Gastrointestinal reflux contributes to laryngopharyngeal symptoms that mimic anaphylaxis: COVID-19 vaccination experience

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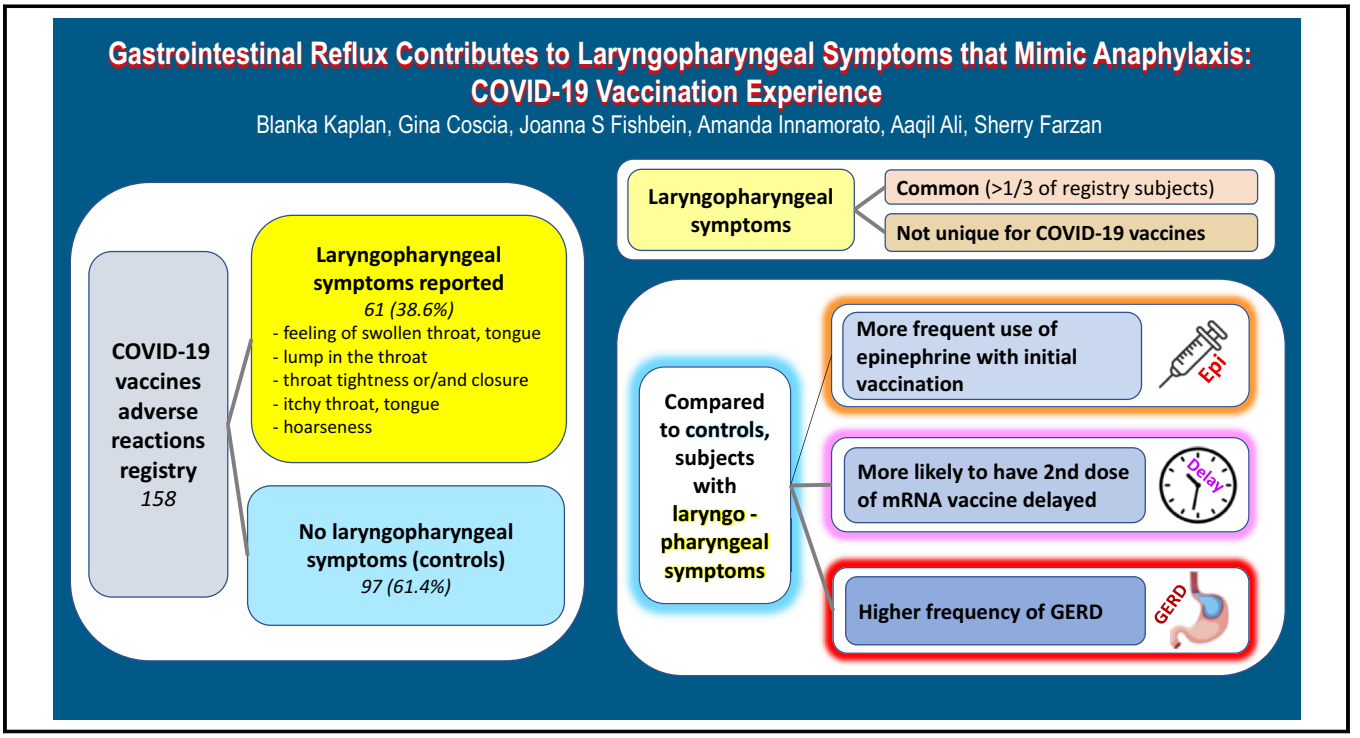
GRAPHICAL ABSTRACT



Background: The sensation of throat closure after vaccination is concerning for anaphylaxis and leads to vaccine hesitancy.
Objectives: We characterized patients who developed laryngopharyngeal symptoms (LPhS) after coronavirus disease 2019 (COVID-19) vaccination and assessed risk factors for these symptoms.
Methods: The study analyzed data from the COVID-19 vaccines adverse reactions registry (December 14, 2020, to June 13, 2022). Outcomes included the incidence of postvaccination LPhS and use of epinephrine. We identified and compared risk factors for COVID-19 postvaccination reactions between subjects with and without LPhS.
Results: A total of 158 subjects were enrolled onto the registry. LPhS were reported in 61 subjects (38.6%), of whom 52 (85.2%) received a subsequent dose. With initial vaccination, the use of epinephrine was higher in subjects with LPhS (20%) compared to those without (6%; $P = .0094$). Fifty-two subjects (85.2%) with LPhS received a subsequent COVID-19 vaccine dose with milder or no symptoms, and none needed treatment with epinephrine. Those with LPhS were more likely to have a history of drug allergies ($P = .02$), severe medication allergies ($P = .03$), gastroesophageal reflux disease ($P = .018$), and need for antireflux medications ($P = .0085$) compared to controls.
Conclusions: In our registry, postvaccination LPhS were common. LPhS can mimic anaphylaxis and lead to more frequent use of epinephrine. Gastroesophageal reflux disease was more frequent in these subjects. Patients with subjective throat closure sensation can safely receive subsequent vaccine doses with close observation and reassurance. LPhS are not

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unique to COVID-19 vaccines. Patient and provider education regarding the role of gastroesophageal reflux disease as a risk factor for LPhS with vaccination can improve vaccine uptake. (J Allergy Clin Immunol Global 2024;3:100176.)

