

MISS JILL DE WIT (Orcid ID : 0000-0001-5080-1453)  
MR JOAN E.E. TOTTÉ (Orcid ID : 0000-0002-3231-4720)

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**The prevalence of antibody responses against *Staphylococcus aureus* antigens in patients with atopic dermatitis: a systematic review and meta-analysis**

**Running title**

Anti-*Staphylococcus aureus* antibody responses in atopic dermatitis

**Authors and affiliations**

J. de Wit,<sup>1</sup> J.E.E. Totté,<sup>1</sup> F.J.M. van Buchem,<sup>1</sup> S.G.M.A. Pasmans<sup>1</sup>

<sup>1</sup>Department of Dermatology, Erasmus University Medical Centre, Rotterdam, the Netherlands

**Corresponding author during publication process**

J. de Wit

Department of Dermatology, Erasmus University Medical Centre Rotterdam  
Burgemeester 's Jacobplein 51, 3015 CA, Rotterdam, The Netherlands

j.dewit.1@erasmusmc.nl, +31 10 70 40110

**Corresponding author post-publication**

S.G.M.A. Pasmans

Department of Paediatric Dermatology, Sophia Children's Hospital, Erasmus University  
Medical Centre Rotterdam, Wytemaweg 80, 3015 CN, Rotterdam, The Netherlands

s.pasmans@erasmusmc.nl

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### **Conflict of interest**

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### **What's already known about this topic?**

- *Staphylococcus (S.) aureus* is implicated as a causal factor in the pathogenesis of atopic dermatitis (AD).
- An altered immune response towards various *S. aureus* antigens might contribute to inflammation.
- Current literature reports varying prevalences of antibodies against *S. aureus* antigens in AD.

### **What does this study add?**

- The prevalence of immunoglobulin (Ig) E against staphylococcal superantigens (SEA, SEB) is increased in AD patients compared to healthy controls.
- Literature on IgG and IgA mediated humoral immune responses is very limited.

### **ABSTRACT**

*Staphylococcus (S.) aureus* plays a role in the pathogenesis of atopic dermatitis (AD), possibly via the expression of various virulence antigens. An altered antibody response towards these antigens might contribute to inflammation. We aimed to provide an overview of the varying prevalences and odds of antibody responses against *S. aureus* antigens in AD patients. Data were systematically obtained from Embase, Medline, Web of Science, Scopus, Cochrane, PubMed and Google Scholar (up to February 12<sup>th</sup> 2016). We selected all original observational and experimental studies assessing anti-staphylococcal antibodies in serum of

AD patients. Prevalences and odds ratios (ORs) of immunoglobulin (Ig) E, IgG, IgM, IgA against *S. aureus* in AD patients versus healthy controls were pooled using the random-effects model. We calculated  $I^2$  statistics to assess heterogeneity and rated study quality using the Newcastle-Ottawa Scale. Twenty-six articles (2369 patients) were included of which 10 controlled studies. Study quality was fair to poor. AD patients had higher prevalences of IgE against staphylococcal enterotoxin (SE) A (OR 8.37, 95% CI 2.93-23.92) and SEB (OR 9.34, 95% CI 3.54-24.93) compared to controls. Prevalences of anti-staphylococcal IgE were 33% for SEA, 35% for SEB and 16% for toxic shock syndrome toxin (TSST)-1. However, study heterogeneity and imprecision should be taken into consideration when interpreting the results. Data on IgG, IgM and IgA as well as other antigens are limited. In conclusion, AD patients more often show an IgE antibody response directed against *S. aureus* superantigens compared to healthy controls supporting a role for *S. aureus* in the AD pathogenesis.

