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Allergic symptoms after mRNA COVID-19 vaccination and risk of incomplete vaccination

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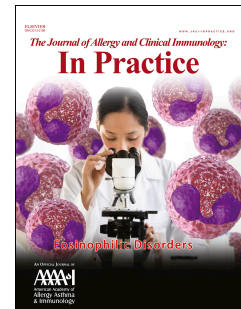
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Allergic symptoms after mRNA COVID-19 vaccination and risk of incomplete vaccinationLacey B. Robinson, MD, MPH¹⁻³Adam B. Landman, MD^{3,4}Erica S. Shenoy, MD, PhD^{3,5}Dean Hashimoto, MD^{3,6}Xiaoqing Fu, MS²Carlos A. Camargo, Jr., MD DrPH^{1-3, 7}Paige Wickner, MD, MPH^{3,8}Kimberly G. Blumenthal, MD, MSc¹⁻³¹Division of Rheumatology, Allergy, and Immunology, Department of Medicine, Massachusetts

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Role of Funder/Sponsor Statement

The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Access to Data and Data Analysis

Dr. Blumenthal, Dr. Robinson and Ms. Fu had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Dr. Blumenthal, Dr. Robinson and Ms. Fu additionally conducted data analysis.

Conflicts of Interest

Dr. Blumenthal reports grants from the American Academy of Allergy Asthma and Immunology (AAAAI) Foundation, CRICO, and MGH, outside the submitted work.

Dr. Landman reports personal fees from Abbott Medical Device Cybersecurity Council, outside the submitted work. Dr. Wickner reports grants from CRICO, outside the submitted work. The remaining authors have nothing to disclose.

CLINICAL IMPLICATIONS

Allergic symptoms after dose one of mRNA COVID-19 vaccine may contribute to incomplete vaccination. However, most patients with mild or non-immediate symptoms can safely complete vaccination. Allergists must be prepared to counsel patients to prevent incomplete vaccination.

CLINICAL COMMUNICATION

Allergic reactions have been reported after Coronavirus Disease 2019 (COVID-19) mRNA vaccination. Anaphylaxis to the first dose is a contraindication to subsequent mRNA vaccination; however, many mild or nonimmediate allergic symptoms are not.^{1,2} We sought to determine if self-reported allergic symptoms were associated with incomplete vaccination.

We prospectively studied Mass General Brigham (MGB) employees who received their first dose of mRNA COVID-19 vaccine between (12/16/2020 and 2/1/2021, with follow-up through 03/15/2021, eMethods). For the 3 days after vaccination, which was captured in the electronic health record, employees completed symptom surveys through e-mail, text, phone, or employee smartphone application links. Self-reported allergic symptoms included: itching or rash (other than at the injection site), hives, swelling and/or respiratory symptoms (Repository Text). MGB allergists were available to assess any employees who self-reported a symptom more severe than itching and rash between doses.

We determined the frequency of self-reported allergic symptoms using the number of dose one survey respondents as the denominator. We compared frequencies using chi-squared tests, considering a 2-sided p-value <0.05 statistically significant. The primary outcome was incomplete mRNA COVID-19 vaccination (i.e., did not receive dose two). We used a multivariable logistic regression model to assess the association of self-reported allergic symptoms and incomplete vaccination. We adjusted for age, sex, race, vaccine manufacturer, MGB site and eligibility group. We also considered the exposure of severe allergic symptoms (respiratory symptoms plus one of the following: itching or rash other than injection site, hives or

swelling). This study was approved by the MGB Human Research Committee. Analyses were conducted in SAS version 9.4 (Cary, NC).

Of 61,057 employees who received their first dose of a COVID-19 mRNA vaccine, 22,683 (37%) received Pfizer-BioNtech and 38,374 (63%) received Moderna. Symptom surveys were completed by 50,167 (83%) employees. Self-reported allergic symptoms were reported by 1,261 employees after dose one (2.5%; 95%CI 2.4%-2.6%); 576 (46%) received an allergy/immunology consultation.

Overall, 50,269 (99%) received the second vaccine dose. Incomplete vaccination occurred in a total of 348 (0.7%) employees: 43 (3%) who self-reported allergic symptoms after dose one versus 305 (0.6%) who did not. Incomplete vaccination was more common among women and differed by MGB site, but not by race or eligibility group (Table 1).

Self-reported allergic symptoms after dose one was associated with an increased odds of incomplete vaccination (adjusted odds ratio (OR) 5.15, 95%CI: 3.75,7.06, $p < 0.001$, Table 2).

Self-reported severe allergic symptoms were rare and associated with a markedly increased odds of incomplete vaccination (unadjusted OR 23.19, 95%CI: 9.74, 55.22 < 0.001).

