ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

Incidence of vaccine-related anaphylaxis from Brazil's National Immunization Program

Incidência de anafilaxia relacionada às vacinas do Programa Nacional de Imunizações

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ABSTRACT

Vaccine-related anaphylaxis is a rare health event, and its incidence requires further investigation in Brazil. The objective of this study was to describe the incidence of anaphylaxis as an event supposedly attributed to vaccination and immunization (ESAVI) associated with the Brazilian National Immunization Program (PNI). A retrospective study was conducted with data extracted from the PNI ESAVI notification system between January 2021 and May 2023, with ethical approval and registration in Plataforma Brasil. Among 290,101 adverse events reported, 84 cases closed with the descriptor "anaphylaxis" or "anaphylactic shock" were identified, mainly concentrated in the South and Southeast regions. Children aged 0 to 9 years were predominantly affected, with a higher incidence in women and white individuals. In absolute numbers, anaphylaxis was associated mainly with the AstraZeneca/Fiocruz (viral vector), Pfizer Comirnaty (mRNA), and CoronaVac (inactivated virus) COVID-19 vaccines, while the highest relative incidence was with the anti-rabies vaccine (2.8 cases per million doses administered). The overall incidence was 0.14 per million vaccine doses. No deaths were reported. Underreporting of vaccine-related anaphylaxis is relevant and highlights the importance of maintaining robust systems for surveillance and management of allergic reactions within vaccination programs. This study corroborates global trends in the rarity of vaccine-related anaphylaxis. The low incidence of this event, regardless of recipient demographics, provides further evidence of the safety of COVID-19 vaccines and other vaccines included in the PNI.

Keywords: Vaccination, anaphylaxis, immunization programs, vaccination hesitancy, immediate hypersensitivity.

RESUMO

A incidência de anafilaxia pós-vacinal é um evento de saúde raro e carece de melhor detalhamento no Brasil. Neste estudo, objetivou-se descrever a incidência de anafilaxia como evento supostamente atribuído à vacinação e imunização (ESAVI) das vacinas do Programa Nacional de Imunizações (PNI). Foi realizado estudo retrospectivo com dados extraídos do sistema de notificação de ESAVI do PNI entre 01/2021 e 05/2023 com aceitação na Plataforma Brasil e aprovação ética. Foram identificados 84 casos encerrados com o descritor "anafilaxia" ou "choque anafilático" entre 290.101 eventos adversos notificados, concentrados principalmente nas regiões Sul e Sudeste. Crianças de 0 a 9 anos foram predominantemente afetadas, com maior incidência em mulheres e indivíduos brancos. A anafilaxia associou-se em números absolutos principalmente às vacinas COVID-19, destacando os fabricantes AstraZeneca/Fiocruz (vetor viral), Pfizer Comirnaty (RNAm) e CoronaVac (inativada), e a maior taxa de incidência foi com a vacina antirrábica (2,8 por milhão de doses aplicadas). A incidência global foi de 0,14/milhão de doses aplicadas. Entre os desfechos não foi relatado óbito. A subnotificação de casos é relevante e sublinha a importância de manter sistemas robustos de vigilância e manejo de reações alérgicas em programas de vacinação. Este estudo segue tendências mundiais da raridade da anafilaxia relacionada às vacinas. Os dados reforçam a segurança das vacinas COVID-19 e demais vacinas existentes no PNI, independente da demografia analisada.

Descritores: Vacinação, anafilaxia, programa de imunização, hesitação vacinal, hipersensibilidade imediata.