## INTRODUCTION

Atopic dermatitis (AD) is a multifactorial disorder that arises from interactions between immune dysregulations, genetic predisposition, skin barrier defects and environmental factors.<sup>1,2</sup> Both the lesional and non-lesional skin as well as the nose of AD patients are more likely to be colonized with *Staphylococcus (S.) aureus* compared to healthy controls.<sup>3</sup> Recent studies have shown that abundance of *S. aureus* is associated with AD severity, suggesting a causal role for *S. aureus* in the pathogenesis of AD.<sup>2,4-9</sup> However, the exact mechanisms by which *S. aureus* aggravates inflammation in AD are not fully understood.<sup>10</sup> *S. aureus* expresses a variety of virulence factors that could contribute to AD inflammation. Based on their biological function these antigens can be divided in four groups: (1) Microbial Surface Components Recognizing Adhesive Matrix Molecules (MSCRAMMs) such as Clumping factor A (ClfA) that helps *S. aureus* adhere to the host cells, (2) cell membrane damaging molecules such as alpha toxin which can induce keratinocyte cell death, (3) household enzymes such as Lipase that provides cell nutrition and (4) immune modulating proteins (superantigenic and non-superantigenic).<sup>10-13</sup> The latter include the group of staphylococcal superantigens which have the ability to activate mast cells and T-cells directly resulting in the release of pro-inflammatory cytokines.<sup>5,14-16</sup> Expression of these *S. aureus* antigens varies between the different *S. aureus* isolates. However, it has been proven difficult to identify associations between the genetic composition of *S. aureus* strains and AD.<sup>17-22</sup>

Evaluation of the antibody response to these *S. aureus* antigens gives an indication of the antigens that are expressed by the bacterium *in vivo* and will give insight into how the immune system of AD patients counteracts these antigens. This might help understand the role of *S. aureus* in the AD pathogenesis as well as the mechanisms by which *S. aureus* causes inflammation. Since 1982 several studies reported serum antibodies against *S. aureus* in patients with AD.<sup>23-35</sup> However, the prevalences of anti-staphylococcal antibodies in these studies vary widely. This is probably due to low sample sizes and different methods used to detect antibodies (e.g. ELISA, AlaSTAT). Moreover, studies often focus on few antigens and/or antibody classes.

The aim of this systematic review is to provide an overview of the pooled prevalence and odds of antibodies (immunoglobulin (Ig) E, IgG, IgM and IgA) against *S. aureus* antigens in serum of patients with AD compared to healthy controls. Additionally, we reviewed the relationship between AD severity and anti-*S. aureus* antibodies.

## **MATERIALS AND METHODS**

### ***Studies***

All original observational and experimental human studies were included. No restrictions were made to publication date and language. Case reports were excluded.

### ***Study participants***

Patients of all ages with AD, irrespective of disease severity, and presence of anti-*S. aureus* antibodies were included. Healthy controls were defined as persons who do not have AD neither an atopic constitution (food allergy, asthma, allergic rhinitis) nor another skin disease.

### ***Study outcomes***

The primary outcome is the proportion of AD patients with antibodies (IgE, IgG, IgM, IgA) in serum against *S. aureus* antigens compared to healthy controls. The secondary outcome is the relationship between AD severity and anti-staphylococcal antibodies.

### ***Search strategy***

The systematically electronic search was conducted in Embase, Medline, Web of Science, Scopus, Cochrane, PubMed and Google Scholar up to February 12<sup>th</sup> 2016 (Table S1). A cross reference check was performed to identify other relevant studies.

### ***Study selection and data extraction***

Initially, all studies identified in the systematic search were screened for relevance by title and abstract. Duplicates and studies that did not meet our inclusion criteria were excluded (Appendix S1). Remaining articles were assessed for eligibility by full text review.

Translation of non-English studies was conducted officially. Study selection and data extraction were performed independently by two researchers (JT and FvB or JdW and FvB). Disagreements were resolved and consensus was reached. If one population was described in different articles, we included the study with the most detailed description of the results. The methodological quality of the articles was scored based on an adapted version of the Newcastle Ottawa Scale (NOS).<sup>3</sup> Studies could reach a maximum score of 9 points for case-control studies and 5 points for uncontrolled studies. Using a scoring algorithm, the controlled studies were classified as being of poor, fair or good methodological quality, based on their NOS scores (Appendix S2).<sup>36</sup> The overall quality of evidence was discussed according to the principles of the GRADE approach (i.e. limitations in study design or execution, inconsistency of results, indirectness of evidence, imprecision, publication bias).<sup>37</sup>

