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Original Article

Immediate adverse events to the yellow fever vaccine in egg-allergic children

Eventos adversos imediatos à vacina febre amarela em crianças alérgicas ao ovo

Bianca Noleto Ayres Guimarães[1], Tânia Cristina de Mattos Barros Petraglia[1], Ana Karolina Barreto Berselli Marinho[2], Adauto Dutra Moraes Barbosa[3]

ABSTRACT

Introduction: The yellow fever vaccine is grown in embryonated chicken eggs and may be contraindicated for egg-allergic individuals. When indicated, it should be applied with caution, after testing and desensitization. Its safety in egg-allergic patients is still poorly studied. **Objective:** To describe a pediatric population referred for egg allergy, with or without a confirmed diagnosis, and cases of immediate-type adverse events to the yellow fever vaccine at a reference center for special immunobiologicals. **Material and methods:** This cross-sectional study collected retrospective data from children between 9 months and 12 years of age who were vaccinated for yellow fever between 2018 and 2019 and had a history of egg allergy. **Results:** In the 829 children diagnosed with presumed egg allergy, a higher prevalence of symptoms was identified after egg exposure, with detectable specific IgE for egg, egg white, and/or egg albumin. Yellow fever vaccine tests were performed in 25 children suspected of severe allergy or anaphylaxis to eggs, and 15 (60%) tested positive to the vaccine after desensitization. Only 11 (1.3%) cases of immediate adverse events to the vaccine occurred, all classified as non-serious events that especially involved the skin (local reaction and rash or urticaria). Most events occurred in children under 2 years of age, those symptomatic after egg ingestion, and those with high levels of specific IgE to egg white. **Conclusion:** This study demonstrated that the yellow fever vaccine can be safely administered to egg-allergic children, including those with a history of anaphylaxis, in an appropriate environment and with specialized professionals.

Keywords: Yellow fever vaccine, egg hypersensitivity, anaphylaxis, desensitization, drug-related side effects and adverse reactions.

RESUMO

Introdução: A vacina contra a febre amarela é cultivada em ovos embrionados de galinha e por isso pode estar contraindicada em indivíduos alérgicos ao ovo. Quando indicada, deve ser aplicada com cautela, após atendimento especializado para avaliação de testes e necessidade de dessensibilização. Sua segurança nos alérgicos ao ovo ainda é pouco estudada. **Objetivo:** Descrever uma população pediátrica encaminhada por alergia ao ovo, com ou sem diagnóstico comprovado, e os casos de eventos adversos do tipo imediata à vacina contra a febre amarela em um centro de referência para imunobiológicos especiais (CRIE). **Material e métodos:** Estudo transversal realizado com coleta de dados retrospectivos de crianças entre 9 meses e 12 anos de idade, vacinadas contra a febre amarela com história de alergia ao ovo, no período de 2018 a 2019. **Resultados:** Dentre as 829 crianças, com diagnóstico presumido de alergia ao ovo, foi identificada uma maior prevalência de sintomáticos após exposição ao ovo, com IgE específica detectável para ovo, clara de ovo e/ou ovoalbumina. Testes para vacina febre amarela foram realizados em 25 crianças com suspeita de alergia grave ou anafilaxia ao ovo, sendo 15 (60%) positivos com a vacina aplicada após dessensibilização. Foram evidenciados apenas 11 (1,3%) casos de evento adverso imediato à vacina, todos classificados como evento adverso não grave e com acometimento especial da pele (reação local e exantema ou urticária). A maioria dos eventos ocorreu em menores de 2 anos, nos sintomáticos após ingesta de ovo e naqueles com altos valores de IgE específica para clara de ovo. **Conclusão:** Este estudo evidencia que a vacina contra a febre amarela pode ser aplicada em crianças alérgicas ao ovo, de forma segura, inclusive naquelas com história de anafilaxia, desde que em ambiente adequado e com profissionais especializados.

Descritores: Vacina contra febre amarela, anafilaxia, dessensibilização imunológica, hipersensibilidade a ovo, efeitos colaterais e reações adversas relacionados a medicamentos.