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Introduction

Anaphylaxis is a serious hypersensitivity reaction that can be fatal if not treated appropriately. This is part of the definition proposed in 2020 by the World Allergy Organization, which characterizes anaphylaxis as a sudden, severe event that can involve the upper and lower airways and/or cardiocirculatory system, occurring with or without skin lesions and with or without circulatory shock.[1]

Depending on the definition, method, and geographic area, the estimated lifetime prevalence of anaphylaxis is 0.3-5.1%, with a 26.5-54% chance of recurrence over a follow-up period of 1.5-25 years.[2] The most common causes are medications, foods, and poison from insects of the *Hymenoptera* order.[3]

Vaccine-related anaphylaxis is a rare event, with an incidence of 1 in 100,000-1,000,000 administered doses.[4] McNeil et al. found an incidence of 1.31 per million (95% CI 0.90-1.84), i.e., only 33 cases of anaphylaxis occurred in 25 million doses, with no age group being predominant. The highest incident rates were for the trivalent influenza vaccine (1.35; 95% CI, 0.65-2.47), followed by monovalent influenza (1.83; 95% CI, 0.22-6.63), and there was an 85% prevalence of allergic comorbidities in these patients.[5] Regarding COVID-19 vaccines, a recent systematic review found a combined incidence rate of 5.58 per million doses (95% CI, 3.04-8.12) for the Pfizer-BioNTech mRNA vaccine and the Moderna vaccine and 9.31 per million doses for the Pfizer-BioNTech vaccine alone.[6]

In allergic reactions (with a type I hypersensitivity reaction mechanism), other vaccine components may be involved in addition to the antigen, such as suspension medium, which could may contain remnants of vaccine production culture media (eg, eggs), adjuvants to enhance antibody production (eg, aluminum hydroxide), stabilizers (eg, gelatin, sugars, and amino acids), preservatives (eg, 2-phenoxyethanol and thimerosal), antibiotics, yeast, and latex.[5,7,8] This also includes substances that increase vaccine solubility, particularly in COVID-19 vaccines. Both the Pfizer-BioNTech and Moderna vaccines contain polyethylene glycol (PEG), a substance previously implicated in immediate IgE-mediated reactions.[9] The AstraZeneca/Fiocruz vaccine contains polysorbate 80, a substance used in many medications and biological therapies, which can sensitize the patient, resulting in subsequent post-vaccination reactions.[8]

Because post-vaccination health events are not always due to the vaccine itself and a causal relationship cannot always be determined at the time of notification, they have been called "events supposedly attributable to vaccination or immunization" (ESAVI) by the Pan American Health Organization. ESAVI may be related to variables, such as vaccine batch quality, application scheduling error, other health conditions, or to the vaccine itself, which could include its components, the application device, or the personal protective equipment of those who administer the vaccine.[10] Establishing causality requires a systematic investigation of individual and populational evidence surrounding the event based on a structured methodology[11] following World Health Organization criteria.[12]

If an immediate hypersensitivity reaction is confirmed, subsequent procedure can then be determined, which could include contraindication for subsequent doses, vaccination under supervision, changing to a formulation without the implicated component, dose fractionation, or vaccination without additional precautions.[13] Increased knowledge of allergens and vaccine reactions and appropriate investigation can also affect vaccine hesitancy[14], a complex phenomenon[15] that World Health Organization has classified as one of the top 10 threats to global health since 2019.[16]

The Brazilian National Immunization Program, which was founded 5 decades ago, was designed to reduce deaths from preventable diseases. Brazil has been an innovator in investigating post-vaccination adverse events[17], including surveying and cataloging anaphylactic reactions, and providing safety data on routinely used vaccines to health professionals and the population. Pursuant to these goals, we investigated the incidence of anaphylaxis as an adverse event of vaccines used in the National Immunization Program and demographically characterized anaphylaxis cases, describing the comorbidities and reported symptoms, classifying cases according to Brighton criteria, describing the causality of anaphylactic events, and reporting the outcomes and conduct upon receiving the final notifications.

Methods

This was an observational, retrospective, descriptive study of national ESAVI notifications registered on the Unified Health System's electronic

notification platform (*e-SUS Notifica*). Anonymized data were obtained from all ESAVI notifications made between January 2021 and May 2023 by the Department of Immunization and Vaccine-Preventable Diseases. To complement the analyses, other data were also obtained from the Unified Health System[18] regarding the total number of doses administered by each immunizer during the same period. For COVID-19 vaccines, the number of administered doses were also made publicly available on the *Vacinômetro* (Vaccinometer) platform, developed by the Secretariat of Information and Digital Health's Department of Monitoring and Evaluation.[19]

