema*, is a common chronic inflammatory skin condition of

Abbreviations used

AD: Atopic dermatitis

ISAAC: International Study of Asthma and Allergies in Childhood

OR: Odds ratio

UK: United Kingdom

children and adults and a significant public health burden in many parts of the world.^{1,2} The prevalence of AD appears to have risen substantially in many countries in recent decades,³ a phenomenon that has been attributed variously to changes in lifestyle, nutrition, and other environmental factors.⁴⁻⁶ The exposures implicated in increasing the risk of AD include high socioeconomic status,^{7,8} low birth order,⁹ reduced crowding in the home,¹⁰ improved hygiene,¹¹ reduced breast-feeding,¹² and eradication of endoparasites.¹³ However, the etiology of AD remains poorly understood, particularly in developing countries, where there has been relatively little effort expended to investigate risk factors for the development of AD.

We have previously reported an increased prevalence of AD in urban compared with rural locations in Jimma, southwest Ethiopia.¹⁴ We have now performed a new case-control study of environmental risk factors for AD in young children in the Jimma area to investigate the early life risk factors associated with AD in urban and rural populations. Our primary hypothesis was that there would be an inverse association between helminthic endoparasite infestation and the occurrence of AD.

METHODS

Study area and target population

Jimma zone is a province in southwest Ethiopia with a population of approximately 2.6 million inhabitants, 120,000 of whom live in the urban area of Jimma town. Jimma is a tropical area with an altitude ranging from 1500 to 2000 m above sea level, and the temperature ranges from 0°C in November to 37°C in March. In 2003, we performed an initial cross-sectional survey targeting all children age 1 to 5 years living in the urban area of Jimma, and in 11 rural farmers' association areas in the Mana and Seqa-chekorsa (Shebe) districts, approximately 50 km from urban Jimma. We used these data to identify groups for more detailed investigation in a nested case-control study and for a diagnostic validation study.^{14a}

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Data collection

Phase 1: initial screening survey. In August and September 2003, we surveyed all children age 1 to 5 years in the study area by house-to-house visits guided by a map of the kebele (the smallest governmental administration unit) or farmers' association map. We used a brief interviewer-administered questionnaire to obtain information from parents or other caregivers on the occurrence of itchy skin conditions to identify possible cases. Questions included the first 3 International Study of Asthma and Allergies in Childhood (ISAAC) study questions for eczema¹⁵: (1) "Has your child ever had an itchy rash which was coming and going for at least 6 months?" (2) "Has your child had this itchy rash at any time in the last 12 months?" and (3) "Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, around the neck, around the ears or eyes?" We also asked the United Kingdom (UK) working party criteria screening question¹⁶: "In the last 1 year, has your child had an itchy skin condition—by itchy we mean scratching or rubbing the skin?"

Phase 2: nested case-control study. From the screening survey, we identified as possible cases all children who gave positive responses to the first 2 ISAAC questions and/or to the UK diagnostic criteria screening question. We also drew a random subsample of all children who participated in the screening survey, irrespective of their questionnaire responses, as a source of controls. The number of children in the random subsample was determined to be approximately equal to the number of possible cases. All of these children were revisited and examined by a pediatric dermatologist (A.H.), and a clinical diagnosis was made. We also collected further detailed information on skin conditions, including the remaining UK diagnostic criteria questions for eczema.¹⁶

Cases for the current study were defined according to the ISAAC protocol criteria of positive responses to all 3 ISAAC eczema questions. Controls were children from the random subsample who did not qualify as cases (Fig 1). To check the consistency of our findings, we repeated the analysis by using case and control definitions confirmed by clinical examination, and by using an alternative case definition based on the full UK diagnostic criteria.

At the second visit (to all possible cases and the random subsample), we also collected information on potential risk factors and confounders, including details of pregnancy and lactation, vaccinations, infections, fruit and vegetable intake, treatment (previous intake of antibiotics and antihelminths), family conditions, and housing conditions. Skin prick tests to *Dermatophagoides pteronyssinus*, cockroach (*Blatella germanica*), eucalyptus, and histamine (positive) and saline (negative) controls were performed, and results were read after 15 minutes. A skin test result was considered positive when the corrected (allergen – saline control) mean skin wheal diameter was ≥ 2 mm. A fresh stool sample was collected from all study subjects and examined for the presence of intestinal parasites by formalin-ether sedimentation.¹⁷ Intensity of parasite infection was categorized by using the same (tertile) cutoffs for each parasite as in our previous study of asthma in this population.¹⁸ Children who were not at home at the time of the second visit were revisited the next day.