### ***Statistical analysis***

A meta-analysis was performed using a random-effects model in case of  $\geq 2$  available studies. We extracted the prevalences of anti-staphylococcal antibodies in AD patients and controls from the included studies. If required we calculated prevalences with the available raw data. The prevalences of anti-staphylococcal antibodies were pooled. Furthermore, in controlled studies these prevalences in patients and controls were compared, expressed as ORs with a 95% confidence interval (CI). Antibody prevalences were descriptively presented for single studies. When the antibody prevalence in the control group was 0% an OR could not be calculated and a continuity correction factor using the Mantel-Haenszel method was added to both the patient and control group (based on the unbalanced group ratio).<sup>38,39</sup> Heterogeneity was assessed using the Higgins  $I^2$  test.<sup>40,41</sup> Nevertheless,  $I^2$  should be interpreted cautiously in small meta-analyses.<sup>42</sup> In case of substantial ( $I^2$  50-90%) or considerable ( $I^2$  75-100%) heterogeneity sources were explored using subgroup analysis for the variables age, method of antibody identification and geographic region of the study centres ( $\geq 10$  available studies). Possible publication bias was assessed in case of  $\geq 10$  studies using funnel plots and Egger's test ( $P$ -value  $< 0.05$ ).<sup>43,44</sup> Analyses were performed using Comprehensive Meta-Analysis Version 2.2 (Biostat, Englewood, NJ). This systematic review was conducted and reported

according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.<sup>45</sup>

## RESULTS

### *Study characteristics and quality*

The literature search identified 2789 studies. After removal of duplicates 1323 studies remained. Screening on title and abstract yielded 113 full text articles. Finally, 26 articles with a total of 2369 patients were included for further analysis (Fig. 1).<sup>24,25,27-35,46-60</sup> Twenty-one articles reported the sex of the patients with a mean percentage of males of 53.4% (range 28.1-81.8).<sup>25,28-30,33-35,46-49,51-60</sup> The mean age was 24.1 years (range 4.4-68.9), reported in 15 articles.<sup>25,28-30,33,34,46-49,51,53-55,58</sup> Thirteen articles scored the AD severity using the SCORing Atopic Dermatitis (SCORAD) with 3 articles reporting a mean of 33.6 (range 32.2-36.0) corresponding with moderate AD.<sup>30,32-35,46,47,49-52,57,59,61</sup> Nine articles used other scoring criteria for the AD severity.<sup>25,28,29,31,48,54-56,58</sup> Most studies were conducted in Europe and Asia. Methods for identification of anti-staphylococcal antibodies consist mainly of radioimmunoassay (RIA) tests, enzyme-linked immunosorbent assays (ELISA) and AlaSTAT assays, an enzyme-immunoassay method for the measurement of allergen specific IgE (Table S2). One study measuring multiple antibodies used both a RIA test for IgE and an ELISA for IgG.<sup>31</sup> NOS scores of the 11 controlled studies were rated as good (n=1), fair (n=5) and poor (n=5).<sup>24,25,27-33,36,53,60</sup> The main reason for downgrading the quality of these studies was incomparability of the patient and control groups. The quality scores of the 15 studies without a control group varied between 2 and 4 points out of 5 (Table S2 and Appendix S2).<sup>34,35,46-52,54-59</sup>

### *Prevalence of antibodies against S. aureus*

#### *IgE*

Twenty-four studies including 2206 patients reported the prevalence of anti-staphylococcal IgE.<sup>24,25,27-31,33-35,46-59</sup> These studies predominantly determine the antibody response against staphylococcal enterotoxin (SE) A, SEB, SEC, SED and toxic shock syndrome toxin (TSST)-1 (19, 23, 7, 3 and 10 studies, respectively) (Table S3).<sup>24,25,27-31,34,35,46-59</sup> Pooled prevalences of anti-staphylococcal IgE in patients were 33% for SEA (95% CI 23-45;  $I^2$  94.23)<sup>24,25,27-</sup>