The sample consisted of 290,101 ESAVI notifications, which were searched using the descriptors "anaphylaxis" and "anaphylactic shock" in the "post-investigation diagnosis" and "investigation closure" column. Relevant notifications were included in the analysis. It should be noted that all cases of anaphylaxis were closed with an ICD-10 code of unspecified anaphylactic shock (T78.2) or unspecified allergy (T78.4: in these, the term "anaphylaxis" was found in the investigation tab's reaction field). ESAVI notifications whose investigation closure column did not include the aforementioned descriptors were excluded. The National Immunization Program uses the criteria of Brighton et al.[20] to determine whether a notification describes a case of anaphylaxis.

Based on the results, we performed a demographic analysis of the population, including state, age group, sex, race, comorbidities, symptoms, the incidence of confirmed cases of anaphylaxis and/or anaphylactic shock (both overall and for each immunization agent), and the attributed causality, including reclassification according to the Brighton criteria.

It should be noted that, in the state of São Paulo, data on COVID-19 vaccinations (including ESAVI reports and the total number of doses) were recorded in its own information system, separate from the federal system. Thus, any other COVID-19 data from that state found in parallel systems (such as the *Vacinômetro* platform) were also removed from the analysis.

This study's ethics committee approval is registered on Plataforma Brasil (CAPPesq/SGP decision 6.083.162; CAAE 69358023.3.0000.0068), including exemption from informed consent.

Results

Of the 290,101 notifications during the study period, 84 were confirmed as anaphylaxis or anaphylactic shock, of which 2 duplicates and 12 notifications with inconsistent data were excluded. The majority of the notifications (56 [66%]) were from the southern and southeastern regions and the Federal District, as shown in Figure 1. Not counting São Paulo (due to the aforementioned data system discrepancy), the state with the most cases was Rio de Janeiro (19%).

The predominant age group for anaphylactic events was 0-9 years of age (20 [24%]), especially 0-5 years (15 [17.8%]), followed by 40-49 years (16 [19%]), as shown in Figure 2. Most events (56 [67%]) events occurred in females. Regarding self-reported race, the cases were mainly White (41 [49%]) or of mixed race (26 [31%]), as shown in Figure 3.

The most frequently reported comorbidity was allergy (9), including asthma (2 cases), allergy to analgesic agents (2 cases), allergy to drugs, medications, or biological substances (1 case), and unspecified allergy (5 cases).

Of the 84 notifications confirmed as anaphylaxis, 69 (82%) occurred after isolated vaccine applications and 15 (18%) after combined immunization. Of the cases due to an isolated vaccine, 54 (65%) were COVID-19 vaccines (Figure 2), with the highest absolute number for Oxford-AstraZeneca-Fiocruz (21 [25%]), followed by Pfizer-BioNTech (15 [18%]), (14 [17%]) and Pfizer-BioNTech pediatric (4 [5%]). Three cases occurred due to arachnid (1 [1%]) and scorpion (2 [2%]) antivenom (Figure 4). Of the anaphylaxis cases associated with isolated vaccines, the majority occurred after the first/only dose (52 [75%]), followed by the second (11 [16%]), and third dose/booster (6 [9%]).

The overall incidence of post-vaccination anaphylactic events was 0.14 per million doses. Among isolated vaccines, the rabies vaccine had the highest incidence rate: 2.80 per million (Table 1), followed by the 23-valent pneumococcal polysaccharide vaccine (1.53 per million), and the Pfizer–BioNTech pediatric COVID-19 vaccine (0.31 per million). Among adult COVID-19 vaccines, the Oxford-AstraZeneca-Fiocruz and CoronaVac (Sinovac-Butantan) vaccines had the same incidence (0.18 per million), followed by Pfizer-BioNTech (0.10 per million) and Janssen (0.05 per million). The overall incidence rate for all COVID-19 vaccines was 0.14 per million (Table 1).

