



Primary care provider-reported prevalence of vaccine and polyethylene glycol allergy in Canada



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ABSTRACT

Background: The coronavirus disease 2019 pandemic has highlighted the importance of accurate capture of vaccine, and vaccine component, allergy. There remains a gap in the prevalence literature from the perspective of direct primary care provider (PCP) reporting at a population level.

Objective: To determine the prevalence of PCP-documented vaccine and polyethylene glycol (PEG) allergy using electronic medical record data from the Canadian Primary Care Sentinel Surveillance Network.

Methods: Retrospective cohort study using the Canadian Primary Care Sentinel Surveillance Network repository. Machine learning algorithms were applied to evaluate for vaccine allergy documentation, and Anatomic Therapeutic Chemical codes were used for PEG allergy or allergy to common injectable medications containing PEG (CIMCP).

Results: The prevalence of PCP-documented vaccine allergy in Canada was 0.037% (395/1,055,677) and of PEG allergy was 0.0009% (10/1,055,677). In total, 0.01% of patients had a documented allergy to either PEG or CIMCP (135/1,055,677). None of the patients with PEG allergy had a documented allergy to a CIMCP. Patients with vaccine allergy and PEG allergy were significantly more likely to have other atopic comorbidities, including asthma ($P < .001$ for both), eczema ($P < .001$ and $P = .001$, respectively), rhinitis ($P = .002$ and $P < .001$, respectively), and food allergy ($P < .001$ for both). Significantly higher rates of depression ($P < .001$ and $P < .001$, respectively) and anxiety ($P = .003$ and $P < .001$, respectively) were found in those with vaccine allergy, or PEG allergy, than those without vaccine allergy or PEG allergy.

Conclusion: This is the first study to estimate the prevalence of vaccine and PEG allergy in a national cohort that uses PCP documentation, revealing a low reported rate of vaccine allergy and PEG allergy.

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Introduction

Vaccination is an important contributor to global public health. A leading driver of global vaccine hesitancy is concern on adverse reactions from vaccination.^{1,2} Although local injection site reactions are common and constitutional symptoms after vaccine administration occur, allergic (immunoglobulin E-mediated) reactions are rare, occurring at a rate of approximately 1.3 per million vaccine doses administered, with vaccine-induced fatality related to anaphylaxis exceptionally rare.³

The coronavirus disease 2019 (COVID-19) pandemic has infected more than 125 million individuals and led to more than 2.7 million deaths as of March 25, 2021.⁴ There are now 2 messenger RNA (mRNA) vaccines and 3 adenovirus vector vaccines approved by emergency use authorization in multiple countries around the world. With vaccine rollout, in particular to the mRNA vaccines, there have been reports of reactions concerning for anaphylaxis among vaccine

recipients, with most reporting atopic comorbidities.⁵ The most recent data from the Centers for Disease Control and Prevention indicate a total of 66 events per 17,524,676 doses (or 3.7 events per million vaccinations), all of which have recovered with standard therapy.⁶

Both mRNA vaccines contain polyethylene glycol (PEG), and the only labeled contraindication to use these vaccines is an allergy to PEG or another vaccine ingredient.⁷ Historically, allergic reactions to PEG are rarely reported in the literature, limited thus far to case reports.^{8,9} Although PEG is a suspect allergen of the mRNA vaccine, it has not been confirmed as the cause of reactions. As a result, further insight into pre-existing risk of PEG allergy has become critical to successful vaccination implementation for the COVID-19 vaccine.

The COVID-19 pandemic has also highlighted the importance of accurate capture of vaccine, and vaccine component, allergy. There remains a gap in the prevalence literature from the perspective of direct primary care provider (PCP) reporting at a population level. A system wherein there is exclusive PCP reporting could increase specificity, and potentially elucidate causality more accurately.

The goal of this study is to determine the prevalence of PCP-reported vaccine allergy, and PEG allergy in children and adults using electronic medical record (EMR) data from providers participating in the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) before the pandemic. To the best of our knowledge, this is the first such study in North America involving a nationally representative population-level PCP-reported database.

