

Stepwise single-dose oral egg challenge: a multicenter prospective study

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Clinical Implications

- The stepwise single-dose oral food challenge, starting with a low dose and progressing to medium doses, is an effective and safe approach that enables children with egg allergies to avoid complete elimination and contributes to improving daily food allergy management.

TO THE EDITOR:

Oral food challenges (OFCs) are important for the management and diagnosis of food allergies.¹ OFCs can enable children to avoid the complete elimination of the causative food^{2,3} and may accelerate oral tolerance.^{4,5} Stepwise OFCs were recommended in the 2017 Japanese food allergy guidelines.⁶ We previously reported the usefulness and safety of stepwise^{2,3} and single-dose OFCs.⁷ Because these previous studies were retrospective single-center trials,^{2,7} they had an inherent bias that may have caused low positive rates of OFCs. To make up for this shortcoming, the present study with a multicenter design was conducted to confirm the safety and effectiveness of stepwise single-dose OFC.

Stepwise single-dose OFC for heated egg was performed at 4 hospitals and 3 pediatric clinics from April 2016 to October 2017 in children who previously experienced an adverse reaction immediately after exposure. We first undertook single low-dose OFC for heated egg (protein dose: 250 mg; equivalent to 1/25 whole egg) (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Next, children who tolerated the single low-dose OFC proceeded to single medium-dose OFC for heated egg (769 mg; equivalent to 1/8 whole egg) within 12 months. The symptoms induced by the challenge and their severity are described in Table 1 and Table E2, available in this article's Online Repository at www.jaci-inpractice.org. After obtaining a negative result for the single low- or medium-dose OFC, children were allowed to consume egg protein up to the recommended doses.

Written consent was obtained from all guardians. This study was approved by the ethics committee of the Sagami National Hospital (Approval number: 2016-2-18) (see Methods section in this article's Online Repository at www.jaci-inpractice.org).

Of 297 children, 45 did not meet our eligibility criteria (Figure 1; Tables E3 and E4, available in this article's Online

Repository at www.jaci-inpractice.org). Of the 252 children enrolled, 26 (10%) experienced egg-related anaphylaxis. The median age of the children was 1.7 years. The median levels of serum specific IgE (sIgE) to egg white and ovomucoid were 14.3 and 7.5 kU_A/L, respectively.

As shown in Figure 1, 200 children with egg allergies (79%) passed the single low-dose OFC. Thereafter, 164 children underwent a single medium-dose OFC at a median of 99 days after completing the single low-dose OFC. Of these children, 148 (90%) passed the single medium-dose OFC. Reactive and tolerant subjects differed significantly in age, egg white sIgE levels, and ovomucoid sIgE levels (Table E5 in this article's Online Repository at www.jaci-inpractice.org). Probability curves based on OFC results for the single low- and medium-dose OFCs are displayed in Figure E1, available in this article's Online Repository at www.jaci-inpractice.org. We predicted that approximately 50% of children would have a reaction to egg white (sIgE levels >100 kU_A/L; Table E6 in this article's Online Repository at www.jaci-inpractice.org).

Among the 52 single low-dose OFC-positive children, 1 (2%) had a severe reaction (barking cough that immediately improved with adrenaline inhalation). Moreover, 13 (25%) and 38 (73%) children had mild and moderate symptoms, respectively. No patient needed intramuscular adrenaline injection. Those with mild or moderate symptoms repeated low-dose OFC (Figure E2 in this article's Online Repository at www.jaci-inpractice.org). Among the 16 single medium-dose OFC-positive children, 4 (25%) and 12 (75%) had mild and moderate symptoms, respectively. No severe reactions occurred. The median times until the onset of the initial symptoms were 61 and 48 minutes in the single low- and medium-dose OFCs, respectively (Table 1).

This is the first multicenter prospective study to examine the effectiveness and safety of stepwise single-dose OFC. Most children passed low or medium doses safely. In terms of the safety of our OFC protocol, the 50% predictive decision point of the single low-dose OFC was an egg white sIgE level >100 kU_A/L. Therefore, OFC can be acceptable even in children with high sIgE levels to egg white or ovomucoid. Moreover, the positive rate of the low-dose OFC in this study was similar to that reported in previous studies; in contrast, that of the medium-dose OFC was only 10%, which is much lower than the 36% reported in a previous study.² In this study, most children who passed the single low-dose OFC also passed the single medium-dose OFC after a short period. Therefore, it is reasonable to perform a single medium-dose OFC soon after confirming the negative results of a single low-dose OFC.