A total of 65 different symptoms were reported among the 84 event notifications. The most frequent

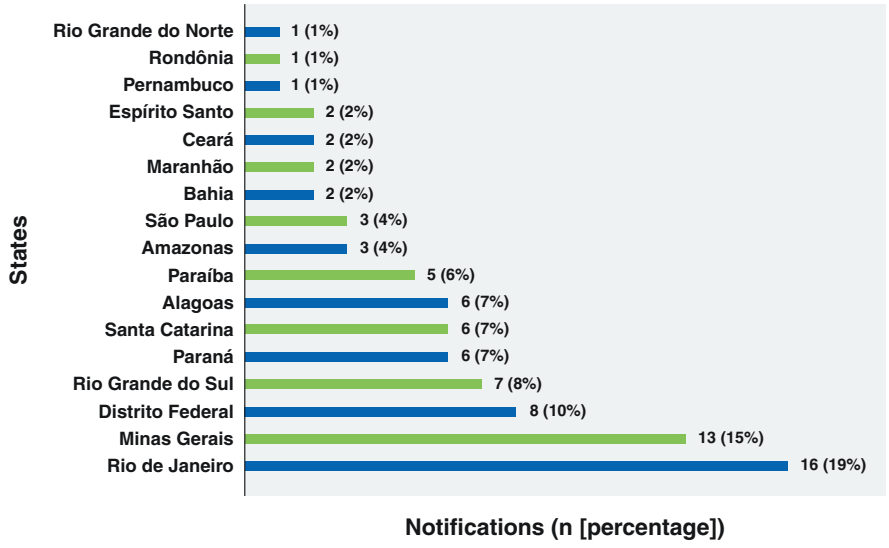

Figure 1
Distribution of anaphylaxis cases reported to the Brazilian National Immunization Program between January 2021 and May 2023 (n = 84)

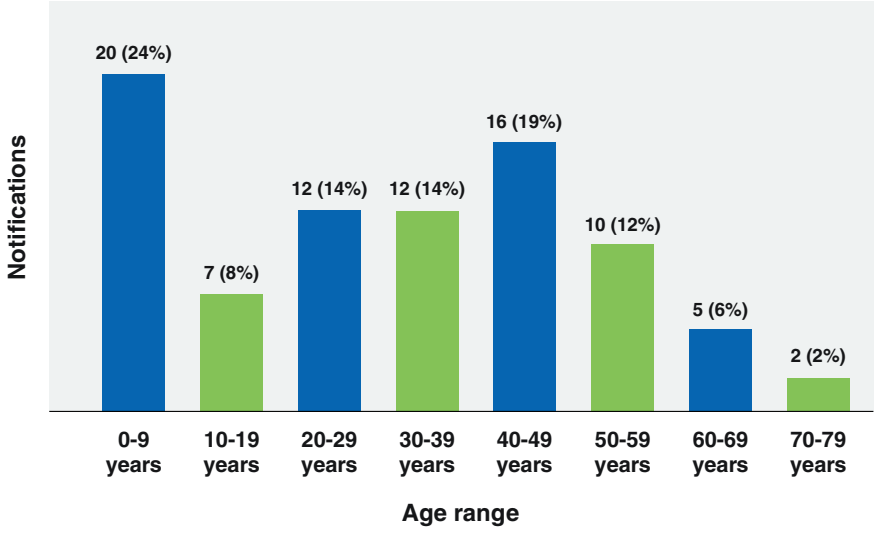

Figure 2
Age distribution of anaphylaxis cases reported to the Brazilian National Immunization Program between January 2021 and May 2023 (n = 84)

