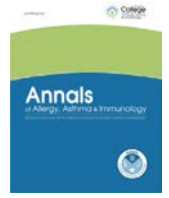




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Letters

Emergency department visits for vaccine-related severe allergic reactions among US adults: 2006–2018



Vaccine-related severe allergic reactions are of growing public concern given reports of anaphylaxis after messenger RNA (mRNA)–based vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),¹ the virus that causes coronavirus disease 2019 (COVID-19) and may contribute to vaccine hesitancy and incomplete vaccination.² Little is known on previous trends in health care utilization for vaccine-related severe allergic reactions among the US adult population.³ Understanding these trends over time, especially before the COVID-19 pandemic, may be helpful to contextualize COVID-19 vaccine-related allergic reactions and inform public understanding of the overall risk of vaccine-related severe allergic reactions.

Our objectives were to characterize the trends in rates of emergency department (ED) visits for vaccine-related severe allergic reactions among the US adult population from 2006 to 2018 and to evaluate factors associated with these severe allergic reactions (including anaphylaxis). We performed cross-sectional analyses of (1) ED visits for vaccine-related severe allergic reactions among US adults (≥ 18 years) using a nationally representative sample of US ED visits, the Nationwide Emergency Department Sample (NEDS), Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality,⁴ and (2) severe allergic events requiring ED care from a national passive reporting system, the Vaccine Adverse Event Reporting System (VAERS).⁵ The NEDS is the largest all-payer US ED database that provides nationally representative data from approximately 145 million ED visits each year using discharge data from 990 hospitals located in 36 States and the District of Columbia.

Vaccine-related severe allergic reactions were determined in NEDS using the following International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification (ICD-9 or 10-CM) diagnostic codes for anaphylaxis, guided by previous studies³: ICD-9-CM code 999.4 (anaphylactic shock-serum) for years 2006 to 2010; ICD-9-CM codes 999.4 (anaphylactic shock-serum), 999.42 (anaphylactic reaction owing to vaccination), and 999.52 and 995.0 (other serum reaction owing to vaccination and other anaphylactic reaction) for years 2011 to 2015 quarter 3; ICD-10-CM codes T80.52

(anaphylactic reaction owing to vaccination), T80.62 and T78.2 (other serum reaction owing to vaccination and anaphylactic shock, unspecified), T88.1 and T78.2 (other complications after immunization, not elsewhere classified, and anaphylactic shock, unspecified), T50.Z95 and T78.2 (adverse effect of other vaccines and biological substances and anaphylactic shock, unspecified), T50.B95 and T78.2 (adverse effect of other viral vaccines and anaphylactic shock, unspecified), and Z88.7 and T78.2 (allergy status to serum and vaccine and anaphylactic shock, unspecified) for years 2015 quarter 4 to 2018.

For identification of severe allergic events in VAERS,^{5,6} cases occurring within 0 to 1 day of vaccination were included if the following terms of the Medical Dictionary for Regulatory Activities were documented: anaphylactic reaction, anaphylactic shock, and anaphylactoid reaction. In addition, cases occurring within 0 to 1 day of vaccination were included if major or minor skin, respiratory, or cardiovascular symptoms or minor gastrointestinal symptoms were documented in combination based on the Brighton Collaboration criteria (levels 1 to 3 of diagnostic certainty).⁷

We used US Census population estimates for the respective years to determine population rates.⁸ Chronic conditions were identified using the Healthcare Cost and Utilization Project Chronic Condition Indicator. Documented epinephrine use for the visits was determined by the following codes: Healthcare Common Procedure Coding System Current Procedural Terminology code J0170 for years 2006 to 2010 and code J0171 for years 2011 to 2018. Focusing on NEDS, we constructed a multivariable logistic regression model to identify factors associated with severe allergic reactions, defined as hospitalization, cardiac arrest, intubation, or death.

From 2006 to 2018, US adults experienced approximately 4027 (95% confidence interval [CI], 3654–4400) vaccine-related severe allergic reactions resulting in ED visits. The rate of these severe allergic reactions resulting in ED visits decreased over time, from 1.73 to 0.94 visits per million population per year (P for trend $< .001$) (Fig 1). The VAERS captured less vaccine-related severe allergic reactions resulting in ED events ($n = 1412$) and a lower rate of severe allergic reactions resulting in ED events (0.27–0.36 events per million population per year; P for trend $> .30$), with events most often associated with influenza vaccines. Most vaccine-related severe allergic reactions resulting in ED visits involved patients who were of female sex ($n = 2571$; 64%), had private insurance ($n = 2193$; 54%), visited urban hospitals ($n = 3124$; 78%), or had a chronic condition ($n = 2257$; 56%). Few ED visits had documented epinephrine use ($n = 267$; 7%).