30,34,35,46-48,50,51,53,54,56-59, 35% for SEB (95% CI 27-43;  $I^2$  91.36)<sup>24,25,27-31,34,35,46-59</sup>, 14% for SEC (95% CI 8-22;  $I^2$  78.26)<sup>24,34,46,47,52,56,58</sup>, 5% for SED (95% CI 1-16;  $I^2$  70.49)<sup>24,34,47</sup> and 16% for TSST-1 (95% CI 10-25;  $I^2$  85.28)<sup>24,27,34,35,46-48,52,56,58</sup> (Table 1 and Fig. S1a-e). There was a great variation in prevalence between studies (0.8-78.8% for SEA, 1.4-72.9% for SEB, 5.4-40.0% for SEC, 0.0-10.7% for SED and 1.4-53.3% for TSST-1) probably resulting in the substantial to considerable heterogeneity. One study showed a prevalence of 35.8% of fibronectin-binding protein (FBP) specific IgE, another study found a prevalence of 48.1% of IgE against lipoteichoic acid (LTA).<sup>27,33</sup> Undetectable to very low prevalences of IgE against the staphylococcal antigens SEE, SEI, SEH, SEK, SEJ, exfoliative toxin (ET)-1 and ETA were found in several single studies (Table 2).<sup>24,31,47</sup>

### *IgG, IgM and IgA*

Prevalences of IgG against *S. aureus* antigens were determined in 4 studies.<sup>31,32,55,60</sup> The pooled prevalences of IgG against SEB, reported in 2 studies (114 patients), was 64% (95% CI 42-81;  $I^2$  78.84) (Fig. S1f).<sup>55,60</sup> Besides, in single studies the IgG prevalences were 77.0% for SEA, 77.0% for TSST-1 and 34.6% for ETA.<sup>31,60</sup> IgG subclass 2 (IgG<sub>2</sub>) was found in 87.0% of the AD patients against SEB and in 61.5% against SEC<sub>1</sub>.<sup>32</sup> Only one study determined anti-staphylococcal IgM and detect antibodies against SEB in 62.5% of the AD patients (Table 2).<sup>55</sup> None of the selected articles studied anti-staphylococcal IgA.

### *Odds of antibodies against S. aureus*

Of the 26 articles 11 studies compared AD patients to healthy controls (759 patients vs. 328 controls).<sup>24,25,27-33,53,60</sup> Nine studies reported the prevalence of anti-staphylococcal IgE (596 patients vs. 189 controls).<sup>24,25,27-31,33,53</sup> These studies mainly described antibody responses against SEA and SEB (7 and 8 articles, respectively).<sup>24,25,27-31,53</sup> Pooled analyses showed that anti-staphylococcal IgE was found significantly more often in the serum of patients compared to controls with an OR of 8.37 for SEA (95% CI 2.93-23.92;  $P < 0.001$ ;  $I^2$  0.00)<sup>24,25,27-30,53</sup> and 9.34 for SEB (95% CI 3.54-24.93;  $P < 0.001$ ;  $I^2$  0.00)<sup>24,25,27-31,53</sup> (Table 3 and Fig. S2a-b). A pooled OR of IgE against TSST-1, reported in 2 studies (83 patients vs. 20 controls), was 23.33 (95% CI 0.47-1153.93,  $P = 0.114$ ,  $I^2$  0.00) (Table 3 and Fig. S2c).<sup>24,27</sup> Prevalences of other antigens, including SEC, SED, ETA, ET-1, FBP and LTA, were described in single controlled studies and pooled estimates could not be provided.<sup>24,27,31,33</sup> The prevalences of all these *S. aureus* antigens were equal or increased in patients compared to controls (Table 4). Since most antibody prevalences in control groups were 0% the ORs could not be calculated.

Prevalences of IgG in patients and controls were compared in 3 studies.<sup>31,32,60</sup> Compared to controls, patients were found to have higher IgG prevalences to ETA and SEB and lower prevalences of IgG to SEA and TSST-1.<sup>31,60</sup> In patients, the IgG<sub>2</sub> prevalence to SEC<sub>1</sub> was lower and to SEB higher compared to controls.<sup>32</sup> However, most differences in prevalences between patients and controls were small. No studies compared the anti-staphylococcal IgM or IgA response between patients and controls.

### ***Subgroup analysis***

Subgroup analyses of the variables age, method of antibody identification and geographic region of the study centres were performed to detect possible sources of heterogeneity. The prevalences of IgE against SEA, SEB and TSST-1 did not significantly differ between children and adults (31% vs. 27%, 25% vs. 38% and 13% vs. 12%, respectively). Studies using the ELISA method showed higher pooled prevalences of IgE against SEA, SEB and TSST-1 compared to studies using RIA tests (61% vs. 19%, 47% vs. 25% and 18% vs. 12%, respectively). Lastly, studies conducted in Asia showed higher pooled prevalences of IgE to SEA, SEB and TSST-1 compared to studies conducted in Europe (51% vs. 24%, 48% vs. 28% and 18% vs. 15%, respectively) (Table 1).