Methods

The CPCSSN is Canada's only primary care practice-based multidisease sentinel surveillance system. The CPCSSN extracts, de-identifies and processes EMR data from 1235 primary care providers in 8 provinces and 1 territory in Canada. Patients (N = 1,055,677) were included in our cohort if they had at least 1 encounter with a CPCSSN provider (family physicians, nurse practitioners, and community pediatricians) between January 1, 2016, and December 31, 2018. This study accessed the billing, health condition (problem list), encounter diagnosis, medication, patient and provider characteristics, and allergy tables from the CPCSSN repository.

Unlike billing and health condition (problem list) tables, the allergy tables derived from EMR data do not contain diagnostic codes (ie, Systemized Nomenclature of Medicine, International Classification of Diseases, Ninth Revision [ICD-9] or Tenth Revision, or International Classification of Primary Care). Therefore, we developed and applied machine learning algorithms to evaluate semi-structured text in the allergy table of the CPCSSN data repository for documentation of a vaccine allergy. A subsample of the semi-structured text in the allergy table was reviewed and categorized by 2 researchers, and any disagreement in coding was adjudicated by the supervising clinician scientist. An algorithm was developed to expand this categorization to the entire CPCSSN network. A manual validation was performed to compare the categorization from the developed algorithm with the chart review. We used the chart review to further categorize any records that were not categorized owing to spelling errors, abbreviations, or similar but different terminology. This process was continued until all vaccine allergy records were categorized. eTable 1 outlines the terms that were categorized into vaccine allergy. Patients may have had more than 1 type of vaccine allergy recorded.

We identified patients as having a "PEG allergy" if documentation was present correlating to the relevant Anatomic Therapeutic Chemical (ATC) code (A06AD15). We identified allergy to common

injectable medications containing PEG (CIMCP)⁵ based on relevant ATC codes (Table 1). Nevertheless, this algorithm was not designed to detect the results of confirmatory testing or consultation reports.

Covariates

Patient age was calculated at the index date of December 31, 2018. We used the ICD-9 and the ATC code for medications to identify conditions and medications of interest. Previously validated case definitions were applied to evaluate prevalence of asthma and depression.¹⁰ Several conditions of interest were also included although formal validation studies have not been conducted to evaluate the sensitivity and specificity of these definitions. Conditions of interest included eczema (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] starting with 691, 692), rhinitis (ICD-9-CM starting with 477, 472), and anxiety (ICD-9-CM starting with 300). We have also included autism (ICD-9-CM starting with 299) and attention-deficit hyperactivity disorder (ICD-9-CM starting with 314). The presence of a diagnosed condition of interest required 2 ICD-9 codes from the encounter diagnosis or billing table or 1 ICD-9-CM from the health conditions table. ATC codes from the medication table were used to indicate a prescription for an eczema treatment (D02A, D07, D11AH), steroid—all routes with the exception of ophthalmic (S02B, S03B, H02, A07EA, C05AA, H02AB, R01AD, R03BA, S01BA, S01BB, S01BC, S01CA, S01CB), or an epinephrine autoinjector (C01CA24). Urban clinic location was determined using the clinics 6-digit postal code from a Canadian Metropolitan Area (population $\geq 100,000$ people). Annual visit frequency and annual medication rate were determined by calculating the mean from the total for each year (2016, 2017, and 2018). We identified patients within the CPCSSN who had documentation of an allergy, including food, stinging insect, environment, medication, or vaccine allergy. Patients with documentation of a vaccine allergy were assessed for a "second allergy" listed in the allergy table in addition to the vaccine allergy of interest (ie, at least 1 food, stinging insect, environment, or medication allergy).

Statistical Analysis

We characterized patients with, and without, documentation indicating a vaccine or PEG allergy in the EMR using descriptive statistics, including mean, SD, and frequency. Furthermore, χ^2 and *t* tests were used to understand patients with and without a vaccine or PEG allergy. An age- and sex-adjusted multivariable logistics regression model evaluated the association between documentation of a vaccine allergy (yes vs no) and patient (atopic comorbidities (yes vs no), depression (yes vs no), anxiety (yes vs no), second allergy (yes vs no), provider factors (sex [female vs male]), and clinic location (urban vs rural). We report the odds ratios (ORs) and 95% confidence intervals (CIs). Statistical analyses were conducted using SAS V9.4 (SAS Institute Inc, Cary, North Carolina).

