

Clinical Communications

Single-dose yellow fever vaccination is well tolerated in egg-allergic children despite positive intradermal test to the vaccine

Marc-Antoine Bédard, MD, FRCPC^a,
 François Graham, MD, MSc, FRCPC^{a,b},
 Louis Paradis, MD, FRCPC^{a,b},
 Kathryn Samaan, MD, FRCPC^a, Philippe Bégin, MD, PhD^{a,b},
 and Anne Des Roches, MD, FRCPC^a

Clinical Implications

- Yellow fever vaccine intradermal skin test results are often positive in egg-allergic and egg-sensitized children. Despite the positive skin test results, many children appear to be able to safely receive the vaccine as a single dose without reaction.

Yellow fever (YF) disease is a *Flavivirus* transmitted by *Aedes aegypti* mosquitoes across 45 countries worldwide. No treatment is specific against this disease, increasing the need for vaccination prophylaxis. The YF vaccine is safe and effective, conferring long-term immunity in over 95% of the people vaccinated. Over 550 million doses have been administered since its production in 1937. Anaphylactic reactions to YF vaccine have been estimated to occur in 0.42 to 1.8 per 100,000 vaccinations.¹ The egg protein content has long been incriminated, but gelatin used as a stabilizing agent could explain some of the reactions. The ovalbumin content varies depending on the lots tested, but in 1 study was found to be between 2.43 and 4.42 µg/mL.² Skin testing and graded dosing protocol appear in the vaccine package insert (YF-VAX; Sanofi Pasteur, Swiftwater, Penn).³ This graded protocol is generally well tolerated, although some immediate reactions have been reported.⁴

This retrospective study includes 24 pediatric patients with confirmed egg allergy or egg sensitization who received vaccination against YF in 1 step (n = 14), 3 steps (n = 1) and 5 steps (n = 9) (Figure 1). Data were collected from June 1998 to November 2019. Patients were diagnosed with egg allergy if they had a clinical history of reaction after egg ingestion and a positive confirmation test such as a positive skin prick test (SPT) (mean wheal diameter >3 mm or greater than the negative control) or an egg white specific IgE >0.35 kUA/L (Tables E1 and E2, available in this article's Online Repository at www.jaci-inpractice.org). Patients were considered to be egg sensitized if they had never introduced eggs in their diet but had a positive confirmation test. Patients were excluded if data confirming the allergy were missing or if the confirmation tests were performed more than 1 year before the vaccination. Patients had 1/100 YF vaccine intradermal (ID) test before the vaccination. The criterion for a positive ID test result was defined as a wheal diameter >3 mm larger than the negative control with surrounding erythema.

In the context of this retrospective study, the number of steps for the vaccination was at the physician's discretion. However, after reviewing all cases, most physicians used either a 1-step (100% of the vaccine dose) or 5-step protocol (1%, 10%, 20%, 30%, and 40% of the total dose) with injections every 20 minutes. Only 1 patient received a 3-step protocol with an injection every 30 minutes (10%, 30%, and 60% of the total dose). The fact that the YF vaccine is compulsory for some countries' admission has helped our vaccination rate. No patient refused the vaccination, and only 1 declined skin testing before a well-tolerated single-step injection. Even though the majority of the patients had a positive 1/100 YF vaccine ID test result (20/24; 83%), there were no allergic reactions reported. YF vaccine ID tests were also performed in 10 adult controls and were negative. Also, 2 patients with egg white specific IgE over 100 kUA/L and 1 patient with the history of anaphylaxis (egg white specific IgE at 53.4 kUA/L) tolerated the vaccination in 1 step.

To our knowledge, this is the first study where egg-allergic or egg-sensitized patients with the positive YF ID test result received the vaccine in 1 step, without a graded challenge or desensitization protocol (n = 12). As mentioned earlier, none of these patients developed an allergic reaction, including patients who had a previous anaphylactic reaction to egg or specific IgE >100. This might be explained by the low egg-protein content of YF vaccine, which is likely below the reaction threshold in a high proportion of egg-allergic patients. The estimated eliciting dose of egg protein to cause a reaction in 1% of the egg-allergic population (ED01) by ingestion is 0.2 mg.⁵ The considerably lower quantities of egg protein reported in YF vaccines (2–4 mcg per dose) would seem unlikely to cause a reaction, although it is possible that an eliciting dose by injection would be lower than that by ingestion.²