Although the PRACTALL guidelines⁸ recommend a general challenge schedule comprising 3, 10, 30, 100, 300, 1000, and 3000 mg of food protein at intervals of at least 20 minutes, this interval may be too short.⁷ Moreover, these intervals lead to overdosing of causative foods. Indeed, most children in the present study experienced symptoms >60 minutes after starting OFC. Accordingly, for an egg challenge, clinicians should carefully monitor children for >60 minutes after the last intake. In the Peanut Allergen Threshold Study, most children with peanut allergies could consume very low doses (1.5 mg) of the

TABLE 1. Data related to the severity of reactions induced during a positive challenge and the subsequent treatment

	Low-dose egg reactivity (n = 52)	Medium-dose egg reactivity (n = 16)
Organ system affected		
Skin	34 (65%)	6 (75%)
Respiratory	8 (15%)	5 (63%)
Gastrointestinal	34 (65%)	8 (38%)
Neurological	0 (0%)	0 (0%)
Cardiovascular	0 (0%)	0 (0%)
Severity		
Mild (grade 1)	13 (25%)	4 (25%)
Moderate (grade 2)	38 (73%)	12 (75%)
Severe (grade 3)	1 (2%)	0 (0%)
Total severity score		
1	14 (27%)	3 (19%)
2	31 (60%)	11 (69%)
3	5 (10%)	1 (6%)
4	1 (2%)	1 (6%)
5	1 (2%)	0 (0%)
Time of symptoms		
Initial symptoms (min)	61 (25-102)	48 (28-90)
Maximum symptoms (min)	80 (50-138)	65 (49-100)
Disappearing symptoms (min)	120 (84-180)	133 (86-153)
Treatment		
Antihistamine (oral)	34 (65%)	13 (81%)
Antihistamine (intravenous or intramuscular)	6 (12%)	1 (6%)
Steroid (oral)	15 (29%)	6 (38%)
Steroid (intravenous)	1 (2%)	0 (0%)
Fluid infusion (intravenous)	1 (2%)	0 (0%)
β2 stimulant inhalation	5 (10%)	4 (25%)
Adrenaline inhalation	1 (2%)	0 (0%)
Adrenaline (intramuscular)	0 (0%)	0 (0%)
No treatment	6 (12%)	0 (0%)

Data are presented as median (interquartile range) or n (%), as appropriate. Severity of symptoms was defined based on the severity of the organ symptom that was most affected (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). Total severity score was defined as the grade of cardiovascular symptoms + the grade of respiratory symptoms + the maximum grade of other symptoms (Table E2).

single-dose OFC.⁹ Our study also identified the doses of egg that the children could safely consume. This safely consumable dose will help improve the quality of food allergy management.

Our study had several limitations. First, OFCs were not double blinded and placebo controlled. However, most children were aged 0 or 1 year, and most induced symptoms were objective; therefore, an assessment bias is likely limited. Second, 36 children who passed the single low-dose challenge did not undergo a medium-dose challenge. However, this would provide little if any effect (Figure E3 in this article's Online Repository at www.jaci-inpractice.org). Third, children suspected of an egg allergy who did not experience previous immediate reactions were not included. Therefore, studies should be conducted to confirm the safety and effectiveness of this approach for various food allergens and in children suspected of food allergies.

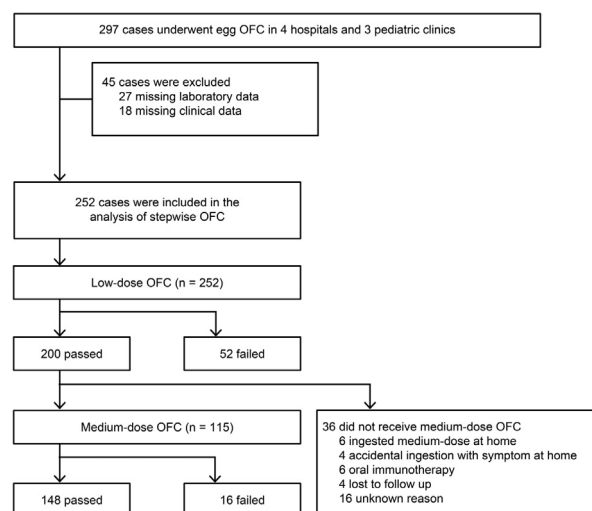


FIGURE 1. Patient enrollment. A stepwise oral food challenge (OFC) (low- and medium-dose OFC; Table E1, available in this article's Online Repository at www.jaci-inpractice.org) was administered.