Key words: *COVID-19, vaccine, adverse reaction, mRNA, GERD, LPR, epinephrine, vaccination delay, anaphylaxis, allergy, hypersensitivity, immunization stress-related response*

Timely and effective vaccination is the best available prophylactic tool to decrease morbidity and mortality of infectious diseases. Allergic reactions to vaccines are rare and mostly mild.[1] During the rollout of novel coronavirus disease 2019 (COVID-19) vaccines, the initial estimated anaphylaxis rate was almost 10 times higher for the Pfizer-BioNTech COVID-19 vaccine (BNT162b2) than the general rate for other vaccines. Although recent publications reported a lower COVID-19 vaccine anaphylaxis rate, it still exceeds the historical estimated rate for other vaccines, at 4.8-7.91 and 1.31 cases per million doses administered, respectively.[2-4] Thus, more than 2 years into the largest vaccination campaign in history, concern remains that severe allergic reactions are more frequent with COVID-19 vaccines.

Anaphylaxis is a severe, potentially fatal allergic reaction that is diagnosed clinically and demands immediate recognition and treatment. Because there is no standardized, confirmatory test for anaphylaxis, clinically validated National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network[5] and World Allergy Organization[6] criteria were established to aid in the diagnosis of anaphylaxis. In addition, the Brighton collaboration criteria[7] were specifically created for immunization-associated anaphylaxis and were widely used to report adverse reactions after COVID-19 vaccination. Concerns about overdiagnosis of anaphylaxis based on current criteria led to recent reevaluation of the Brighton collaboration case definition for anaphylaxis.[8]

Clinically, presentation with acute respiratory, cardiac, and/or dermatologic symptoms after exposure to a potential allergen is consistent with an allergic reaction. Subjective complaints of throat discomfort, including feelings of throat tightness/closing, swollen tongue, and hoarseness, raise clinicians' concern for a severe allergic reaction. The goals of this study were to characterize patients who developed postvaccination laryngopharyngeal symptoms (LPhS) that can mimic anaphylaxis, compare them to patients without LPhS, and assess risk factors for these symptoms.

Abbreviations used

BNT162b2:	Pfizer-BioNTech COVID-19 vaccine
COVID-19:	Coronavirus disease 2019
GERD:	Gastroesophageal reflux disease
ISSR:	Immunization stress–related response
LPhS:	Laryngopharyngeal symptoms
LPR:	Laryngopharyngeal reflux
mRNA-1273:	Moderna COVID-19 vaccine
PEG:	Polyethylene glycol
SOB:	Shortness of breath
VCD:	Vocal cord dysfunction

METHODS

Study design

This study prospectively enrolled patients evaluated in the Division of Allergy and Immunology at Northwell Health for COVID-19 vaccine reactions from December 14, 2020, to June 13, 2022. A COVID-19 registry was established to record and monitor adverse reactions to COVID-19 vaccines. Written consent was obtained from all subjects; patients who declined participation in the registry were excluded. This study was approved by the institutional review board of the Feinstein Institutes of Medical Research at Northwell Health.

Information about adverse reactions with COVID-19 vaccination, treatment, and medical history were collected from the patients and review of medical records. A questionnaire was used for structured data collection (see the Methods in the Online Repository available at www.jaci-global.org). Patients who presented with a feeling of swollen and/or thick tongue, swollen throat, lips, uvula, lump in the throat, throat tightness or/and closure, itchy throat and/or tongue, and hoarseness were included in the LPhS group. The control group included all registry patients without LPhS. For our purposes here, we defined the initial vaccine dose as the first dose of COVID-19 vaccine that resulted in allergic or adverse symptoms. Subsequent vaccinations were received after the reaction-provoking dose. Patients with a history of a COVID-19 vaccine reaction were offered subsequent dose administration at the Northwell Health high-risk COVID-19 vaccine clinic. Patients were premedicated, vaccinated, and observed for at least 1 hour, or longer if any concerning allergic symptoms were reported. Premedications included antireflux medications (H_2 receptor antagonists or/and proton pump inhibitors) with or without H_1 antihistamines. All supervising physicians were allergy specialists, trained in recognition and treatment of allergic reactions, including anaphylaxis. Symptoms during a subsequent COVID-19 vaccine dose, premedication, and treatment drugs were recorded. Baseline and postvaccination tryptase level data were collected for those with symptoms concerning for anaphylaxis. Delay in vaccination was defined as an interval of longer than 6 weeks between receiving the first and second mRNA vaccines. Comparisons were performed among patients who received mRNA vaccines. Data of one patient who experienced adverse symptoms with the Janssen vaccine and developed more significant LPhS, including persistent dysphonia and dysphagia after receiving the Moderna COVID-19 vaccine (mRNA-1273) booster, were analyzed as an mRNA vaccine reaction.

