Received: 14 June 2021 | Revised: 28 July 2021 | Accepted: 6 August 2021

DOI: 10.1111/pai.13631

SUPPLEMENT ARTICLE

WILEY

Hypersensitivity reactions to vaccines in children: from measles to SARS-CoV-2

Carlo Caffarelli[1] | Lucia Liotti[2] | Annamaria Bianchi[3] | Paolo Bottau[4] | Silvia Caimmi[5] | Giuseppe Crisafulli[6] | Fabrizio Franceschini[2] | Claudia Paglialunga[7] | Francesca Saretta[8] | Francesca Mori[9]

[1]Dipartimento Medicina e Chirurgia, Clinica Pediatrica, Università di Parma, Parma, Italy

[2]UOC Pediatria, Azienda Ospedaliero-Universitaria "Ospedali Riuniti", Ancona, Italy

[3]Pediatric Unit, San Camillo Forlanini Hospital, Roma, Italy

[4]UOC Pediatria e Neonatologia, Ospedale di Imola, Imola, Italy

[5]Pediatric Clinic, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy

[6]Dipartimento di Pediatria, UO Allergologia, Università di Messina, Messina, Italy

[7]UOC di Pediatria, Azienda Ospedaliera-Universitaria "Consorziale-Policlinico", Ospedale Pediatrico Giovanni XXIII, Bari, Italy

[8]Dipartimento Materno-Infantile Azienda Sanitaria, SC Pediatria, Ospedale Latisana-Palmanova, Universitaria Friuli Centrale, Udine, Italy

[9]Allergy Unit, Meyer Children's Hospital, Florence, Italy

Correspondence
Carlo Caffarelli, Clinica Pediatrica, Dipartimento Medicina e Chirurgia, Università di Parma, 43126 Parma, Italy,
Phone:+390521702207.
Email: carlo.caffarelli@gmail.com

Funding information
None.

Editor: Michele Miraglia Del Giudice

Abstract

Allergic individuals at risk for hypersensitivity reactions to measles vaccine marketed for a long time are well established. On the other hand, risk factors for hypersensitivity reactions to the new mRNA COVID-19 vaccines currently include a history of allergy, allergy to excipient of the vaccine, or hypersensitivity reactions to the first dose of COVID-19 vaccine. In the last two cases, the recipient should be assessed by an allergist before vaccination to share a decision on the choice of vaccination. Studies on skin testing accuracy and desensitization protocols to the COVID-19 vaccines and the efficacy of potential alternatives in patients with confirmed hypersensitivity reactions to the first COVID-19 vaccine are necessary to improve the safety of COVID-19 vaccines.

KEYWORDS
children, COVID-19, hypersensitivity reaction, influenza, measles, SARS-CoV-2, vaccine, yellow fever

1 | INTRODUCTION

Hypersensitivity reactions (HR) can be elicited by a vaccine component or, more rarely, by the immunizing antigen.[1] The incidence of HRs to vaccines ranges from 1 case per 50,000 doses to 1 per 1,000,000 doses.[2] Local reactions are the most frequent, benign, not at risk of severe systemic involvement, and do not contraindicate further doses.1 Systemic HRs to vaccines appearing within minutes to 4 h are defined as immediate, while delayed reactions, including urticaria-angioedema, maculopapular rashes, thrombocytopenia, Arthus reaction, and purpura, occur within hours or days after exposure.[1]

2 | SYSTEMIC HYPERSENSITIVITY REACTIONS TO EXCIPIENTS OF MEASLES VACCINE

Vaccination is still denied to many children because of false contraindications, for example, in egg-allergic children for measles-mumps-rubella-varicella (MMR/MMRV) vaccine or influenza vaccine. Nowadays, these vaccines are considered safe because of the very low amounts of ovalbumin (0–1 ng/ml) and the poor correlation between reactions after vaccination and egg allergy.[2] Therefore, no precaution is required for egg-allergic children who receive MMR/MMRV or influenza vaccine. In yellow fever (YF) vaccines, ovalbumin concentration is higher than in MMR/MMRV or influenza vaccines. Therefore, in egg-allergic patients, a skin prick test (1:10 and 1:1) and then an intradermal test (1:100) with YF vaccine should be performed, and when positive, the dose should be given through a graded protocol under medical supervision. Children with HRs to MMR/MMRV vaccine should be investigated for allergy to other components, including gelatin. Gelatin can trigger HR also in the Japanese encephalitis vaccine and YF vaccine.

