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## Safety of an inactivated COVID-19 vaccine in patients with wheat-dependent exercise-induced anaphylaxis

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COVID-19;  
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safety;  
allergic reactions

### Abstract

**Background:** Inactivated vaccines against coronavirus disease-2019 (COVID-19) offer an effective public health intervention to mitigate this devastating pandemic. However, little is known about their safety in patients with wheat-dependent exercise-induced anaphylaxis (WDEIA).

**Methods:** We recruited 72 WDEIA patients and 730 healthy matched controls who received an inactivated COVID-19 vaccine. Participants were monitored for 4 weeks after each immunization for adverse reactions and completed questionnaires regarding local and systemic reactions at 7 and 28 days after each vaccination. For those who had received the COVID-19 vaccine prior to enrollment, adverse event data were obtained retrospectively.

**Results:** Local and systemic adverse events occurred at similar rates in the WDEIA group and the control group. In both groups, injection-site pain and fatigue were the most common local and systemic reactions, respectively. Compared with healthy controls, more allergic events were reported in the WDEIA group (after dose 1, 0.5% vs. 4.2%,  $p=0.019$ ; after dose 2, 0% vs. 1.4%,  $p=0.089$ ). Allergic reactions mainly manifested as rash, urticaria, and edema, which were mild and controllable. No serious allergic events were reported.

**Conclusions:** The adverse event profile of inactivated COVID-19 vaccine did not differ between WDEIA patients and healthy controls. The risk of allergic reactions in patients with WDEIA seems higher, but no anaphylaxis was reported, and the allergic reactions were controllable. Inactivated COVID-19 vaccines appear to be well-tolerated in WDEIA patients, but patients with potential allergy risks should be cautious.

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## Introduction

Globally, the devastating coronavirus disease 2019 (COVID-19) pandemic resulting from infection by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) continues to cause high morbidity and mortality.<sup>1</sup> As of October 11, 2021, over 234 million cases of SARS-CoV-2 infection have been reported worldwide, and almost 4.8 million patients have died.<sup>2</sup> High vaccine uptake is the most effective preventative measure to contain this pandemic. Regulatory authorities have approved several vaccines, including inactivated whole-virus vaccines, recombinant protein subunit vaccines, vectored vaccines, and mRNA vaccines.<sup>3,4</sup>

Published reports indicate that 32 to 81% of individuals with anaphylaxis following COVID-19 vaccination had a history of allergic reactions to other exposures, including foods.<sup>5,6</sup> However, a few studies have addressed the safety of COVID-19 vaccines in patients with food allergies.<sup>7</sup> Wheat-dependent exercise-induced anaphylaxis (WDEIA), a distinct type of immunoglobulin E (IgE)-mediated food allergy, is a life-threatening allergic disease that manifests as hypotension or anaphylactic shock.<sup>8</sup> In China, about 37% of food-induced anaphylaxis cases are caused by wheat.<sup>9</sup> The inactivated SARS-CoV-2 vaccine, the type used most widely in China,<sup>10,11</sup> prevents infection with SARS-CoV-2 by stimulating the immune system and inducing an intense and persistent immune response,<sup>12</sup> but its safety among patients with WDEIA remains unknown. We aimed to compare adverse events associated with an inactivated COVID-19 vaccine in WDEIA patients versus those in healthy controls.

## Materials and methods

### Study design and participants

We conducted this cross-sectional survey from June 2021 to September 2021 at Peking Union Medical College Hospital (PUMCH)—a tertiary allergy center. A total of 72 WDEIA patients and 730 healthy controls who had received at least one dose of the inactivated SARS-CoV-2 vaccine were recruited for this study. All patients with WDEIA enrolled in the study meet the following criteria<sup>13</sup>: (1) anaphylaxis manifestation as determined according to the World Allergy Organization (WAO) systemic allergic reaction grading system (grades 4 or 5)<sup>14</sup>; (2) anaphylaxis occurring in the presence of physical activity, nonsteroidal anti-inflammatory drugs, or alcohol within 6 h of wheat ingestion; (3) allergen-specific IgE test results against  $\omega$ -5 gliadin or gluten of  $\geq 0.35$  KUA/L; and (4) a wheat-elimination diet prevented patients from experiencing anaphylaxis. Healthy control individuals were recruited during physical check-ups at the same hospital. Individuals with allergic disorders, including food allergies, allergic rhinitis, allergic asthma, atopic dermatitis, and chronic urticaria, were excluded from the control group. All participants volunteered to participate in this study and signed a written informed consent. The study protocol was approved by the ethics committee of PUMCH.