Study outcomes

Presence of LPhS and use of epinephrine for initial and subsequent vaccinations were assessed. We examined risk factors for reactions to COVID-19 vaccines, including history of allergic reactions, anxiety, presence and frequency of gastroesophageal reflux disease (GERD), and treatment with antireflux medications before vaccination. History of any and severe allergic reactions to medications, vaccines, food, intravenous contrast, venom, and latex was reported. Severity of prior allergic reactions was documented by allergy specialists according to patient report and recorded history. Severe reactions included anaphylaxis, systemic symptoms suggestive of anaphylaxis, and severe cutaneous adverse drug reactions. Frequency of risk factors were compared between laryngopharyngeal and control groups. Incidence of LPhS, depending on the type of mRNA COVID-19 vaccine

TABLE I. Patient characteristics and vaccination data

Characteristic	All patients	LPhS	No LPhS	*P* value
No. of patients	158	61 (38.6)	97 (61.4)	
Age at vaccination (years), mean ± SD	44.8 ± 15.8	47.6 ± 12.9	43.1 ± 17.3	.06
Sex				.02
Female	34 (85)	57 (93.4)	77 (79.4)	
Male	24 (15)	4 (6.6)	20 (20.6)	
Race				.57*
White	93 (59)	38 (62.3)	55 (56.7)	
African American/Black	19 (12)	7 (11.5)	12 (12.4)	
Asian	12 (8)	3 (4.9)	9 (9.3)	
Native American/Alaskan/Pacific Islander	2 (1)	0	2 (2)	
Unknown/declined	32 (20)	13 (21.3)	19 (19.6)	
Ethnicity				.06
Hispanic	20 (13)	6 (9.8)	14 (14.4)	
Non-Hispanic	117 (74)	42 (68.9)	75 (77.3)	
Unknown	21 (13)	13 (21.3)	8 (8.3)	
Type of COVID-19 vaccine received				.001
BNT162b2	100 (63.3)	48 (78.7)	52 (53.6)	
mRNA1-1273	56 (35.4)	12 (19.7)	44 (45.4)	
Janssen†	2 (1.3)	1 (1.6)	1 (1)	NA
Vaccine dose that caused initial reaction				.5
First	135 (85.4)	52 (85.2)	83 (85.6)	
Second	17 (10.8)	8 (13.1)	9 (9.3)	
Booster (third)	6 (3.8)	1 (1.6)	5 (5.2)	
Exact dates for first and second mRNA vaccination available	122 (77.2)	51 (83.6)	71 (73.2)	
Second dose of mRNA vaccine delayed (>6 weeks)	67 (54.9)	36 (70.6)	31 (43.7)	.0032
No delay in vaccination	55 (45.1)	15 (29.4)	40 (56.3)	

Data are presented as nos. (%) unless otherwise indicated.
NA, Not applicable.
*Comparison was done between White, African America/Black, Asian with Native American/Alaskan/Pacific Islander, and unknown.
†Data from those who received the Janssen vaccine were excluded from inferential analysis.

received, and delay in receiving the second dose of the initial vaccination series were also examined.

Statistical analysis

Descriptive statistics were computed for the overall sample and by LPhS status (ie, frequencies and proportions for categorical factors, and means and standard deviations or medians and interquartile ranges for continuous factors). Either the chi-square test or the Fisher exact test was used to compare categorical risk factors according to presence of LPhS, as appropriate. Either 2-sample *t* test or Wilcoxon rank sum test was used to compare continuous factors between the 2 groups, as appropriate.

RESULTS

Baseline characteristics

A total of 190 adult subjects were evaluated for COVID-19 vaccine adverse reactions, of whom 158 consented to participate in the COVID-19 vaccines adverse reactions registry. Overall, 134 (85%) were female, and the median (Q1-Q3) age was 44.9 (36.0-54.0) years (Table I). All but 2 subjects had reactions to mRNA vaccines. Most subjects (135 [85.4%]) experienced a reaction to the first vaccine dose. LPhS were reported in 61 subjects (38.6%), of whom 52 (85.2%) went on to receive a subsequent dose (Fig 1). Ninety-seven control subjects (61.4%) reported various symptoms, including rashes (flushing, pruritus, hives, nonurticarial rashes, and large injection-site reactions), swelling, tachycardia, hypertension, dizziness, lymphadenopathy, tingling, paresthesia, and anaphylaxis.