Prick by prick to gelatin and gelatin-specific IgE (sIgE) detection should be performed in children with a history of possible gelatin allergy or a history of reactions to vaccines containing gelatin. Children with negative IgE tests should undergo an oral gelatin challenge. In case of gelatin hypersensitivity, a gelatin-free vaccine should be given. If unavailable, a graded-dose protocol allows getting the dose without harm. Gelatin contains galactose-α-1,3-galactose (α-gal). Case series of HRs to Zoster vaccine or concurrent injection of MMR, varicella, and diphtheria-tetanus-pertussis/oral polio (DTaP/IPV) vaccines in patients with α-gal allergy and low gelatin sIgE were reported. These vaccines should be cautiously used in patients with α-gal allergy. Single studies showed that HRs to DTaP/IPV in patients allergic to cow's milk might be related to milk traces in vaccines. So, patients with milk allergy should be monitored for 1 h after receiving such vaccines. HRs related to the presence of antibiotics in vaccines are not well demonstrated.[1] The patients with latex allergy should be vaccinated with latex-free equipment.

Key Messages

Gelatin and potentially α-gal allergy should be considered in children before measles-mumps-rubella-varicella (MMR/MMRV) vaccination. At present, risk factors for hypersensitivity reactions to the new mRNA COVID-19 vaccines are allergy history, allergy to vaccine components, and hypersensitivity reactions to the first COVID-19 vaccine. Diagnostic approaches need to be developed.

3 | COVID-19 VACCINES

Among hundreds of new COVID-19 vaccines, two adenovirus-vector COVID-19 vaccines, Oxford-AstraZeneca, Johnson & Johnson's Janssen, and two mRNA COVID-19 vaccines, Pfizer/BioNTech BNT162B2 and Moderna mRNA-1273, have been approved in Western countries.

During the post-marketing assessment, the Centers for Disease Control and Prevention (CDC) reported an anaphylaxis incidence of 11.1 cases per million doses after 1,893,360 first doses of the mRNA Pfizer-BioNTech COVID-19 vaccine in December 2020 and 2.5 cases per million doses after 4,041,396 first doses of Moderna COVID-19 vaccine in January 2021.[3,4] From December 2020 to January 2021, anaphylaxis incidence decreased to 4.7 per million doses for Pfizer-BioNTech COVID-19 vaccine, but it remained unchanged for Moderna vaccine.[5] In April 2021, 0.46 cases of anaphylaxis per million doses after 120,774,248 shots of the Pfizer-BioNTech vaccine were reported. The incidence of anaphylaxis seems low with the higher number of people vaccinated. However, a prospective study in 64,900 employees showed a higher incidence of anaphylaxis (0.027% with Pfizer-BioNTech 0.023% with Moderna), raising doubts on the CDC reporting system.[6] One anaphylaxis was confirmed with Johnson & Johnson's Janssen vaccine in 288,368 recipients.[7] Overall, most anaphylactic reactions to COVID-19 vaccines developed in females.[3-7] Anaphylaxis occurred in 86% of cases within 30 min after Pfizer-BioNTech vaccine and 90% of cases within 15 min after Moderna vaccine.[3,4] No fatality has been reported.[3-7]

Protocols for stratifying the risk for reactions to COVID-19 vaccines have been proposed.[8] Risk factors for HRs to mRNA COVID-19 vaccines are the history of allergy to foods, drugs, vaccines, dog, cat, hymenopter, and jellyfish venom, iodinated contrast media or gadolinium, allergy to vaccine excipients, polyethylene glycol (PEG)/polysorbate-80 (PS-80), and HR to the first dose of COVID-19 vaccine.[5,6] However, HRs may develop in recipients without risk factors, so COVID-19 vaccines should be administered in an equipped setting to treat anaphylaxis and with trained staff.[5,6] In patients with previous anaphylaxis, a history of allergy is not a contraindication. However, a protracted observation period of 30 min is recommended.

In individuals with HR to COVID-19 vaccine components or the first dose of COVID-19 vaccines, allergist and recipient should

discuss available options to make a shared decision on vaccination. Attention should be paid to some points. Vaccines are a successful healthcare intervention. Both mRNA COVID-19 vaccines contain PEG 2000, triggering IgE-mediated anaphylactic reaction to the first shot of the vaccines in allergic individuals.[9] Both adenovirus-vector COVID-19 vaccines contain PS-80 cross-reacting with PEG because of common antigenic determinants. PS-80 shows low clinical reactivity in humans. It has been suggested that a patient with a self-reported unproven history of allergy to drugs or industrial products containing PS-80 or PEG, especially if tolerated an influenza vaccine or an injected preparation containing PS-80, may receive the Janssen/Johnson & Johnson COVID-19 vaccine and be monitored for 30 min.[8] Prick tests and intradermal tests might be a diagnostic option for PEG allergy.[8] However, PEG skin testing can trigger allergic reactions, including anaphylaxis. Moreover, negative results of PEG/PS-80 skin tests cannot exclude significant allergy.[9] Therefore, when PEG allergy is suspected, clinicians and patients should achieve a shared decision on performing both skin tests inappropriate settings and, regardless of skin testing results, vaccines. Patients with PEG anaphylaxis should avoid COVID-19 vaccines with PEG/PS-80.[8] Currently, in patients who reacted to the first vaccine dose, the second dose should not be given. In these patients, the safety and accuracy of skin testing with COVID-19 vaccines or PEG/PS-80 needs to be clarified. Data are lacking on tolerance of future vaccination with different COVID-19 vaccines. The safety of the desensitization protocol is uncertain.