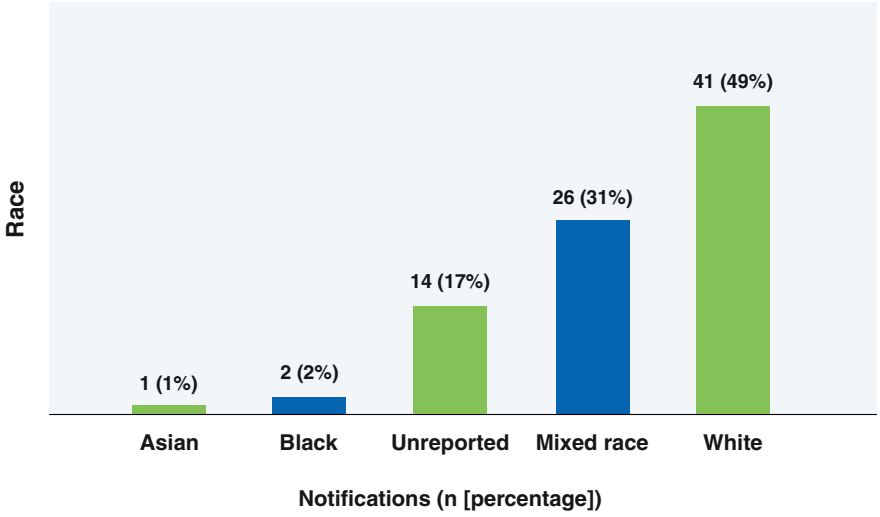

Figure 3
Distribution by race of anaphylaxis cases reported in the Brazilian National Immunization Program between January 2021 and May 2023 (n = 84)

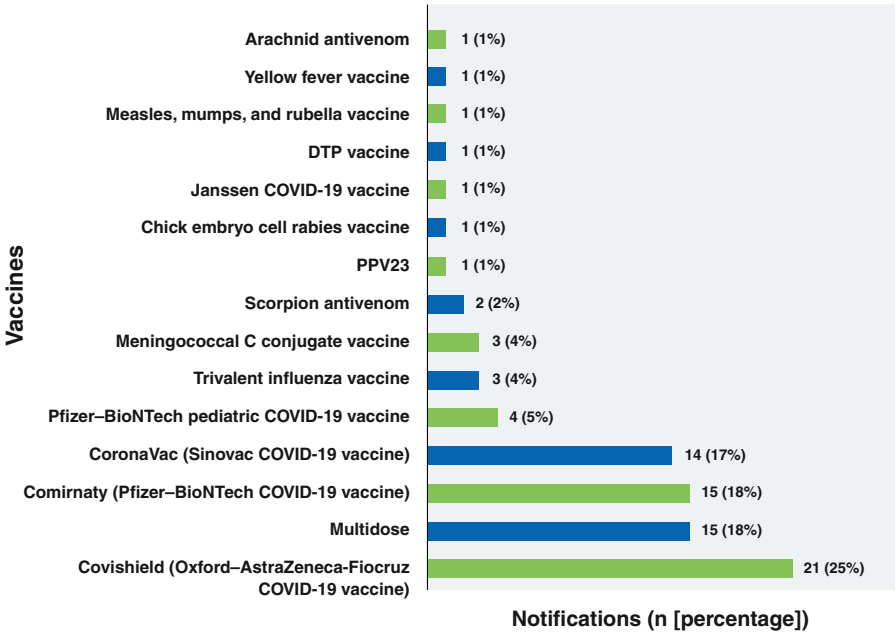

Figure 4
Percentage of confirmed anaphylaxis cases for each Brazilian National Immunization Program vaccine between January 2021 and May 2023, excluding cases of multidose anaphylaxis (n = 84)

DTP= diphtheria, pertussis, and tetanus; PPV23 = 23-valent pneumococcal polysaccharide vaccine.

Table 1
Incidence rate (IR) of anaphylaxis per million doses for Brazilian National Immunization Program vaccines, except for COVID-19 vaccines in the state of São Paulo and cases due to antivenom or multidose application (in descending order by IR)

Vaccine	Doses	Cases	IR per million
Rabies	357,271	1	2.80
PPV23	654,479	1	1.53
Comirnaty (Pfizer–BioNTech) COVID-19, pediatric	13,102,289	4	0.31
Meningococcal C conjugate	14,826,616	3	0.20
Oxford-AstraZeneca-Fiocruz	117,597,423	21	0.18
CoronaVac (Sinovac-Butantan)	76,235,510	14	0.18
DTP vaccine	10,157,454	1	0.10
Comirnaty (Pfizer–BioNTech) COVID-19	153,684,896	15	0.10
Measles, mumps, and rubella	16,845,804	1	0.06
Yellow fever	16,833,464	1	0.06
Janssen COVID-19	22,049,722	1	0.05
Trivalent influenza vaccine	135,344,321	3	0.02

DTP = diphtheria, pertussis, and tetanus; PPV23 = 23-valent pneumococcal polysaccharide.

were anaphylaxis (23), dry cough (13), dyspnea (12), anaphylactic shock (10), glottis edema (8), allergic reaction (7), pruritus (7), urticaria (6), edema (6), facial edema (6) and headache (5).