LPhS group

LPhS were present in 61 subjects (38.6%). Fifty-three subjects (86.9%) in this group had other associated respiratory, cardiac, dermatologic, and/or gastrointestinal symptoms (Table II). Concomitant respiratory symptoms were reported in 23 subjects (37.7%), including shortness of breath (SOB) without wheezing (20 [87.0%]), cough (4 [17.4%]), and self-reported wheezing (1 [4.3%]). The subject with wheezing, 3 subjects (75%) with cough, and 12 (60%) with subjective SOB had known asthma. Tachycardia and hypertension were the only cardiac symptoms observed. None of the subjects developed respiratory failure, hypotension, or shock. None of the LPhS patients had a history of vocal cord dysfunction (VCD).

Most symptoms started within 1 hour (50 [81.9%]) and resolved within a day (37 [60.7%]) (Fig 2). Twenty-five subjects (41.0%) developed symptoms after the standard 15-minute observation period ended. Symptoms lasted over 24 hours in 23 subjects (37.7%), of whom 6 (9.8%) reported symptoms lasting for over a month. Among 61 subjects with LPhS, there was a significantly higher proportion of Pfizer-BioNTech COVID-19 vaccine recipients (BNT162b2) versus mRNA-1273 vaccine recipients in the laryngopharyngeal group (78.7% and 19.7%, respectively) compared to control subjects (53.6% and 45.4%, respectively) ($P = .001$) (Table I).

Concern for anaphylaxis

With initial vaccination, a total of 18 patients received epinephrine for presumed anaphylaxis. Epinephrine was administered to 12 (19.7%) LPhS subjects compared to 6 (6.2%) in the

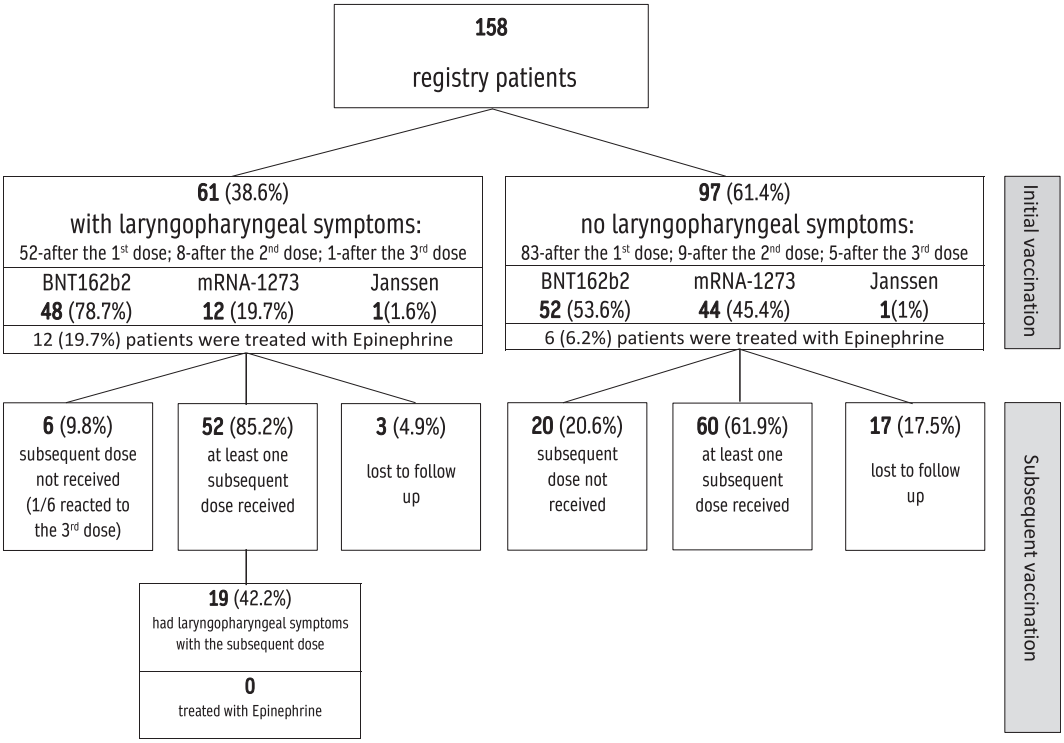

FIG 1. Patients (N = 158) provided informed consent for inclusion of their cases in a COVID-19 vaccine adverse reactions registry.

control group (P = .0094). Two of 6 control subjects received epinephrine on days 4 and 14 after vaccination, therefore inconsistent with immediate IgE-mediated COVID-19 vaccine–induced anaphylaxis. One control subject fulfilled old level 2 Brighton criteria,[7] and 3 subjects developed transient adverse symptoms inconsistent with anaphylaxis. None of the LPhS group subjects needed epinephrine with subsequent vaccination (Fig 1).

