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Safety of MMR vaccination evaluated in children with food and gelatin allergy in Iran

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Abstract

Background Vaccination is essential for building immunity across various populations, and governments consider it a cornerstone of public health. This study aims to investigate the prevalence of gelatin allergy among infants with food allergies who have received previous vaccinations and were referred to this center for Measles-Mumps-Rubella (M.M.R.) vaccine administration.

Methods This study, conducted at the Immunology Children's Medical Center (CMC) Hospital in Tehran, Iran, aimed to explore the prevalence of gelatin allergy in infants with food allergies undergoing M.M.R vaccine injections. The cross-sectional study included children diagnosed with food allergies, confirmed by allergy specialists, and who provided consent. The methodology involved different tests based on the severity of food allergies. For children with mild food allergies, a gelatin prick test preceded MMR vaccination. Those with severe food allergies or a history of vaccine reactions underwent skin prick tests with various gelatins and the MMR vaccine. Positive results led to graded dose vaccinations. Data, including clinical questions, were recorded using a standard vaccination questionnaire.

Results Results from 163 evaluated children (average age: 16.85 months) revealed that 8% were allergic to gelatin. Notably, all gelatin-allergic patients had a positive family history of atopia. A significant association existed between gelatin allergy and a positive intradermal vaccine test. No significant relationships were found with gender, age, food allergens, infant milk type, antihistamine use, blood history, or product use.

Conclusion The study concludes that a gelatin-free vaccine is preferable for allergic patients. In cases where such a vaccine isn't available, a skin test with the vaccine is recommended before full-dose administration. The findings emphasize the importance of considering family history and intradermal vaccine tests in managing gelatin allergies during vaccinations.

Keywords Allergy, Gelatin, MMR vaccination

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Introduction

Food allergies are an important health issue, especially in children, and are increasing worldwide [1, 2]. Among the various allergens, attention has been drawn to bovine gelatin because of its possible association with food allergy in the digestive tract [3, 4]. Gelatin is widely used in foods, pharmaceuticals, and vaccines, including Measles, Mumps, and Rubella (M.M.R) vaccines [5]. However, there have been concerns about its potential to trigger gelatin allergies, especially in individuals who already have food allergies [6, 7].

In recent years, the safety and efficacy of vaccines, including the M.M.R vaccine, have been the subject of considerable debate [6, 8]. Despite the important role of vaccination in the prevention of infectious diseases, adverse events, including allergies, have been reported to stick to administration. This has led to increased awareness of potential allergens, such as gelatin in vaccines.

Iran, like many other countries, has a high prevalence of food allergies among children [9–12]. Food allergy prevalence in children in Iran is reported to be high, with available data indicating a range of approximately 1.8–7.5% in infants under one year old, and around 0.49–0.6% in adults. Additionally, studies suggest that food allergies affect about 6–10% of the population across different communities, with specific allergens such as cow's milk, eggs, and peanuts showing significant sensitization rates among children [13, 14].

Understanding the frequency of gelatin allergy in children with existing food allergies and its potential association with M.M.R vaccination is essential for ensuring the safety and efficacy of immunization programs. Therefore, this study aims to investigate the frequency of gelatin allergy in children with food allergies and its relationship with M.M.R vaccination specifically in the Iranian population.

Several studies have explored the potential association between gelatin allergies and adverse reactions following vaccination, particularly with the M.M.R vaccine [8, 15–17]. Notably, alpha-gal syndrome (AGS) has emerged as a significant factor in understanding these reactions [8]. AGS is a serious food allergy to red meat that is triggered by the oligosaccharide galactose-α-1,3-galactose (alpha-gal), which is present in most mammals [18, 19]. This condition typically arises after individuals are bitten by certain types of ticks, leading to sensitization to alpha-gal and subsequent allergic reactions upon exposure to mammalian products, including gelatin derived from cows or pigs [20–22].

Nakayama et al. (2019) reported complications of anaphylaxis following vaccination, highlighting gelatin allergies as one of the contributing factors [23]. Similarly, de Silva et al. (2017) identified positive reactions to cow gelatin and other allergenic components in immediate allergies to vaccines containing cow or pig content [24]. The presence of cow gelatin in vaccines has been linked to acute reactions in patients with alpha-gal sensitivity [25]. In these patients, symptoms can occur two to six hours after exposure to alpha-gal-containing products, which complicates diagnosis and management [26]. Patients with AGS often experience a range of symptoms from mild hives and gastrointestinal issues to severe anaphylaxis, which underscores the importance of recognizing this sensitivity when evaluating adverse vaccine reactions [20]. Understanding the correlation between alpha-gal sensitivity and acute allergic reactions is crucial for healthcare providers when assessing patients who report adverse events following vaccination [27, 28].