There is a lack of data evaluating the sensitivity and specificity of the YF ID test. As shown recently in a study by Gerhardt et al,⁴ this test seems to have a good sensitivity because none of the 48 proven egg-allergic patients with negative YF ID test results reacted to a full dose of YF vaccine. Interestingly, in our study, only 4 of 24 patients had negative YF ID test results. The difference could be due to the vaccine itself. Brazil has developed a national YF vaccine from Bio-Manguinhos-Fiocruz (Rio de Janeiro), which could produce fewer false positives in egg-allergic patients. We also found the positive predictive value (PPV) of the YF ID test to be extremely low in our population. When considering only the patients vaccinated in 1 step (Table 1), the observed PPV here was 0% (0%–26%) and the observed specificity calculated for tolerance to a direct single-dose challenge was 14.3% (2 true negatives and 12 false-positive ID tests; 1.8%–42.8%). The specificity increased to 16.7% (4 true negatives and 20 false-positive ID tests; 4.7%–37.4%) when redistributing untested patients following the Bayesian approach to control for inverse workup bias (verification bias). Future larger studies are required to better characterize the diagnostic performance of the YF ID test, but, overall, its diagnostic accuracy appears to be very poor in our population.

Moreover, parents are often reluctant to accept repeated invasive procedures for treatment of their children, as is the case with YF vaccine, which can be associated with significant

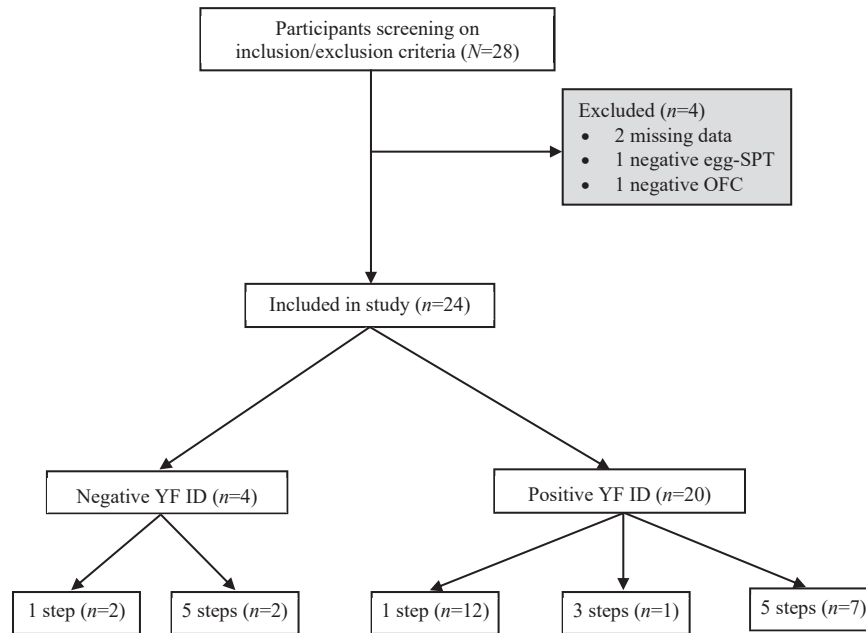


FIGURE 1. Distribution of the injection protocol based on the YF ID test. *OFC*, Oral food challenge; *SPT*, skin prick test; *YF ID*, yellow fever vaccine intradermal test result.

TABLE I. Characteristics of patients with positive YF ID who received the vaccination in 1 step

Patient	Age (y)	Sex	Initial reaction type with egg	Tolerate eggs in baked good (yes/no)	Egg white specific IgE (kUA/L)	Egg white SPT (mm)	YF ID (mm)	YF vaccination tolerated
1	1	M	Never eaten	Y	0.64	7.5	15	Yes
2	10	F	Immediate urticaria	N	1.04	15.5	8	Yes
3	15	M	Never eaten	N	>100	12.5	11	Yes
4	13	M	Never eaten	N	>100	10.5	11	Yes
5	1.5	M	Never eaten	N	—	11	11.5	Yes
6	1.5	M	Never eaten	N	7.72	14	7	Yes
7	14	F	Immediate urticaria	N	10	12	10	Yes
8	9 mo	M	Immediate urticaria and angioedema	N	—	12	11	Yes
9	4.5	F	Immediate urticaria	Y	52.4	15	16	Yes
10	3	M	Immediate angioedema, vomiting, and shortness of breath	N	53.4	25	13	Yes
11	2	F	Never eaten	N	0.96	12	10	Yes
12	10 mo	M	Immediate urticaria	Y	—	10	6	Yes

SPT, Skin prick test; *YF ID*, yellow fever intradermal test (1/100).