Ethics approval for all aspects of the study was obtained from the relevant committees in Nottingham and Jimma. Consent was obtained from parents or caregivers after a verbal explanation of the study supported by a written information sheet.

Analysis

All data were entered into the Statistical Package for the Social Sciences version 11.0 (SPSS Inc, Chicago, Ill) and analyzed by multiple logistic regression, with adjustment where appropriate for age, sex, and urban or rural residence. Because we have previously

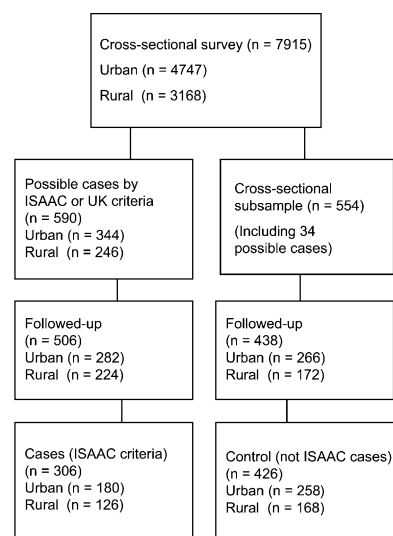


FIG 1. Subject recruitment and response.

observed and reported different risk factors for other allergic disease in the urban and rural populations of Jimma,^{19,20} we looked for effect modification by urban or rural area by fitting a statistical interaction with site of residence; where the associations differed between the urban and rural areas, results are stratified by site. Our power calculation presumed that we would obtain detailed information on at least 250 cases of AD, and with a control sample of equal size, we would have approximately 90% power to detect an odds ratio (OR) of 0.5 in relation to parasite infection.

RESULTS

Response rate and prevalence

Screening information from the brief questionnaire was obtained from 7915 children age 1 to 5 years (mean, 3 years). Because there are no census data available, the participation rate is unknown, but anecdotally, there were few refusals. Of these participants, 4012 (51%) were boys and 3903 (49%) girls, and 4747 (60%) were from the urban and 3168 (40%) from rural areas (Fig 1). Information was provided for 75% of participants by a parent, 11% by an older sibling, and the remainder by another family or household member. We identified 590 possible cases in the survey, 350 of which met the full ISAAC diagnostic criteria, so the prevalence of AD by the ISAAC criteria in this population was 4.4%. We generated a random subsample of 554 individuals from all participants (34 of whom had already been identified as possible cases), and were able to follow-up and perform detailed assessments for 438 (79%), and for 506 (86%) of the possible cases. Of the 186 lost to follow-up, 13 were reported to have died, 82 had changed their address, 65 were not available for study at either home visit, and 26 refused. The distribution of boys to girls, age, and urban-rural site of residence (Fig 1) of those in the detailed study was similar to that of respondents in the initial screening survey.

TABLE I. Association of demographic and socioeconomic characteristics with AD defined by the ISAAC diagnostic criteria

	Cases	Controls	OR (95% CI)	Age, sex, and site-adjusted OR (95% CI)
Total	306	426		
Male	55.2	50.0	1	
Female	44.8	50.0	0.81 (0.60-1.09)	
Age (y)				
1	19.0	17.6	1	
2	24.2	21.1	1.06 (0.67-1.68)	
3	22.2	17.1	1.20 (0.75-1.94)	
4	17.3	24.2	0.66 (0.41-1.07)	
5	17.3	20.0	0.81 (0.50-1.31)	
Urban	58.8	60.6	1	
Rural	41.2	39.4	1.07 (0.80-1.45)	
Highest parental education				
No education	20.3	28.2	1	1
Elementary	35.9	30.0	1.66 (1.12-2.48)	1.70 (1.13-2.55)
Secondary	43.8	41.8	1.46 (1.00-2.13)	1.65 (1.07-2.55)
Father's occupation				
Civil servant	23.2	23.0	1	1
Farmer	39.2	43.9	0.89 (0.61-1.30)	0.60 (0.35-1.01)
Other	37.6	33.1	1.13 (0.76-1.67)	1.07 (0.71-1.59)
Income group				
Low	68.0	65.7	1	1
Medium	25.5	24.2	1.02 (0.72-1.44)	1.01 (0.71-1.43)
High	6.5	10.1	0.63 (0.36-1.10)	0.65 (0.36-1.15)