This study was approved by the Health Research Ethics Board at the University of Manitoba (HS21787 [H2018:189]).

Results

Within our cohort, the prevalence of PCP-reported vaccine allergy in Canada was 0.037% (395/1,055,677; 370 cases per million persons). Of those with reported vaccine allergy, 23% were of male sex with a median age of 58.7 years (Table 2). Most (87.2%) were seen in urban clinics. Among those with a vaccine allergy, there were significantly higher rates of other allergic comorbidities, including asthma (*P* <

Table 1
Characteristics of Patients Who Visited a Primary Care Provider Participating in Canadian Primary Care Sentinel Surveillance Network With or Without Documentation of a Vaccine Allergy in Their Electronic Medical Record

Variable name	Patients without documentation of a vaccine allergy in the EMR, n = 1,055,282	Patients with documentation of a vaccine allergy in the EMR, n = 395	P value
N = 1,055,677			
Patient characteristics			
Patient sex, n (% male)	469,763 (44.5)	91 (23.0)	<.001
Patient age, median (IQR)	44.8 (23.8)	58.7 (22.2)	<.001
Pediatric patient (≤ 18)	281,823 (26.7)	65 (16.5)	<.001
≥ 1 or more atopic comorbidities	333,040 (31.6)	181 (45.8)	<.001
Asthma ^a	128,736 (12.2)	77 (19.5)	<.001
Eczema ^a	198,349 (18.8)	121 (30.6)	<.001
Rhinitis ^a	78,386 (7.4)	45 (11.4)	.002
Autism	3805 (0.4)	0	.23
ADHD	22,959 (2.9)	5 (1.3)	.21
Depression	188,000 (17.8)	97 (24.6)	<.001
Anxiety	259,050 (24.6)	122 (30.9)	.003
Visit frequency, mean (SD)	2.7 (2.9)	4.2 (3.9)	<.001
Annual number of prescriptions, mean (SD)	2.0 (2.6)	4.0 (3.9)	<.001
Eczema medication	266,739 (25.3)	140 (35.4)	<.001
Steroid medication	371,521 (35.2)	214 (54.2)	<.001
Epinephrine autoinjector	29,312 (2.8)	41 (10.4)	<.001
Second allergy	125,974 (11.9)	164 (41.5)	<.001
Food allergy	39,239 (3.7)	64 (16.2)	<.001
Stinging insect allergy	21,764 (2.1)	33 (8.4)	<.001
Medication allergy	161,951 (15.4)	212 (53.7)	<.001
Allergy to ≥ 3 medications	15,451 (1.5)	73 (18.5)	<.001
Environment allergy	49,413 (4.7)	62 (15.7)	<.001
Provider characteristics			
Urban clinic	925,965 (88.9)	342 (87.2)	.29
Provider age, mean (SD)	50.8 (10.9)	51.9 (11.3)	.07

Abbreviations: ADHD, attention-deficit hyperactivity disorder; EMR, electronic medical record; IQR, interquartile range.

^aAtopic comorbidities include ≥ 1 diagnosis in the EMR for asthma, eczema, rhinitis epinephrine autoinjector: C01CA24.Eczema medication: D02A[^], D07[^], and D11AH[^]. Steroid medication: S02B[^], S03B[^], H02[^], A07EA[^], C05AA[^], H02AB[^], R01AD[^], R03BA[^], S01BA[^], S01BB[^], S01BC[^], S01CA[^], and S01CB[^]. Secondary allergy: documentation in the EMR of a food allergy, stinging insect allergy, environment allergy, and medication allergy.