In conclusion, this multicenter study confirmed that a stepwise single-dose OFC will help children with egg allergies avoid complete elimination of an egg and minimize the effect of complete elimination. We hope this will contribute to improving food allergy management.

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Conflicts of interest: M. Ebisawa serves on the DBV Technologies Scientific Advisory Board. The rest of the authors declare that they have no relevant conflicts of interest.

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METHODS

Oral food challenge test

A stepwise oral food challenge (OFC) for egg with low-dose OFC and medium-dose OFC was administered to confirm tolerance acquisition safely at 4 hospitals and 3 clinics from April 2016 to October 2017. A stepwise OFC was administered according to European Academy of Allergology and Clinical Immunology guidelines.^{E1} The symptoms and associated severity are described in Table E3. We included patients who first underwent a single low-dose OFC for heated egg (250 mg; equivalent to 1/25 whole egg) (Table E1). Patients who tolerated the single low-dose OFC underwent the single medium-dose OFC for heated egg (769 mg; equivalent to 1/8 of whole egg) within 6 months. The amount of protein was confirmed to be similar using enzyme-linked immunosorption (Table E2). We did not divide the challenge food and administered it all at the same time. We observed symptoms for 2 hours after patients consumed the challenge foods. The symptoms and associated severity are described in Table E3. After a negative result for the single low-dose OFC or single middle-dose OFC, patients were allowed to consume up to the recommended doses of egg protein as previously described.^{E2}

ImmunoCAP analysis

Serum levels of specific IgE (sIgE) against egg white, ovomucoid, milk, and wheat (Immuno CAPTM; Thermo Fisher Scientific/Phadia, Uppsala, Sweden) were measured within 6

months of OFC. If the sIgE for causative foods was >100 kU_A/L, a dilution measurement was applied.

Statistical methods

Data were expressed as median values and interquartile ranges. The Mann-Whitney *U* test or Fisher's exact test was used, and a *P* value $<.05$ was considered statistically significant. We calculated the serum IgE concentration level in which approximately 5%, 10%, 50%, 90%, and 95% of the patients are predicted to have a reaction (5%, 10%, 50%, 90%, and 95% predictive decision points, respectively) using probability curves, as previously described.^{E3,E4} To create probability curves and determine the predictive decision points, we used regression analysis after logarithmic transformation of sIgE values.^{E4}

$$\text{Logit}(\Pr[Y = 1 | \ln(kU_A/L)]) = \alpha + \beta \ln(kU_A/L)$$

Values of predictive decision points were applied within ranges for the exact sIgE value.

All analyses were performed using SPSS software (version 24.0 SPSS Inc., Chicago, Ill).

Ethical considerations

This prospective study was approved by the ethical committee of Sagami-hara National Hospital (Approval number: 2016-2-18). Written consent was obtained from all patients or guardians. All data were anonymized before the analysis. This study was registered with a clinical trial registry (UMIN000013026).

