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Frequency of allergic reactions in egg allergic patients after receiving the yellow fever vaccine

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Abstract
Background: Immunization with live attenuated viral yellow fever vaccine (YFV) grants effective immunity in most cases, and is recommended and prioritized for residents and travelers of endemic countries. YFV is seldom administered to egg-allergic patients (EAP) since it is cultivated in embryonated chicken eggs and may contain residual egg proteins, being a problem for egg-allergic residents and travelers of endemic countries.
Objective: Describe the frequency of allergic reactions after YFV administration in confirmed EAP from an allergy outpatient center in Bogotá, Colombia.
Methods: An observational, retrospective, cross-sectional, and descriptive study was conducted from January 2017 to December 2019. EAP whose allergy was confirmed with a positive Skin Prick Test (SPT) and/or egg protein-specific IgE levels who hadn't received the YFV were included. Every patient had an SPT, severe EAP, and an additional Intradermal Test (IDT) done with the vaccine. If the vaccine SPT and IDT were negative, the YFV was administered as a single dose; if either were positive, the YFV was administered in graded doses. Statistical analysis was done in Stata16MP.
Results: Seventy one patients were included, 24 (33.8%) of those had a history of egg anaphylaxis. All patients had negative YFV SPTs, and two of the five YVF IDTs were positive. Two patients, with previous egg-anaphylaxis, presented allergic reactions to the vaccine.
Conclusions: YFV did not trigger allergic reactions in EAP without history of egg-anaphylaxis. With further research, safe single-dose vaccination to this population could be considered; however, patients with previous egg-anaphylaxis should be evaluated by an allergist before vaccination.

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Introduction

Yellow fever (YF) is a viral zoonotic disease transmitted by vectors endemic to several tropical countries.[1] According to the World Health Organization (WHO), the global burden is approximately up to 150,000 cases yearly, and 35% of untreated severe cases are mortal. However, the global incidence might be 10–250 times greater.[1] Since its introduction, the yellow fever vaccine (YFV) has proven to be the most effective way to prevent this disease,[1-8] granting 90% protection 10 days after its administration, and a single lifetime dose is sufficient.[1-5,8] YF vaccination is, therefore, important and required for residents and travelers of endemic regions.[5,9,10]

The WHO contraindicates the YFV application in patients with severe egg allergy,[1] and the manufacturers contraindicate its application in all egg-allergic patients (EAP),[11-15] as its cultivation in embryonated-chicken-eggs may represent a higher risk of adverse reactions in these populations because it contains residual ovalbumin and other egg proteins.[10] It is indicated that EAP should be evaluated by allergy specialists to determine if the vaccine ought to be administered in a single dose or graded doses, and/or at a specialized attention center.[4,16-18] These recommendations can be barriers leading to delays or even abstention of vaccination, increasing the risk of exposure in endemic regions.[19]

Other vaccines are also produced in chicken-embryos (e.g., Influenza) or chicken-fibroblasts (e.g., MMR, Rabies).[4,16,17,19-24] Vaccines produced in embryos have greater concentrations of residual egg proteins than those produced in fibroblasts.[4,16,20] Recent evidence has demonstrated that vaccination of EAP with Influenza (ovalbumin ≤1.0–1.6 ug/dose)[25] and MMR (ovalbumin ≤ 1.0 ng/dose)[25] is not associated with an increased frequency of allergic reactions in contrast with non-EAP. Consequently, the administration of Influenza and MMR vaccines in this population is now considered safe in a single dose,[2,8,25] compared to the YFV, which theoretically, has the highest ovalbumin content, and thus, isn't considered safe in EAP.[4,9,21]