.001), eczema ($P < .001$), rhinitis ($P = .002$), and food allergy ($P < .001$), and significantly higher rates of prescribed allergy medications ($P < .001$) vs those without vaccine allergy. Patients with vaccine allergy were significantly more likely to have a diagnostic code for a second allergy (food, stinging insect, environmental, medication) recorded in their charts ($P < .001$). Rates of depression (24.6% vs 17.8%; $P < .001$) and anxiety (30.9% vs 24.6%; $P = .003$) were significantly higher among those with reported vaccine allergy than those without. The most common vaccine causing a potential reaction was influenza (87.6%; 346/395) followed by MMR (11.4%; 45/395); 10 patients had reported allergy to more than 1 vaccine (eTable 2). In the logistic regression analysis (Table 3), those with an atopic comorbidity (OR,

Table 2
Age- and Sex-Adjusted Logistic Regression of Vaccine Allergy Among Patients With an Appointment to a Canadian Primary Care Sentinel Surveillance Network Provider Between January 1, 2016, and December 31, 2018

Variable name	Odds ratio (95% confidence interval)	P value
N = 1,055,677		
Atopic comorbidity ^a	1.4 (1.14-1.76)	.001
Depression	1.2 (0.9-1.39)	.28
Anxiety	0.9 (0.8-1.3)	.99
Second allergy	4.1 (3.3-5.1)	<.001
Female provider (vs male provider)	1.1 (0.9-1.4)	.31
Urban clinic (vs rural)	1.3 (0.97-1.77)	.07

Abbreviation: EMR, electronic medical record.

^aAtopic comorbidities include ≥ 1 diagnosis in the EMR for asthma, eczema, and rhinitis.

1.4; 95% CI, 1.14-1.76) and a second allergy (OR, 4.1; 95% CI, 3.3-5.1) had higher odds of PCP-reported vaccine allergy compared with those without an allergic comorbidity or second allergy listed in their charts.

The PCP-reported prevalence of PEG allergy in Canada was 0.0009% (10/1,055,667; 9.5 cases per million persons). In total, 135 patients had a reported allergy to either PEG or CIMCP (135/1,055,667; 0.01%; 127 cases per million persons) (Table 1). None of the 10 patients with PEG allergy had a reported allergy to a CIMCP.

Table 3
Polyethylene Glycol or Common Injectable Medication Containing Polyethylene Glycol Allergy Among Patients With an Appointment to a Primary Care Provider Participating in Canadian Primary Care Sentinel Surveillance Network Between January 1, 2016, and December 31, 2018

Medication	Frequency
N = 1,055,677	
Macrogol (A06AD15)	10
Methylprednisolone acetate (H02AB04)	19
Methoxy polyethylene glycol epoetin beta (Micera) (B03XA03)	0
Pegfilgrastim (Neulasta) L03AA13	0
Medroxyprogesterone acetate (Depo-Provera) (G03DA02, G03AC06, G03AA08, G03AA17, G03FA12, L02AB02)	56
Brilliant Blue G Ophthalmic Solution (TissueBlue)—key word search	0
Sulfur hexafluoride (Lumason) (V08DA05)	45
Biomatoprost implant (Durysta)—key word search	0
Trastuzumab (L01XC03, L01XC41, L01XC14)	2
Rilonacept (Arcalyst) (L04AC04)	0
Perflutren lipid microsphere (Definity) (V08DA01, V08DA04)	3
Total	135

Table 4
Allergy to Polyethylene Glycol, or Common Injectable Medication Containing Polyethylene Glycol, Among Patients With an Appointment to a Primary Care Provider Participating in in Canadian Primary Care Sentinel Surveillance Network Between January 1, 2016, and December 31, 2018

Medication	No allergy to Macroglol or a new medication, n = 1,055,542	Macroglol (A06AD15) and injectable medications containing PEG, n = 135	P value (χ^2 or Fisher's exact test)
N = 1,055,677			
Patient sex, n (% female)	585,223 (55.5)	117 (88.0)	<.001
Patient age, mean (SD)	44.8 (23.8)	53.3 (20.0)	<.001
≥1 or more atopic comorbidities	333,157 (31.6)	64 (48.1)	<.001
Asthma ^a	128,781 (12.2)	32 (24.1)	<.001
Eczema ^a	198,431 (18.8)	39 (29.3)	.001/.001
Rhinitis ^a	78,408 (7.4)	23 (17.3)	<.001
Depression	188,042 (17.8)	55 (41.4)	<.001
Anxiety	259,105 (24.6)	67 (50.4)	<.001
Visit frequency, mean (SD)	2.7 (2.9)	5.0 (5.2)	<.001
Annual number of prescriptions, mean (SD)	1.97 (2.6)	4.0 (4.0)	<.001
Eczema medication	266,821 (25.3)	58 (43.6)	<.001
Steroid medication	371,649 (35.2)	86 (64.7)	<.001
Epinephrine autoinjector	29,349 (2.8)	7 (5.3)	.08
Second allergy	205,089 (19.4)	125 (94.0)	<.001
Food allergy ^a	39,289 (3.7)	14 (10.5)	<.001/<.001
Stinging insect allergy	21,793 (2.1)	Supp	.44
Medication allergy (excluding PEG and CIMCP)	120,690 (11.4)	75 (56.4)	<.001
Allergy to ≥3 medications	15,482 (1.5)	42 (31.6)	<.001
Environment allergy	49,430 (4.7)	45 (33.8)	<.001
Provider characteristics			
Urban clinic (vs rural clinic)	926,197 (88.9)	110 (83.3)	.04
Provider age, mean (SD)	50.8 (10.9)	49.3 (10.0)	.14