Demographic associations

Compared with controls from the random sample who did not meet the ISAAC AD criteria, cases of AD tended to be younger (though not significantly so) and of more educated parents (Table I). There was a significant association with father's occupation after adjusting for age, sex and site of residence ($P = .04$) such that the risk of AD tended to be lower in children of farmers; this effect was apparent only in the urban area, the rural population being predominantly farmers. There was no relation between AD risk and sex, family income, or residence in urban or rural areas.

Association with allergen skin sensitization

There was no overall association between allergen skin sensitization and AD. However, this association differed between urban and rural areas, with the odds of AD tending to be increased in subjects who had positive skin test results in the urban area (significantly so in relation to eucalyptus; Table II) and reduced in the rural area.

Effect of parasite infection

The most common parasites were *Ascaris lumbricoides*, present in 28% of the cross-sectional subsample; *Trichuris trichiura* in 26%; and *Necator americanus* (hookworm) in 4%, with no *Schistosoma* or other parasites. There was no evidence that the risk of AD was reduced in the presence of any 1 or more parasite infections (Table III); indeed, the risk of AD was significantly higher in the presence of any parasite

infection, with this effect predominantly caused by *Trichuris*. This association tended to be stronger in the urban area, although the interaction was not statistically significant. Hookworm infection had no clear effect. There was also no evidence that the risk of AD was influenced by the intensity of parasite infection (all P values $> .6$). A total of 52% of children had received an antihelminth treatment at some time in the past, but this was unrelated to AD.

Maternal and early life factors

There were no significant associations between AD risk and feeding practices, or with family size or antibiotic use by the child (Table IV), but there was a significant reduction in risk associated with vaccination (age, sex, and site-adjusted OR, 0.64; 95% CI, 0.47-0.88), most notably with DPT or polio vaccination. Most children had had both of these vaccinations or neither. The risk of AD was increased in children with a history of malaria (OR, 2.18; 95% CI, 1.53-3.10) but was unrelated to other infections, including measles and pertussis (data not shown). There were too few children reported to be premature (3%) to assess the effect of gestation on AD risk.

Home lifestyle

Cases were less likely to use wood for fuel every day, more likely to use electricity every day, and more likely to live in a house with a corrugated iron rather than a thatched roof (Table V). Insecticide use in the home was also associated with increased risk of AD. All of these effects tended to be stronger in the urban area, though not

TABLE II. Association of AD (ISAAC criteria) with allergen skin sensitization (2 mm or more greater than saline)

	Urban			Rural		
	Cases	Controls	Age and sex-adjusted OR (95% CI)	Cases	Controls	Age and sex-adjusted OR (95% CI)
Dust mite sensitization						
No	74.3	76.3	1	79.0	76.5	1
Yes	25.7	23.7	1.14 (0.72-1.78)	21.0	23.5	0.88 (0.50-1.54)
Cockroach sensitization						
No	92.2	94.4	1	95.2	94.6	1
Yes	7.8	5.6	1.36 (0.62-2.95)	4.8	5.4	0.87 (0.30-2.54)
Eucalyptus sensitization						
No	86.6	94.8	1	92.7	89.2	1
Yes	13.4	5.2	2.67 (1.31-5.45)	7.3	10.8	0.63 (0.27-1.47)
Any sensitization						
No	61.5	68.3	1	69.4	67.5	1
Yes	38.5	31.7	1.35 (0.90-2.03)	30.6	32.5	0.91 (0.55-1.52)

significantly so. Cases and controls were equally likely to use kerosene (35% vs 36%); few (2.8%) ever used gas. Cases were more likely to have access to a piped water source and less likely to have the river as their only source of drinking water. Cases also tended to have a higher fruit intake. There was no significant relation between AD and having animals living in the home, type of flooring or walls of the home, type of mattress, or the presence of a smoker in the home.