### Assessment of local adverse events

Injection-site pain, itch, and rash were measured on the following scale: mild (not affecting daily activity), moderate (slightly affecting daily activity), severe (significantly affecting daily activity), and grade 4 (resulting in emergency department visit or hospitalization). Redness, swelling, and induration were assessed according to the following scale: mild (2.0 to 5.0 cm in diameter), moderate ( $>5.0$  to 10.0 cm in diameter), severe ( $>10.0$  cm in diameter), and grade 4 (for redness: necrosis or exfoliative; for swelling or induration: necrosis).

### Assessment of systemic adverse events

Fever was assessed according to the following scale: mild,  $37.3$  to  $<38^\circ\text{C}$ ; moderate,  $\geq 38.0$  to  $<38.5^\circ\text{C}$ ; severe,  $\geq 38.5$  to  $<39.5^\circ\text{C}$ ; and grade 4,  $\geq 39.5^\circ\text{C}$ . The additional scale of systemic adverse events was as follows: diarrhea (mild: 1 to 3 times per 24 h; moderate: 4 to 5 times per 24 h; severe:  $\geq 6$  times per 24 h), vomiting (mild: 1 to 2 times per 24 h; moderate:  $>2$  times per 24 h; severe: requiring intravenous hydration), decreased appetite, nausea, new or worsened muscle pain, new or worsened joint pain, dizziness, headache, cough, fatigue, stuffy nose, runny nose, and chill (mild: not affecting daily activity; moderate: slightly affecting daily activity; severe: significantly affecting daily activity); grade 4 for all reactions required an emergency department visit or hospitalization. Allergic events were determined according to the WAO systemic allergic reaction grading system.<sup>14</sup>

### Data collection

Between June 2021 and September 2021, questionnaires were sent to participants via social media to obtain demographic information (sex, age, and nationality) and data on adverse events that occurred within the 4 weeks after each vaccination. Adverse events were recorded and verified by investigators.

### Statistical analysis

Continuous data are presented as means and were compared using Student's *t*-tests. Categorical outcomes are expressed as frequencies and percentages and were compared using chi-square or Fisher's exact tests. Statistical calculations were carried out using SPSS 25.0 software (SPSS Inc., Chicago, IL, USA). Hypothesis testing was two-sided, and  $p < 0.05$  was considered statistically significant.

## Results

### Demographic characteristics of the study population

A total of 72 WDEIA patients and 730 healthy controls were recruited in this study, all of whom had received the first

**Table 1** Demographic characteristics of the study population.

Characteristics	WDEIA group	Control group	p <sup>a</sup>
<b>Dose 1</b>			
	N=72	N=730	
Mean age (years)	42.4 (19-79)	40.8 (16-76)	0.287
Male (%)	37 (51.4)	388 (53.2)	0.775
Han nationality (%)	72 (100)	730 (100)	
<b>Dose 2</b>			
	N=70	N=729	
Mean age (years)	42.6 (19-79)	40.8 (16-76)	0.237
Male (%)	37 (52.9)	387 (53.1)	0.971
Han nationality (%)	70 (100)	729 (100)	

WDEIA, wheat-dependent exercise-induced anaphylaxis. Number (%) or mean (range) reported.

<sup>a</sup>Chi-square test for categorical variables, *t*-test for continuous variables.

dose of inactivated COVID-19 vaccine. Two participants in the WDEIA group and one in the healthy control group did not receive the second dose of inactivated COVID-19 vaccine. The baseline characteristics, including age, gender, and nationality, did not differ in both groups (Table 1).

## Local reactions

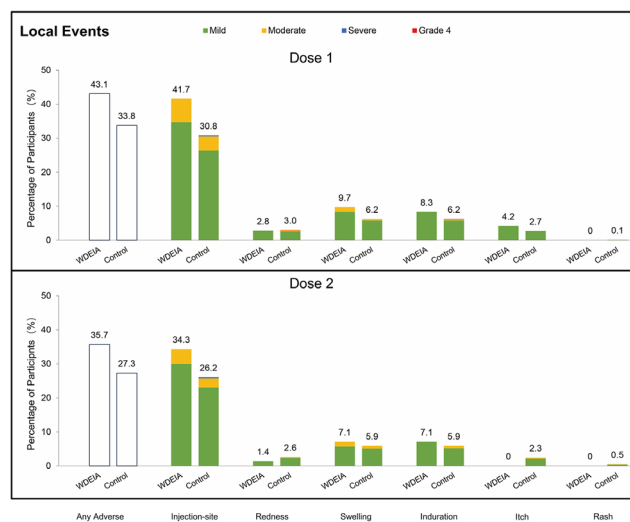
The proportion of participants reporting local reactions was similar between the WDEIA group and the control group (after dose 1, 43.1% vs. 33.8%,  $p=0.117$ ; after dose 2, 35.7% vs. 27.3%,  $p=0.134$ ). Injection-site pain, injection-site swelling, and induration were the most common local reactions in each group (Figure 1). Most of the local reactions in both groups were mild-to-moderate and resolved within a week.