Schmidle, Paul, et al. (2017) observed acute reactions in alpha-gal-sensitive patients following MMR and Zoster vaccines, which were attributed to the content of cow gelatin. This suggests that gelatin allergies may play a role in adverse reactions to vaccines [8].

In Brazil, Freitas et al. (2013) conducted a study on patients with immediate reactions to vaccines, finding that symptoms such as conjunctivitis, periorbital swelling, hives, fever, and facial swelling were reported. Notably, no fatalities were reported, and the onset of symptoms occurred within an average of 42 min after vaccination [29].

Eseverri et al. (2023) conducted a study in Spain that categorized sensitivity reactions following MMR vaccination into six distinct categories based on their potential causes. These categories include: 1- Infectious agents or their products, 2- Auxiliary materials, 3- Stabilizers (e.g., gelatin), 4- Preservatives (e.g., thiomersal), 5- Antibiotics (e.g., neomycin), 6- Biological media (e.g., chicken fetal cell cultures). It is important to clarify that these categories represent different types of components that may be associated with adverse reactions, rather than implying that all six agents directly caused adverse events in every case [30]. This classification underscores the diverse range of potential allergens and vaccine components that could trigger sensitivity reactions in individuals, highlighting the complexity of vaccine-related allergic responses.

In the United States, Pool et al. (2002) reported anaphylaxis reactions following M.M.R vaccine administration at a rate of approximately 1.8 per million injectable doses. It is important to clarify that the M.M.R vaccine does contain gelatin, which is used as a stabilizer. This component has been associated with allergic reactions in some individuals [6]. This indicates the importance of monitoring and understanding potential allergic reactions associated with vaccines.

Patja et al. (2001) conducted a study involving 36 patients with anaphylaxis following the M.M.R vaccine. Although the specific details of the study were not

mentioned, it suggests that anaphylactic reactions to the MMR vaccine have been documented in a subset of individuals [31].

These studies collectively highlight the potential link between gelatin allergies and adverse reactions following M.M.R vaccination. Understanding the frequency and nature of these reactions is crucial for ensuring the safety and efficacy of immunization programs, particularly in populations with a high prevalence of food allergies like Iran.

We believe the results of this study provide valuable insights into the prevalence of gelatin allergy among children with food allergies in Iran. Additionally, it will shed light on the potential association between gelatin allergy and M.M.R vaccination, and help further the discussion on vaccine safety The findings may have implications for vaccine development and guidelines to help health professionals make informed decisions about vaccination strategies for children with food allergies. On the whole, investigation of the frequency of gelatin allergy in children with food allergies and the association with M.M.R vaccination is important to ensure vaccination people protection measures are safe and effective, especially in countries like Iran where food allergy is common.

Method

This is a cross-sectional study conducted at the immunology clinic of the Children's Medical Center (CMC) Hospital in Tehran, Iran. The study aimed to investigate the prevalence of gelatin allergy (i.e. mammalian gelatin) in children with food allergies, taking into account various factors such as gender, age, type of food allergens consumed, family history of atopy, type of milk consumption in infants, results of previous diagnostic tests, response to the prick test during the visit, previous medical history, history of gelatin consumption in infants and mothers, history of atopy in the child, history of antihistamine use, history of blood and blood product consumption, and history of sensitivity to previous vaccinations. The study period spanned from March 21, 2021, to August 23, 2022.

Table 1 Categorizing food allergies from mild to severe

Severity Grade	Description	Symptoms/Criteria
Grade 1	Mild reactions	Isolated local reactions (e.g., urticaria, localized swelling)
		Minimal gastrointestinal symptoms (e.g., mild nausea, stomach cramps)
Grade 2	Moderate reactions	Symptoms affecting two or more organ systems (e.g., moderate skin reactions with gastrointestinal symptoms)
		Persistent abdominal pain, vomiting, or diarrhea
Grade 3	Severe reactions	Significant respiratory distress (e.g., wheezing, stridor)
		Cardiovascular symptoms (e.g., hypotension, tachycardia)
Grade 4–5	Life-threatening reactions	Anaphylaxis requiring emergency intervention

Children who were referred to the immunology clinic at CMC Hospital during this period due to food allergies and had their diagnosis confirmed by an allergy and clinical immunology specialist were included in the study after obtaining consent. Patients with a history of mild food allergy were permitted to receive the M.M.R. vaccine after undergoing bovine and porcine gelatin prick tests with positive and negative controls. If no suspected allergic or anaphylactic symptoms were observed, they were discharged one hour later.