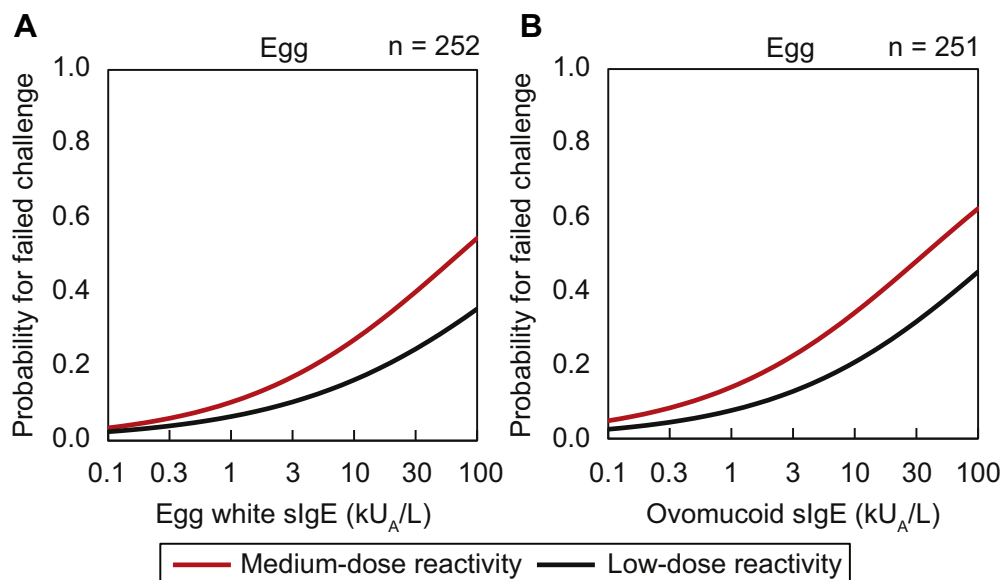


FIGURE E1. Fitted probability curve demonstrating stepwise oral food challenge (OFC) outcomes with respect to IgE levels against **A** egg white and **B** ovomucoid. The probability curve was subdivided by the total cumulative dose of low-dose OFC and medium-dose OFC. *sIgE*, Specific IgE.

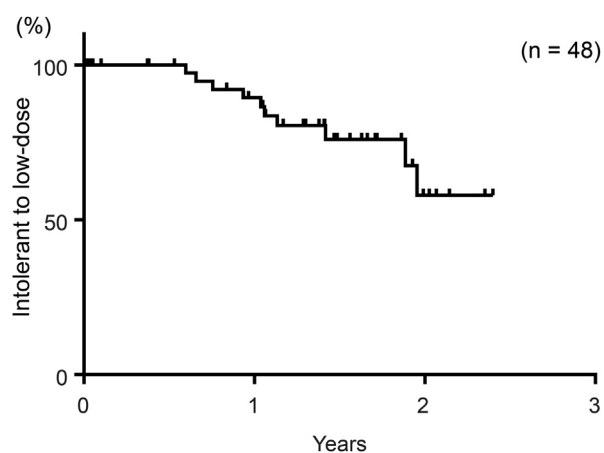


FIGURE E2. Proportion of patients who underwent repeated testing after a positive result on the low-dose oral food challenge (OFC). Patients who reacted to a single low-dose OFC were advised to avoid exposure completely and were rechallenged with a low-dose OFC yearly (at a median of 347 days after positive single low-dose OFC). This graph shows the result of rechallenges for low-dose OFC.

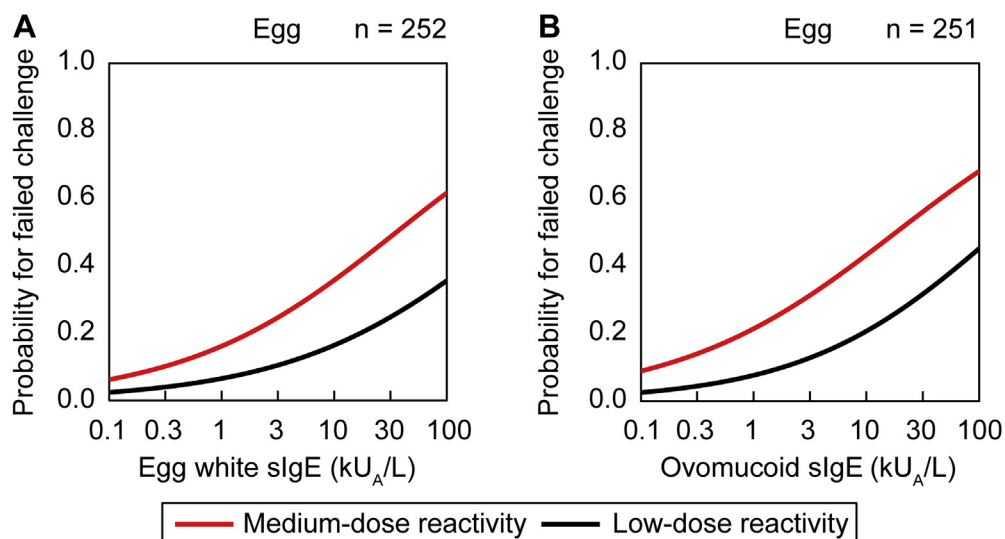


FIGURE E3. Fitted probability curve demonstrating stepwise oral food challenge (OFC) outcomes with respect to IgE levels against **A** egg white and **B** ovomucoid. The probability curve was subdivided by the total cumulative dose of low-dose OFC and medium-dose OFC. Thirty-six patients did not receive medium-dose OFC. Patients who consumed medium doses at home ($n = 6$) were assumed to be tolerant to the medium dose. The remainder ($n = 30$) were assumed to be reactive to the medium dose. *sIgE*, Specific IgE.