Of the 1,261 with self-reported allergic symptoms after dose one, 1,218 received dose two and 860 (70%) completed the dose two symptom survey. Among the 860 survey respondents, there were 146 (17%) with recurrent allergic symptoms but none were severe.

In a prospective cohort of employees receiving mRNA COVID-19 vaccination, self-reported allergic symptoms (reported by 2.5% after dose one) were associated with 5-fold increased odds of incomplete vaccination. The vast majority of individuals (97%) with self-reported allergic symptoms safely completed the vaccination series.

The two currently authorized mRNA COVID-19 vaccines require a two-dose vaccination series.^{3,4} The implications of incomplete vaccination remain unclear, but decreased vaccine efficacy and/or durability are the primary public health concern.

Study limitations include the use of self-reported data, although the cohort included healthcare workers, and therefore data reliability may be high. Hospital employees had direct access to MGB allergists and allergy protocols for dose two administration, a level of specialist access unlikely to be reproduced on a population level. As such, these findings likely represent a “best care scenario,” biasing results towards the null and likely to be a larger factor in other US populations that are not healthcare employees and do not have easy access to specialist care.

An estimated 6.3 million adults in the United States may experience allergic symptoms after mRNA COVID vaccination, and this study warns that ~200,000 are at risk of incomplete vaccination. Most patients with mild or nonimmediate symptoms can safely complete their vaccination.^{5,6}

138 In fact, recent estimates from the Centers for Disease Control and Prevention found that ~8% of
139 adults in the US have not completed the mRNA COVID-19 vaccination series.⁷ Our data suggest
140 that allergic symptoms may contribute to incomplete vaccination. Clinicians, particularly
141 allergists, need to be aware of this risk and prepared to provide counseling to reduce the impact
142 of incomplete vaccination.

143

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REFERENCES

1. COVID-19 Vaccination. United States Centers for Disease Control and Prevention, United States; Published March 4, 2021. Available at: <https://www.cdc.gov/vaccines/covid-19/index.html>. Accessed on March 25, 2021.
2. Blumenthal KB, Robinson LB, Camargo CA Jr, Shenoy ES, Banerji A, Landman AB, Wickner P. Acute allergic reactions to mRNA COVID-19 vaccines. JAMA. Published online March 08, 2021.
3. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020;383(27):2603-2615.
4. Baden LR, El Sahly HM, Essink B, Kootloff K, Frey S, Novak S, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021; 384:403-416.
5. Blumenthal KG, Freeman EE, Saff RR, Robinson LB, Wolfson AF, Foreman RK, et al. Delayed large local reactions to mRNA-1273 vaccine against SARS-CoV-2. N Engl J Med. 2021 Apr 1;384(13):1273-1277.
6. Kelso JM, Greenhawt MJ, Li JT, Nicklas RA, Bernstein DI, Blessing-Moore J, et al. Adverse reactions to vaccines practice parameter: 2012 update. J Allergy Clin Immunol. 2012;130(1):25-43.
7. Robbins, R. Millions are skipping their second doses of COVID vaccines. The New York Times. 2021. April 26. Sect. B; Page 1.

TABLES

Table 1. Characteristics of employees with incomplete mRNA COVID vaccination				
	No. (%)			
	Incomplete Vaccination (n = 348)	Any self-reported allergic symptoms after dose one^a (n = 43)	No self-reported allergic symptoms after dose one (n = 305)	P value
Age, mean (SD)	41 (14)	43 (13)	41 (14)	0.21
Sex				0.08
Male	77 (22)	5 (12)	72 (24)	
Female	271 (78)	38 (88)	233 (76)	
Race				0.31
White	228 (66)	31 (72)	197 (65)	
Black	31 (9)	3 (7)	28 (9)	
Asian	19 (5)	4 (9)	15 (5)	
Other/Unknown	70 (20)	5 (12)	65 (21)	
Vaccine manufacturer				0.17
Moderna	244 (70)	34 (79)	210 (69)	
Pfizer-BioNTech	104 (30)	9 (21)	95 (31)	
MGB Site ^b				0.004
1	126 (36)	8 (19)	118 (39)	
2	107 (31)	13 (30)	94 (31)	
3	26 (7)	8 (19)	18 (6)	
4	89 (26)	14 (33)	75 (25)	
Eligibility Group ^c				0.71
A	9 (28)	11 (26)	88 (29)	
B	67 (19)	8 (19)	59 (19)	
C	51 (15)	9 (21)	42 (14)	
D	58 (17)	7 (16)	51 (17)	
E	42 (12)	3 (7)	39 (13)	
Missing	31 (9)	5 (12)	26 (9)	

^aSelf-reported allergic symptoms included itching or rash (other than injection site) in 27 (8%), hives in 13 (4%), swelling in 12 (3%), respiratory in 13 (4%) and potentially severe (respiratory plus at least one other symptom) in 6 (2%).