Baseline tryptase levels were available in 31 subjects from the LPhS group and 29 control subjects, and postreaction levels were obtained in 6 and 1 subject, respectively. Three additional subjects in the LPhS group had postreaction levels without basal levels. None of the postreaction tryptase levels was elevated compared to baseline. One LPhS group subject had baseline elevated tryptase level that did not change after the reaction.

Dysphonia

Five subjects developed hoarseness after initial COVID-19 vaccination. All but one subject denied history of dysphonia. None of them had active voice problems at the time of vaccination. Dysphonia was mild, resolved within few hours, and did not recur with subsequent vaccination in 2 of these 5 subjects. The other 3 subjects developed severe persistent dysphonia after receiving the first COVID-19 mRNA vaccine. One of them received a subsequent BNT162b2 vaccine and developed dysphonia 30 minutes after the vaccination. Her dysphonia after receiving the second COVID-19 vaccination was more severe and lasted over 6 weeks, which was longer than with the first dose. Another subject, who had mild subjective LPhS after receiving the Janssen vaccine, developed dysphonia and dysphagia the day after receiving mRNA-1273 booster that lasted over a month. The third patient declined subsequent vaccination. Dysphonia was observed and documented by an otolaryngologist and/or allergist in all 3 patients with persistent symptoms.

LPhS with subsequent dose

Among the 52 (85.2%) laryngopharyngeal group subjects who received a subsequent mRNA COVID-19 vaccine, 19 (36.5%) developed LPhS. Most subjects (46 [88.9%]) received the subsequent dose at the Northwell Health high-risk clinic under a physician's supervision. Subjects reported upper airway, tongue, or throat swelling; lump or knot in the throat; throat or tongue feeling thick, sore, scratchy, or irritated; and numbness of throat or/and tongue. Objective findings during the observation period were noted in 2 patients: cough and hoarseness in patients with mast cell activation syndrome and dysphonia, respectively. Vital signs and physical examination results, including oral and respiratory examinations, were normal in all patients. Four subjects reported subjective chest tightness and SOB. Two of these subjects had a known history of asthma, another had asthma and mast cell activation syndrome, and one had Sjögren syndrome–associated lung disease. Two subjects had subjective pruritus without rash, and 1 had palpitations. All symptomatic subjects, except the 2 with dysphonia, reported that symptoms were milder compared to the initial vaccination.

Premedication and treatment of LPhS for subsequent vaccination

According to the initial recommendations,[9] subjects receiving subsequent vaccination after an initial reaction were premedicated with H_1 antihistamines. Subjects with LPhS were also premedicated with famotidine. Our typical recommendation was to

TABLE II. Associated symptoms with initial vaccination for LPhS patients

Symptom	No. (%)
No. (%) with data	61 (100)
Isolated LPhS	8 (13.1)
Respiratory symptoms	23 (37.7)
Hypoxemia	0
Bilateral wheeze/bronchospasm*	1 (4.3)
Respiratory distress including at least 2 of tachypnea, increased use of accessory respiratory muscles, recession, cyanosis, and grunting	0
Stridor	0
Decreased peak flow	0
Cough	4 (17.4)
Difficulty breathing without wheeze or stridor	20 (87.0)
Sneezing, rhinorrhea	0
Gastrointestinal symptoms	11 (18.0)
Diarrhea	2 (18.2)
Abdominal pain	4 (36.4)
Nausea	5 (45.5)
Vomiting	2 (18.2)
Cardiac symptoms	19 (31.1)
Measured hypotension/low blood pressure	0
Uncompensated shock by at least 3 of: tachycardia, cap refill >3 seconds, reduced central pulse volume, decreased/loss of consciousness	0
Reduced peripheral circulation by at least 2 of the following: tachycardia and cap refill >3 seconds without hypotension, decreased consciousness	0
Decreased or loss of consciousness without uncompensated shock or peripheral circulation above	0
Hypertension	11 (57.9)
Tachycardia	14 (73.7)
Dermatologic symptoms	35 (57.4)
Generalized urticaria/hives or generalized erythema/redness	26 (74.3)
Angioedema† (local or generalized)	10 (28.6)
Generalized pruritus with skin rash	14 (40.0)
Generalized pruritus without skin rash	8 (22.9)
Generalized prickling sensation	0
Local injection-site urticaria/hives	1 (2.9)
Red, itchy eyes	1 (2.9)

Patients may have had >1 symptom.
*Wheezing in 1 patient was self-reported and was not recorded in emergency room records.
†Angioedema refers to nonlaryngopharyngeal swelling.

take famotidine 20 mg and cetirizine 10 mg or fexofenadine 180 mg the night before and 1 hour before vaccination. Subjects who were receiving therapy with H_2 receptor antagonists for their initial vaccination reaction were additionally premedicated with proton pump inhibitors, and vice versa. As we gained a better understanding of adverse effects of COVID-19 vaccines, subjects with isolated LPhS were premedicated only with antireflux medications. Maintenance asthma medications for people with asthma who developed SOB with their initial vaccination were optimized, and they took 2 puffs of short-acting bronchodilator 1 hour before vaccination.