Approximately one-third of these ED visits (weighted $n = 1364$; 34%) were considered severe, defined as resulting in hospitalization (weighted $n = 1335$; 34%), cardiac arrest or intubation (weighted $n = 271$; 7%), or death ($n < 10$, 1%). After controlling for age, sex,

2006 to 2018

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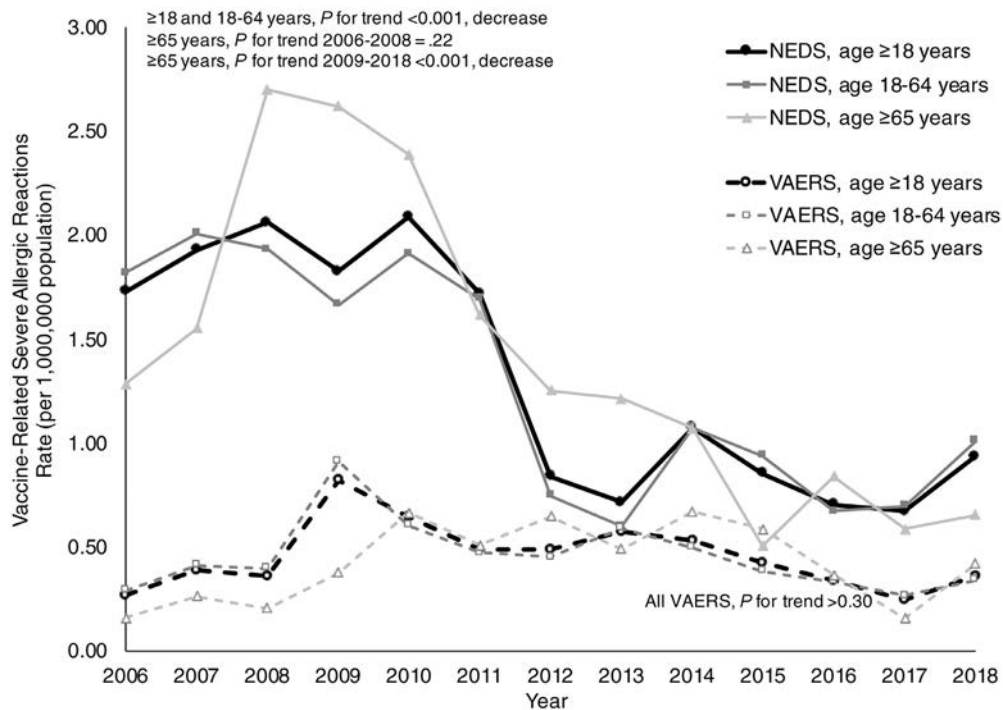


Figure 1. ED visit rates for vaccine-related severe allergic reactions per million population by age group and data source, 2006 to 2018. ED, emergency department; NEDS, Nationwide Emergency Department Sample; VAERS, Vaccine Adverse Event Reporting System.

primary payer, geographic region, urban vs rural hospital, and presence of chronic conditions, factors associated with vaccine-related severe allergic reactions included increasing age (odds ratio [OR], 2.24; 95% CI, 1.04-4.86 for ≥ 65 years compared with ages 18-24 years), male sex (OR, 1.56; 95% CI, 1.08-2.24 compared with female sex), public insurance (OR, 1.84; 95% CI, 1.18-2.82 compared with private insurance), or having any chronic condition (OR, 14.36; 95% CI, 8.88-23.21).

Using nationally representative data, we report that vaccine-related severe allergic reactions resulting in ED visits among adults were rare and decreased considerably from 2006 to 2018, before the COVID-19 pandemic. Vaccine-related anaphylaxis had previously been estimated to be 1.3 cases per million vaccine doses given from 2009 to 2011.³ Slightly higher rates of anaphylaxis have been reported after administration of mRNA COVID-19 vaccinations, with recent estimates of 7.9 cases per million vaccinations.¹ Previous reports of vaccine-related anaphylaxis may not be comparable to our findings given that we report population-based rates. Similar to studies on mRNA COVID-19 vaccines, we found that passive reporting of vaccine-related events through VAERS underestimated the rates.⁹

Reassuringly, death from vaccine-related severe allergic reactions was exceedingly rare. Older adults, especially more than or equal to 65 years, were more likely to experience vaccine-related severe allergic reactions compared with younger adults, which may be secondary to preexisting comorbidities. Older adults have been noted to have increased risk of fatal anaphylaxis, especially secondary to drug-related anaphylaxis.¹⁰ Documented epinephrine use was noted to be low perhaps secondary to prehospital use or inadequate documentation.

Limitations include potential coding errors and minimal clinical information, including lack of allergist-performed diagnostic testing to confirm vaccine-related severe allergic reactions such as anaphylaxis. Nevertheless, we have used national data from the following 2 different sources to capture health care utilization for vaccine-related severe allergic reactions: (1) voluntarily reported data (VAERS) and (2) a population-based sample of ED discharges based on physician diagnosis (NEDS). Together, these data may provide a more comprehensive picture of trends in vaccine-related severe allergic reactions.