### ***Relationship between AD severity and antibodies against *S. aureus****

Considering the low number of studies reporting a mean SCORAD we could not calculate an overall association between AD severity and anti-staphylococcal antibodies. However, several individual studies reported a significant association between superantigen-specific (e.g. SEA, SEB) IgE and AD severity, measured by SCORAD, the criteria of Rajka or the modified Leicester system.<sup>29,32,55,58</sup> This association could not be confirmed in four comparable studies.<sup>25,28,46,58</sup> Sohn *et al.* looked at IgG against SEB and did not find a relation with AD severity.<sup>55</sup> However, Mrabet-Dahbi *et al.* found that patients with a deficiency of anti-staphylococcal IgG<sub>2</sub> to SEC<sub>1</sub> had a more severe AD phenotype.<sup>32</sup> Based on these contradictory studies, no conclusions can be drawn about the association between the anti-staphylococcal antibody response and severity of AD.

### **Publication bias**

Funnel plots of the pooled prevalence of IgE against SEA, SEB and TSST-1 showed no asymmetry (Fig. S3). Eggers tests had intercepts of 0.52 for SEA (95% CI -4.40-5.44,  $P = 0.826$ ), -0.44 for SEB (95% CI -3.78-2.91,  $P = 0.789$ ) and -0.82 for TSST-1 (95% CI -4.40-2.76,  $P = 0.611$ ) confirming no publication bias.

### **DISCUSSION**

This systematic review includes 26 studies and 2352 AD patients. IgE responses against SEA and SEB in serum were found more often in AD patients compared to healthy controls. IgE, IgG and IgM against a very limited panel of other antigens were reported in single studies. No data are available on anti-staphylococcal IgA. Pooled prevalences of anti-staphylococcal IgE in AD patients are 33% for SEA, 35% for SEB and 16% for TSST-1. Substantial to considerable heterogeneity and imprecision (small studies) limit the quality of evidence and should be taken into consideration when interpreting the results. Subgroup analysis were performed to account for differences in outcome measures (indirectness). Quality of evidence was probably not influenced by publication bias.

Subgroup analyses suggest that the antibody prevalence is dependent on the method of antibody identification (ELISA vs. RIA) and the geographic region of the study centres (Asia vs. Europe). This is in accordance with the study of Taylor *et al.* that found ELISA more sensitive than RIA to detect IgG<sub>1</sub> in mouse.<sup>62</sup> It might also explain the higher prevalence of antibodies in Asia compared to Europe as Asian studies use ELISA techniques more often. Furthermore, ethnicity dependent antibody response has been suggested, at least for TSST-1.<sup>63</sup> Because heterogeneity in subgroup analyses remains high, pooled prevalences and odds were probably also influenced by other variables, like AD severity. Unfortunately, we were not able to explore this as only a few studies reported a mean SCORAD. These individual studies showed contradictory results about the association between AD severity and IgE against predominantly superantigens.

The *S. aureus* antigens SEA and SEB belong to the group of immune-modulators and act as superantigens. This indicates they have the ability to stimulate T-cells directly resulting in T-cell proliferation and cytokine release causing epithelial damage.<sup>14-16</sup> The increased anti-SEA and anti-SEB IgE responses can be the result of increased expression of these antigens by the *S. aureus* bacteria in AD patients, indicating SEA and SEB as one of the bacteria's

mechanisms to aggravate or even initiate inflammation in AD. However, studies included in this systematic review predominantly examined the prevalence of antibodies against the superantigens SEA, SEB and TSST-1 and other common antigens such as ClfA and Lipase were not tested. In addition, SEA, SEB and TSST-1 are only present in respectively 14%, 24% and 14% of the *S. aureus* isolates.<sup>64</sup> These data suggest a bias in the assessment of staphylococcal antigens and indicate also a large genetic diversity amongst the colonized *S. aureus* strains. Furthermore, the increased IgE responses against these antigens may be the result of immunological cross-reactivity, where the corresponding antigen-coding genes of SEA, SEB and/or TSST-1 are not present in the isolate.<sup>65-67</sup>