We utilized the TRESIVAC® vaccine produced by the Serum Institute of India. The vaccine is a live attenuated formulation that contains the following ingredients:

- Measles Virus: Edmonston-Zagreb strain.
- Mumps Virus: Jeryl Lynn strain.
- Rubella Virus: Wistar RA 27/3 strain.

Each dose, when reconstituted, contains not less than:

- 1000 CCID50 of Measles virus.
- 5000 CCID50 of Mumps virus.
- 1000 CCID50 of Rubella virus.

Additionally, the vaccine includes excipients such as gelatin (partially hydrolyzed), D-sorbitol, L-histidine, and others.

However, for patients with a history of severe food allergy or a previous adverse reaction to the vaccine, additional tests were conducted. This included skin prick tests with bovine, porcine, and gelatin, as well as the M.M.R. vaccine itself (as determined by the allergist's decision). If these tests yielded positive results and confirmed the allergy, the child was admitted to the hospital for graded dose vaccination. Table 1 summarizes the classification of food allergies based on severity, providing clear descriptions and examples of symptoms associated with each grade.

Skin tests

In our study, skin tests were conducted to evaluate the presence of gelatin allergy in children with food allergies prior to administering the Measles-Mumps-Rubella (M.M.R.) vaccination. The following methods were employed for skin testing:

Skin Prick testing

- A solution containing mammalian gelatin was prepared at concentrations of 1 mg/mL (1:1000 dilution) for the prick test.
- Control solutions included histamine (positive control) at a concentration of 10 mg/mL and glycerinated saline (negative control).
- The allergens and controls were applied to the skin at least 2 cm apart, and a specialized device was used to scratch the skin, allowing the allergen to penetrate the outer layer.
- The test results were read after 15 to 20 min, with a positive reaction indicated by the formation of a wheal or hive measuring at least 5 mm in diameter.

Intradermal testing

- For intradermal testing, a higher concentration of gelatin was used, typically around 1:100 or 1:500 dilutions.
- Each allergen was injected intradermally to create a wheal, similar to conducting a tuberculin test.
- The results were assessed after 15 to 20 min, with a positive result defined as a wheal larger than the negative control.
- These testing methods were performed in accordance with established guidelines for allergy testing, ensuring that appropriate precautions were taken to monitor for any adverse reactions during and after the tests.

It is important to note that the recommendation for performing skin tests with the MMR vaccine primarily applies to individuals with specific risk factors associated with gelatin allergy, such as a history of anaphylactic reactions to components of the vaccine or significant food allergies. Routine skin testing is not recommended for the general population receiving the MMR vaccine. The study period spanned from March 21, 2021, to August 23, 2022.

Data collection and analyzed

Data collection involved administering a standard vaccination questionnaire and recording clinical questions from the parents. Written consent was obtained, and the phone numbers and information regarding previous and new allergy tests were documented. All collected information was then entered into SPSS statistical software for analysis.

Since the initial community size was unknown, as it was uncertain how many patients would come for vaccination throughout the research period, a sample size of 120 individuals was estimated based on statistical research methods for unknown populations. However, efforts were made to include more than 120 individuals, resulting in a statistical population of 163 participants for this study.

Quantitative variables were reported using mean and standard deviation, while categorical variables were reported using frequency and percentage. For comparing quantitative variables, the T-test was employed for normally distributed variables, while appropriate non-parametric tests were used for non-normally distributed variables. The relationship between qualitative variables was assessed using the Chi-squared test or Fisher's exact test when necessary. All analyses were conducted with a significance level of $p = 0.05$ using SPSS software.

Result

Demographic information of participants

A total of 163 children were included in this research study. The average age of the children was 16.85 months. Out of the 163 children, 66 were girls and 97 were boys. Among them, 31 were born through natural delivery, while 132 were born via cesarean delivery. In terms of gravidity, 111 children were from gravid 1 pregnancies, 40 were from gravid 2 pregnancies, and 12 were from pregnancies with a gravidity of more than 2.

Regarding feeding methods, 83 children did not use formula, while 80 children were fed with formula. Among the children who consumed powdered milk, 33 used amino acid powdered milk, 30 used hydrolyzed powdered milk, 7 used hypoallergenic powdered milk, and 10 used regular powdered milk.

The introduction of supplementary feeding varied among the children, with 92 children starting after 6 months of age and 71 children starting between 4 and 6 months of age.

A total of 140 children had a history of taking antihistamines, while 6 children had a history of receiving blood product injections (Blood product injections refer to the administration of therapeutic substances derived from human blood, which can include various components used to treat specific medical conditions). All the children included in the study were vaccinated with the M.M.R vaccine. Out of these, 33 children had graded vaccination, and 130 children had complete vaccination. None of the children had received any vaccination in the month prior to the study.