WHO prequalified four manufacturers to produce and supply YFVs: Bio-Manguinhos (Brazil), FSUE Chumakov (Russia), Institute Pasteur Dakar (Senegal), and Sanofi Pasteur (France).[26] The ovalbumin concentration of the YFVs isn't published by the manufacturers and varies between them.[2,4,8,9,17,27] Sanofi Pasteur manufactures two YFVs: STAMARIL® (UK), which from extension studies has reported an approximate ovalbumin concentration of 0.067–0.306 ug/dose (mean 0.105 ug/dose),[5,8,25] and YF-VAX® (USA) with 1.22–2.21 ug/dose (mean 1.56 ug/dose).[2,8,9,25] There is no available quantification of the concentration of ovalbumin from the other manufacturers.[3] Furthermore, as heating is not part of the manufacturing process, the allergenicity of the ovalbumin is higher than it would be if the vaccines were heated; this explains why patients who react to raw egg, but tolerate cooked egg, could still react to the vaccine.[4,8]

Adverse reactions that have been described after YF vaccination in EAP are frequently mild: headache, fever, or localized pain and swelling at the injection site.[6,7,28] Anaphylactic reactions occur at an estimated rate of 0.4–1.8 reactions per 100,000 administered doses of YFV.[2,4-7,9,20,25,28-30] Most anaphylactic reactions are reported in patients with allergy to either egg proteins or other constituents of the vaccine, such as gelatin, sorbitol, latex, and antibiotics without a known distribution within this group.[2,4-7,9,20,25,28,29]

Due to the prevalence of YF in endemic countries, its high mortality rate,[1] and the few studies evaluating the safety of the YFV in EAP,[3,5,8] this study aimed to describe the frequency of allergic reactions following YFV administration in EAP. In addition, the population was characterized, the egg and vaccine allergic reactions described, and the delay in vaccination quantified, according to the Colombian immunization program.

Methods

An observational, retrospective, cross-sectional, and descriptive study was conducted from January 2017 to December 2019. Patients from the Fundación Santa Fe de Bogotá (FSFB) – UNIMEQ-ORL allergy outpatient center with confirmed IgE-mediated egg allergy who had not received the YFV vaccine were included. Egg-allergy was confirmed by suggestive history due to urticaria, angioedema, eczema, gastrointestinal symptoms, and/or respiratory symptoms 2 hours after egg consumption in the past 6 months, and positive Skin Prick Test (SPT) and/or specific IgE (sIgE) suggestive of a 95% positive predictive value of egg-allergy diagnosis by oral food challenge (OFC), or positive OFC in the past 6 months. The diagnostic cutoff values for SPT in children of <2 years was a mean wheal diameter ≥ 5 mm[31,32] or in children of ≥ 2 years a mean wheal diameter ≥ 7 mm,[33] and for egg protein sIgE levels in children of <2 years a sIgE ≥ 2 kUA/L[31,33] or in children of ≥ 2 years a sIgE ≥ 7 kUA/L.[33] For patients with history of egg-anaphylaxis in the past 6 months, cutoff values were SPT wheal ≥ 3 mm or sIgE ≥ 2 kUA/L.[31,33] Patients with less than 12 months of age, sensitized to egg without previous egg consumption, who were pregnant, or had a primary or acquired immunodeficiency were excluded. Egg anaphylactic patients were included and their diagnosis and severity were determined in congruence with the criteria proposed by Sampson et al.,[34] World Allergy Organization (WAO),[35] and European Academy of Allergy and Clinical Immunology (EAACI).[36] Considering there was not an epidemiological hypothesis, it was not necessary to perform a sample size calculation.

Every included patient had an SPT with the neat STAMARIL® YFV and additionally patients with history of severe egg anaphylaxis had an Intradermal Test (IDT) with the YFV at 1:100 dilution. Positivity of the YFV SPT was determined when the wheal presented an average diameter ≥3 mm. The YFV IDT was considered positive when the wheal presented a diameter 3 mm larger than the initial wheal diameter. If the YFV SPT and YFV IDT were negative, the STAMARIL® YFV was administered in one step, if either were positive, the vaccine was administered in graded doses with 30 minute intervals (Figure 1) following standardized two-step (0.05 mL and 0.045 mL; 10 and 90%)[6,8] or three-step (0.05 mL, 0.15 mL, 0.30 mL; 10, 30, and 60%)[4] protocols according to medical criteria. After vaccination, patients were observed for 60 minutes to identify possible allergic reactions triggered by the vaccine. Patients were