This is the first systematic review summarising the available data on the prevalence of anti-staphylococcal antibodies in AD patients and the involved antigens. The broad selection criteria (e.g. all languages, only exclusion of case reports and non-original studies) resulted in collecting the majority of articles about this subject and limiting selection bias. However, there are still some limitations in this study. Most articles did not report the AD treatment at time of antibody measurement. The use of antimicrobial therapy might decrease the *S. aureus* load and *S. aureus* antibody titres.<sup>4</sup> Nevertheless, oral antibiotic treatment did not change the skin microbiome in mice.<sup>68</sup> In addition, the anti-inflammatory effect of systemic glucocorticosteroids could both cause a decrease in serum antibody concentrations and might reduce *S. aureus*.<sup>6,69,70</sup> Even emollient monotherapy showed a decrease of *S. aureus* on the skin.<sup>71,72</sup> In the studies that did report the treatment at baseline the therapies consist mainly of topical corticosteroids or no treatment at all (n=9). Secondly, cut-off values of antibody identification methods were highly variable, not mentioned or unclear in and between several methods. Through subgroup analysis we tried to partly correct for this variability. Last, mainly anti-staphylococcal IgE was assessed, which determination was often unsubstantiated or based on results of previous studies. AD patients have frequent high IgE responses to environmental antigens, including *S. aureus*, for example. In addition, IgG is the most common antibody in the extravascular fluid and among others play a role in the neutralization of toxins.<sup>73,74</sup>

To further investigate the role of (the immune response against) *S. aureus* in the AD pathogenesis future studies should focus on other antibody subtypes and other *S. aureus* antigens. IgG subclasses should be measured to detect possible biomarkers for AD severity, such as a selective deficiency in IgG<sub>2</sub> against SEC<sub>1</sub> in the study of Mrabet-Dahbi *et al.*<sup>32</sup>

Besides, assessment of the antibody response against other *S. aureus* antigens, like MSCRAMMs, membrane damaging molecules, housekeeping antigens and other types of immune modulating proteins, might reduce the possibility of an increased IgE response being a secondary phenomenon of increased *S. aureus* colonisation on the AD skin.

### **Conclusion**

This systematic review with meta-analysis shows that AD patients have higher prevalences of IgE against the *S. aureus* antigens SEA and SEB compared to healthy controls, taking the large heterogeneity into consideration. These antigens, belonging to the group of immune-modulators, are known as superantigens and have the ability to cause inflammation and epithelial damage. This supports a role for *S. aureus* in the AD pathogenesis. IgE, IgG and IgM against a very limited panel of other antigens were studied in single studies. No data are available on anti-staphylococcal IgA.