TABLE E1. Stepwise oral food challenge with the amount of protein and amounts of detected egg protein in the challenge foods

Challenge food	Egg protein used	Egg protein measured	Origin of material
Low-dose egg OFC (egg juice)	250 mg	265.8 mg	Egg juice was made using 1 g of cooked egg powder and 39 mL of apple juice (total 40 mL). Cooked egg powder (Kewpie Corporation, Tokyo, Japan) was produced by boiling hen's egg at 95°C for 15 min, followed by pasteurization at 65°C for 20 min, and then spray-drying it.
Medium-dose egg OFC (egg juice)	769 mg	730.5 mg	Egg juice (NH Foods Ltd.) contains cooked egg powder (as above), hydrogenated maltose starch, citrate, fragrance, calcium phosphate, and sweetener (aspartame-L-phenylalanine compounds), and 25 mL of water.
Scrambled egg (45.3 g)		6591.5 mg	
Boiled whole egg (54.2 g)		6749.2 mg	
Raw egg (52.1 g)		6322.2 mg	

OFC, Oral food challenge.

Challenge foods were prepared in the nutrition management room. The amounts of egg protein were measured using the FASTKIT version III enzyme-linked immunosorbent assay egg kit from NH Foods, Ltd. (Osaka, Japan) that detects whole egg protein. In the OFC, the challenge foods were administered all at once.

TABLE E2. Severity of symptoms during the oral food challenge

	1 (mild)	2 (moderate)	3 (severe)
Skin	Localized urticaria, exanthema, wheal, pruritus	Generalized urticaria, exanthema, wheal, pruritus	—
	Swollen eyelid or lip	Swollen face	—
Gastrointestinal tract	Pruritus of the throat or oral cavity	Throat pain	—
	Mild abdominal pain	Moderate abdominal pain	Cramps
	Nausea, emesis, diarrhea	Recurrent emesis, diarrhea	Continuous emesis, loss of bowel control
Respiratory tract	Intermittent cough, nasal congestion, sneezing, rhinorrhea	Repetitive cough	Persistent cough, hoarseness, “barky” cough
	—	Chest tightness, wheezing detectable via auscultation	Audible wheezing, dyspnea, cyanosis, saturation <92%, swallowing or speaking difficulties, throat tightness, respiratory arrest
Cardiovascular	—	Pale face, mild hypotension, tachycardia (increase >15 beats/min)	Hypotension, dysrhythmia, severe bradycardia, cardiac arrest
Neurological	Change in activity level, tiredness	“Light-headedness,” feeling of “pending doom,” somnolence, headache	Confusion, loss of consciousness, incontinence

The severity score was based on the organ system that was most affected by the symptoms. Hypotension was defined as systolic blood pressure <70 mm Hg for children aged 1 mo to 1 y, <70 + (2 × age) mm Hg for children aged 1-10 y, and <90 mm Hg for children aged >11 y. Mild hypotension was defined as systolic blood pressure <80 mm Hg for children aged 1 mo to 1 y, <80 + (2 × age) mm Hg for children aged 1-10 y, and <100 mm Hg for children aged >11 y. Wheezing detectable via auscultation with a stethoscope was defined as mild wheezing. Audible wheezing was defined as wheezing detected without a stethoscope. This severity score was defined in the anaphylaxis guidelines for Japan.^{E5}

Total severity scores were defined as the grade of cardiovascular symptoms + the grade of respiratory symptoms + the maximum grade of other symptoms.^{E6}

TABLE E3. Background difference of patients who did or did not undergo medium-dose oral food challenge (OFC)

	Patients who underwent medium-dose OFC (n = 164)	Patients who did not undergo medium-dose OFC (n = 36)	P value
Sex (male)	101 (62%)	18 (50%)	.260
Age (y), median	1.5 (1.1-3.4)	2.2 (1.3-5.6)	.031
History of anaphylaxis to causative food	18 (11%)	2 (6%)	.539
Atopic dermatitis, current	70 (43%)	12 (33%)	.352
Bronchial asthma, current	12 (7%)	3 (8%)	.736
Allergic rhinitis, current	5 (3%)	2 (6%)	.612
Egg white sIgE (kU _A /L)	9.6 (3.6-27.5)	13.6 (5.7-32.1)	.183
Ovomucoid sIgE (kU _A /L)	4.9 (0.8-19.3)	7.0 (3.5-22.5)	.117
Total IgE (IU/mL)	120 (40-428)	225 (82-679)	.080

OFC, Oral food challenges; sIgE, specific IgE.

