(38.3%) were tested on days 9 to 14. Of the 134 student contacts tested on day 3, 14 (10.4%) were positive for SARS-CoV-2 infection. Of the 839 student contacts tested on days 9 to 14, 40 (4.8%) were positive for SARS-CoV-2 infection. Of the 388 student contacts in high school who were tested, 32 (8.2%) were positive for SARS-CoV-2 infection on days 9 to 14 compared with 8 (1.8%) of 451 student contacts in elementary and middle school who tested positive ($P < .001$; **Table**).

Among 799 student contacts of confirmed COVID-19 cases with a negative test result on days 9 to 14, only 1 student became symptomatic after returning to school and had a positive SARS-CoV-2 test result on day 14 after an initial negative test result on day 9. The virus from this student was genetically distinct from the virus isolated from the confirmed COVID-19 case to which the student had been exposed (GenBank confirmed case: MW307809; GenBank 9-day student contact: MW308137). Loss of instruction decreased by 3649 days with the 9-day testing protocol (8097 days missed) compared with a theoretical 14-day quarantine without testing (11 746 days missed).

Discussion | In this study of a 9-day testing protocol for student contacts of confirmed COVID-19 cases in 1 Florida county, a reduction in loss of instructional time was found that was less than what would have occurred with a 14-day quarantine. There was no evidence that an earlier return to school with a negative test result was linked with subsequent symptomatic illness. Had students returned to school before day 14 without testing on day 9 or thereafter, 8.2% of high school contacts would have returned to school with SARS-CoV-2 infection. These findings should be considered when evaluating the December 2020 CDC recommendation for a 10-day quarantine without testing or a 7-day quarantine with testing.[5]

Limitations of this study include (1) contact testing ranging from days 9 to 14; (2) lack of testing for students who quarantined for 14 days; and (3) use of symptomatic illness alone for follow-up of negative test results.

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Acute Allergic Reactions to mRNA COVID-19 Vaccines

Anaphylaxis to the mRNA COVID-19 vaccines is currently estimated to occur in 2.5 to 11.1 cases per 1 million doses, largely in individuals with a history of allergy.[1] Allergic concerns contribute to vaccine hesitancy; we investigated acute allergic reaction incidence after more than 60 000 mRNA COVID-19 vaccine administrations.

Supplemental content

Methods | We prospectively studied Mass General Brigham (MGB) employees who received their first dose of an mRNA COVID-19 vaccine (12/16/2020-2/12/2021, with follow-up through 2/18/2021) (eMethods in the Supplement). For 3 days after vaccination, employees completed symptom surveys through a multipronged approach including email, text message, phone, and smartphone application links. Acute allergic reaction symptoms solicited included itching, rash,

Table 1. Acute Allergic Reactions Self-reported Through Voluntary Reporting and Multipronged Prospective System Surveillance After mRNA COVID-19 Vaccination

	No. (%) [95% CI]			
	Both mRNA vaccines (n = 64 900)	Pfizer-BioNTech (n = 25 929)	Moderna (n = 38 971)	*P* value
Self-reported allergic reaction[a]	1365 (2.10) [1.99-2.22]	506 (1.95) [1.79-2.13]	859 (2.20) [2.06-2.35]	.03
Confirmed anaphylaxis[b]				
Either criteria	16 (0.025) [0.014-0.040]	7 (0.027) [0.011-0.056]	9 (0.023) [0.011-0.044]	.76
Brighton[c]	14 (0.022) [0.012-0.036]	7 (0.027) [0.011-0.056]	7 (0.018) [0.007-0.037]	.44
NIAID/FAAN[d]	9 (0.014) [0.006-0.026]	4 (0.015) [0.004-0.040]	5 (0.012) [0.004-0.030]	.75
Both criteria	7 (0.011) [0.004-0.022]	4 (0.015) [0.004-0.040]	3 (0.008) [0.002-0.023]	.45

Abbreviations: mRNA, messenger RNA; NIAID/FAAN, National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network.

[a] Itching or rash other than at the injection site (n = 788), respiratory symptoms (n = 342), hives (n = 244), or swelling (n = 191) (see the eAppendix in the Supplement). Numbers do not sum to 1365 because employees could report more than 1 reaction.

[b] See Table 2 for details of reactions.

[c] The Brighton Collaboration[2] case definition uses combinations of symptoms to define levels of diagnostic certainty. Brighton level 1 represents the highest level of diagnostic certainty that a reported case represents anaphylaxis; levels 2 and 3 are successively lower levels of diagnostic certainty; level 4 is a case reported as anaphylaxis but that does not meet the Brighton Collaboration case definition; and level 5 is a case that was neither reported as anaphylaxis nor meets the case definition. This study considered Brighton levels 1 or 2 anaphylaxis cases.