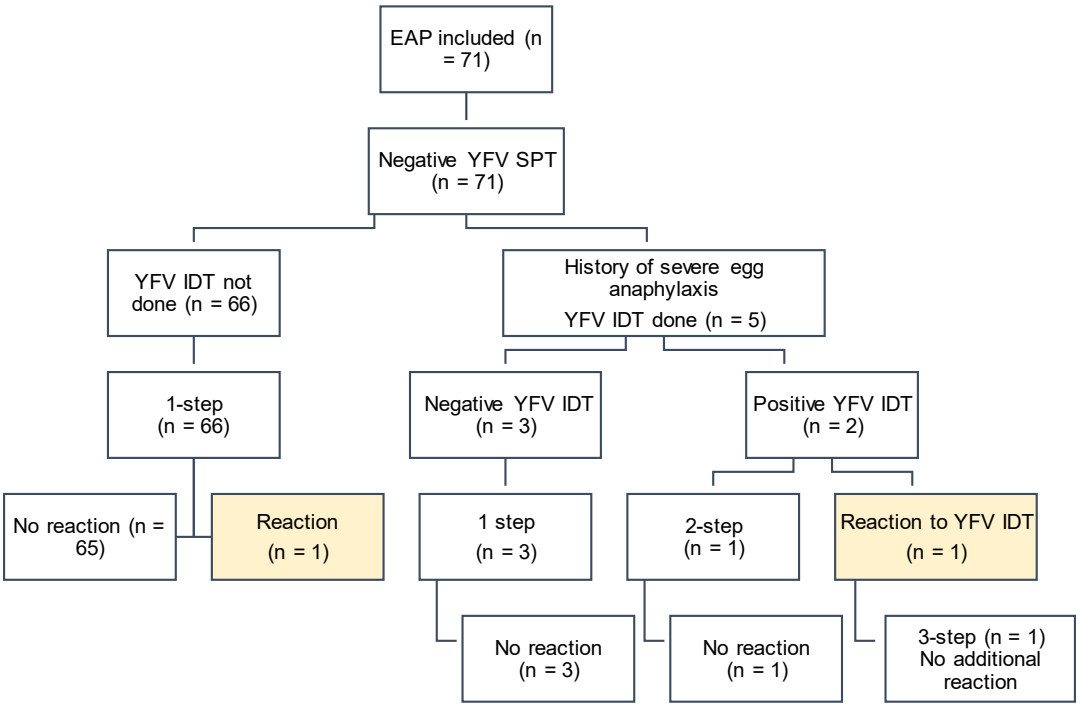

Figure 1 Distribution and outcomes of skin testing and yellow fever vaccination. EAP: egg allergic patients; YFV: Yellow Fever Vaccine; SPT: Skin Prick Test; IDT: Intradermal Test.

not expected to sign an informed consent for the retrospective nature of the study. The study was approved by the FSFB ethics committee (CCEI-11213-2019).

Patients' sociodemographic information, their personal and family history of atopic disease, and their YFV status were collected reviewing their past clinical charts and digitalized in a single survey. The population was characterized, the egg and vaccine allergic reactions described, and the delay in vaccination quantified. Gender, age, allergic history, and egg-allergy characteristics such as presentation, symptoms, time of presentation, and results of diagnostic tests were the variables described. The frequency of allergic reactions after the application of the YFV and the delay in vaccination according to the Colombian immunization program were calculated. Measures of central tendency (means and medians) and dispersion (interquartile ranges) were used for quantitative variables and percentages with absolute and relative frequencies for qualitative variables. The statistical analysis was performed using the Stata 16 MP statistical package.