Among the children, 143 had a positive history of atopy, while 91 children had a positive family history of atopy. Out of the children with a history of atopy, 2 children (1.4%) had eczema, 75 had eczema, 43 had eczema and asthma, and 23 had eczema and allergic rhinitis.

Regarding allergy testing, 17 children had not undergone any allergy tests, 11 children had completed the RIDA test (an enzyme immunoassay used to detect

allergen-specific immunoglobulin E (IgE) antibodies in serum, allowing for the simultaneous assessment of multiple allergens [32]), and 135 children had undergone the skin-prick test (SPT). Among these, 134 children were diagnosed with food allergies, and 29 had multiple allergies. Specifically, the allergy histories included 1 child with a nut allergy, 1 child with a wheat allergy, 52 children with an egg allergy, 6 children with a milk allergy, and 103 children with multiple allergies. Notably, 7 children had a positive prick test; these tests were primarily conducted for common food allergens such as eggs, milk, wheat, and nuts. Additionally, given the context of our study on gelatin allergies, it is important to note that some of these children may have also reacted positively to gelatin or gelatin-containing products.

Thirteen children were found to be allergic to gelatin, out of which 8 had pork allergy, 2 had cow allergy, and 3 had both allergies. Thirty-three children had positive intradermal tests for vaccine allergy. Among the remaining 80 children, neither the mother nor the child had a history of consuming gelatin. In 55 children, only the mother had a history of consuming gelatin, while in 1 patient only the child had a history of consuming gelatin, and in 27 patients, both the mother and the child had a history of consuming gelatin.

The type of allergy observed in the children varied, with 54 children having delayed allergies, 18 children experiencing anaphylaxis, and 61 children having urticaria.

Statistical analysis of the results

There was no statistically significant difference in the prevalence of gelatin allergy between boys and girls ($p = 0.076$). Similarly, there was no statistically significant relationship between gelatin allergy and delivery type ($p = 0.465$). However, there was a significant relationship between the type of allergic reaction and gelatin allergy ($p = 0.02$), with urticaria being the most common allergic reaction in children with gelatin allergy.

The average age of children allergic to gelatin was found to be 21.93 months (+5.08), whereas the average age of those not allergic to gelatin was 11.79 months (+0.96). However, this difference in age was not statistically significant ($p = 0.14$). None of the children allergic to gelatin were found to be allergic to food allergens, but this difference was also not statistically significant ($p = 0.084$).

Interestingly, all children allergic to gelatin had a positive family history of atopy, indicating a significant relationship between gelatin allergy and a positive family history of atopy ($p = 0.001$). Additionally, all children allergic to gelatin had a personal history of atopy, but no significant relationship was found between gelatin allergy and a positive personal history of atopy ($p = 0.372$).

There was no significant relationship between gelatin allergy and the type of milk consumed (breast milk or formula) ($p = 0.57$), as well as no statistically significant relationship between gelatin allergy and a history of allergy to previous vaccines ($p = 0.226$). Similarly, there was no significant relationship between gelatin allergy and allergy in the vaccine prick test ($p = 0.098$).

Furthermore, no significant relationship was found between gelatin allergy and a history of gelatin consumption in the child or mother ($p = 0.975$), or a history of antihistamine use ($p = 0.218$). None of the children allergic to gelatin had a history of injecting blood products, and there was no significant relationship between gelatin allergy and a history of injecting blood products ($p = 1.0$).

Lastly, 12 children with a positive gelatin allergy also had a positive intradermal allergy test to the vaccine, indicating a significant relationship between gelatin allergy and allergy in the intradermal vaccine test ($p < 0.0001$) (Table 2).

Discussion

Gelatin is added to vaccines as a preservative and stabilizer to protect the vaccine from adverse conditions during storage and to keep the vaccine safe and effective. The amount of gelatin in the vaccine varies between 15 micrograms and more than 15,500 micrograms per vaccine dose [33, 34]. The highest amount of gelatin is found in M.M.R, rabies, varicella-zoster, oral typhoid and yellow fever vaccines, and smaller amounts up to 2000 micrograms per dose are found in diphtheria-tetanus-pertussis vaccine and influenza vaccine. Severe allergic reactions to gelatin have been described for M.M.R [33, 35], varicella [36–38], yellow fever [39], and Japanese encephalitis vaccines. In the past, Japanese studies reported high rates of positive gelatin-specific IgE (86–100%) in patients with anaphylactic reactions to M.M.R and chickenpox vaccines. In contrast, US and European studies showed a lower rate of positive specific IgE (14–28%) in the same patients [31, 33]. The inconsistency between the results can be attributed to the different types of gelatin used in the vaccine. In the 1990s, low molecular weight highly hydrolyzed porcine gelatin was added as a stabilizer to M.M.R vaccines in the United States. However, semi-hydrolyzed bovine gelatin with a small amount of high molecular weight was used in Japan in those years. A second explanation for the high incidence of gelatin allergy in Japan could be the existence of a genetic predisposition [40]. HLA DR 9 type is common in Japanese patients [41]. Hydrolyzed gelatin was removed from the DTP vaccine in 1999. After removing gelatin from vaccines or changing the gelatin to less sensitive highly hydrolyzed porcine gelatin, vaccine-induced anaphylaxis was significantly reduced in Japan [40]. Children with allergies to red meat (beef, pork, lamb) or milk are at increased risk of vaccine reactions due to gelatin [42]. These patients have positive specific IgE levels for beef, lamb, pork and milk. Although