Based on the described symptoms, the event notifications were classified according to the Brighton criteria. The majority of cases (41 [49%,]) were certainty level 1, followed by level 4 (32 [38%]), level 5 (5 [6%]), level 3 (4 [5%]), and level 2 (2 [2%]).

Regarding the location and type of care offered to patients during the event, the facilities and complexity varied. Many patients underwent observation at a basic health unit for ≤ 24 hours (31 [37%]), followed by outpatient care at a clinic or doctor's office (14 [17%]), hospitalization for > 24 hours (13 [15%]), and admission to an intensive care unit (2 [2%]). This information was not reported in 24 (29%) cases.

The outcome was reported in 65 (77%) of the event notifications, including 81% reported as cured without sequelae and 19% still in follow-up at the time of study completion. No deaths were reported among the cases. The decisions regarding future vaccination at case closure are shown in Figure 5.

Discussion

As far as we know, this was the first national survey on anaphylaxis incidence based on Brazilian National Immunization Program data. The low number of ESAVI notifications during the study period is relevant, since it could indicate underreporting. The study data were from a critical phase of the COVID-19 pandemic, during which treatment seeking would have been somewhat limited. Due to the focus on COVID-19 vaccines during the pandemic, other vaccination coverage was reduced. Health care professionals may also have failed to recognize the signs and symptoms of anaphylaxis, resulting in a lower number of diagnoses

and notifications. Training health professionals to recognize anaphylaxis in a timely manner will ensure greater notification, adequate treatment, and favorable outcomes.

The 84 cases of post-vaccination anaphylaxis were mainly concentrated in the southern and southeastern regions and the Federal District, especially the state of Rio de Janeiro, where 19% occurred. However, since these are absolute numbers, this could merely be indicative of the greater population in these regions. There could also be regional variation in anaphylaxis awareness in different health care networks, in addition to heterogeneous notification routines in different states and municipalities.

The most affected age group was children 0-9 years of age, especially the 0-5 year sub-group, although occurrences were very rare. At this age, patients are more frequently exposed to vaccines and their immune system is still immature. This group also has a higher prevalence of allergies to vaccine components and a higher incidence of infections, which can influence reactions.[21] Furthermore, young children are closely and consistently observed by a caregiver, which increases the chance of noticing an adverse reaction. The rarity of anaphylaxis in this age group is another endorsement for the safety of National Immunization Program vaccines.

In line with the findings of a previous cohort, women and girls were predominantly affected[5], which also agrees with other studies that have confirmed sexual dimorphism in antigenic response and adverse reactions to certain vaccines.[22,23] However, the number of doses applied to each sex and whether this would affect the incidence rate is unknown.

There was a higher prevalence of cases among Whites, followed by individuals of mixed race, confirming previously documented trends.[5,24] This demographic profile could indicate either a greater tendency to report adverse events or some as yet unknown biological susceptibility.