Results

The study included 71 confirmed EAP who were vaccinated against YF in one step (n = 69), two steps (n = 1), and three steps (n = 1) (Figure 1). On average, their first allergic reaction to egg was at 9.37 months of age (IQR = 7.0–12.0) (Table 1), and their first consult with an allergy specialist was at 18 months of age (IQR = 12.0–19.0). All patients included had a positive SPT and/or sIgE suggestive of a 95% positive predictive value of egg-allergy diagnosis by OFC, and no patient required an OFC in the previous 6 months; therefore, none were performed within the included patients. The median age for YF vaccination was 20 months (IQR = 18.0–27.0), meaning that 50% of this population had a vaccination delay of 2 months or more according to the Colombian immunization program. Furthermore, a high frequency of allergic history was found within the population: 54.9% presented multiple food allergies, 52.1% atopic dermatitis, 22.5% allergic rhinitis, and 9.9% asthma. In addition, out of all patients with food allergies, 28 [71.8%] were allergic to Cow's milk, 10 [25.6%] to fruits, and 10 [25.6%] to fish.

Table 1 describes the symptoms of allergic reactions to egg presented within the study group. Cutaneous reactions were the most reported as expected. Anaphylaxis was found with a frequency of 24 [33.8%], most of these [79.2%] being moderate. Egg preparation was also a determinant of the frequency of allergic reactions after egg consumption: 59.3% reacted after consuming raw egg (e.g., soft-boiled, fried with a runny yolk, mayonnaise), 35.6% after consuming cooked egg (e.g., hard-boiled, scrambled, well-cooked omelet), and 5.2% after consuming baked products containing egg.

All 71 patients underwent YFV SPT and all were negative (Figure 1), and five with history of severe egg-anaphylaxis also had an YFV IDT done of which only two were positive. The YFV was administered in one step to the 66 patients who had negative YFV SPT and to the 3 patients with history of severe egg-anaphylaxis who had an additional negative YFV IDT. Of those, 68 tolerated the vaccine without presenting a reaction, while one, with a history of moderate egg anaphylaxis, presented urticaria on the face 10 minutes after administration, which quickly subsided with an antihistamine (Table 2). The other two patients, who had positive YFV IDT, were vaccinated in graded doses. One tolerated the YFV in two steps (10 and 90%) without presenting a reaction, while

Table 1 Sociodemographic and egg allergy characteristics of the study population.

Variables	n	%
Total patients (n)	71	
Gender (male)	40	56.3
Age (months) at first allergic reaction to egg*	9.37*	2.78*
Age (months) at first consultation with an allergy specialist*	18.0*	16.30*
Personal history of allergy		
Rhinitis	16	22.5
Asthma	7	9.9
Atopic dermatitis	37	52.1
Food allergy	39	54.9
Family history of allergy (parents or siblings)		
Rhinitis	22	31.0
Asthma	17	23.9
Atopic dermatitis	13	18.3
Food allergy	2	2.8
Symptoms of allergic reaction to egg		
Urticaria	44	62.0
Angioedema	36	50.7
Eczema	18	25.4
Gastrointestinal symptoms	11	15.5
Respiratory symptoms	13	18.3
Anaphylaxis	24	33.8
Other	2	2.8
Severity of anaphylaxis**/***		
Moderate	19	79.2
Severe	5	20.8
Egg allergy diagnostic tests****	**<2 years old**	**≥ 2 years old**
SPT to egg (mm)	6.73 (3.0–19.0)	7.70 (4.5–13.0)
SPT to egg yolk (mm)	6.0 (4.0–11.0)	7.04 (5.0–16.0)
SPT to egg white (mm)	6.38 (3.0–13.0)	7.66 (4.0–12.0)
SPT to ovalbumin (mm)	6.52 (3.0–12.0)	7.34 (4.0–10.0)
SPT to ovomucoid (mm)	7.04 (4.0–14.0)	7.45 (4.5–13.0)
sIgE to egg (kU/L)	10.27 (0.63–32.7)	17.26 (0.35–34.2)
sIgE to egg yolk (kU/L)	16.13 (0.57–100.0)	12.59 (0.36–100.0)
sIgE to egg white (kU/L)	27.28 (0.65–100.0)	23.03 (0.35–100.0)
sIgE to ovalbumin (kU/L)	15.44 (0.35–100.0)	17.36 (0.65–100.0)
sIgE to ovomucoid (kU/L)	12.74 (0.35–76)	4.32 (0.41–17.0)
Age (months) at receipt of YFV*	25.86*	19.63*