Multivariate analyses

In a multivariate model, which included all of the statistically significant effects described, the strongest independent predictors of AD were age (adjusted OR for age 5 years compared with age 1 year, 0.60; 95% CI, 0.36-1.01; test for linear trend, $P = .009$), vaccination (OR, 0.68; 95% CI, 0.49-0.94), history of malaria (OR, 2.07; 95% CI, 1.44-2.97), infection with *Trichuris* (OR, 1.61; 95% CI, 1.14-2.26), increased fruit intake (OR for more than 1/wk, 1.97; 95% CI, 1.18-3.30), and water source (risk of AD was highest in subjects who had piped water and least in those using water from the river; OR for river vs piped, 0.33; 95% CI, 0.15-0.71).

Use of alternative case and control definitions

At clinical examination, 102 cases were confirmed by a local physician as having AD and 388 controls as not having AD. When we used only cases and controls confirmed by clinical examination, we found associations very similar to those described above; there were significant or borderline significant ($P < .1$) independent effects of older age, malaria, infection with *Trichuris*, and increased fruit intake, and there was an inverse association with vaccination. Cases were more likely to have piped water, but the effect of water source was not statistically significant in multivariate analysis. Very similar associations were also apparent for cases and controls defined according to the UK working party criteria for AD (data not shown).

TABLE III. Parasite presence in association with atopic eczema (ISAAC criteria)

	Cases	Controls	Age, sex, and site-adjusted OR
Any parasite			
No	36.9	47.4	1
Yes	63.1	52.6	1.58 (1.16-2.15)
<i>Trichuris</i>			
No	64.1	74.2	1
Yes	35.9	25.8	1.64 (1.18-2.28)
<i>Ascaris</i>			
No	66.3	71.4	1
Yes	33.7	28.6	1.31 (0.95-1.81)
Hookworm			
No	96.4	96.5	1
Yes	3.6	3.5	1.01 (0.45-2.28)

DISCUSSION

We have conducted, to our knowledge, the largest etiologic study of AD in preschool children in a developing country. In our previous study of AD in adults and children in Jimma 9 years ago, the prevalence of AD was higher in the urban than in the rural population of Jimma, but was only 0.3% overall for children under age 19 years.¹⁴ Our new findings estimate the prevalence in very young children at 4.4%, and in this age group, AD was equally prevalent in the urban and rural areas. Contrary to our study hypothesis, the prevalence of AD tended to be increased in children with intestinal parasite infections, especially *Trichuris*. AD was more common in children of more educated parents but was otherwise unrelated to several of the risk factors for AD identified in studies in developed countries, including breast-feeding or weaning patterns, family size, or crowding in the home.

The validity of our case definitions is a potential limitation of this study, especially in a county in which other skin conditions prevail. The UK working group has provided criteria for AD that have been shown to be reliable and valid for epidemiologic studies in UK

TABLE IV. Maternal and early life factors in association with atopic eczema (ISAAC criteria)

	Cases	Controls	Age, sex, and site-adjusted OR
Maternal age (y)			
<22	21.6	24.6	1
22-25	28.8	30.5	1.08 (0.71-1.63)
26-29	18.6	16.0	1.33 (0.83-2.14)
30-45	31.0	28.9	1.27 (0.84-1.91)
Breast-feeding			
≤12 mo	26.8	22.3	1
12-24 mo	52.3	55.2	0.73 (0.50-1.05)
>24 mo	20.9	22.5	0.76 (0.49-1.18)
Initiation of weaning			
<4 mo	19.0	15.0	1
4-6 mo	67.0	70.0	0.76 (0.51-1.13)
>6 mo	14.1	15.0	0.76 (0.45-1.30)
Any vaccination			
No	39.5	29.3	1
Yes	60.5	70.7	0.64 (0.47-0.88)
DPT vaccination			
No	51.6	40.8	1
Yes	48.4	59.2	0.66 (0.49-0.89)
Polio vaccination			
No	41.5	30.0	1
Yes	58.5	70.0	0.62 (0.45-0.85)
Malaria infection			
No	66.0	79.8	1
Yes	34.0	20.2	2.18 (1.53-3.10)
Number of siblings			
0-1	20.6	21.1	1
2-3	49.3	47.2	1.09 (0.73-1.61)
4 or more	30.1	31.7	0.95 (0.62-1.46)
Antibiotic use by child			
No	61.8	64.1	1
Yes	38.2	35.9	1.09 (0.80-1.48)