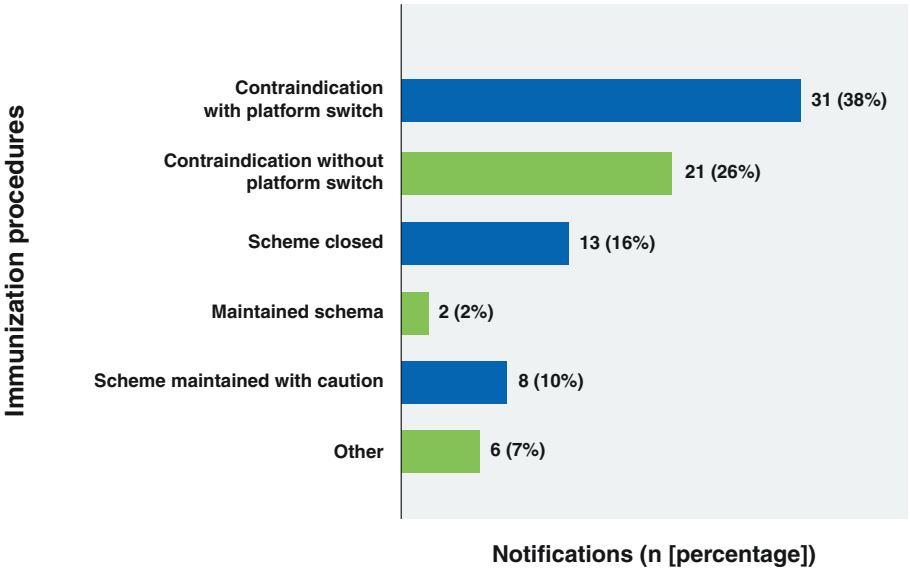

Figure 5
Immunization conduct upon closing anaphylaxis cases reported to the Brazilian National Immunization Program between January 2021 and May 2023 (n = 84)

Regarding comorbidities, 25% of the event notifications mentioned pre-existing conditions, with allergies being the most common (10%). Atopy has been reported as a factor in individuals with an immunoglobulin E-mediated systemic reaction to vaccine components such as diphtheria and tetanus toxin, although the association was not statistically significant.[25] An ongoing clinical trial[26] is evaluating vaccine reactions among atopic and non-atopic populations, which may shed more light on this risk factor, especially regarding COVID-19 vaccines. In any case, our results reinforce the importance of carefully evaluating atopic patients prior to vaccination. This is especially true for asthmatic patients: due to the association between poor asthma control and severe anaphylactic reaction, this group has shown worse outcomes in all age groups.[27]

Post-vaccination anaphylaxis is a very rare adverse reaction. The incidence rate in our sample was 0.14 per million doses, which is lower than that in a pre-pandemic study (1.31 per million). In this study, the inactivated influenza vaccine had the highest number of events, (although similar to other vaccines) and the rabies vaccine had the highest incidence rate (86 per million)[5], as it did in our sample (2.8 per million).

Rabies vaccines may contain gelatin[4], which is one of the main anaphylaxis-related antigens, having a proven immunoglobulin E-mediated type I allergic response. Regarding alpha-gal syndrome, it is still controversial whether the amount of gelatin contained in vaccines could elicit a reaction.[28,29] The anti-rabies vaccine involved in the reported event was produced by the Butantan Institute and is preferred by the National Immunization Program. This innovative vaccine is Vero cell-derived and free from any animal products, having an excellent safety profile.[17]

The preponderance of anaphylaxis cases associated with COVID-19 vaccines should be interpreted with caution. These were the most frequently applied vaccines during the study period and, despite the highest absolute number of cases, the incidence rate was low (0.045-0.31 [mean 0.14] cases per million). Our incidence rate for COVID-19 vaccines was significantly lower than that reported by the U.S. Centers for Disease Control data (5 per million)[30], which might be explained by underreporting or a lack of investigation into reported cases, which were thus never confirmed as anaphylaxis. This highlights the need to strengthen the surveillance system and improve the notification and training systems for health professionals.