Table 2 Demographic and clinical factors associated with gelatin allergy in children undergoing Measles-Mumps-Rubella vaccination

		Gender				**Total**	**P-value**
		Female		***Male***			
Gelatin Allergy	*No*	64		86		150	0.076
	Yes	2		11		13	
		Gelatin Allergy					
		No		*Yes*			
Delivery	*NVD*	30		1		31	0.465
	CS	120		12		132	
		Gelatin Allergy					
		No		*Yes*			
Type of the Allergy	*Delayed*	83		1		84	0.02
	CS	14		4		18	
	Anaphylaxsis	53		8		61	
		Familiy Atopy Hx					
		No		*Yes*			
Gelatin Allergy	*No*	72		78		150	0.001
	Yes	0		13		13	
		Type of Milk					
		Formula		*Breast Milk*			
Gelatin Allergy	*No*	75		75		150	0.566
	Yes	5		8		13	
		History of allergic reaction to previous vaccination					
		No		*Yes*			
Gelatin Allergy	*No*	128		22		150	0.226
	Yes	9		4		13	
		Prick Test Allergy Status					
		No		*Yes*			
Gelatin Allergy	*No*	145		5		150	0.098
	Yes	11		2		13	
		History of the Gelatine use					
		No one used	*Mother has used*	*Child has used*	*Both mother and child have used*		
Gelatin Allergy	*No*	74	50	1	25	150	0.975
	Yes	6	5	0	2	13	
		Anti-Histamine use History					
		No		*Yes*			
Gelatin Allergy	*No*	23		127		150	0.218
	Yes	0		13		13	
		Blood Transfusion History					
		No		*Yes*			
Gelatin Allergy	*No*	144		6		150	1.000
	Yes	13		0		13	
		Intradermal Allergy Test					
		No		*Yes*			
Gelatin Allergy	*No*	129		21		150	< 0.0001
	Yes	1		12		13	

in the present study, there was no significant relationship between gelatin allergy and the type of milk consumed or milk allergy. In fact, none of the 6 patients who were allergic to milk in this study showed an allergy to gelatin. All children with a previous reaction to foods or vaccines containing gelatin should undergo allergy testing. In the investigations conducted in this study, there was no significant relationship between gelatin allergy and previous allergy to food allergens.

Several studies have highlighted gelatin allergies as contributing factors to complications such as anaphylaxis [23, 24]. Moreover, the presence of cow gelatin in vaccines has been linked to acute reactions in patients with alpha-gal sensitivity [8]. These findings emphasize the

need to understand and monitor potential allergic reactions associated with vaccines.

The results of this study further contribute to our understanding of gelatin allergies and their relationship with specific factors. Notably, there was no significant difference in the prevalence of gelatin allergy between boys and girls, indicating that gender may not be a determining factor in gelatin allergies ($p = 0.076$). Similarly, the type of delivery (vaginal or cesarean) did not show a significant relationship with gelatin allergy ($p = 0.465$).

However, an important finding is the significant relationship between the type of allergic reaction and gelatin allergy ($p = 0.02$). Urticaria was the most common allergic reaction observed in children with gelatin allergy. This suggests that gelatin may be a trigger for urticaria in susceptible individuals. Further investigation into the mechanisms underlying this relationship could provide valuable insights into the immunological response to gelatin allergens.

Although the average age of children allergic to gelatin was higher than those not allergic to gelatin, this difference was not statistically significant ($p = 0.14$). This indicates that age may not be a determining factor in the development of gelatin allergy. Additionally, none of the children allergic to gelatin were found to be allergic to food allergens, although this difference was not statistically significant ($p = 0.084$). This suggests that gelatin allergy may be independent of other food allergies, highlighting the need for specific attention to gelatin as an allergenic component. That while some studies indicate a link between gelatin allergy and other food allergies (such as red meat and milk) [42]. Further research is necessary to fully understand the relationship between gelatin allergy and other food allergies, especially considering the complexities involved in allergic responses.