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## TABLES

**Table 1**

IgE against SEA, SEB, TSST-1, SEC and SED in patients with atopic dermatitis

Antigen (subgroup)	Number of studies	Number of patients	Pooled proportion of patients with detectable antigens (95% CI)	Heterogeneity ( $I^2$ )
<b>SEA</b>				
All studies	19	1852	0.33 (0.23-0.45)	94.23
Studies including age <18	6	507	0.31 (0.11-0.63)	96.56
Studies including age ≥18	7	859	0.27 (0.17-0.42)	88.22
Studies including RIA methods*	8	1139	0.19 (0.12-0.29)	86.36
Studies including ELISA method	3	169	0.61 (0.34-0.82)	86.83
Studies including AlaSTAT method	6	461	0.42 (0.28-0.57)	89.04
Studies including Immunoblot method	1	27	0.48 (0.30-0.66)	-
Studies performed in Europe	11	1220	0.24 (0.16-0.34)	87.87
Studies performed in Asia	7	576	0.51 (0.33-0.70)	93.75
Studies performed in USA	1	56	0.32 (0.21-0.45)	-
<b>SEB</b>				
All studies	23	2111	0.35 (0.27-0.43)	91.36
Studies including age <18	8	631	0.25 (0.13-0.43)	92.73
Studies including age ≥18	8	968	0.38 (0.29-0.48)	84.70
Studies including RIA methods*	11	1418	0.25 (0.18-0.34)	86.77
Studies including ELISA method	4	209	0.47 (0.24-0.72)	89.39
Studies including AlaSTAT method	6	461	0.48 (0.33-0.64)	90.42
Studies including Immunoblot method	1	27	0.63 (0.44-0.79)	-
Studies performed in Europe	12	1304	0.28 (0.21-0.36)	84.70
Studies performed in Asia	10	751	0.48 (0.36-0.61)	90.06
Studies performed in USA	1	56	0.18 (0.10-0.30)	-
<b>SEC</b>				
All studies	7	540	0.14 (0.08-0.22)	78.26
<b>SED</b>				
All studies	3	317	0.05 (0.01-0.16)	70.49
<b>TSST-1</b>				
All studies	10	1110	0.16 (0.10-0.25)	85.28
Studies including age <18	5	631	0.13 (0.05-0.28)	85.00
Studies including age ≥18	3	1039	0.12 (0.05-0.27)	84.65
Studies including RIA methods*	6	918	0.12 (0.05-0.25)	90.38
Studies including ELISA method	2	109	0.18 (0.11-0.26)	0.00
Studies including Immunoblot method	1	27	0.41 (0.24-0.60)	-
Studies performed in Europe	7	945	0.15 (0.07-0.28)	90.09
Studies performed in Asia	2	109	0.18 (0.11-0.26)	0.00
Studies performed in USA	1	56	0.21 (0.13-0.34)	-
Abbreviations: SE, staphylococcal enterotoxin; TSST-1, toxic shock syndrome toxin; RIA, radioimmunoassay; ELISA, enzyme-linked immunosorbent assay; CI, confidence interval				
* CAP fluorescent enzyme immunoassay (FEIA), ImmunoCAP, and UniCAP				

**Table 2**IgE, IgG and IgM against *Staphylococcus aureus* antigens in patients with atopic dermatitis

Antibody	<i>Staphylococcus aureus</i> antigen	Number of studies	Number of patients	(Pooled) proportion of patients with detectable antigens (95% CI)	Heterogeneity ( $I^2$ )
IgE	SEE	1	140	0.01	
	SEI	1	140	0.01	
	SEH	1	140	0.00	
	SEK	1	140	0.00	
	SEJ	1	140	0.00	
	ETA	1	26	0.00	
	FBP	1	95	0.36	
	LTA	1	27	0.48	
IgG	SEA	1	74	0.77	78.84
	SEB	2	114	0.64 (0.42-0.81)	
	TSST-1	1	74	0.77	
	ETA	1	26	0.35	
IgG <sub>2</sub>	SEB	1	77	0.87	
	SEC <sub>1</sub>	1	78	0.62	
IgM	SEB	1	40	0.63	

Abbreviations: Ig, immunoglobulin; SE, staphylococcal enterotoxin; TSST-1, toxic shock syndrome toxin 1; ET, exfoliative toxin; FBP, fibronectin-binding protein; LTA, lipoteichoic acid; CI, confidence interval

**Table 3**

IgE against SEA, SEB and TSST-1 in patients with atopic dermatitis versus healthy controls

<i>Staphylococcus aureus</i> antigen	Number of studies	Number of patients	Number of controls	Pooled OR in patients vs controls (95% CI)	Heterogeneity (I <sup>2</sup> )
SEA	7	475	139	8.37 (2.93-23.92)*	0.00
SEB	8	501	172	9.34 (3.54-24.93)*	0.00
TSST-1	2	83	20	23.33 (0.47-1153.93)	0.00

Abbreviations: SE, staphylococcal enterotoxin; TSST-1, toxic shock syndrome toxin 1; OR, odds ratio; CI, confidence interval  
\* significant result

**Table 4**IgE and IgG against *Staphylococcus aureus* antigens in patients with atopic dermatitis versus healthy controls

Antigen	<i>Staphylococcus aureus</i> antibody	Number of studies	Number of patients	Number of controls	Mean proportion of patients with detectable antigens	Mean proportion of controls with detectable antigens	P-value
IgE	SEC	1	56	15	0.05	0.0	-
	SED	1	56	15	0.05	0.0	-
	ETA	1	26	33	0.00	0.0	-
	ET	1	56	15	0.02	0.0	-
	FBP	1	95	17	0.36	0.0	-
IgG	SEA	1	74	111	0.77	0.88	-
	SEB	1	74	111	0.73	0.69	-
	TSST-1	1	74	111	0.77	0.85	-
	ETA	1	26	14	0.35	0.14	-
IgG <sub>2</sub>	SEB	1	77	27	0.87	0.78	-
	SEC <sub>1</sub>	1	78	28	0.62	0.86	-