1. Hospital Municipal Rocha Maia, Secretaria Municipal de Saúde, Centro de Referência para Imunobiológicos Especiais - Rio de Janeiro, RJ, Brazil.
2. Hospital das Clínicas da Faculdade de Medicina da USP, Serviço de Imunologia Clínica e Alergia/Disciplina de Imunologia Clínica e Alergia - São Paulo, SP, Brazil.
3. Universidade Federal Fluminense, Departamento Materno-Infantil - Rio de Janeiro, RJ, Brazil.

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Introduction

Yellow fever (is a potentially serious viral disease transmitted by mosquitoes to humans and other primates. The most significant outbreak of yellow fever in Brazilian history occurred between 2017 and 2018 (1,376 cases; 35% lethality rate), and the risk of its re-urbanization again became a concern when the outbreak reached the most populous region of the country. Since 2019, the National Immunization Program's vaccination recommendation has been extended nationwide.[1]

Egg protein allergy (EPA), which is prevalent among children[2], may contraindicate the use of yellow fever vaccine due to the risk of adverse reactions, as this vaccine contains egg protein.[3] However, further research is needed to confirm the safety of the yellow fever vaccine in patients with EPA.[4-7] The objective of the present study was to determine the relationship between EPA and allergic reactions to the yellow fever vaccine in children.

Material and methods

This cross-sectional study collected retrospective data from a pediatric population with a history of EPA who were vaccinated for yellow fever at the Reference Center for Special Immunobiologicals (CRIE), Rocha Maia Municipal Hospital, Rio de Janeiro, RJ. We included boys and girls aged from 9 months to 12 years, 11 months, and 29 days who were vaccinated between January 2018 and December 2019. This period was selected due to the ongoing yellow fever outbreak in the city and the high demand for the vaccine.

Children diagnosed with EPA who were referred for yellow fever vaccination received prior care by the service's pediatrician, who performed an anamnesis to assess EPA severity and the risk of immediate adverse events to the vaccine. After an initial medical assessment, children with a history of mild/moderate EPA were given the yellow fever vaccine under 30 to 60 minutes of on-site observation. Those with a severe allergy or anaphylaxis to egg were referred for evaluation by the service's allergist and immediate skin testing for yellow fever vaccine was performed.

The immediate skin test to assess type I hypersensitivity consists of a prick test with the pure vaccine (1:1 dilution), followed by an intradermal test with the diluted vaccine (1:100) if the initial prick test is negative. Children with positive results at any stage of the immediate skin testing received the yellow fever vaccine after desensitization in a safe environment and under continuous monitoring, according to Brazilian Society of Allergy and Immunology (ASBAI) protocol.[4] Immediate reactions considered vaccine adverse events (VAE) were reported to the health surveillance team by the attending physician. According to the Ministry of Health's VAE manual, any events that resulted in hospitalization, significant dysfunction and/or permanent disability, or death or risk of death with immediate clinical intervention to prevent death, were considered severe VAE.[8] An event can be considered mild, moderate, or intense, regardless of its severity, such as intense local hyperemia.[8]

The yellow fever vaccine, manufactured by Bio-Manguinhos® during the national vaccination campaign of 2018, was applied in either the standard dose (0.5 mL) in individuals < 2 years of age and travelers or in the campaign dose (0.1 mL) in those > 2 years of age and non-travelers. Vaccinations were excluded if they were not referred through formal documentation to CRIE due to EPA, if they were revaccinations, or if the patient was not kept under observation after application for the period indicated by the doctor according to protocol.

Data were collected through the Ministry of Health's National Immunization Program Information System and anamneses, including the data used by attending physicians to define EPA severity and report VAE. The following variables were analyzed: age at vaccination, sex, clinical and laboratory information from the anamnesis (on which the referral based), comorbidities and other allergic diseases associated with EPA, immediate skin test results for yellow fever vaccine, vaccine dose and form of application of (with or without desensitization), and VAE during the observation period. The clinical information used to diagnose EPA was stratified into signs and symptoms of EPA prior to vaccination.

When reported, the results of the *in vivo* sensitization test (prick test for egg and/or egg components), which were carried out by the patient's physician prior to evaluation at CRIE, were classified as negative or positive. The oral challenge test was not evaluated in this study due to its limited use in non-specialized services.

The *in vitro* sensitization test, involving specific dosages of serum IgE for egg, egg white, ovalbumin, and/or ovomucoid, was mainly performed using the fluoroenzyme immunoassay method (ImmunoCAP,

Thermo Fisher Scientific, Waltham , MA, USA).[9] When reported, the results were classified as undetectable/detectable. Detectable results (low, moderate, or high) were classified according to the reference values of the clinical analysis laboratories where they were performed. The examination date, when reported, was also collected.