discomfort. This is what led some parents to ask for a 1-step vaccination despite their child's severe allergy. The same multi-step approach was used with influenza vaccination in egg-allergic patients before the H1N1 pandemic. Since then, multicentric prospective studies have confirmed no increased risk of allergic reaction to these vaccines in egg-allergic patients, and this multistep approach is no longer justified. Although this study suggests that direct 1-dose vaccination could be safe in most egg-allergic patients, it has several limitations that must be considered before extending these conclusions to real-life practice. These include its retrospective design and small population size, which is still larger than most studies on this subject to date. Also, 50%

of the patients included had never introduced eggs in their diet and did not undergo oral food challenge before YF immunization to confirm egg allergy. These sensitized patients ($n = 12$) all had an SPT over the 95% PPV threshold (≥ 7 mm or ≥ 2 mm if < 2 years),⁶ suggesting a very high probability of egg allergy. Finally, because of the study's timeframe, the YF vaccine lots were different, and the egg protein content of these vaccines was not determined.

In conclusion, YF vaccination in egg-allergic patients could be safe, even with a 1-step protocol. These results are in the same trend as the recent changes in practice with influenza and measles vaccines, which are considered safe in egg-allergic patients.^{7,8}

However, further prospective studies with larger cohorts of egg-allergic patients with positive YF vaccine ID test results are needed.

^aDepartment of Pediatrics, Section of Allergy and Clinical Immunology, Centre Hospitalier Universitaire Sainte-Justine, Montreal, QC, Canada

^bDepartment of Medicine, Section of Allergy and Clinical Immunology, Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada

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Corresponding author: Anne Des Roches, MD, FRCPC, Department of Pediatrics, Section of Allergy and Clinical Immunology, 3175 Chemin de la Côte-Sainte-Catherine, Montréal, QC H3T 1C5, Canada. E-mail: a.des.roches@umontreal.ca. 2213-2198

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TABLE E1. Characteristics of patients with confirmed egg allergy or sensitization

	Total (n = 24)	+YF ID (n = 20)	1 step (n = 14)	3 steps (n = 1)	5 steps (n = 9)
Sex, n (%)					
Male (n = 17)	17 (70.8)	14 (70)	9 (64.3)	0 (0)	8 (88.9)
Female (n = 7)	7 (29.2)	6 (30)	5 (35.7)	1 (100)	1 (11.1)
Mean age (y)	5.3	5.2	6.2	2.5	4.3
Min-Max	0.73-15.52	0.73-15.52	0.73-15.52	2.5	1-14.1
Initial reaction type, n (%)					
Never ate egg	12 (50)	10 (50)	7 (50)	0 (0)	5 (55.6)
GI reaction	3 (12.5)	2 (10)	1 (7.1)	1 (100)	1 (11.1)
Cutaneous reaction	6 (25)	6 (30)	5 (35.7)	0 (0)	1 (11.1)
Respiratory reaction	2 (8.3)	1 (5)	0 (0)	0 (0)	2 (22.2)
Anaphylaxis	1 (4.2)	1 (5)	1 (7.1)	0 (0)	0 (0)
Tolerate eggs in baked good (n = 23), n (%)					
Yes	7 (30.4)	5 (25)	5 (35.7)	0 (0)	2 (22.2)
No/never tried	16 (69.6)	14 (70)	8 (57.1)	1 (100)	7 (77.8)

GI, Gastrointestinal; +YF ID, positive yellow fever intradermal test result.

TABLE E2. Skin prick test (SPT) and specific IgE

	All patients (n = 24)	Never eater (n = 12)	+YF ID (n = 20)	1 step	3 steps	5 steps
SPT (mm)*						
Egg white SPT (n = 24)	11.56 (7-25)	10.3 (7-14)	12 (8-25)	12.6 (7-25)	9	10.9 (7.5-16.5)
Yolk SPT (n = 22)	5.9 (0-15)	5 (0-15)	6.8 (0-15)	6.6 (0-15)	5	6.2 (3-10)
IgE (kUA/L)*						
Total IgE	1189.1 (21-5439) n = 13	861.6 (21-3191)	1270.6 (21-5439)	939.9 (21-3191)	NA	1587.9 (182-5439)
Egg white specific IgE†	41.23 (0.64 to >100) n = 16	53.14 (0.64 to >100)	41.5 (0.64 to >100)	32.9 (0.64 to >100)	NA	55.1 (7 to >100)
ID YF vaccine						
Positive ID YF vaccine 1/100, n (%)	20 (83)	10 (83)	20 (100)	12 (86)	1 (100)	7 (78)

*Mean (min-max).

ID, Intradermal test result; NA, not available; YF, yellow fever.

†Values >100 kUA/L were approximated at 100 kUA/L for the mean calculation.