Abbreviations: CIMCP, common injectable medication containing polyethylene glycol; EMR, electronic medical record; PEG, polyethylene glycol.

^aAtopic comorbidities include ≥1 diagnosis in the EMR for asthma, eczema, rhinitis, and food allergy. Epinephrine autoinjector: C01CA24. Eczema medication: D02A[^], D07[^], and D11AH[^]. Steroid medication: S02B[^], S03B[^], H02[^] A07EA[^], C05AA[^], H02AB[^], R01AD[^], R03BA[^], S01BA[^], S01BB[^], S01BC[^], S01CA[^], and S01CB[^]. Second allergy includes a food allergy, stinging insect allergy, environment allergy, vaccine allergy, or drug allergy (excluding A06AD15 and all "new_meds"). <5 occurrences.

Similarly, all 125 patients who had an allergy to a CIMCP only listed 1 medication allergy. None of the patients with PEG allergy had a vaccine allergy reported.

Among those with a PCP-reported allergy to PEG, or CIMCP, 12% were of male sex with a mean age of 53.3 years (Table 4). Among those with a reported PEG (or CIMCP) allergy, there were significantly higher rates of other allergic comorbidities, including asthma ($P < .001$), eczema ($P = .001$), rhinitis ($P < .001$), and food allergy ($P < .001$) than those without PEG allergy or an allergy to CIMCP. There were significantly higher rates of prescribed allergy medications ($P < .001$) in those with a reported PEG/CIMCP allergy than those without PEG/CIMCP allergy. Patients with PEG/CIMCP allergy were significantly more likely to have a diagnostic code for a second allergy (food, stinging insect, environmental, medication) recorded in their charts ($P < .001$). Rates of depression (41.4% vs 17.8%; $P < .001$) and anxiety (50.4% vs 24.6%; $P < .001$) were significantly higher among those with reported PEG/CIMCP allergy recorded in their charts compared with those without.

Discussion

This is the first study to estimate the overall prevalence of vaccine and PEG allergy in a nationally representative cohort that uses PCP reporting of the allergy in the EMR. It reveals a low reported rate of vaccine allergy (0.037%) and PEG allergy (0.0009%) across Canada. These issues are particularly timely to discuss, given ongoing concerns with both COVID-19 vaccine allergic reactions, and that these could be attributable to PEG allergy, though these data underscore the low population prevalence of both PEG and vaccine allergy. Historically, the rate of vaccine anaphylaxis is approximately 1 per million doses.

Most of the EMR-reported vaccine allergy was attributable to the influenza vaccine, reported per patient instead of per dose of vaccine provided. It is likely that this is due to influenza vaccine being administered much more frequently than other vaccinations.

These PCP-recorded EMR data provide additional validity of reporting allergy when compared with systems informed by clinician or patient self-reported data. It is also more likely to accurately capture characteristics associated with vaccine or PEG allergy that may help identify potential risk factors. These data reveal a significant association between vaccine allergy and allergic comorbidities, including with depression and anxiety, although this finding lost significance in the regression. Although these data are not implying causality or risk, they indicate potentially novel findings that require further study.