This study was approved by the Research Ethics Committee of the Rio de Janeiro Municipal Secretary of Health (CAAE: 33512620.9.0000.5279).

Results

The sample included a total of 829 children with probable EPA who were vaccinated for yellow fever (Table 1).

Table 1
Sex and age of 829 children vaccinated for yellow fever at the Rocha Maia Municipal Hospital Reference Center for Special Immunobiologicals

Variable	
Sex	**n (%)**
Male	460 (55)
Female	369 (45)
	Total: 829 (100)
Age	
Minimum – Maximum	9 months – 12 years
Median	1 year, 11 months
Mean (years ± SD)	3 ± 2
Age	**n (%)**
9 months	64 (8)
9 months to < 2 years	359 (43)
2 to 5 years	235 (28)
6 to 12 years	171 (21)
	Total: 829 (100)

SD = standard deviation.

Diagnostic criteria for egg protein allergy

The following criteria were used to evaluate a presumed diagnosis of EPA: the presence or absence of signs and symptoms after egg exposure (n = 688[83%]), prick test results for egg and/or its components (n = 190[23%]), and specific serum IgE for egg, egg white, and/or ovalbumin (n = 563[68%]).

In total, 720 (87%) children had symptoms after egg exposure, and/or specific serum IgE, and/or positive prick test results for egg or egg components. For in 12% (n = 97) of the children, no information was found about EPA symptoms or diagnostic tests.

Of the 623 children (91%) with signs and symptoms after egg exposure, 490 (79%) had cutaneous manifestations, 219 (35%) had gastrointestinal manifestations, 67 (11%) had respiratory manifestations, and 48 (8%) had neurological manifestations. Signs and symptoms in more than 1 organ or system occurred in 172 (28%) children. Anaphylaxis or suspected anaphylaxis was described in 22 (4%) children. The most commonly reported signs and symptoms of EPA were: urticaria (58%), dermatitis (29%), vomiting (26%), diarrhea (14%), angioedema (10%), cough (8%), irritability (7%), abdominal pain (6 %), rhinitis (4%), and anaphylaxis (4%). Although information about the range of EPA symptoms and the date of yellow fever vaccination were not reported in most records, in the symptomatic group, 356 (57%) were nursing infants when they received the vaccine.

Among the analyzed egg components, serum IgE levels for egg white (92%), ovalbumin (20%), and egg (17%) were the most frequent. Ovomucoid-specific IgE results were reported in < 1% of the sample. In total, 499 (89%) children had detectable specific serum IgE levels indicative of sensitization to eggs, egg whites, and/or ovalbumin, with 170 (30%) having specific serum IgE levels > 3.50 kU/l, which is considered high. The test date was reported for 176 (31%) children, of whom 95% were aged < 12 months and 81% were aged < 6 months when vaccinated.

Comorbidities, such as other allergic diseases associated with EPA prior to vaccination, were reported in 221 (27%) of the children, distributed as follows: atopic dermatitis (35%), cow's milk protein allergy (28%), other food allergies (8%), rhinitis (26%), and asthma or bronchitis (17%). None of the children were positive for gelatin allergy.

To assess sensitivity to yellow fever vaccine, immediate skin tests were performed in 25 (3%) of the children by the CRIE allergist: 20 who had a history of or suspected anaphylaxis to egg and 5 who had a

clinical history of severe EPA (urticaria and/or intense angioedema). High specific serum IgE values for egg, egg white, and/or ovalbumin were found in 21 of the 22 children with reported results. The prick test was positive in 10 of the 11 reported applications. Of the 22 children with anaphylaxis to egg, only 2 (5 and 6 years old), who had episodes in infancy, did not undergo an immediate skin test for yellow fever vaccine due to subsequent improvement.