Regarding individual COVID-19 vaccines, the Oxford-AstraZeneca-Fiocruz vaccine was the most commonly associated with reactions (25%), followed by Pfizer-BioNTech (18%), and CoronaVac (17%). These vaccines include components such as polysorbate 80 (Oxford-AstraZeneca-Fiocruz) and PEG 2000 (Pfizer-BioNTech), which many reports have identified as the cause of allergic reactions, especially PEG 2000. However, it was later found that the risk of reaction to this vaccine, even among patients who previously reacted to PEG, is extremely low. Thus, due to the strong level of evidence according to Grading of Recommendations, Assessment, Development and Evaluation criteria, vaccination is indicated.[31] Other reactions to PEG with mechanisms involving mast cell activation have been described, such as complement activation-related pseudoallergy, in which IgG and IgM antibodies against PEG activate the complement and lead to mast cell degranulation.[28] CoronaVac uses aluminum hydroxide as an excipient, which has been associated with late local reactions but is not usually involved in immediate reactions.[13] There has also been considerable discussion of non-immunological reactions to vaccines, which can mimic anaphylactic reactions, such as vasovagal response, and immunization stress-related response, which can involve both physical and emotional symptoms and typically has a benign outcome.[4,17,28] Anamnesis and a review of the medical records are essential in the investigation and can guide allergists in differentiating the response type. Skin tests with the vaccine and/or component have low sensitivity and high specificity for stratifying individuals who may have a serious reaction in the second dose. There is no formal recommendation regarding these tests, and they can be performed at the specialist's discretion.[32] The second dose of COVID-19 vaccine is generally well tolerated, even without switching platforms; no clear benefits have been determined from taking gradual doses or premedication.[31] The decision should depend on patient choice in a shared decision model.[32]

In cases of anaphylaxis after combined vaccination, skin tests and component diagnosis may be the only way for patients to continue following their vaccination schedule. The allergist's role is crucial to avoid unnecessary vaccine restriction, thus leaving patients susceptible to vaccine-preventable diseases.[13] However, further evidence is needed to guide such decisions.

The majority (75%) of ESAVI in this study occurred after the initial dose. Other authors have also found this to be the case with COVID-19 vaccines, hypothesizing possible non-allergic causes. When the second dose was administered without changing the platform, a lower frequency of anaphylaxis was observed, and the symptoms that did occur were tolerable.[33]

It should be noted that the majority of cases were classified as Brighton level 1, indicating a high probability of true anaphylaxis, which indicates the importance of surveillance and preparation for serious allergic reactions in vaccination centers. However, our reclassifications were based solely on data from the notification form. For example, in 2 cases classified as Brighton level 5 (i.e., not anaphylaxis) and another 32 cases classified as level 4 (i.e., indeterminate), the notification forms were investigated by the surveillance service according to National Immunization Program protocols, and additional information (from medical records, for example) led to confirmation of anaphylaxis. Such data discrepancies highlight the importance of correct notification procedures: health professionals must add as much clinical information as possible at the time of notification to strengthen subsequent epidemiological studies based on notification data. In a study of COVID-19 vaccines, Basili et al. reported no significant difference in certainty between Brighton and World Allergy Organization classifications.[34] However, due to a lack of clinical data in the notification forms, we did not undertake such a comparison.

Regarding the World Health Organization's Causality Assessment Protocol for adverse events following immunization, reports in the A1 category were the most contraindicated for future doses of the vaccine. No deaths from anaphylaxis occurred in our sample, and the majority of cases were resolved without sequelae, which aligns with the literature since, despite being a potentially serious event, fatalities are extremely rare.[5,21,35]

Including ICD-11 codes that address various differentials could improve future epidemiological research on vaccine-related anaphylaxis, given that the current classification systems limit the correct description of events, due to which some cases may not be investigated.[36]

As study limitations, in addition to possible underreporting, we highlight the non-inclusion of ESAVI data from the state of São Paulo, since it is the most populous state in the country, thus reducing the absolute number of reported cases.

Conclusions

The incidence rate of anaphylaxis associated with National Immunization Program vaccines was 0.14 cases per million doses during the study period, which reinforces the rare nature of such events and highlights the safety of the program's vaccines. The rabies vaccine had highest incidence rate, whereas COVID-19 vaccines had the highest absolute number of cases. Underreporting was probably relevant and may have impacted the absolute number of events.

Demographic characterization of confirmed anaphylaxis cases revealed a higher incidence among children, women, and Whites. The main type of comorbidity was allergy, which underscores the importance of consulting an allergist when making immunization decisions.

Indication/contraindication for subsequent doses or the decision to switch platforms must be made after rigorous analysis of the facts and possible reaction mechanisms. Our data corroborate the need for robust surveillance and management of allergic reactions in vaccination programs.

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