The proportion of participants reporting local reactions (not severe or grade 4 in severity) was similar after each dose (43.1% vs. 35.7%,  $p=0.371$ ) in the WDEIA group. The proportion of participants reporting local reactions was higher after dose 1 than after dose 2 in the control group (33.8% vs. 27.3%,  $p=0.007$ ).

## Systemic reactions

There was no difference in the incidence of systemic adverse events between patients with WDEIA and controls (after dose 1, 37.5% vs. 30.0%,  $p=0.188$ ; after dose 2, 30.0% vs. 21.3%,  $p=0.092$ ). The most common systemic reactions in each group were fatigue, muscle pain, and dizziness (Figure 2). Patients with WDEIA reported more allergic reactions than did controls after dose 1 (4.2% vs. 0.5%,  $p=0.019$ ). However, there was no statistical difference in the rate of allergic reactions after dose 2 (1.4% vs. 0%,  $p=0.089$ ). Characteristics of these allergic events are shown in Table 2.

The proportion of patients in the WDEIA group reporting systemic events was similar after dose 1 and dose 2 (37.5% vs. 30%,  $p=0.35$ ), but these events were more common after dose 1 than after dose 2 in the control group



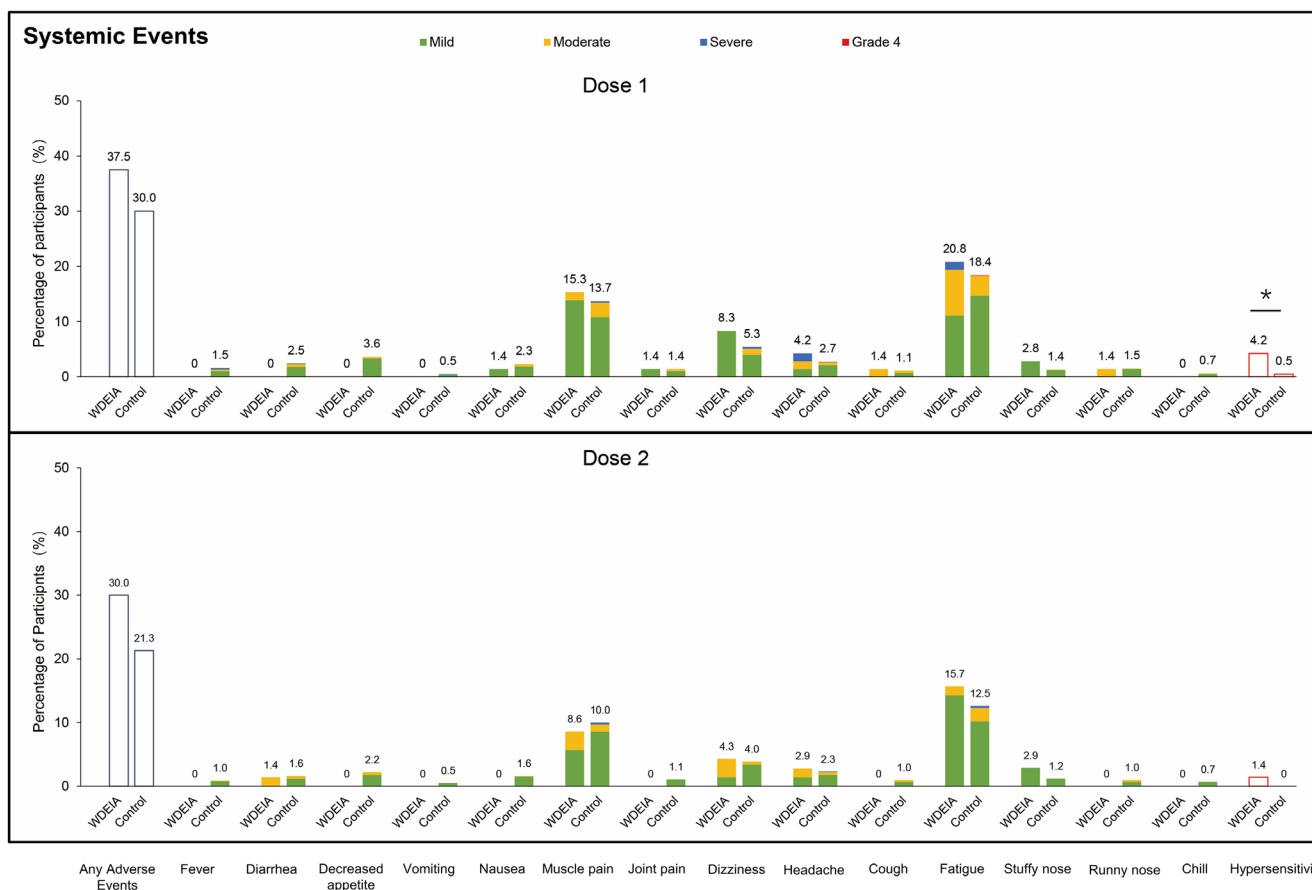
**Figure 1** Local reactions reported within 4 weeks after injection of inactivated COVID-19 vaccine in WDEIA and control groups. There was no significant difference in the incidence of each local adverse event between the two groups ( $p>0.05$ ).  $P<0.05$  was considered statistically significant.