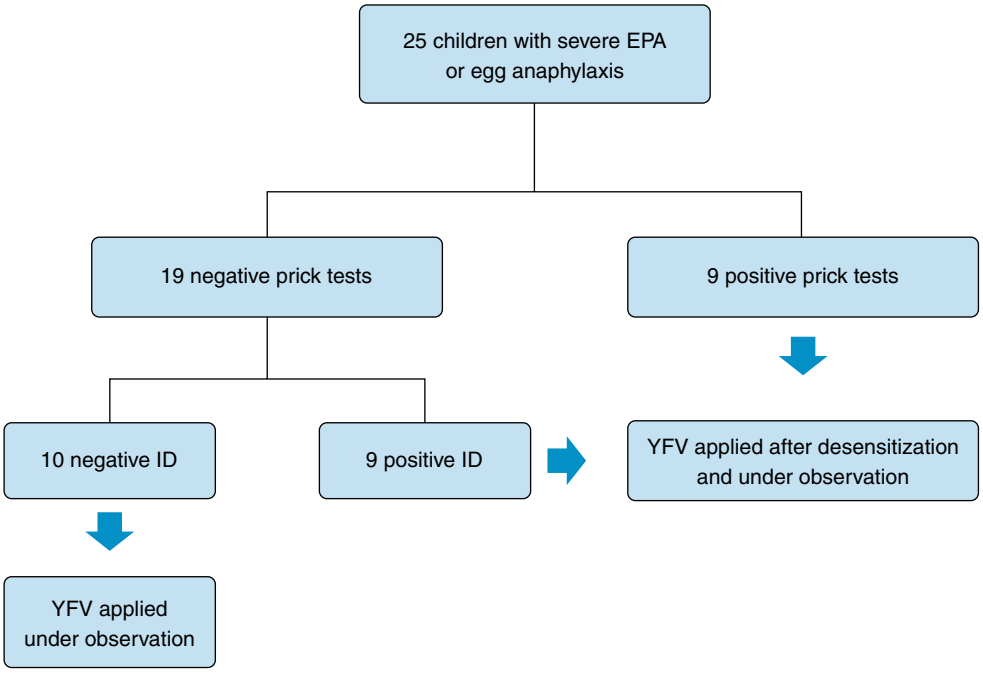
To assess sensitivity to the yellow fever vaccine, a prick test with the pure vaccine was performed, followed by an intradermal test with diluted vaccine (1:100) if the initial results were negative. Of the 25 prick tests performed for yellow fever vaccine, 6 were positive. The 19 children with negative results underwent intradermal testing with the diluted vaccine, of whom 9 were positive. Following the dose escalation (or desensitization) protocol, the 15 (60%) children with a positive test result (prick or intradermal) received the vaccine (Figure 1).

The standard vaccine dose (0.5 mL) was administered to 568 (69%) children. A dose of 0.1 mL (2018 campaign) was applied to 261 (31%) children > 2 years of age. Of the 15 children who received the vaccine after desensitization, 3 received it during the campaign (0.1 mL dose).

Adverse events to yellow fever vaccine

Of the 829 children presumed to have EPA, only 11 (1.3%) had immediate VAE (Table 2). All of these cases were reported as non-serious. No anaphylactic reactions to vaccination were reported.

An 8-year-old child reported mild "shortness of breath", although there were no changes in vital signs and the condition improved during the observation period (case 3). Four (36%) children had an immediate wheal reaction and hyperemia at the application site: 3 of the cases were mild (cases 7, 10 and 11) and 1 was severe (case 8).



EPA = egg protein allergy, ID = intradermal test, YFV = yellow fever vaccine.

Figure 1
Flowchart of immediate skin testing for yellow fever vaccine sensitivity in children with a history of severe egg protein allergy or anaphylaxis at the Rocha Maia Municipal Hospital Reference Center for Special Immunobiologicals

Seven (64%) children had cutaneous manifestations away from the vaccination site: 1 with angioedema (case 9), 4 with urticaria (cases 1, 2, 4, and 6), and 2 with exanthema (cases 5 and 11). Case 5 (an infant) had mild conjunctival hyperemia associated with urticaria. Case 11 (nursing infant) had a mild local reaction within a few minutes that evolved to urticaria 2 hours after vaccination.

Of those who had immediate VAE, 7 (64%) were nursing infants, 8 (73%) had a history of cutaneous manifestations after egg exposure, 1 (9%) was suspected of egg anaphylaxis, 4 (36%) had a history of multiple organ/system manifestations after egg exposure (but no anaphylaxis or simultaneous symptoms), and 7 (64%) had high egg white-specific IgE values (> 3.50 kU/L).