populations²¹ but may have poorer sensitivity elsewhere.^{22,23} The ISAAC criteria for AD, which are based on the initial data from the UK working party, are more inclusive, and as a separate component of this study, we assessed the validity of both the ISAAC and UK working party criteria for the first time in an Ethiopian population. We found that the ISAAC criteria identified more cases (n = 350 of the original survey) than the UK criteria (n = 127), with relatively little loss in positive predictive value compared with a clinical examination as gold standard.^{14a} To maximize the statistical power of our analyses, we have used the ISAAC criteria as primary outcome, but we checked our main findings by using alternative case definitions in our population, first by using only cases and controls confirmed by clinical examination, and second by using the complete UK working party criteria. The direction and size of effects were similar for all of these analyses, although they were sometimes of lessened statistical significance for the latter because of smaller numbers.

The hypothesis that intestinal parasitic infections might protect against AD was based on epidemiologic and immunologic evidence that parasites protect against other

TABLE V. Home lifestyle in association with atopic eczema (ISAAC criteria)

	Cases	Controls	Age, sex, and site-adjusted OR
Crowding in the home			
0.2-2	20.6	23.7	1
2-2.5	29.7	27.7	1.22 (0.80-1.86)
2.5-4.5	29.7	22.3	1.52 (0.99-2.34)
>4.5	19.9	26.3	0.88 (0.56-1.39)
Roof of the house			
Corrugated	75.4	67.6	1
Thatched	24.6	32.4	0.53 (0.35-0.80)
Floor of house			
Mud	84.0	85.9	1
Cement	16.0	14.1	1.18 (0.76-1.83)
Source of water			
Piped	67.3	57.7	1
Well	10.1	7.7	0.82 (0.45-1.47)
River	3.6	9.4	0.26 (0.13-0.54)
Spring	19.0	25.1	0.41 (0.25-0.67)
Cigarette smoker			
No	78.1	79.1	1
Yes	21.9	20.9	1.07 (0.75-1.54)
Wood as fuel			
Never/sometimes	24.2	16.9	1
Every day	75.8	83.1	0.57 (0.39-0.84)
Electricity as fuel			
Never/sometimes	39.5	46.7	1
Every day	60.5	53.3	2.63 (1.55-4.48)
Animals living in the house			
No	51.3	47.2	1
Yes	48.7	52.8	0.86 (0.63-1.17)
Vegetable intake			
Never	9.8	10.9	1
<1/wk	35.5	43.9	0.93 (0.55-1.58)
>1/wk	54.9	45.5	1.40 (0.83-1.55)
Fruit intake			
Never	10.1	15.0	1
<1/wk	35.9	46.7	1.21 (0.74-2.00)
>1/wk	53.9	38.3	2.29 (1.40-3.77)
Insecticide use			
No	81.0	85.9	1
Yes	19.0	14.1	1.53 (1.01-2.32)

atopic disease.¹³ Indeed, we have previously shown in the Jimma population that individuals with certain intestinal parasite infections, especially hookworm, have a lower risk of wheezing and asthma.^{18,19} There have been very few studies looking directly at the association of AD with intestinal parasites, but none of the available data, including the findings from the current study, support a hypothesis of a similar protective effect of intestinal parasites in AD.^{24,25} Hookworm and some other parasites are associated, at least temporarily as they enter the body, with skin irritation, and if this were misclassified as AD, our results would be biased toward a positive association. Alternatively, a protective effect of parasites may be specific to asthma and may relate to organ-specific suppression of allergic inflammation in the airways¹⁹

rather than a more general effect on allergic disease. Unlike studies from elsewhere,^{25,26} intestinal parasites did not appear to protect against allergen sensitization in the Jimma population.^{18,19}