(30% vs. 21.3%,  $p=0.0001$ ). In patients with WDEIA, every single patient (1.4%) experienced severe headache and fatigue, respectively, after the first dose of vaccine; no grade 4 systemic reactions were reported in this group.

## Discussion

To date, limited data are available on the safety of COVID-19 vaccines in food-allergic patients.<sup>15</sup> Reactions after vaccination are categorized as local and systemic reactions<sup>16</sup>; mild local reactions are mostly attributed to nonspecific inflammation caused by the injection itself or by the injection of foreign materials. Local reactions may additionally result from type III or type IV hypersensitivity.<sup>16</sup> This study found that the incidence of local adverse reactions was similar between a group of WDEIA patients and a matched group of healthy controls. Injection-site pain was the most common local reaction in both groups. Consistent with our results, Zhang et al.<sup>10</sup> found that injection-site pain was the most common adverse reaction in healthy adults (21% in the 3  $\mu$ g group, 26% in the 6  $\mu$ g group). Similarly, Xia et al.<sup>17</sup> demonstrated that 24% (34/144) of vaccine recipients reported injection-site pain, which was the most common injection-site adverse event. Our findings were similar to those of other inactivated COVID-19 vaccines in older healthy adults.<sup>18</sup> Generally, the proportion of reported local reactions was similar between the WDEIA group and healthy controls in our study.

In the current study, the incidence of local adverse events in the WDEIA group was identical after dose 1 and after dose 2. However, in the control group, the proportion of reported local reactions was higher after dose 1 than after dose 2. Recent studies on the safety of inactivated COVID-19 vaccines have mainly focused on analyzing the



**Figure 2** Systemic reactions reported within 4 weeks after injection of inactivated COVID-19 vaccine in WDEIA and control groups. \*p<0.05.

**Table 2** Characteristics of cases of hypersensitivity events following receipt of inactivated COVID-19 Vaccine.

Age, year	Sex	Reaction onset after dose 1	Signs and symptoms	WAO grading system	Treatment	Outcome	Reception of dose 2
<b>WDEIA group</b>							
49	Male	3 days	Generalized urticaria	1	Antihistamines	Recovered after 2 h	Yes, no allergic events
58	Male	6 days	Generalized urticaria, swollen lip and face	1	Antihistamines	Recovered after 1 h	Yes, similar events occurred 9 h after dose 2
34	Female	5 h	Generalized urticaria	1	Antihistamines	Recovered after 1 h	Yes, no allergic events
<b>Control group</b>							
35	Male	24 h	Diffuse erythematous rash	1	Antihistamines	Lasted for more than 2 months	No
31	Female	4 days	Diffuse pruritic rash	1	Unknown	Lasted for 2 weeks	Yes, no allergic events
32	Male	3 days	Diffuse pruritic rash	1	No	Lasted for 2 weeks	Yes, no allergic events
52	Male	5 min	Generalized urticaria	1	Antihistamines, dexamethasone	Recovered after 20 min	Yes, no allergic events

WAO: World Allergy Organization; WDEIA: wheat-dependent exercise-induced anaphylaxis.

overall adverse reactions after two vaccinations, but did not note the differences in the incidence of adverse reactions after each vaccination.<sup>19</sup>