Table 2
Immediate adverse events following yellow fever vaccination at the Rocha Maia Municipal Hospital Reference Center for Special Immunobiologicals

Case	Age, sex	Clinical condition of EPA	IgE [a] (kU/l)	Prick test for egg	Comor-bidities	IST for YFV	Dose (mL)	Reaction to YFV
1	3 y, F	NI	Egg white: 4.5	NI	NI	No	0.5	Mild rash
2	5 y, M	Urticaria, abdominal pain, cough and bronchospasm	NI	Pos.	NI	No	0.1	Mild urticaria
3	8 y, F	Angioedema	Egg white: 4.94	Pos.	NI	No	0.1	"Shortness of breath"
4	1 y, M	Anaphylaxis	Egg white: 23.5	NI	NI	Yes [b]	0.5	Mild urticaria
5	10 m, M	Urticaria	Egg white: 1.4	NI	CMPA	No	0.5	Mild rash
6	1 y, M	Urticaria and vomiting	Egg white: 12	NI	NI	No	0.5	Urticaria and conjunctival hyperemia
7	10 m, F	Urticaria and dermatitis	Egg white: 14	Pos.	DA	No	0.5	Mild local reaction
8	2 y, M	Urticaria and rhinitis	Egg white: 85.1	Pos.	CMPA, rhinitis and asthma	No	0.5	Intense local reaction
9	10 m, F	Irritability	Egg white: 0.22	NI	Denied	No	0.5	Angioedema
10	1 y, F	Asymptomatic (no direct egg exposure)	Egg white: 3.75	Pos.	CMPA	No	0.5	Mild local reaction
11	1 y, F	Urticaria and vomiting	NI	NI	Denied	No	0.5	Mild local reaction and urticaria after 2 hours

CMPA = cow's milk protein allergy, IST = immediate skin test, NI = not informed, Pos. = positive, YFV = yellow fever vaccine.
[a] IgE for egg, egg white, and/or ovalbumin; [b] Positive prick test for yellow fever vaccine.

Of the 15 children with positive immediate skin test (prick/intradermal) results for yellow fever vaccine, only 1, who had a previous history of anaphylaxis to egg, had a reaction (urticaria) during the desensitization process (case 4). No children with negative immediate skin test results had a reaction to the vaccine.

Children who reacted to the vaccine were discharged under medical supervision. None of the children required intravenous medication, oxygen therapy, or adrenaline. According to the VAE notifications, 4 other children who received the yellow fever vaccine at CRIE were reported as having late and non-severe exanthema reactions 6 hours after application; these were not considered immediate-type reactions.

Discussion

The present study evaluated a population of 829 patients with probable EPA, a significant sample compared to other published studies.[5,10-17] Among the demographic factors, age proved to be relevant, since most of the children were < 5 years of age, in whom EPA is more common, especially at < 2 years of age, when EPA is even more prevalent.[2,7]

In the CRIE risk assessment, the symptomatology criteria (specific serum IgE values or immediate response test results) were the most commonly used types in routine diagnosis and classification of allergy severity and in clinical practice.[7,9] In 87% of the children, at least 1 diagnostic criterion was present, and no information was found on asymptomatic children with negative test results, which suggests that the majority of this population did have EPA.

Egg sensitization, detected by specific serum IgE to egg, egg white, and/or ovalbumin, was identified in the majority of the children, of whom 170 had high values (> 3.5 kU/L). Ovomucoid-specific IgE was rarely reported by the referring physicians, and it was not found in isolation in any child. It is unclear why so few were tested for this specific IgE, and it was not possible to investigate this issue in detail. The detection of specific IgEs has been considered indicative of food sensitization, although this generally only points to the need for a double-blind placebo-controlled oral challenge test to diagnose EPA. However, the oral challenge test, considered the gold standard for diagnosing EPA, was not reported in the children's records, probably because it requires a supervised environment, is seldom available in clinical practice[9], and most children are clinically diagnosed without it.[7]

Other IgE-mediated allergic diseases (cow's milk protein allergy, atopic dermatitis, rhinitis, and asthma) were prevalent in the group with reported comorbidities. It is known that a history of allergic diseases can be a risk factor for hypersensitivity reactions to vaccines.[5,12,13]

Most delays in yellow fever vaccination are due to EPA, because it requires prior guidance from a health professional and referral to a specialized center for application.[4,8,18]