An interesting finding is the significant relationship between gelatin allergy and a positive family history of atopy ($p = 0.001$). This highlights a potential genetic predisposition to gelatin allergy, indicating that individuals with a family history of atopy may be at higher risk of developing gelatin allergies. However, no significant relationship was found between gelatin allergy and a positive personal history of atopy ($p = 0.372$). This suggests that while familial factors may play a role, individual factors may also contribute to the development of gelatin allergy.

Other factors examined in this study, such as the type of milk consumed, history of allergy to previous vaccines, and a history of gelatin consumption in the child or mother, did not show a significant relationship with gelatin allergy. This implies that these factors may not be major contributors to the development of gelatin allergies in children.

An important finding is the significant relationship between gelatin allergy and allergy in the intradermal vaccine test ($p < 0.0001$). This indicates that individuals with gelatin allergies may exhibit a positive response to intradermal allergy tests, suggesting a specific immunological sensitivity to gelatin allergens in the vaccine.

It is important to note that this study has some limitations. The sample size may not be representative of the entire population, and the study design may have inherent biases. Additionally, the study did not investigate the specific mechanisms underlying gelatin allergies, which could provide further insights into the immunological response.

Finally, this study adds to the existing literature on gelatin allergies and their potential association with adverse reactions following vaccination. The results indicate that gelatin allergy may be related to the type of allergic reaction, positive family history of atopy, and positive intradermal allergy test to the vaccine. Further research is needed to explore the underlying mechanisms and to develop strategies for identifying individuals at risk of gelatin allergies. Understanding the relationship between gelatin allergies and adverse vaccine reactions is crucial for ensuring the safety and efficacy of immunization programs, particularly in populations with a high prevalence of food allergies.

Conclusion

In this study, we analyzed 163 patients and found that 13 patients (8%) had confirmed gelatin allergy. Our findings revealed a significant association between gelatin allergy and positive family history of atopy, and skin test but we did not find gelatin allergy gender, age, specific food allergy, type of infant milk, or antihistamines -We did not find any significant correlation between factors such as history of use, history of blood and blood products.

Considering the presence of gelatin in vaccines, it is important to prioritize gelatin-free vaccines for patients with gelatin allergy. The gelatin content in vaccines can range from 500 g/0.5 ml to 12 mg/0.5 ml, which is not negligible for individuals with gelatin sensitivity. In cases where a gelatin-free vaccine is not available and vaccination is necessary, we recommend conducting a skin test with the specific vaccine prior to administration. Based on the results of the skin test, children with negative reactions can safely receive the full dose of the vaccine, while those with positive reactions should receive the vaccine in graded doses to ensure their safety.

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Author contributions
M.SH. was responsible for the study conception and design. At the same time, M.M. supervised the whole study. M.SH. prepared the first draft of the manuscript and revised the manuscript. M.K., F.A., M.G., and M. Ma did the analysis of the results, made critical revisions to the paper for important

intellectual content, and supervised the study. All authors have read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
All provider participants who took part in the standard vaccination questionnaire provided informed consent. We emphasized to the participants that their information would be kept confidential during the data collection phase to ensure their privacy was respected. It is important to note that our study involved young children, and therefore, we obtained a letter of consent from their parents or legal guardians. The study protocol was reviewed and approved by the Ethics Committee of Tehran Medical University, Tehran, Iran (ID: IR.TUMS.CHMC.REC.1400.236). Additionally, all methods employed in the study adhered to the relevant guidelines and regulations, including the Declaration of Helsinki.

Competing interests
The authors declare no competing interests.

Consent for publication
Not applicable.