LPhS with subsequent vaccination were reported by 19 women (31.1%), of whom 16 (84%) received symptomatic treatment at their supervising physician's discretion (see Table E1 in this article's Online Repository at www.jaci-global.org). Oral H_1 and H_2 antihistamines were provided to most patients. Postvaccination cough and chest tightness in people with asthma were treated with inhaled/nebulized bronchodilators. The subject with a mast cell activation syndrome received intramuscularly administered diphenhydramine. Subjects who developed dysphonia were treated with oral prednisone, proton pump inhibitors, H_1 antihistamines, and H_2 receptor antagonists.

Risk factors

The prevalence of anxiety (40.8%), asthma (37.3%), history of allergic reaction to medications (44.9%), and GERD (58.7%) in our cohort was overall high (Table III). There was no significant difference in prevalence of anxiety, asthma, and history of allergic reactions to vaccines, foods, intravenous contrast, venom, or latex between laryngopharyngeal and control groups. Subjects with LPhS were more likely to have a history of overall drug allergies ($P = .02$), severe medication allergies ($P = .03$), a history or symptoms of GERD ($P = .018$), and a prescription for an antireflux medication or are receiving daily medications for reflux/GERD ($P = .0085$). Frequency of heartburn and reflux symptoms did not correlate with incidence of postvaccination LPhS ($P = .64$). All 3 subjects with persistent dysphonia and 1 of 2 subjects with mild hoarseness had known GERD. Sixteen subjects (26.2%) with LPhS after COVID-19 vaccination reported a history of LPhS with medications (10 [62.6%]), non–COVID-19 vaccines (5 [31.3%]), or both (1 [6.3%]).

Delay in completing initial vaccine series

Among the 156 subjects in the cohort who experienced a reaction to their initial COVID-19 mRNA vaccine, the dates of first and second vaccination were available for 122 subjects. Sixty-seven (54.9%) of these subjects were delayed more than 6 weeks in receiving their second vaccine dose. The proportion of subjects with vaccination delay was significantly higher among LPhS subjects (36/51, 70.6%) compared to those without LPhS (31/71, 43.7%, $P = .0032$) (Table I).

DISCUSSION

The data from the Northwell Health COVID-19 adverse vaccine reactions registry demonstrate 4 main findings. First, postvaccination LPhS are common but are not consistent with anaphylaxis. Second, patients presenting with LPhS are more likely to receive epinephrine compared to those without these symptoms. Third, GERD is a risk factor for the development of LPhS after COVID-19 vaccination. Fourth, delay in receiving the second dose of mRNA vaccine was significantly more common among LPhS subjects compared to controls.

Most cases reported as anaphylaxis during the COVID-19 vaccine rollout did not meet anaphylaxis criteria after careful review.[10] Respiratory symptoms in our laryngopharyngeal group were predominantly subjective, and there were no cases of respiratory or circulatory compromise. None of the subjects vaccinated in our high-risk COVID-19 vaccine clinic, including those with LPhS, required epinephrine. Furthermore, subjects who reported

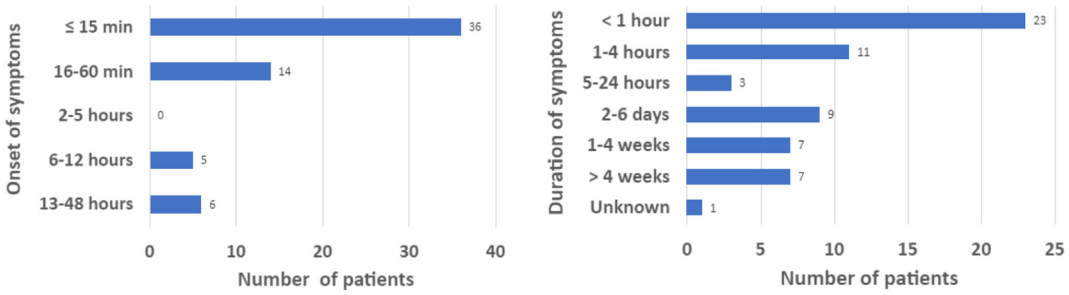

FIG 2. Onset *(left)* and duration *(right)* of LPhS after initial COVID-19 vaccination.