For those with reported PEG allergy, although this rate increases 10-fold when PEG-containing medications are included, it still remains very low. Importantly, among this cohort, none of the patients with PEG allergy had a reported allergy to an injectable medication containing PEG, and no patient had more than 1 of the injectable medications containing PEG listed as an allergy. This could potentially imply that there is little cross-reactivity to (or between) medications that contain PEG as an excipient, or that any cross-reactivity may be limited by the molecular weight content or absolute concentration of PEG in that medication. The lack of cross-reactivity noted in this data set could possibly imply a limited likelihood of clinically relevant issues that may develop in someone with a primary PEG allergy and an allergy to a PEG-containing item, such as a vaccine. This study also describes a significant association between vaccine/PEG allergy and allergic comorbidities, anxiety and depression. To the best of our knowledge, this is the first such study to document these associations.

Allergic reactions to PEG have been reported in the literature, and anti-PEG immunoglobulin E has been identified.^{9,11} PEG-associated anaphylaxis can often occur on first known exposure to PEG or PEG-modified (PEGylated) therapeutics.¹¹ It is suspected that risk of anaphylaxis increases with increasing PEG molecular weight and concentration.¹² A 2016 review of immediate-type hypersensitivity to PEG identified 37 case reports of allergic reactions in the literature but did not comment on allergic comorbidities.⁸ Cross-sensitization between PEGs of various molecular weights, PEGylated drugs, and

PEG derivatives was described. A recently published case series of 5 confirmed PEG allergies, the largest case series to date, documented anaphylaxis in 4/5 cases, all of which were caused by PEG in medications.¹² This case series also did not comment on allergic comorbidities.¹¹

A key limitation of our estimates is that we relied on provider documentation of an allergy within the allergy section of the EMR which could both over- or underestimate the true rate of allergy, although it implies that the vaccine or medication in question would be withheld from the patient based on presumed allergy. Despite the processing of the allergy terms having been validated, it is possible that the algorithm may have failed to capture some cases of reported PEG allergy and it is possible that some cases of PEG allergy remain unreported, being attributed to another agent or classified as idiopathic, given this is a relatively uncommon and potentially poorly recognized allergen. Conversely, it is also possible that the prevalence was overestimated as this algorithm was not designed to detect the results of confirmatory testing or consultation reports, and cases that do not represent true allergy may have been counted. This data set does not contain more specific information on the nature of the reaction that occurred. It is also possible that associations between PEG/vaccine allergy and other atopic conditions could indicate that patients with these diseases are more likely to also have PEG or vaccine allergy, or that patients with these conditions or their providers are more likely to characterize symptoms as allergic. Lastly, we cannot say for certain that this sample is representative of all primary care practices. Nevertheless, the patient population within the CPCSSN practices is representative of the general population in Canada when compared with other national data sources.¹³ It is unclear how this rate would generalize to the United States or other high-income nations.

In conclusion, our study reveals a very low prevalence of PCP-reported vaccine allergy in Canada and provides some initial data on patient characteristics associated with vaccine allergy, an identified unmet need within our specialty.¹⁴ This data set provides a baseline of EMR-reported vaccine and PEG allergy before the COVID-19 pandemic. This study can therefore serve to evaluate increases in documented allergies during the COVID-19 pandemic and characterize vaccine reactions to ensure that as allergists, we code vaccine reaction information accurately to provide a precise presentation of risks and benefits to our patients.

Our study also reveals an exceedingly low prevalence of PCP-reported PEG allergy in Canada. Although this is not to dismiss the importance of this molecule as a potentially relevant allergen, decision-makers should keep the overall low baseline rate of PEG allergy in perspective when considering policy recommendations regarding PEG-containing pharmaceutical products, including COVID-19

vaccines, and potential risk of reactivity. The pros and cons of an approach to PEG allergy and COVID vaccination are detailed elsewhere and are beyond the scope of this report.^{5,15,16} Replication of this type of study in similar data sets of other countries is necessary to refine the certainty and accuracy of prevalence estimates.