*Values reported in mean and standard deviation; **Relative frequencies calculated upon patients with history of anaphylaxis; ***Severity of anaphylaxis determined according to Muraro Grading score for the severity of anaphylactic reactions.[36]; ****Values reported in mean (min – max) according to age group (<2 years old or ≥2 years old).

the other presented urticaria 5 minutes after the YFV IDT that resolved with antihistamine and oral corticosteroids, reason why the vaccine was administered in three steps (10, 30, and 60%) and was tolerated (Table 2). The frequency of allergic reactions following YFV administration in EAP was 2.8% (95% CI: [0.34–9.8%]) (Table 3) of the study population and 8.3% of the patients with a history of egg anaphylaxis, and the manifestations were mild being hives in both cases. None of the patients without a history of egg anaphylaxis reacted after the administration of the YFV.

Discussion

Similar to other Latin American tropical countries, in the FSFB, egg-allergy is the fourth most frequent self-reported food allergy with an estimated frequency of 0.21.[37] The administration of vaccines in EAP has become a concern for health personnel and a barrier for their vaccination access, often being delayed and occasionally denied,[5,19,24] representing a problem in Latin American countries like Colombia. YFV is contraindicated in patients with severe egg allergy[1]; thus, these patients must be evaluated by an allergy specialist to determine if the vaccine should be administered in graded doses.[4,16–18] However, Influenza and MMR vaccines, which also contain residual egg proteins, are already considered safe for patients with egg allergy and are administered as a single dose in regular vaccination sites.[2,8,25] The European Union legislation has established 2.0 μg/mL (1.0 μg/0.5 mL) as the maximum egg protein concentration allowed, as it has been demonstrated to be a safe amount in patients with previous egg anaphylaxis.[4,38,39]

Table 2 Description of allergic reaction in EAP after receiving the YFV*.

Patients	n	Reacted (n)	Reacted (%)	Characteristics
YFV SPT (–) YFV IDT (ND)	66	1	1.5%	15 month-old male with no atopic history, other allergies, or family atopic history. Presented first allergic reaction to cooked egg at 7 months of age with urticaria, angioedema, and repetitive vomiting, classified as moderate anaphylaxis. Confirmation of egg-allergy by diagnostic SPT and sIgE (SPT wheal: egg = 6 mm, egg white = 7 mm, egg yolk = 5 mm, ovalbumin = 7 mm, ovomucoid = 5 mm; sIgE: egg-white = 61 kUA/L, egg-yolk = 81 kUA/L, ovalbumin = 35.5, ovomucoid 5.83). Last reaction before vaccination had been 6 months before. Presented a mild reaction with urticaria on the face 10 minutes after YFV administration in one step, was administered loratadine, and subsided 40 minutes after.
YFV SPT (–) YFV IDT (–)	3	0	0.0%	-
YFV SPT (-) YFV IDT (+)	2	1	50.0%	20 month-old male with history of atopic dermatitis and anaphylaxis to cow's protein, and father with history of allergic rhinitis, asthma, and atopic dermatitis. Presented first allergic reaction to cooked egg at 8 months of age with irritability, urticaria, angioedema, rhinorrhea, cyanosis, abdominal cramping, and repetitive vomiting, classified as severe anaphylaxis. Confirmation of egg-allergy by diagnostic SPT and sIgE (SPT wheal: egg white = 5 mm, egg yolk = 5 mm, ovalbumin = 6 mm, ovomucoid = 5 mm; sIgE: total = 502 kUA/L, egg white = 53 kUA/L, egg yolk = 7.11 kUA/L, ovalbumin = 10.9 kUA/L). Last reaction before vaccination had been 2 months before. Presented a mild reaction with urticaria 5 minutes after the positive YFV IDT that resolved with antihistamine and oral corticosteroids, and later tolerated YFV vaccination in three steps (10, 30, and 60%)
Total	71	2	2.8%	

EAP: egg allergic patients; YFV: Yellow Fever Vaccine; SPT: Skin Prick Test; IDT: Intradermal Test; ND: not done; (–): negative; (+): positive. *Severity of anaphylaxis determined according to Muraro Grading score for the severity of anaphylactic reactions.[36]

Table 3 Frequencies of allergic reaction in EAP after receiving the YFV*.