TABLE III. Risk factors, stratified by LPhS status

Risk factor	Overall (N = 158)	LPhS (n = 61)	No LPhS (n = 97)	*P* value
Anxiety; no. (%) with data	130 (82)	54 (89)	76 (78)	
History of anxiety	53 (40.8)	26 (48.1)	27 (35.5)	.15
Asthma; no. (%) with data	158 (100)	61 (100)	97 (100)	
History of asthma	59 (37.3)	28 (45.9)	31 (32.0)	.08
History of allergic reactions of any severity;* no. (%) with data	158 (100)	61 (100)	97 (100)	
Medications	71 (44.9)	36 (59.0)	35 (36.1)	.02
Vaccines	19 (12.0)	10 (16.4)	9 (9.3)	.18
Food	55 (34.8)	23 (37.7)	32 (33.0)	.72
Intravenous contrast	19 (12.0)	11 (18.0)	8 (8.2)	.09
Venom	31 (19.6)	11 (18.0)	20 (20.6)	.38
Latex allergy	13 (8.2)	7 (11.5)	6 (6.1)	.35
History of severe allergic reactions;* no. (%) with data	158 (100)	61 (100)	97 (100)	
Medications	26 (16.5)	15 (26.0)	11 (11.3)	.03
Vaccines	5 (3.2)	2 (3.3)	3 (3.1)	.99
Food	23 (14.6)	9 (14.8)	14 (14.4)	.99
Intravenous contrast	8 (5.1)	6 (9.8)	2 (2.1)	.06
Venom	8 (5.1)	5 (8.2)	3 (3.1)	.26
Latex allergy	8 (5.1)	4 (6.6)	4 (4.1)	.49
GERD; no. (%) with data	150 (95)	58 (95)	92 (95)	
History or symptoms of GERD	88 (58.7)	41 (70.7)	47 (51.1)	.018
Frequency of heartburn; no. (%) with data	82 (93)	38 (93)	44 (94)	
3 or more times a week	38 (46.3)	20 (52.6)	18 (40.9)	.64
1-2 times a week	17 (20.7)	8 (21.1)	9 (20.5)	
1-3 times a month	20 (24.4)	7 (18.4)	13 (29.5)	
Less than once a month	7 (8.5)	3 (7.9)	4 (4.1)	
Antireflux medications; no. (%) with data	154	58	96	
Prescribed or daily antireflux medications	40 (26.0)	22 (37.9)	18 (18.8)	.0085

*History of allergic reactions to medications, vaccines, food, intravenous contrast, venom, and latex is not mutually exclusive.

a severe reaction to the initial vaccination went on to receive a subsequent full vaccine dose and a booster, with mild or no symptoms, except subjects with persistent dysphonia.

An acute elevation of tryptase indicates mast cell degranulation in anaphylaxis and is thought to correlate with more severe symptoms.[11] Only a few patients had their tryptase level checked at the time of the initial reaction, but none of the patients with available data had an acute rise in tryptase levels. Taken together, subjective LPhS, a reaction on the first exposure to COVID-19 vaccines, milder or absent symptoms on repeat exposure, symptom resolution without epinephrine, and lack of tryptase elevation are inconsistent with anaphylaxis.

Subjects with LPhS were much more likely to have received epinephrine compared to controls. This underscores the significance of laryngopharyngeal manifestations in a provider's clinical decision making and the potential for overdiagnosis of anaphylaxis. Prompt recognition and treatment of anaphylaxis is of paramount importance, but subjective throat and tongue complaints alone should not be considered symptoms of anaphylaxis.

Polyethylene glycol (PEG), the excipient in mRNA vaccines, was initially blamed for allergic reactions to COVID-19 vaccinations. PEG is a common excipient for oral and injectable medications, but anaphylaxis to PEG is extremely rare.[12] Subsequent publications demonstrated that PEG is not responsible for severe hypersensitivity reactions,[13-15] and people with severe PEG allergy are able to tolerate mRNA vaccines.[16,17] Non–IgE-mediated mechanisms to explain COVID-19 vaccine reactions, including complement activation–related pseudoallergy (aka CARPA), have been proposed[18-20] but not demonstrated.

A recent nested case–control study found that immunization stress–related response (ISSR) accounted for 85% of adverse reactions after mRNA-1273 vaccine.[21] ISSR, formerly called immunization anxiety-related reaction,[22] includes nonallergic symptoms that are precipitated by the stress of immunization.[23] LPhS fall under the umbrella of ISSR. Postnasal drip, VCD, laryngospasm, anxiety, laryngopharyngeal reflux (LPR), and GERD contribute to LPhS and can mimic stridor in anaphylaxis. Correlations have been observed between GERD/LPR and allergic rhinitis,[24] vocal cord disease,[25,26] and anxiety.[27,28] Female sex, young age, history of allergies, and anxiety are reported risk factors for ISSR[21] and acute-onset hypersensitivity events[29] to COVID-19 vaccines. In line with these reports, anxiety and asthma were frequent in our cohort, but their prevalence did not differ between the LPhS and control groups.