[d] NIAID/FAAN clinical criteria[3] for the diagnosis of anaphylaxis must meet 1 of the following criteria: (1) acute onset with involvement of skin and/or mucosal tissue and either (a) respiratory compromise or (b) reduced blood pressure or associated symptoms of end organ dysfunction; (2) 2 or more of the following occur after exposure to a likely allergen for that patient: (a) involvement of skin or mucosal tissue, (b) respiratory compromise, (c) reduced blood pressure or associated symptoms, or (d) persistent gastrointestinal symptoms; and (3) reduced blood pressure after exposure to a known allergen for that patient.

hives, swelling, and/or respiratory symptoms (eAppendix in the Supplement).

To identify anaphylaxis, allergists/immunologists reviewed the electronic health records of employees (1) reporting 2 or more allergy symptoms, (2) described as having an allergic reaction in MGB safety reports, (3) logged by the on-call MGB allergy/immunology team supporting employee vaccination, and (4) referred to MGB allergy/immunology. Episodes were scored using the Brighton Criteria[2] and the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria.[3] Confirmed anaphylaxis required meeting at least 1 of these 2 sets of criteria.

We described characteristics and outcomes of anaphylaxis cases. We calculated incidence rates and 95% CIs of self-reported acute allergic reactions and confirmed anaphylaxis, using vaccine administrations as the denominator. We compared frequencies using χ^2 tests, considering a 2-sided *P* value of .05 statistically significant. Analyses were conducted in SAS version 9.4. This study was approved by the MGB Human Research Committee with a waiver of informed consent.

Results | Of 64 900 employees who received their first dose of a COVID-19 vaccine, 25 929 (40%) received the Pfizer-BioNTech vaccine and 38 971 (60%) received the Moderna vaccine. At least 1 symptom survey was completed by 52 805 (81%).

Acute allergic reactions were reported by 1365 employees overall (2.10% [95% CI, 1.99%-2.22%]), more frequently with the Moderna vaccine compared with Pfizer-BioNTech (2.20% [95% CI, 2.06%-2.35%] vs 1.95% [95% CI, 1.79%-2.13%]; *P* = .03) (**Table 1**). Anaphylaxis was confirmed in 16 employees (0.025% [95% CI, 0.014%-0.040%]): 7 cases from the Pfizer-BioNTech vaccine (0.027% [95% CI, 0.011%-0.056%]) and 9 cases from the Moderna vaccine (0.023% [95% CI, 0.011%-0.044%]) (*P* = .76).

Individuals with anaphylaxis were a mean age of 41 (SD, 13) years, and 15 (94%) were female (**Table 2**); 10 (63%) had an allergy history and 5 (31%) had an anaphylaxis history. Mean time to anaphylaxis onset was 17 (SD, 28; range, 1-120) minutes. One patient was admitted to intensive care, 9 (56%) received intramuscular epinephrine, and all recovered. Three employees, with prior anaphylaxis history, did not seek care.

Discussion | In this prospective cohort of health care employees, 98% did not have any symptoms of an allergic reaction after receiving an mRNA COVID-19 vaccine. The remaining 2% reported some allergic symptoms; however, severe reactions consistent with anaphylaxis occurred at a rate of 2.47 per 10 000 vaccinations. All individuals with anaphylaxis recovered without shock or endotracheal intubation.

The incidence rate of confirmed anaphylaxis in this study is larger than that reported by the Centers for Disease Control and Prevention based on passive spontaneous reporting methods (0.025-0.11 per 10 000 vaccinations).[1] However, the overall risk of anaphylaxis to an mRNA COVID-19 vaccine remains extremely low and largely comparable to other common health care exposures.[4] Although cases were clinically compatible with anaphylaxis, the mechanism of these reactions is unknown.

Most of the vaccine recipients with anaphylaxis had allergy histories, with 31% having prior anaphylaxis. However, given that approximately 5% of adults have severe food allergy histories[5] and 1% of adults have severe drug allergy histories,[6] this MGB employee cohort likely included almost 4000 individuals with severe food or medication allergy histories who were safely vaccinated.

Limitations of this study include the use of self-reported data. However, cohort participants were largely health care workers, and therefore self-reported data reliability may be

Table 2. Anaphylaxis Cases After mRNA COVID-19 Vaccination (n = 16)

Characteristics	No. (%)		
	Both mRNA vaccines (n = 16)	Pfizer-BioNTech (n = 7)	Moderna (n = 9)
Age, mean (SD), y	41 (13)	41 (14)	41 (13)
Female	15 (94)	6 (86)	9 (100)
Prior allergic reactions	10 (63)	3 (43)[a]	7 (78)[b]
Prior anaphylaxis	5 (31)	1 (14)	4 (44)
Symptoms			
Pruritus, urticaria, and/or angioedema	14 (88)	6 (86)	8 (89)
Sensation of throat closure, cough, wheeze, and/or dyspnea	14 (88)	6 (86)	8 (89)
Hypotension and/or tachycardia	7 (44)	3 (43)	4 (44)
Nausea, vomiting, and/or diarrhea	8 (50)	3 (43)	5 (56)
Minutes to onset, mean (SD) [range]	17 (28) [1-120]	14 (7) [10-30]	19 (38) [1-120]
Symptom timing			
≤15 min	14 (88)	6 (86)	8 (89)
≤30 min	15 (94)	7 (100)	8 (89)
Received epinephrine	9 (56)	6 (86)	3 (33)
Treatment setting[c]			
Emergency department	9 (56)	4 (57)	5 (56)
Hospitalization	1 (6)	1 (14)	0
Intensive care unit	1 (6)	1 (14)	0
Brighton level[d]			
1	1 (6)	0	1 (11)
2	13 (81)	7 (100)	6 (67)
3	2 (13)	0	2 (22)
NIAID/FAAN criteria[e]	9 (56)	4 (57)	5 (56)
Severity[f]			
Grade I	7 (44)	3 (43)	4 (44)
Grade II	9 (56)	4 (57)	5 (56)
Grade III	0	0	0
Grade IV	0	0	0
Elevated tryptase[g]	1 (6)	0	1 (11)