Data are expressed as n (%) or median values, with 25% to 75% interquartile ranges provided in parentheses.

TABLE E4. Background of patients

	(n = 252)
Sex (male)	152 (60%)
Age (y), median	1.7 (1.2-4.6)
History of immediate reaction to egg	252 (100%)
History of anaphylaxis to egg	26 (10%)
Atopic dermatitis, current	109 (43%)
Bronchial asthma, current	23 (9%)
Allergic rhinitis, current	12 (5%)
Egg white sIgE (kU _A /L)	14.3 (4.8-33.8)
Ovomucoid sIgE (kU _A /L)	7.5 (1.6-24.5)
Total IgE (IU/mL)	172 (53-611)

sIgE, Specific IgE.

Data are expressed as n (%) or median values, with 25% to 75% interquartile ranges provided in parentheses. In 1 patient, ovomucoid sIgE data were missing.

TABLE E5. Background differences of patients who reacted and tolerated low-dose or medium-dose oral food challenge (OFC)

	Low-dose OFC		<i>P</i> value	Medium-dose OFC		<i>P</i> value
	Reactive (n = 52)	Tolerant (n = 200)		Reactive (n = 16)	Tolerant (n = 148)	
Sex (male)	33 (64%)	119 (60%)	.636	12 (75%)	89 (60%)	.290
Age (y), median	4.2 (1.9-6.4)	1.5 (1.2-5.4)	<.001	2.9 (1.3-7.9)	1.4 (1.0-2.9)	.023
History of anaphylaxis to causative food	6 (12%)	20 (10%)	.798	2 (13%)	16 (11%)	.835
Atopic dermatitis, current	27 (52%)	82 (41%)	.162	6 (38%)	64 (43%)	.793
Bronchial asthma, current	8 (15%)	15 (8%)	.102	0 (0%)	12 (8%)	.609
Allergic rhinitis, current	5 (10%)	7 (4%)	.076	2 (13%)	3 (2%)	.075
Egg white sIgE (kU _A /L)	33.0 (14.2-89.8)	10.8 (4.0-28.2)	<.001	14.6 (3.8-23.9)	9.1 (3.5-29.0)	.885
Ovomucoid sIgE (kU _A /L)	22.6 (10.5-73.0)	5.6 (1.1-19.3)	<.001	7.6 (2.0-19.9)	4.7 (0.7-19.3)	.300
Total IgE (IU/mL)	608 (93-1355)	137 (47-445)	<.001	141 (52-1120)	120 (37-414)	.291

sIgE, Specific IgE.

Data are expressed as n (%) or median values, with 25% to 75% interquartile ranges provided in parentheses. Two hundred egg-allergic patients (79%) passed single low-dose OFC. Consequently, 164 patients underwent single medium-dose OFC at a median of 99 d after completing single low-dose OFC. Of these, 148 egg-allergic patients (90%) passed single medium-dose OFC.

TABLE E6. Clinical efficacy of antigen-specific IgE for predicting positive oral food challenge (OFC)

Group	5% predicted probability	10% predicted probability	50% predicted probability	90% predicted probability	95% predicted probability
Low-dose OFC (egg white sIgE)	0.5	2.8	375.7	n.e.	n.e.
Medium-dose OFC (egg white sIgE)	0.2	0.9	69.3	n.e.	n.e.
Low-dose OFC (ovomucoid sIgE)	0.4	1.8	147.9	n.e.	n.e.
Medium-dose OFC (ovomucoid sIgE)	0.1	0.5	37.0	n.e.	n.e.

n.e., Not estimated; sIgE, specific IgE.

IgE values are presented in kU_A/L. The exact ranges of egg white sIgE and ovomucoid sIgE were 0.1-731 and 0.1-342 kU_A/L, respectively. Thus, we did not calculate the values outside of these ranges.

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