The most common local reactions to mRNA COVID-19 vaccines are delayed or very delayed, followed by local injection site reactions. Most patients with the first dose reactions tolerated the second dose without HRs even if a rash, commonly less severe, may recur.[10] Delayed injection site reactions are generally self-limited and appear not to recur with the second dose.

4 | CONCLUSIONS

Findings on the safety of the measles vaccine marketed for a long time show that individuals with gelatin allergy and potentially with α-gal allergy are at risk for allergic reactions. So far, risk factors for HRs to the new COVID-19 vaccines include the history of allergy, reactions to vaccine's excipients, or the first dose of COVID-19 vaccine. In the last two cases, the recipient should be assessed by an allergist. Risks and benefits should be considered before making a shared decision on testing and the next vaccination. Studies on skin testing accuracy and desensitization protocols to the COVID-19 vaccines and the efficacy of potential alternatives in patients with confirmed HR to a first COVID-19 vaccine are necessary to improve the safety of COVID-19 vaccines.

ACKNOWLEDGEMENTS

Open Access funding provided by Universita degli Studi di Parma within the CRUI-CARE Agreement. [Correction added on 11-May-2022, after first online publication: CRUI-CARE funding statement has been added.]

CONFLICT OF INTERESTS

Authors declared that they have no conflict of interests.

AUTHOR CONTRIBUTIONS

Carlo Caffarelli involved in conceptualization writing the review, and editing. **Lucia Liotti, Annamaria Bianchi, Paolo Bottau, Silvia Caimmi, Giuseppe Crisafulli, Fabrizio Franceschini, Claudia Paglialunga, and Francesca Saretta** involved in writing the review and editing. **Francesca Mori** involved in conceptualization, supervision, writing the review, and editing.

ORCID

Carlo Caffarelli https://orcid.org/0000-0001-7710-6995
Lucia Liotti https://orcid.org/0000-0002-5699-2796
Silvia Caimmi https://orcid.org/0000-0003-0515-524X
Giuseppe Crisafulli https://orcid.org/0000-0001-5602-8668
Francesca Saretta https://orcid.org/0000-0001-9443-5483
Francesca Mori https://orcid.org/0000-0001-7483-0128

REFERENCES

1. Franceschini F, Bottau P, Caimmi S, et al. Evaluating children with suspected allergic reactions to vaccines for infectious diseases. *Allergy Asthma Proc*. 2018;39:177-183.
2. Sarti L, Lezmi G, Mori F, et al. Diagnosis and management of hypersensitivity reaction to vaccines. *Expert Rev Clin Immunol*. 2020;16:883-896.
3. CDC. COVID-19 Response Team Food and Drug Administration. Allergic reactions including anaphylaxis after receipt of the first dose of Pfizer-BioNTechCOVID-19 vaccine—United States, December 14-23. *MMWR Morb Mortal Wkly Rep*. 2021;70:46-51.
4. CDC. COVID-19 Response Team Food and Drug Administration. Allergic reactions including anaphylaxis after receipt of the first dose of Moderna COVID-19 vaccine - United States, December 21, 2020-January 10, 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70:125-129.
5. Shimabukuro TT, Cole M, Su JR. Reports of anaphylaxis after receipt of mRNA COVID-19 Vaccines in the US—December 14, 2020–January 18, 2021. *JAMA*. 2021;325:1101-1102.
6. Blumenthal KG, Robinson LB, Camargo CA Jr, et al. Acute allergic reactions to mRNA COVID-19 Vaccines. *JAMA*. 2021;325:1562-1565.
7. Takuva S, Takalani A, Garrett N, et al. Thromboembolic events in the South African Ad26.COV2.S vaccine study. *New Engl J Med*. 2021;385(6):570-571. https://doi.org/10.1056/NEJMc2107920.
8. Banerji A, Wolfson AR, Wickner PG, et al. COVID-19 vaccination in patients with reported allergic reactions: Updated evidence and suggested approach. *J Allergy Clin Immunol Pract*. 2021;9:2135-2138.
9. Sellaturay P, Nasser S, Islam S, et al. Polyethylene glycol (PEG) is a cause of anaphylaxis to the Pfizer/BioNTech mRNA COVID-19 vaccine. *Clin Exp Allergy*. 2021;51:861-863.
10. McMahon DE, Amerson E, Rosenbach M, et al. Cutaneous reactions reported after Moderna and Pfizer COVID-19 vaccination: A registry-based study of 414 cases. *J Am Acad Dermatol*. 2021;85:46-55.

How to cite this article: Caffarelli C, Liotti L, Bianchi A, et al. Hypersensitivity reactions to vaccines in children: from measles to SARS-CoV-2. *Pediatr Allergy Immunol*. 2022;33(Suppl. 27):58–60. https://doi.org/10.1111/pai.13631