Abbreviations: mRNA, messenger RNA; NIAID/FAAN, National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network.

[a] Allergies to (1) dexamethasone and propranolol, (2) penicillin and measles, mumps, and rubella vaccine, and (3) venom, tree nuts, shellfish, aspirin, and sulfites.

[b] Allergies to (1) gadolinium, (2) tree nuts and sulfonamide antibiotics, (3) sulfonamide antibiotics and cat dander, (4) peanuts, tree nuts, and morphine, (5) shellfish, tree nuts, and sulfonamide antibiotics, (6) ciprofloxacin, and (7) peanut, penicillin, sulfonamide antibiotics, and gadolinium.

[c] Highest level of care reported. There were 3 employees who did not seek treatment, 1 employee who was treated in an urgent care clinic, and 1 employee who was treated in the Mass General Brigham health system vaccine clinic.

[d] The Brighton Collaboration[2] case definition uses combinations of symptoms to define levels of diagnostic certainty. Brighton level 1 represents the highest level of diagnostic certainty that a reported case represents anaphylaxis; levels 2 and 3 are successively lower levels of diagnostic certainty; level 4 is a case reported as anaphylaxis but that does not meet the Brighton Collaboration case definition; and level 5 is a case that was neither reported as anaphylaxis nor meets the case definition. This study considered only Brighton level 1 or 2 as anaphylaxis cases. Brighton level 3 cases met NIAID/FAAN clinical criteria.[3]

[e] NIAID/FAAN clinical criteria[3] for the diagnosis of anaphylaxis must meet 1 of the following criteria: (1) acute onset with involvement of skin and/or mucosal tissue and either (a) respiratory compromise or (b) reduced blood pressure or associated symptoms of end organ dysfunction; (2) 2 or more of the following occur after exposure to a likely allergen for that patient: (a) involvement of skin or mucosal tissue, (b) respiratory compromise, (c) reduced blood pressure or associated symptoms, or (d) persistent gastrointestinal symptoms; and (3) reduced blood pressure after exposure to a known allergen for that patient.

[f] Grade I, cutaneous symptoms; grade II, measurable but not life-threatening symptoms; grade III, life-threatening symptoms; grade IV, cardiac and/or respiratory arrest. Based on a scale of anaphylactoid reactions in *Lancet*. 1977;1(8009):466-469.

[g] Tryptase measurement was captured acutely in 5 cases (32%). An elevated tryptase level was defined as either above the upper limit of normal or >(2 + 1.2 × baseline tryptase level). One patient with a baseline tryptase level of 4.3 ng/mL had an acute tryptase level of 7.7 ng/mL associated with Moderna vaccine anaphylaxis.

high. The use of vaccine administrations as the denominator for allergic reaction incidence may have resulted in some inaccuracy. Although study methods might have missed cases of potential anaphylaxis, comprehensive prospective surveillance methods were used, and symptom survey alone captured 81% of all vaccinated employees. A northeastern US cohort may not be generalizable.

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COMMENT & RESPONSE

Fractional Flow Reserve Treatment and Major Adverse Cardiac Events in Patients With Coronary Artery Disease

To the Editor The study by Dr Sud and colleagues,[1] which measured single-vessel fractional flow reserve (FFR) in patients with coronary artery disease, demonstrated that percutaneous coronary intervention (PCI) was associated with a lower rate of major adverse cardiac events for ischemic lesions on FFR but a higher rate of major adverse cardiac events for nonischemic lesions, compared with those not receiving PCI. While these findings support an FFR-based threshold for PCI procedures, we are concerned about its use in patients with heart failure. The authors do not appear to have considered the potential influence of central venous pressure in the analysis of FFR measurement in patients with heart failure included in their study. The mean right atrial pressure, when in the normal range, is considered to have a negligible influence on FFR measurement.[2,3] However, an elevated central venous pressure, often seen in patients with heart failure, may have an important effect on FFR measurement, which may influence the determination of coronary artery lesion severity.[4] Therefore, the results of this large retrospective analysis should be interpreted cautiously for patients with heart failure.

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In Reply The concern raised by Dr Rigatelli and Mr Zuin regarding our study[1] involves the influence of heart failure on FFR