Abbreviations: Ig, immunoglobulin; SE, staphylococcal enterotoxin; TSST-1, toxic shock syndrome toxin 1; ET, exfoliative toxin; FBP, fibronectin-binding protein

## FIGURE LEGENDS

Figure 1

Flow chart of search strategy and study selection

Table 1

IgE against SEA, SEB, TSST-1, SEC and SED in patients with atopic dermatitis

Abbreviations: SE, staphylococcal enterotoxin; TSST-1, toxic shock syndrome toxin; RIA, radioimmunoassay; ELISA, enzyme-linked immunosorbent assay; CI, confidence interval

\* CAP fluorescent enzyme immunoassay (FEIA), ImmunoCAP, and UniCAP

Table 2

IgE, IgG and IgM against *Staphylococcus aureus* antigens in patients with atopic dermatitis

Abbreviations: Ig, immunoglobulin; SE, staphylococcal enterotoxin; TSST-1, toxic shock syndrome toxin 1; ET, exfoliative toxin; FBP, fibronectin-binding protein; LTA, lipoteichoic acid; CI, confidence interval

Table 3

IgE against SEA, SEB and TSST-1 in patients with atopic dermatitis versus healthy controls

Abbreviations: SE, staphylococcal enterotoxin; TSST-1, toxic shock syndrome toxin 1; OR, odds ratio; CI, confidence interval

\* significant result

Table 4

IgE and IgG against *Staphylococcus aureus* antigens in patients with atopic dermatitis versus healthy controls

Abbreviations: Ig, immunoglobulin; SE, staphylococcal enterotoxin; TSST-1, toxic shock syndrome toxin 1; ET, exfoliative toxin; FBP, fibronectin-binding protein

Figure S1a-f

Forest plots of prevalence meta-analyses

- (a) IgE against SEA in patients with atopic dermatitis
- (b) IgE against SEB in patients with atopic dermatitis
- (c) IgE against SEC in patients with atopic dermatitis

- (d) IgE against SED in patients with atopic dermatitis
- (e) IgE against TSST-1 in patients with atopic dermatitis
- (f) IgG against SEB in patients with atopic dermatitis

Figure S2a-c

Forest plots of odds meta-analyses

- (a) IgE against SEA in patients with atopic dermatitis versus healthy controls
- (b) IgE against SEB in patients with atopic dermatitis versus healthy controls
- (c) IgE against TSST-1 in patients with atopic dermatitis versus healthy controls

Figure S3a-c

Funnel plots for publication bias

- (a) IgE against SEA in patients with atopic dermatitis
- (b) IgE against SEB in patients with atopic dermatitis
- (c) IgE against TSST-1 in patients with atopic dermatitis

Table S1

Electronic search

Table S2

Study characteristics per study

Full reference details are provided in Appendix S3 (see Supporting Information)

<sup>a</sup> Only abstract available

<sup>b</sup> Number of patients included in study (characteristics refer to this number) /number of patients included in the outcome

<sup>c</sup> Control group included in the study but the outcome was not reported

Abbreviations: N, number of patients or controls; y, year; mo, months; AD, atopic dermatitis; NOS, Newcastle-Ottawa Scale; S. aureus, Staphylococcus aureus, med, median; AB, antibiotics; UV, ultraviolet, SCORAD, SCORing Atopic Dermatitis; Ig, immunoglobulin; FEIA, fluorescent enzyme immunoassay; SE, staphylococcal enterotoxin; TSST-1, toxic shock syndrome toxin 1; FBP, fibronectin-binding protein; ET, exfoliative toxin; LTA, lipoteichoic acid

Table S3

Studies reporting IgE antibodies against *Staphylococcus aureus* antigens in patients with atopic dermatitis

Abbreviations: SE, staphylococcal enterotoxin; TSST-1, toxic shock syndrome toxin 1; ET, exfoliative toxin; FBP, fibronectin-binding protein; LTA, lipoteichoic acid

Appendix S1

Inclusion criteria for selecting studies for this systematic review

Appendix S2

Quality assessment score

Appendix S3

Supplementary references