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References

1. Prescott SL, Pawankar R, Allen KJ, Campbell DE, Sinn JK, Fiocchi A, et al. A global survey of changing patterns of food allergy burden in children. World Allergy Organ J. 2013;6:1–12.
2. Loh W, Tang ML. The epidemiology of food allergy in the global context. Int J Environ Res Public Health. 2018;15(9):2043.
3. Ebo D, Stevens W. IgE-mediated food allergy–extensive review of the literature. Acta Clin Belg. 2001;56(4):234–47.
4. Tedner SG, Asarnoj A, Thulin H, Westman M, Konradsen JR, Nilsson C. Food allergy and hypersensitivity reactions in children and adults—A review. J Intern Med. 2022;291(3):283–302.
5. Kelso JM. The gelatin story. J Allergy Clin Immunol. 1999;103(2):200–2.
6. Pool V, Braun MM, Kelso JM, Mootrey G, Chen RT, Yunginger JW, et al. Prevalence of anti-gelatin IgE antibodies in people with anaphylaxis after measles-mumps-rubella vaccine in the united States. Pediatrics. 2002;110(6):e71–e.
7. Kelso JM, Jones R, Yunginger J. Anaphylaxis to measles, mumps, and Rubella vaccine mediated by IgE to gelatin. J Allergy Clin Immunol. 1993;91(4):867–72.
8. Schmidle P, Mehlich J, Brockow K, Darsow U, Biedermann T, Eberlein B. Gelatin-containing vaccines for varicella, Zoster, measles, mumps, and Rubella induce basophil activation in patients with alpha-gal syndrome. Int Arch Allergy Immunol. 2021;182(8):716–22.
9. Kalmarzi R, Ataee P, Homagostar G, Tagik M, Ghaderi E, Kooti W. Evaluation of the frequency of food allergens based on skin Prick test in children in Kurdistan Province–Iran. Allergol Immunopathol. 2018;46(1):45–57.
10. Fathi SM, Tavakol M, Rezaei N, Movahedi M, Aghamohammadi A, Shariat M et al. Impact of IgE-mediated food allergy on parental quality of life in Iranian patients. Iran J Allergy Asthma Immunol. 2016:372–80.
11. Nabavi M, Hoseinzadeh Y, Ghorbani R. Prevalence of food allergy in asthmatic children under 18 years of age in Semnan-Iran in 2007–2008. Koomesh. 2010;11(3).
12. Varasteh AR, Fereidouni M, Shakeri MT, Vahedi F, Abolhasani A, Afsharian MS, et al. Prevalence of allergic disorders among the population in the City of Mashhad, Northeast Iran. J Public Health. 2009;17:107–12.
13. Shoormasti RS, Sabetkish N, Kazemnejad A, Vahabi N, Fazlollahi M, Pourpak Z. Are the most common food allergens in an Iranian atopic population compatible with worldwide reports? A systemic review and meta-analysis with molecular classification of frequent allergens. Allergol Immunopathol. 2019;47(6):604–18.
14. Fazel M, Azizi A, Daniar A, Tabatabaei F-S, Kalantari A. Epidemiology of food allergies in children with asthma in Gorgan, Northern Iran: a Cross-Sectional Population-Based study. Int J Pediatr. 2023;11(2):17397–404.
15. Pool V, Braun MM, Kelso JM, Mootrey G, Chen RT, Yunginger JW, et al. Prevalence of anti-gelatin IgE antibodies in people with anaphylaxis after measles-mumps Rubella vaccine in the united States. Pediatrics. 2002;110(6):e71. https://doi.org/10.1542/peds.110.6.e71. Epub 2002/11/29.
16. McNeil MM, DeStefano F. Vaccine-associated hypersensitivity. The Journal of allergy and clinical immunology. 2018;141(2):463–72. Epub 2018/02/08. https://doi.org/10.1016/j.jaci.2017.12.971. PubMed PMID: 29413255; PubMed Central PMCID: PMCPMC6602527.
17. Kumagai T, Yamanaka T, Wataya Y, Saito A, Okui T, Yano S, et al. A strong association between HLA-DR9 and gelatin allergy in the Japanese population. Vaccine. 2001;19(23):3273–6. https://doi.org/10.1016/S0264-410X(00)00555-7.
18. Stone CA, Hemler JA, Commins SP, Schuyler AJ, Phillips EJ, Peebles RS, et al. Anaphylaxis after Zoster vaccine: implicating alpha-gal allergy as a possible mechanism. J Allergy Clin Immunol. 2017;139(5):1710–3. e2.
19. Kiewiet MBG, Apostolovic D, Starkhammar M, Grundström J, Hamsten C, van Hage M. Clinical and serological characterization of the α-Gal Syndrome—Importance of atopy for symptom severity in a European cohort. J Allergy Clin Immunology: Pract. 2020;8(6):2027–e342. https://doi.org/10.1016/j.jaip.2020.02.016.
20. Platts-Mills TAE, Li RC, Keshavarz B, Smith AR, Wilson JM. Diagnosis and Management of Patients with the α-Gal Syndrome. The journal of allergy and clinical immunology In practice. 2020;8(1):15–23.e1. Epub 2019/10/01. https://doi.org/10.1016/j.jaip.2019.09.017. PubMed PMID: 31568928; PubMed Central PMCID: PMCPMC6980324.
21. Commins SP. Diagnosis & management of alpha-gal syndrome: lessons from 2,500 patients. Expert Rev Clin Immunol. 2020;16(7):667–77.
22. Reddy S, Yi L, Shields B, Platts-Mills T, Wilson J, Flowers RH. Alpha-gal syndrome: a review for the dermatologist. J Am Acad Dermatol. 2023;89(4):750–7.
23. Nakayama T. Causal relationship between immunological responses and adverse reactions following vaccination. Vaccine. 2019;37(2):366–71.
24. de Silva R, Dasanayake W, Wickramasinhe G, Karunatilake C, Weerasinghe N, Gunasekera P, et al. Sensitization to bovine serum albumin as a possible cause of allergic reactions to vaccines. Vaccine. 2017;35(11):1494–500.
25. Stone CA Jr., Commins SP, Choudhary S, Vethody C, Heavrin JL, Wingerter J et al. Anaphylaxis after vaccination in a pediatric patient: further implicating alpha-gal allergy. The journal of allergy and clinical immunology In practice. 2019;7(1):322-4.e2. Epub 2018/06/19. doi: 10.1016/j.jaip.2018.06.005. PubMed PMID: 29913263; PubMed Central PMCID: PMCPMC6295282.
26. Commins SP. Diagnosis & management of alpha-gal syndrome: lessons from 2,500 patients. Expert Rev Clin Immunol. 2020;16(7):667–77. https://doi.org/10.1080/1744666x.2020.1782745. Epub 2020/06/24.
27. Macdougall JD, Thomas KO, Iweala OI. The meat of the matter: Understanding and managing Alpha-Gal syndrome. ImmunoTargets Therapy. 2022;11:37–54. https://doi.org/10.2147/itt.s276872. Epub 2022/09/23.
28. Dreskin SC, Halsey NA, Kelso JM, Wood RA, Hummell DS, Edwards KM, et al. International consensus (ICON): allergic reactions to vaccines. World Allergy Organ J. 2016;9(1):32. https://doi.org/10.1186/s40413-016-0120-5. Epub 2016/09/30.
29. Freitas DR, Moura E, Araújo G, Cardoso A, Scheidt P, Ferraz E, et al. Investigation of an outbreak of hypersensitivity-type reactions during the 2004 National measles-mumps-rubella vaccination campaign in Brazil. Vaccine. 2013;31(6):950–4.
30. Eseverri JL, Ranea S, Marin A. Adverse reactions to vaccines. Allergol Immunopathol. 2003;31(3):125–38.
31. Patja A, Mäkinen-Kiljunen S, Davidkin I, Paunio M, Peltola H. Allergic reactions to measles-mumps-rubella vaccination. Pediatrics. 2001;107(2):e27–e.
32. Hwang H, Kwon J, Kim JY, Lee HH, Oh CE, Choi G-S. The RIDA allergy screen versus the Phadiatop test in 430 consecutive patient specimens. Lab Med. 2016;47(1):20–9.
33. Sakaguchi M, Inouye S. IgE sensitization to gelatin: the probable role of gelatin-containing diphtheria–tetanus–acellular pertussis (DTaP) vaccines. Vaccine. 2000;18(19):2055–8.
34. Kelso JM. Potential food allergens in medications. J Allergy Clin Immunol. 2014;133(6):1509–18.