Patients	n	Reacted (n)	Reacted (%)
All patients	71	2	2.8
Stratified by history of egg anaphylaxis			
EAP without history of egg anaphylaxis	47	0	0.0
EAP with history of egg anaphylaxis	24	2	8.3
Stratified by severity of egg anaphylaxis			
EAP with history of moderate egg anaphylaxis	19	1	5.3
EAP with history of severe egg anaphylaxis	5	1	20.0
Stratified by IDT result			
YFV SPT (–) and YFV IDT (ND)	66	1	1.5
YFV SPT (–) and YFV IDT (–)	3	0	0.0
YFV SPT (–) and YFV IDT (+)	2	1	50.0

EAP: egg allergic patients; YFV: Yellow Fever Vaccine; SPT: Skin Prick Test; IDT: Intradermal Test; ND: not done; (–): negative; (+): positive. *Severity of anaphylaxis determined according to Muraro Grading score for the severity of anaphylactic reactions.[36]

Theoretically, YFVs contain the highest residual egg concentration compared to the Influenza and MMR vaccines, and could result in more frequent allergic reactions in EAP.[4,9,21,22,24] The Influenza vaccine, which is also produced in chicken embryos, contains ≤1.0–1.6 ug/0.5 mL of ovalbumin,[8,17,18,25] and it has been demonstrated to be safe to administer to patients with a history of egg allergy or egg anaphylaxis in their usual vaccination center without the need of graded doses if it contains less than 0.6–1.0 ug/0.5 mL of egg protein.[4,16,23] The ovalbumin concentration of YFVs varies according to the vaccine and manufacturer, and this information isn't available in the packaging; thus, through extension studies, it has been calculated for Sanofi Pasteur vaccines (Table 4),[2,5,8,25] and for other manufacturers there is no estimate available. STAMARIL®, the vaccine used in Colombia and in this study,[40] contains an approximate concentration of 0.067–0.306 ug/0.5 mL (mean 0.105 ug/0.5 mL) of ovalbumin,[5,8,25] in addition to other allergens such as sorbitol E430, lactose, natural rubber, or polyisoprene,[8] while YF-VAX® contains approximately 1.22–2.21 ug/0.5 mL (mean 1.56 ug/0.5 mL) of ovalbumin and other allergens such as sorbitol, gelatin (7,500 ug/dose), and latex from the plug.[2,8,9,25]

Considering the aforementioned, STAMARIL®YFV has an ovalbumin content much lower than 1.0 μg/0.5 mL (2.0 μg/mL) and could be considered safe for administration in EAP following the European Union legislation,[4,37,38] probably without desensitization.[25] Besides, according to Roukens who conducted a study with seven patients, 0.1 mL of the YFV is sufficient to induce antibodies to trigger a

Table 4 Ovalbumin concentration in MMR, Influenza, and YF vaccines.

Vaccine	MMR[25]	STAMARIL®[5,8,25]	Influenza[8,17,18,25]	YF-VAX®[2,8,9,25]
[ovalbumin]	≤ 1.0 ng/0.5 mL	0.067–0.306 ug/0.5 mL	≤ 1.0–1.6 ug/0.5 mL	1.22–2.21 ug/0.5 mL
Mean [ovalbumin]	-	0.105 ug/0.5 mL	-	1.56 ug/0.5 mL

MMR: Measles, Mumps, and Rubella; YF: Yellow Fever.

protective reaction to the YF virus in EAP.[28] Consequently, protocols for YF vaccination in EAP could be reassessed as it has been done with the Influenza and MMR vaccines.