Moreover, as we have previously shown for asthma,²⁷ AD was more weakly associated with allergen sensitization in the Jimma population, especially those living in the rural areas, than in more developed societies. The only significant relationship was with eucalyptus sensitization in the urban area, and this result may have arisen by chance as a result of multiple hypothesis testing. Nevertheless, we tested for eucalyptus because there is a large eucalyptus plantation on the outskirts of Jimma, and this finding highlights the importance of considering allergens other than those most relevant to allergy in Western society. A reduction in the degree of atopy in AD populations living in developing countries has been documented in a recent review of the association between atopy and AD.²⁸ Indeed, more than 60% of AD cases in this study were not atopic according to the allergens tested in our survey, calling into question the validity of the term *atopic* within AD and providing further support to the nomenclature committee of the World Allergy Organization's recent call for revising nomenclature for allergic disorders.²⁹

This study found no effect of several risk factors that have long been linked to AD, including breast-feeding or stage of weaning, birth order, or crowding in the home. Our previous study in an older population in Jimma also found no protective effect of family size on risk of AD,¹⁴ and one possibility is that these are all markers for an exposure or exposures that are more homogeneous, and therefore less predictive of AD, in the Ethiopian population. Exposure to infection is a potential explanation for these effects, but at first sight, there is little in our data to support the hypothesis that exposure to childhood infection protects against allergy. There was no association with specific childhood infections apart from a positive relationship with malaria. This may be a chance finding. Skin rashes are not a reported clinical feature of malaria, so this association, if real, is difficult to explain. In both the current and previous studies in Jimma, vaccination against infection has tended to be negatively associated with AD and other allergic disease. However, the association that we found with the source of the child's drinking water and increased AD in those using piped water, which is consistent with recent data from Ecuador showing a weak protective effect of drinking river water on the development of atopy,³⁰ might be explained through increased exposure to enteric infections, which may be more relevant in protecting against the development of atopy.³¹ The association of AD with better parental education, which was our only marker of socioeconomic status, was largely explained by other factors such as the source of drinking water, and could also be a marker for better hygiene. The unexpected association of AD with high fruit intake may similarly reflect a more healthy, and at the same time, a more hygienic lifestyle.

In conclusion, we have shown that the etiology of AD in young Ethiopian children differs in several respects from

that reported in the developed world. Further studies of AD in developing countries may help in isolating important factors in the development of the condition.

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Correction

With regard to the November 2004 article entitled "Immune responses to mosquito saliva in 14 individuals with acute systemic allergic reactions to mosquito bites" (2004;114:1189-94): In Table II (page 1191), the data pertaining to individual no. 10 were presented incorrectly and no. 11 was missing. A correct version of the Table is presented here:

TABLE II. Demographics of 14 individuals with systemic allergic reactions to mosquito bites

Individual no.	Age (y)	Sex	Systemic symptoms-signs	Country	New arrival
1	12	F	Urticaria, wheezing	US (MN)	No
2	7	M	Angioedema, urticaria	US (MN)	No
3	3	F	Angioedema of face	US (VA)	No
4	14	F	Anaphylactic reactions	US (NC)	No
5	5	M	Urticaria, angioedema, nausea, vomiting	US (NC)/Syria	Yes
6	22	M	Angioedema, dyspnea, loss of consciousness	US (NY)	Yes
7	23	M	Urticaria, dyspnea	US (NY)	Yes
8	>18	M	Angioedema, wheezing	US	No
9	>18	M	Angioedema, urticaria	US	No
10	>18	M	Reported as anaphylactic reaction	US	No
11	29	M	Urticaria, angioedema, respiratory and presyncopal-type symptoms	Canada (ON)	No
12	32	F	Urticaria, hypotension (blood pressure 80/50)	Germany	No
13	21	F	Angioedema, loss of consciousness	Switzerland	No
14	>18	M	Angioedema, decreased consciousness	Japan	Yes

Treatment of the acute reaction included one or more of the following: epinephrine, H₁-antihistamine (usually diphenhydramine), glucocorticoid, intravenous fluids, oxygen, and inhaled β_2 -adrenergic agonist. Participants 2, 6, 7, and 13 received immunotherapy with mosquito whole-body extract after their systemic allergic reaction to mosquito bites (rush immunotherapy in participants 6, 7, and 13). Participant 5 received prophylactic cetirizine.