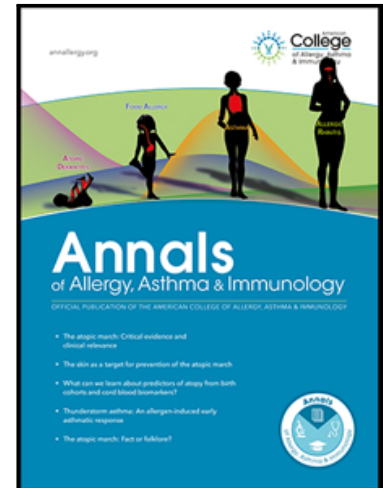


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Emergency department visits for vaccine-related severe allergic reactions among US adults: 2006-2018

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Keywords: anaphylaxis, COVID-19, vaccine, allergy, Emergency Department, adult

Abbreviations: Emergency Department (ED)

Nationwide Emergency Department Sample (NEDS)

United States (US)

Vaccine Adverse Event Reporting System (VAERS)

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Vaccine-related severe allergic reactions are of growing public concern given reports of anaphylaxis after COVID-19 mRNA vaccination¹ and may contribute to vaccine hesitancy and incomplete vaccination.² Little is known about prior trends in healthcare utilization for vaccine-related severe allergic reactions among the United States (US) adult population.³ Understanding these trends over time, especially prior to 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 objective was to characterize trends in rates of emergency department (ED) visits for vaccine-related severe allergic reactions among the US adult population from 2006-2018 and to examine 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 Quality⁴ and 2) severe allergic events requiring ED care from a national passive reporting system, the Vaccine Adverse Event Reporting System (VAERS).⁵ NEDS is the largest all-payer US ED database which 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 *International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification* diagnostic codes for anaphylaxis, guided by prior studies³: ICD-9-CM code 999.4 (Anaphylactic Shock-Serum) for years 2006-2010; ICD-9-CM code 999.4 (Anaphylactic shock-serum), 999.42 (Anaphylactic reaction due to vaccination), 999.52 and 995.0 (Other serum reaction due to vaccination and Other anaphylactic reaction) for years 2011-2015 Quarter 3; ICD-10-CM code T80.52 (Anaphylactic reaction due to vaccination), T80.62 and T78.2 (Other serum reaction due to vaccination and Anaphylactic shock, unspecified), T88.1 and T78.2 (Other complications following 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), Z88.7 and T78.2 (Allergy status to serum and vaccine and Anaphylactic shock, unspecified) for years 2015 Quarter 4-2018.

For identification of severe allergic events in VAERS,^{5,6} cases occurring within 0-1 days of vaccination were included if the following MedDRA terms were documented: anaphylactic reaction, anaphylactic shock, and anaphylactoid reaction. Additionally, cases occurring within 0-1 days of vaccination were included if major or minor skin, respiratory, or cardiovascular symptoms or minor gastrointestinal symptoms were documented in combination based on Brighton Collaboration criteria (levels 1 through 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 HCUP Chronic Condition Indicator (CCI). Documented epinephrine use for the visits were determined by the following codes: Healthcare Common Procedure Coding System Current Procedural Terminology (CPT) code J0170 for years 2006-2010, and CPT code J0171 for years 2011-2018. 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 2006-2018, US adults experienced approximately 4027 (95% 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 <0.001) (see **Figure**). 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 to 0.36 events per million population per year; P for trend >0.30), with events most commonly associated with influenza vaccines. Most vaccine-related severe allergic reactions resulting in ED visits involved patients who were female ($n=2571$; 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%).

Roughly 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, primary payer, geographical region, urban/rural hospital, and presence of chronic conditions, factors associated with vaccine-related severe allergic reactions included increasing age (OR, 2.24; 95% CI, 1.04-4.86 for ≥ 65 years compared to age 18-24 years), male sex (OR, 1.56; 95% CI, 1.08-2.24

compared to female sex), public insurance (OR, 1.84; 95% CI, 1.18-2.82 compared to 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 significantly decreased from 2006 to 2018, prior to the COVID-19 pandemic. Vaccine-related anaphylaxis had previously been estimated to be 1.3 cases per million vaccine doses given from 2009-2011.³ 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 rates.⁹

Reassuringly, death from vaccine-related severe allergic reactions were exceedingly rare. Older adults, especially ≥ 65 years, were more likely to experience vaccine-related severe allergic reactions compared to younger adults, which may be secondary to preexisting co-morbidities. 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 pre-hospital 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 including anaphylaxis. However, we have used national data from two different sources to capture healthcare 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.