The incidence of systemic adverse reactions was similar between the WDEIA group and healthy controls. In line with previous studies in healthy participants,<sup>10,20</sup> fatigue was the most common systemic reaction in both WDEIA patients and healthy controls in this study. Several studies have reported that fatigue was one of the more common adverse events, but that fever (in 3-4%) was the most commonly reported.<sup>17,18</sup> In contrast, we found the incidence of fever to be relatively lower in healthy controls in our study, and no participants in the WDEIA group reported fever. Currently, the sample size of available reported studies is relatively small, which may account for the variation in the reported incidence of adverse reactions. Most of the adverse events in WDEIA patients were of mild-to-moderate severity, similar to that reported elsewhere in healthy participants.<sup>17,18</sup>

This study found that patients with WDEIA reported higher incidence of allergic reactions than did healthy controls. By the present results, 0 to 4% of healthy participants reported hypersensitivity after receiving the inactivated COVID-19 vaccine.<sup>10,17,18,20</sup> However, there is a lack of reports on hypersensitivity events in allergic patients after inactivated vaccine injection. The Th2-type immune response to vaccine antigens has been reported to be more pronounced among atopic individuals.<sup>16</sup> The most common allergic reactions were urticaria and angioedema in WDEIA patients, which is consistent with previous studies.<sup>10</sup> No anaphylaxis was reported in our study.

The reported contraindications to the COVID-19 vaccine include patients who have a history of systemic allergic reaction to the first dose of vaccine, or those who have severe allergic reaction to the vaccine component. However, atopic history is not a preset contraindication for immunization. COVID-19 vaccination has been permitted for those with a history of food-induced anaphylaxis once they were observed for 30 min after vaccination.<sup>12,16,21</sup> Patients with WDEIA may be prone to allergic reactions after vaccination, but in this study no anaphylaxis was reported, and the allergic symptoms were controllable.

Allergic reactions to vaccines are generally not attributable to their active ingredients but rather to inert substances.<sup>12,21</sup> The main excipients used in the inactivated SARS-CoV-2 vaccine are disodium hydrogen phosphate, sodium dihydrogen phosphate, and aluminum hydroxide.<sup>11</sup> Aluminum hydroxide adjuvant is helpful to modulate and enhance immune responses, which can induce type IV hypersensitivity (contact allergy and injection-site maculopapular rash), but no immediate hypersensitivity reactions to it have been reported.<sup>16,22,23</sup> The pathogenic allergens and pathophysiology of vaccine-induced allergic reactions associated with inactivated SARS-CoV-2 vaccines remain unknown.

Allergic reactions to vaccines are either acute at onset or delayed.<sup>22</sup> Typically, most acute-onset allergic reactions are type I hypersensitivity reactions mediated by preformed IgE antibodies, usually starting within 4 h of exposure to the relevant allergen.<sup>22</sup> Acute hypersensitivity occurring 48 h after immunization with inactivated COVID-19 vaccine has been described.<sup>10</sup> Delayed-type reactions

occur hours or days after exposure. Rashes were the most common reported signs of delayed-type reactions, which may not be immunologically mediated or even reproducible on re-exposure.<sup>22,24</sup> It is difficult to diagnose and differentiate these reported allergic reactions clinically.

This study describes the adverse events of an inactivated COVID-19 vaccine in WDEIA patients. As most studies to date have focused on evaluating the safety of the inactivated vaccine in healthy volunteers,<sup>10</sup> investigating the safety of inactivated COVID-19 vaccine in WDEIA patients may provide an important reference for clinicians treating these patients. However, this study has several limitations. WDEIA is a relatively rare disorder, and we were only able to recruit 72 participants for this study in the given period. To detect adverse events more comprehensively, larger sample sizes are needed. Furthermore, most questionnaires were collected retrospectively, and prospective studies are required to verify our results. Given that this was a single-center experience in China, other countries using different vaccines may have difference incidence of reactions. Lastly, this study only focused on the safety of inactivated COVID-19 vaccines; their efficiency specific to patients with WDEIA remains to be evaluated.

## Conclusion

Patients with WDEIA had a similar incidence of most adverse reactions to inactivated COVID-19 vaccines as did a group of matched healthy controls. The risk of allergic reactions in patients with WDEIA seems higher; however, no anaphylaxis was reported in our cohort, and allergic symptoms were controllable. Therefore, patients with WDEIA appear to tolerate inactivated COVID-19 vaccines well, but clinicians should pay attention to the potential risks of allergic reactions.

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