^bMGB vaccination sites included academic medical centers, community hospitals and local vaccine clinics. Sites 1 and 2 are academic medical centers and sites 3 and 4 include community hospitals and local sites.

^cEligibility group were designed by location of employee work, beginning with Wave A ambulatory location for COVID-19 evaluation/testing/care, emergency departments, inpatient and observation units, laboratories working with COVID-19, occupational health clinics, patient homes (home health), and urgent care centers. Wave B included primary care, periprocedural areas and radiation oncology. Wave C included all other outpatient clinical care areas, laboratories and outpatient radiology. Wave D included all other hospital-based employees, including hospital workers who worked both remotely and in the hospital. Wave E included all other eligible employees.

Table 2. Incomplete vaccination among employees by self-reported allergic symptoms after dose one of mRNA COVID-19 vaccination

Incomplete Vaccination	No self-reported allergic symptoms (OR, 95%CI)	<u>Any</u> self-reported allergic symptoms after dose one (OR, 95%CI)	P value
Number of events	305	43	-
Unadjusted	1.00 (ref)	5.68 (4.11, 7.85)	< 0.001
Adjusted^a	1.00 (ref)	5.15 (3.75, 7.06)	< 0.001
Incomplete Vaccination	No self-reported allergic symptoms (OR, 95%CI)	<u>Severe</u> self-reported allergic symptoms after dose one (OR, 95%CI)	P value
Number of events	305	6	
Unadjusted	1.00 (ref)	23.19 (9.74, 55.22)	< 0.001

^aMultivariable model adjusted for age, sex, race, vaccine manufacturer, MGB site, wave of vaccine eligibility
Abbreviations, OR, odds ratio, 95%CI, 95% confidence interval

Repository Text

Allergic symptoms after mRNA COVID-19 vaccination and risk of incomplete vaccination

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eMethods

Mass General Brigham (MGB) began employee Coronavirus disease 19 (COVID-19) vaccination on December 16, 2020. Vaccination occurred across 17 vaccine clinics in phases with the earliest vaccinations (wave A) in employees whose primary location of work included: ambulatory location for COVID-19 evaluation/testing/care, emergency departments, inpatient and observation units, laboratories working with COVID-19, occupational health clinics, patient homes (home health), and urgent care centers. Wave B included primary care, periprocedural areas and radiation oncology. Wave C included all other outpatient clinical care areas, laboratories and outpatient radiology. Wave D included all other hospital-based employees, including those who performed some remote work and also worked in the hospital perform remote work. Wave E included all other eligible employees. The only allergy-related exclusion criterion for initial vaccination was a history of a severe allergic reaction (e.g., anaphylaxis) to a component of the vaccine (e.g., polyethylene glycol or polysorbate 80). After vaccination in the MGB vaccine clinics, employees were observed for 15 or 30 minutes according to guidelines set by the Centers for Disease Control and Prevention.

Any potential allergic reactions associated with vaccination observed in the vaccine clinics were documented in the employee's electronic health record (EHR). For allergic reactions, pages to a dedicated MGB allergy/immunology pager, implemented December 17, 2020 to support employee vaccination, were encouraged. MGB allergists maintained a shared pager log and all potentially allergic reactions were specialist-documented in the employee's EHR. Filing of 1) a Vaccine Adverse Event Reporting System report and 2) a safety report was encouraged for all

possible anaphylactic reaction events. Each MGB-affiliated hospital sent MGB allergists COVID-19 vaccine-related safety reports biweekly during employee vaccination.

Daily for 3 days after vaccination, employees were contacted regarding post-vaccination symptoms through a multi-pronged approach including e-mail, text message, phone, and employee smartphone application links; symptom checks were completed through a web-based Research Electronic Data Capture (REDCap) survey or telephone. Survey completion was defined as full completion of at least one of the three post-vaccine symptom surveys. Employees with possible allergic events identified from the pager, safety reports, or self-reports (more severe than itching and rash alone) were referred to MGB allergists for evaluation and dose two guidance with specified protocols.

eAppendix: Employee Symptom Survey—Allergy Question

Version 1. December 17 through December 31 2020

Have you had any of the following allergic symptoms over the past day? (check all that apply)

- ☐ Rash or itching (other than at injection site)
- ☐ Hives
- ☐ Swollen lips, tongue, eyes, or face
- ☐ Wheezing, chest tightness or shortness of breath
- ☐ None of the above

Version 2. January 1, 2021 through present

Over the past day, have you had any of the following allergic symptoms? (check all that apply)

- ☐ Rash or itching (other than where you got your shot)
- ☐ Hives (itchy, raised bumps that can look like mosquito bites)
- ☐ Swollen lips, tongue, eyes, or face
- ☐ Wheezing, chest tightness or shortness of breath that has continued since your shot
- ☐ None of the above