Our data demonstrate a significantly higher frequency of GERD and use of daily and/or prescription antireflux medications in the LPhS group compared to controls. It is unclear why only a few people who have LPR/GERD develop LPhS. We posit that there is an interplay of multiple factors, including GERD/LPR, postnasal drip, and anxiety that lead to LPhS in a stress-provoking situation. Symptoms of postnasal drip, which can be triggered by environmental allergens, nonallergic exposure, or acute nasopharyngitis, as well as symptoms of reflux and anxiety are affected by multiple factors and can change from day to day. We believe that variabilities in these symptoms, triggered by severity and activity of underlying medical conditions at the time of vaccination, rather than a specific vaccine or medication, contribute to LPhS. This would explain why some people tolerated their first COVID-19 vaccine but had nonallergic symptoms with a second vaccination or a booster.

Unfortunately, we did not have the ability to perform diagnostic laryngoscopies in the acute setting to exclude VCD, but none of the LPhS patients in our cohort had a history of VCD recorded in their charts. Importantly, while laryngoscopy is the reference standard for a diagnosis of VCD, paradoxical vocal cord adduction may not be always demonstrated as a result of the intermittent nature of this condition. Only 50% of patients who underwent laryngoscopy for strongly suspected VCD/inducible laryngeal obstruction after COVID-19 vaccination had their diagnosis confirmed in a case series of 10 patients.[30]

Our finding that BNT162b2-vaccinated patients were more likely to develop LPhS compared to mRNA-1273 implies that these symptoms are not mRNA dependent because mRNA-1273 contains a much higher quantity of mRNA. Furthermore, these symptoms are not unique to COVID-19 vaccination. More than a quarter of our patients with LPhS reported a history of similar symptoms with unrelated vaccines and/or medications.

Adverse vaccine reactions led to a delay in completing the initial COVID-19 vaccination series in our cohort. Subjects with LPhS were more likely to have their second vaccination delayed compared to those without these symptoms. Whether or not this affected the incidence and morbidity of COVID-19 infection in our cohort is unknown. While anxiety and stress are hard to control, treatment of underlying disorders such as GERD and asthma may minimize adverse reactions. Furthermore, vaccination of susceptible patients under the supervision of a clinician trained in recognition and management of anaphylaxis can encourage vaccination and reduce epinephrine treatment when not indicated. Patient education about reflux symptoms, rather than attributing subjective symptoms to anxiety, can reassure patients and reduce vaccine hesitancy. Further research is needed to validate these findings for COVID-19 and other vaccines, as well as to determine if pretreatment with antireflux medications can decrease LPhS.

To our knowledge, this is the first study that characterized postvaccination LPhS, identified GERD as a risk factor, highlighted the more frequent use of epinephrine in patients presenting with these symptoms, and demonstrated a significant delay in receiving the subsequent COVID-19 vaccine dose compared to controls. The ability to vaccinate patients at the high-risk COVID-19 vaccine clinic was a powerful tool that allowed immunizations to take place under close supervision of allergy specialists, who are skilled in evaluating and managing allergic symptoms, including anaphylaxis.

Our study has several limitations. First, GERD symptoms were self-reported in some patients and therefore were not confirmed by endoscopy in every patient. Second, laryngoscopies were not performed to exclude VCD. Third, our study was not powered to evaluate the effect of pretreatment with antireflux medications. Fourth, the number of subjects is relatively small, which is reflective of a very low incidence of allergic reactions to vaccines.

In conclusion, postvaccination LPhS were common in our registry. The importance of these findings goes beyond COVID-19 vaccines because LPhS occur with other vaccine and drug reactions. Prompt diagnosis and treatment of anaphylaxis remain paramount. However, LPhS can be misdiagnosed as anaphylaxis and are likely to be treated with epinephrine. People with GERD are more likely to develop LPhS. Close observation during immunization and reassurance of these patients can ensure timely completion of necessary vaccinations.

DISCLOSURE STATEMENT

Disclosure of potential conflict of interest: G. Coscia and S. Farzan were members of the Regional Respiratory Field Medical Advisory Board–Northeast Sanofi outside the submitted work. S. Farzan has received a grant from the American College of Allergy, Asthma & Immunology outside the submitted work. The rest of the authors declare that they have no relevant conflicts of interest.

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Key messages

- **Postvaccination LPhS occur frequently and are not unique to COVID-19 vaccines.**
- **Presentation with LPhS leads to more frequent use of epinephrine and delay in receiving a subsequent vaccine dose.**
- **GERD is a risk factor for the development of LPhS.**

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