Although anaphylactic and hypersensitivity reactions to yellow fever vaccine have been reported[19-22], few studies have evaluated adverse events to the vaccine in patients with EPA. Four studies that performed desensitization protocols for yellow fever vaccine in patients with anaphylaxis to egg found no serious VAE.[5,12,13,16] The present study found a history or suspicion of egg anaphylaxis in 4% (n = 22) of the vaccinated children. This number is probably an underestimate, since 28% of the children had signs and symptoms of EPA in more than one organ or system, but no information on anaphylaxis or the time between symptoms was provided. Anaphylaxis is often underdiagnosed, particularly in children.[23]

Immediate skin tests for yellow fever vaccine (prick tests, followed by intradermal tests if negative) were performed in 25 children suspected of severe allergy or anaphylaxis to egg, of which 15 (60%) were positive (6 prick tests and 9 intradermal tests). This percentage is high compared to other studies of children with EPA. Sharma et al. (2020) evaluated 11 children with EPA and performed prick tests on 7 (2 anaphylactic), all of which were negative. Only 1 underwent an intradermal test, which was also negative.[13] Gerhardt et al. (2019) tested yellow fever vaccine in 43 children with proven egg allergy (7 anaphylactic), finding negative prick test results in all cases and positive intradermal tests in 6 (14%).[12] Likewise, Julião et al. (2018) performed prick tests for yellow fever vaccine in 5 children with EPA (2 anaphylactic), finding negative results in all cases and positive intradermal results in 2 cases.[16] The higher number of positive immediate skin test results in the present study could be explained by the fact that the sample was selected for greater EPA severity, with 19 (76%) considered anaphylactic to egg. Following negative prick test results for the yellow fever vaccine with intradermal tests resulted in a higher number of positive results, as occurred in in other studies.[12,16]

Gerhadt et al. found an immediate reaction in 3 of the 6 children with positive intradermal test results who were desensitized to yellow fever vaccine, concluding that intradermal tests can help predict a higher risk of vaccine reaction.[12] In the present study, the 9 desensitized patients with positive intradermal test results had no VAE, and only 1 infant with positive test results reacted with immediate urticaria to the yellow fever vaccine. Intradermal tests can be more painful and difficult to perform in infants, presenting a greater possibility of skin irritation and false-positive results.[13] Larger studies are needed to determine the sensitivity and specificity of immediate skin tests for yellow fever vaccine.

Egg is one of the most frequently associated vaccine components with immediate hypersensitivity reactions.[24-26] Eleven (1.3%) cases of immediate VAE occurred in our sample, all defined as non-serious, which was suggestive of severe EPA and a likely risk of immediate reaction to yellow fever vaccine.

Studies of large populations who received the yellow fever vaccine have shown low rates of immediate reaction suggestive of hypersensitivity.[19,22,27] However, in studies on patients with EPA, the actual frequency of VAE has not been defined due to population variability and the small number of affected individuals.[5,10-17]

Most VAE in our sample occurred in infants who were symptomatic after egg exposure and had high egg white-specific IgE values. This suggests that VAE are likely related to age and EPA severity. However, these results are not comparable due to a lack of studies with large samples of EPA patients.[5,10-17]

Urticaria was the most commonly reported symptom in EPA diagnostic criteria, as well as in immediate reactions to the yellow fever vaccine. This corroborates large population studies, which do not specifically assess EPA, but frequently report urticaria in hypersensitivity events and immediate reactions to the yellow fever vaccine.[19,22]

We were unable to associate vaccine dosage with the occurrence of adverse events. Most VAE in this study were occurred after a dose of 0.5 mL (91%). However, the 0.1 mL dose (2018 campaign) was applied to 32% of the sample, all > 2 years of age, when EPA prevalence/severity usually decreases.[2,7]

Although we studied a significant population of children with presumed EPA, there were no anaphylactic reactions to the yellow fever vaccine. The few observed VAE were classified as non-serious, although immediate reactions did occur in children without a history of severe EPA.

The yellow fever vaccine testing protocol, followed by desensitization for patients with positive results, made yellow fever vaccination safer in children with severe EPA. Based on these results, we conclude that the yellow fever vaccine can be safely applied to children with EPA after evaluation by a specialist and in an appropriate and supervised environment.

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Corresponding author:
Bianca Noleto Ayres Guimarães
E-mail: biancanoleto@hotmail.com