35. Sakaguchi M, Inouye S. Systemic allergic reactions to gelatin included in vaccines as a stabilizer. Jpn J Infect Dis. 2000;53(5):189–95.
36. Kumagai T, Yamanaka T, Wataya Y, Umetsu A, Kawamura N, Ikeda K, et al. Gelatin-specific humoral and cellular immune responses in children with immediate-and nonimmediate-type reactions to live measles, mumps, Rubella, and varicella vaccines. J Allergy Clin Immunol. 1997;100(1):130–4.
37. Singer S, Johnson CE, Mohr R, Holowecky C. Urticaria following varicella vaccine associated with gelatin allergy. Vaccine. 1999;17(4):327–9.
38. Sakaguchi M, Yamanaka T, Ikeda K, Sano Y, Fujita H, Miura T, et al. IgE-mediated systemic reactions to gelatin included in the varicella vaccine. J Allergy Clin Immunol. 1997;99(2):263–4.
39. Sakaguchi M, Nakayama T, Inouye S. Food allergy to gelatin in children with systemic immediate-type reactions, including anaphylaxis, to vaccines. J Allergy Clin Immunol. 1996;98(6):1058–61.
40. Franceschini F, Bottau P, Caimmi S, Crisafulli G, Lucia L, Peroni D, et al. Vaccination in children with allergy to Non active vaccine components. Clin Translational Med. 2015;4(1):1–8.
41. Kumagai T, Yamanaka T, Wataya Y, Saito A, Okui T, Yano S, et al. A strong association between HLA-DR9 and gelatin allergy in the Japanese population. Vaccine. 2001;19(23–24):3273–6.
42. Bogdanovic J, Halsey NA, Wood RA, Hamilton RG. Bovine and Porcine gelatin sensitivity in children sensitized to milk and meat. J Allergy Clin Immunol. 2009;124(5):1108–10.

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