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References

1. The Lancet Child Adolescent Health. Vaccine hesitancy: a generation at risk. *Lancet Child Adolesc Health*. 2019;3(5):281.
2. Kulkarni S, Harvey B, Prybylski D, Jalloh MF. Trends in classifying vaccine hesitancy reasons reported in the WHO/UNICEF Joint Reporting Form, 2014–2017: use and comparability of the Vaccine Hesitancy Matrix [e-pub ahead of print]. *Hum Vaccin Immunother*. doi:10.1080/21645515.2020.1859319, accessed April 1, 2021.
3. Kelso JM, Greenhawt MJ, Li JT, et al. Adverse reactions to vaccines practice parameter 2012 update. *J Allergy Clin Immunol*. 2012;130(1):25–43.
4. Johns Hopkins Coronavirus Resource Center. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU). Available at: <https://coronavirus.jhu.edu/map.html>. Accessed April 1, 2021.
5. Banerji A, Wickner PG, Saff R, et al. mRNA vaccines to prevent COVID-19 disease and reported allergic reactions: current evidence and suggested approach. *J Allergy Clin Immunol Pract*. 2021;9(4):1423–1437.
6. Centers for Disease Control and Prevention. Severe allergic reactions from COVID-19 vaccine. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html#:~:text=Anaphylaxis%20after%20COVID%2D19%20vaccination,and%20immediately%20treat%20the%20reaction>. Accessed December 30, 2020.
7. Centers for Disease Control and Prevention. What to do if you have an allergic reaction after getting a COVID-19 vaccine. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/allergic-reaction.html>. Accessed April 1, 2021.
8. Wenande E, Garvey LH. Immediate-type hypersensitivity to polyethylene glycols: a review. *Clin Exp Allergy*. 2016;46(7):907–922.
9. Stone CAJ, Liu Y, Relling MV, et al. Immediate hypersensitivity to polyethylene glycols and polysorbates: more common than we have recognized. *J Allergy Clin Immunol Pract*. 2019;7(5):1533–1540. e8.
10. Williamson T, Green ME, Birtwhistle R, et al. Validating the 8 CPCSSN case definitions for chronic disease surveillance in a primary care database of electronic health records. *Ann Fam Med*. 2014;12(4):367–372.
11. Zhou Z-H, Stone CA, Jakubovic B, et al. Anti-PEG IgE in anaphylaxis associated with polyethylene glycol. *J Allergy Clin Immunol Pract*. 2021;9(4):1731–1733. e3.
12. Sellaturay P, Nasser S, Ewan P. Polyethylene glycol-induced systemic allergic reactions (anaphylaxis). *J Allergy Clin Immunol Pract*. 2021;9(2):670–675.
13. Queenan JA, Williamson T, Khan S, et al. Representativeness of patients and providers in the Canadian Primary Care Sentinel Surveillance Network: a cross-sectional study. *CMAJ Open*. 2016;4(1):E28–E32.
14. Dreskin SC, Halsey NA, Kelso JM, et al. International Consensus (ICON): allergic reactions to vaccines. *World Allergy Organ J*. 2016;9(1):32.
15. Murphy KR, Patel NC, Ein D, et al. Insights from American College of Allergy, Asthma, and Immunology COVID-19 vaccine task force: allergic reactions to mRNA SARS-CoV-2 vaccines. *Ann Allergy Asthma Immunol*. 2021;126(4):319–320.
16. Greenhawt M, Abrams EM, Oppenheimer J, et al. The COVID-19 pandemic in 2021: avoiding overdiagnosis of anaphylaxis risk while safely vaccinating the world. *J Allergy Clin Immunol Pract*. 2021;9(4):1438–1441.