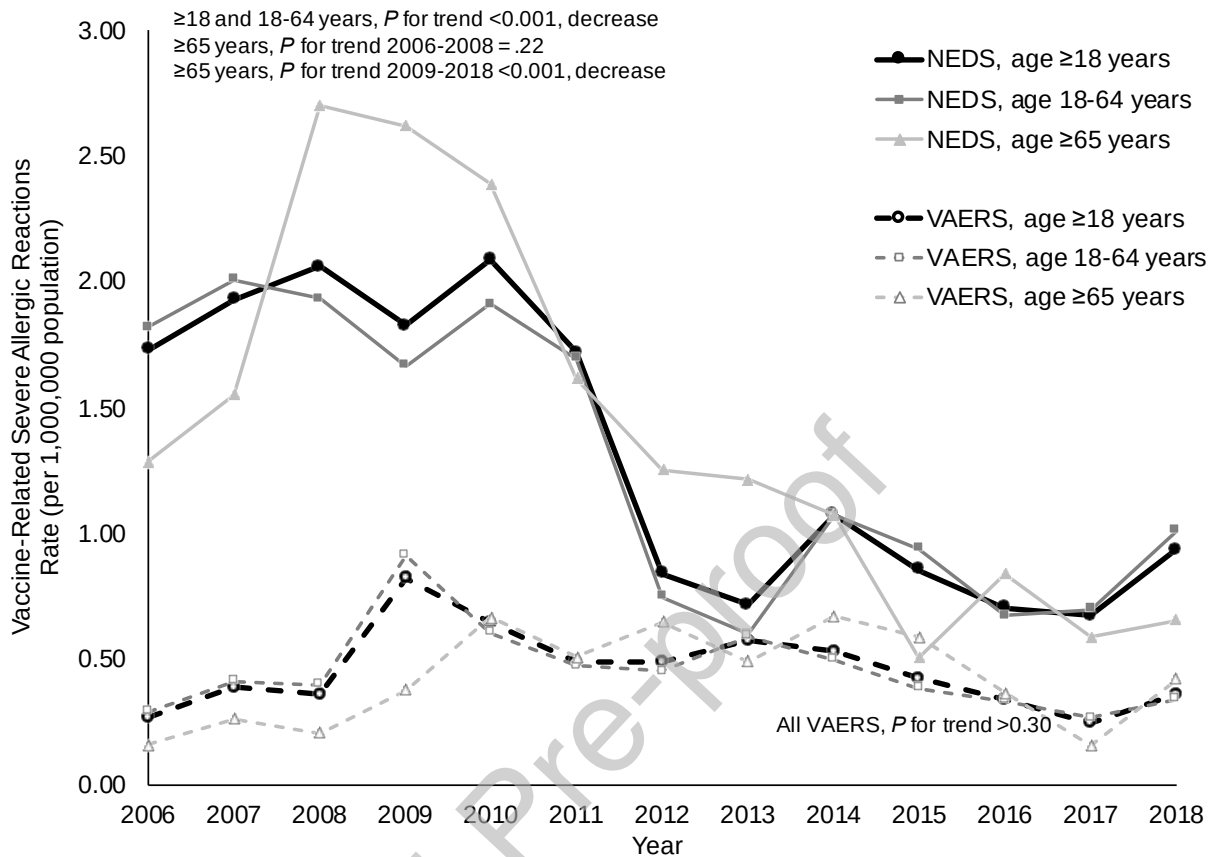
Vaccine-related severe allergic reactions are rare and healthcare utilization for these severe allergic reactions decreased from 2006 to 2018 (before the COVID-19 pandemic). Reassuringly fatal vaccine-related allergic reactions were exceedingly rare. Recognition, diagnosis, and appropriate treatment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

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ED visit rates for vaccine-related severe allergic reactions per million population by age group and data source, 2006-2018



Abbreviations: NEDS, National Emergency Department Sample; VAERS, Vaccine Adverse Event Reporting System.