The results within the study group were exploratory and could suggest a history of egg anaphylaxis as a risk factor for presenting a reaction following the YFV administration, as both patients shared this trait, highlighting no severe events were evidenced; however, further observational longitudinal studies are necessary to confirm these findings. In a study carried out in Australia (Table 5), similar results were found: of the 11 patients included, 2 reacted mildly to the graded administration of the STAMARIL® vaccine, 1 of them having a history of egg anaphylaxis and a positive YFV SPT to the vaccine, and neither underwent an IDT to the YFV.[8] However, in a study conducted in Brazil, of the 58 EAP included, 6 of them presented mild-moderate reactions to the graded administration of the Biomanguinhos-Fiocruz vaccine (unknown ovalbumin concentration).[3] It is striking that these patients presented a negative YFV SPT but a positive YFV IDT, suggesting that the YFV IDT could be a possible predictor.[3] In a similar Canadian study, 24 egg-allergic or egg-sensitized patients were included, and all underwent a YFV IDT, and 20 of them had a positive result.[2] The YF-VAX® vaccine was administered in one step to two negative YFV IDT patients and 12 positive YFV IDT patients, in three steps to one positive YFV IDT patient, and in five steps to seven positive YFV IDT patients, none of whom presented an adverse reaction to the vaccine.[2] When comparing the Brazilian and Canadian studies, the difference in the vaccine might explain the varying results to the YFV IDTs.[2,3] In our study, only five YFV IDTs were realized; hence, the results and conclusions about vaccine IDT are not comparable; thus, larger studies are required to identify and better characterize the diagnostic performance and predictive value to elucidate these contradictory results.[2]

The YFV was administered as a single dose with no associated adverse reactions to 68 of the 71 included patients (95.8%) in our study. Similarly, in the Canadian study, the YFV was also administered in one step with no adverse reaction to 14 of the 24 included patients (58.3%).[2] Cancado et al. report the safe administration of the Biomanguinhos-Fiocruz YFV in a one-step protocol to more than 64% of EAP and a total of 93.7% tolerated the vaccine including those undergoing a four-step protocol (EAP with positive SPT or IDT to the YFV), and the frequency of reaction to the vaccine was of 6.3%, most of them mild, with only one case of anaphylaxis.[39,41] These results (Table 5) imply that the administration of the YFV could be safe in EAP, even in a one-step protocol, following the same trend for Influenza and MMR vaccines now considered safe in EAP. Further prospective studies with larger cohorts are still needed to confirm this conclusion.

When administering the vaccine in graded doses to the two patients who had a positive YFV IDT in our study, two different protocols were used. With one patient, a two-step (10 and 90%) protocol was followed, while with the other patient, a three-step (10, 30, and 60%) protocol was followed. There are multiple recommended administration protocols, without a consensus between them: two step (0.05 mL and 0.045 mL; 10 and 90%)[6,8] with intervals of 30–60 minutes, three step (0.05 mL, 0.15 mL, 0.30 mL; 10, 30, and 60%) with 30-minute intervals,[4] four step (1:10, 0.05 mL; pure, 0.5 m, 0.15 mL, and 0.3 mL; <1, 10, 30, and 60%) with intervals of 15 to 30 minutes,[10,39,41] and five step (1:10, 0.05 mL; 0.05 mL, 0.1 mL, 0.15 mL and 0.2 mL) with intervals of 15 minutes,[3,27] which is recommended by the American Academy of Pediatrics (AAP). Establishing a unified protocol to determine the appropriate administration of the YFV could aid in better evaluating the impact of desensitization on EAP.

Compared with other studies, delay in vaccination was quantified, due to the obligatory nature of its administration in Colombia at 18 months of age. Vaccination was carried out between 12 and 134 months of age, with a median of 20 months (IQR = 18.0–27.0). This means that 50% of the study group experienced a delay of 2 months or more, presenting a substantial risk for the population in an endemic area such as Colombia.