Supplementary Data

eTable 1

Vaccine Allergy Terms

DTPA-HBV-IPV/HIB
 18 MO IMMUNIZATION
 1ST ROUND IMMUNIZATIONS
 ADACEL
 AREPANRIX
 BOOSTRIX
 BOOSTRIX-POLIO (PF) INTRAMUSCULA
 DDAVP
 DE 2 VACCINS DU 6 MOIS ET 9 MOIS
 DIP, PERT (ACELL), TET, POLIO VACC
 DIPHTHERIA, TETANUS, ACELLULAR P
 DIPHTHERIA-PERTUSSIS-POLIOMYELIT
 DPT-POLIO-HIB COMBO PACK
 DPT/POLIO
 DPT/POLIO/HIB
 DPTP
 DPTP AND HIB
 DPTP OR MMR
 DTAP-P-HIB-HEP B
 DTP IMMUNIZE
 FIVE YEAR VACCINATION
 FLU SHOT
 FLU VACCINE
 FLUVIRAL
 FLUZONE SYRINGE
 H1N1 FLU VACCINE
 HEP A AND HEP B COMBINED
 HEP B
 HEP B VACCINE -> HIVES AT THE SC
 HEPATITIS B
 HEPATITIS B VACCINE
 HEPATITIS B VIRUS VACCINES - HIV
 HPV VACCINE
 IMMUNIZATION
 IMMUNIZATION 6 MO
 IMMUNIZATIONS
 INFLUENZA
 INFLUENZA IMMUNIZATION
 INFLUENZA VACCINE
 INFLUENZA VACCINE 2017 FLUZONE Q
 INFLUENZA VACCINE AGRIFLU
 INFLUENZA VIRUS VACCINE 20MG
 INFLUENZA VIRUS VACCINE TVS 2012
 LIVE VACCINES
 M-M-R II (PF)
 M-M-R III
 MEASLES, MUMPS & RUBELLA VIRUS V
 MEASLES, MUMPS, AND RUBELLA VACC
 MEASLES, MUMPS, RUBELLA, VARICEL
 MEASLES, MUMPS & RUBELLA VACCINE LI
 MENINGOCOCC GRP C CNJ-DPHT CRM
 MENINGOCOCCAL A, C, Y, W-135 POL
 MENINGOCOCCAL VACCINE
 MENJUGATE
 MENJUGATE 10 MCG/0.5 ML INTRAMUS
 MENJUGATE VIAL
 MENJUGATE/VARICELLA
 MMR
 MMR ALLERGY
 MMR II VACCINE
 MMR II VIRUS VACCINE
 MMR II VIRUS VACCINE LIVE ATTENU
 MMR INJECTION
 MMR VACCINE
 MMR-V
 PCN
 PEDIACEL
 PEDIACEL VACCINE VIAL
 PENTACEL
 PENTACEL INJ

PENTACEL VACCINE
 PNC
 PNC (ANAPHYLAXIE)
 PNC (RASH PAN CORPOREL)
 PNC (RASH)
 PNC (URTICAIRE)
 PNC - RASH
 PNC CF INFO SUPPLÉMENTAIRE
 PNEUMOCOCC 7-VAL CONJ-DIP CRM
 PNEUMONIA
 PNEUMONIA VACCINE
 PREVNAR VACCINE VIAL
 QUAD
 QUADRACEL
 QUADRACEL - SUSPENSION
 QUADRACEL IMMUNIZATION
 QUADRACEL VACCINE
 QUADRACEL VACCINE VIAL
 QUADRICEL
 RABIES IMMUNIZAT
 SEIZURE AFTER VARICELLA OR QUAD
 SOME VACCINES
 TETANUS TOXOID
 TWUNRIX JUNIOR
 VACCINE
 VACCINE - 2 MONTH? PENTASEL
 VACCINE SUSPENSION
 VACCINES
 VARICELLA VACCINE
 VARICELLA VIRUS VACCINE
 VARICELLA VIRUS VACCINE LIVE SUB
 VARICELLA, LIVE ATTENUATED
 VARIVAX
 VARIVAX 1350 UNIT
 VARIVAX III
 VARIVAX III 1350U/0.5ML
 VARIVAX III 1350UNIT
 VARIVAX INJECTION? -ASTHMA ATTAC
 VARIVAX VACCINE
 VAXIGRIP VACCINE

eTable 2

Documented Vaccine Allergy Among Canadian Primary Care Sentinel Surveillance Network Patients With an Appointment Between January 1, 2016, and December 31, 2018, by Vaccine Name

name_calc	Frequency	Percent (%)
BCG	1	0.25
DTaP	8	1.96
DTaP-Hib	1	0.25
Influenza	346	84.80
MMR	45	11.03
Not specified	1	0.25
Pneumovax	3	0.74
Rotavirus	1	0.25
Varicella	2	0.49
Total	408	

Abbreviations: BCG, Bacillus Calmette-Guéri; DTaP, diphtheria, tetanus, pertussis; Hib, *Haemophilus influenzae* type b; MMR, .

(continued)