Vaccine-related severe allergic reactions are rare and health care utilization for these severe allergic reactions decreased from 2006 to 2018 (before the COVID-19 pandemic). Reassuringly, fatal vaccine-related allergic reactions were exceedingly rare. Recognition, diagnosis, and appropriate treatment of vaccine-related severe allergic reactions should be considered important components of public health vaccination efforts.

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Delayed hypersensitivity to the Comirnaty coronavirus disease 2019 vaccine presenting with pneumonitis and rash



Clinical trials have supported the efficacy of vaccines for the prevention of coronavirus disease 2019 (COVID-19) infection, and widespread vaccination is now seen as a cornerstone in preventing mortality.¹ Postapproval surveillance has however revealed rare but significant vaccine-associated complications, including thrombosis with thrombocytopenia syndrome after the adenovirus vector ChAdOX1-S and Janssen vaccines² and myocarditis with messenger RNA-based vaccines.³ This has highlighted the importance of ongoing pharmacovigilance and prompt reporting of suspected vaccine-associated adverse events. Here, we present a case of inflammatory pneumonitis and fixed rash after a second dose of the BioNTech Comirnaty COVID-19 vaccine with delayed hypersensitivity seen on skin testing.

A 55-year-old woman presented to hospital 6 days after the second dose of the Comirnaty COVID-19 vaccine with malaise, fever, cough, and an abdominal rash. She had tolerated the first dose, 3 weeks before, with brief pain at the injection site but no other signs of reactogenicity.

The patient initially tolerated the second vaccination, but a large, fixed, confluent, erythematous, nontender rash emerged over her right lower abdomen 48 hours after the dose. Notably, there were no accompanying skin changes over the injection site. The rash remained in a fixed distribution thereafter and did not improve with oral antimicrobial therapy. At 4 days from vaccination, she then developed a persistent nonproductive cough accompanied by progressive dyspnea, rigors, nausea, and anorexia, which eventually prompted her presentation to hospital.

On presentation, the patient was hypoxic with oxygen saturation of 91% on room air and febrile at 39.6°C. Blood investigations revealed lymphopenia with a lymphocyte count of $0.4 \times 10^9/L$ and markedly elevated inflammatory markers with C-reactive protein of 512 mg/L but no other significant organ dysfunction. Multifocal bilateral lung infiltrates were found on chest x-ray examination with confluent changes in the right lower lobe.

The patient was commenced on intravenous ceftriaxone and azithromycin for presumed community-acquired pneumonia but remained persistently febrile and hypoxic. A computed tomography scan of the chest on the second day of admission revealed bilateral, multifocal ground-glass changes with peribronchial thickening (Fig 1). Bronchoscopy was performed 2 days later with visible clear mucoid secretions, and atypical bronchial cells were found on

cytology results. Microbiological investigation results on bronchial washings were negative, including Gram stain, bacterial and fungal culture, viral polymerase chain reaction, microscopy for acid-fast bacilli, and *Mycobacterium tuberculosis* polymerase chain reaction.

Given the lack of response to broad-spectrum antibiotics, a noninfective inflammatory pneumonitis related to vaccination was considered, particularly in light of the abdominal rash. On the third day of admission, prednisone 25 mg daily was added to ongoing antibiotics; within 24 hours, there was resolution of the fever, improvement in the patient's symptoms, and downtrend in inflammatory markers. Topical 0.1% methylprednisone ointment was applied to the abdominal rash, which resolved after several days. Results of skin histopathology, taken on the day of admission, subsequently revealed mixed dermatitis with perivascular eosinophils and negative direct immunofluorescence, consistent with a drug reaction.

The patient was discharged on the sixth day of admission and completed a further week of oral antibiotics and tapering prednisone with complete resolution of symptoms. Owing to the atypical cells on bronchoscopy sample cytology, a positron emission tomography scan was performed 1 month later, which revealed mild glucose avidity in the right middle lobe and lingula, consistent with resolving inflammation but no other pulmonary lesions. Skin prick and intradermal testing to the Comirnaty COVID-19 vaccine demonstrated no immediate reaction, but a large 38 × 45-mm intradermal reaction to the 1:10 dilution of the vaccine was seen at 48 hours, consistent with delayed hypersensitivity.

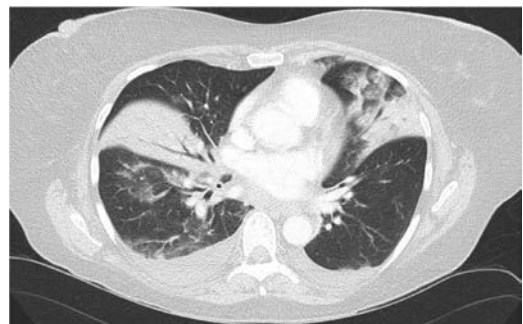


Figure 1. Computed tomography of the chest with axial view revealing diffuse ground-glass changes and peribronchial thickening on day 2 of the patient's hospital admission.

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