Limitations

The single-center retrospective design of the study limited the number of cases evaluated, and the information obtained from the consulted medical records; thus, missing data or underregistration could have occurred and the results and conclusions depend on the quality of the medical records. Considering patients with history of possible egg allergy and egg SPT of 3 mm may also undergo restrictions and delays in the application of the YFV, we did not include the patients we found with egg SPT of 3–5 mm, with no egg OFC, who were vaccinated and tolerated the YFV, as they did not meet our chosen criteria for true clinical egg allergy.[31-33] In addition, within our group we did not find any patients who required a diagnostic egg OFC in the previous 6 months, compared with other studies, reason why no patients with an egg OFC were included.[3] Furthermore, and relevant to our conclusions and recommendations, and considering the results from Brazilian and Canadian studies, evaluating the association between an allergic reaction to the vaccine and YFV IDT positivity could have been valuable[2,3] for which a more established protocol on which patients benefit from an YFV IDT could have been helpful.

Table 5 Available studies on YF vaccination of EAP.

Article	Year	Country	# of included EAP	# of egg-anaphylactic patients	YFV	YFV SPT	YFV IDT	YFV administration protocol	# of EAP vaccinated	# of reactions
Bédard MA., et al. Single-dose yellow fever vaccination is well tolerated in egg-allergic children despite positive intradermal test to the vaccine[2]	2021	Canada	24	1	YF-VAX®	ND	4 (–)	1 step	2	0
								5 step	2	0
							20 (+)	1 step	12	0
								3 step	1	0
								5 step	7	0
Sharma K., et al. Yellow Fever Vaccination in Egg-Allergic Children[8]	2020	Australia	11	3	STAMARIL®	4 ND 7 (–)	10 ND 1 (–)	1 step	1	0
								2 step	9	1*
								3 step	1	0
Gerhardt CMB., et al. Safety of yellow fever vaccine administration in confirmed egg-allergic patients[3]	2020	Brazil	58	24	Biomanguinhos-Fiocruz	58 (–)	48 (–)	1 step	48	0
							10 (+)	5 step	10	6 (4*/6)
Cancado LB., et al. Yellow Fever Vaccine (YFV) for Patients with Egg Allergy: Protocol Proposal[41]	2019	Brazil	79	Unknown	Biomanguinhos-Fiocruz	64 (–)	67 (–)	1 step	52	1
						15 (+)	12 (+)	4 step	27	0
Cancado LB., et al. Yellow fever vaccine and egg allergy[39]	2019	Brazil	132	Unknown	Biomanguinhos-Fiocruz	115 (–)	109 (–)	1 step	92	Unknown
						17 (+)	23 (+)	4 step	40	0
**García, M., et al. Frequency of Allergic Reactions in Egg Allergic Patients After Receiving the Yellow Fever Vaccine.	2023	Colombia	71	24	STAMARIL®	71 (–)	66 ND	1 step	69	1*
							3 (–)			0
							2 (+)	2 step	1	0
								3 step	1	1*
Total			375	52		28 ND 315 (–) 32 (+)	76 ND 232 (–) 67 (+)	276 1 step 99 graded protocol		10 (2.67%)

*History of egg anaphylaxis; **This study.
ND: Not done; (–): Negative; (+): Positive; YF: Yellow Fever; EAP: egg-allergic patients; YFV: Yellow Fever Vaccine; SPT: Skin Prick Test; IDT: Intradermal Test.

Conclusion

In conclusion, of the 71 patients with a clinical history of egg allergy and a high probability of clinical relevance, two with history of egg anaphylaxis presented a positive reaction during the administration of the YFV. Whether the type of reaction presented with the egg (e.g., anaphylaxis) is associated with tolerance or not to the YFV should be confirmed to possibly consider safe single-dose YF vaccination in EAP. However, it is still recommended that patients with a history of egg anaphylaxis are evaluated by allergy specialists before the administration of the YFV, without it being a barrier. In YF endemic areas, vaccination should be favored, and delays avoided. More studies and data are still needed to further evaluate the safety and administration protocol of the YFV in EAP[3,5,19] and to determine the value of the YFV IDT as a predictor of allergic reactions to the vaccine in EAP.

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