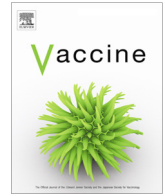




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Short communication

Anaphylaxis rates associated with COVID-19 vaccines are comparable to those of other vaccines



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ABSTRACT

We retrieved data on 8940 anaphylaxis cases post-COVID-19 vaccination from the US Vaccine Adverse Event Reporting System and the European EudraVigilance from week 52/2020 through week 31/2021 and compared them with those of other vaccines. Overall, 837,830,000 COVID-19 vaccine doses were delivered in the US and Europe during the study period, for which the vaccine name was known. The mean anaphylaxis rate was estimated at 10.67 cases per 10⁶ doses of COVID-19 vaccines (range: 7.99–19.39 cases per 10⁶ doses depending on the vaccine). COVID-19 vaccines ranked fifth in reported anaphylaxis rates, behind rabies, tick-borne encephalitis, measles-mumps-rubella-varicella, and human papillomavirus vaccines (70.77, 20, 19.8, and 13.65 cases per 10⁶ vaccine doses, respectively). COVID-19 vaccines are within the range of anaphylaxis rates reported across several common vaccines in these two passive reporting systems. These data should be communicated to reassure the general population about the safety profile of COVID-19 vaccines.

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1. Introduction

Almost one year after the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the declaration of the coronavirus disease 2019 (COVID-19) pandemic, the first COVID-19 vaccines were developed and granted emergency use authorization [1]. Currently there are several COVID-19 vaccines in use globally as the key countermeasure to reduce the health, societal, and economic consequences of the pandemic and accelerate return to normality [2]. Nevertheless, in several countries the expected benefits of COVID-19 vaccines were hampered by vaccine hesitancy, some of which were driven by safety concerns and mistrust of authorities on the basis of the rapid deployment and approval of COVID-19 vaccines [2,3], the newness of the vaccine platforms, and other issues. Adverse events including anaphylaxis were reported post-COVID-19 vaccination, presumably due to the polyethylene glycol component of the novel mRNA vaccines, and received significant attention in social media [4,5]. However,

adverse events following vaccination with commonly administered vaccines are not infrequent and most cases are not serious. Conversely, serious, life-threatening anaphylaxis cases and associated fatal outcomes are extremely rare post-vaccination [6]. Herein, we estimated the anaphylaxis rates following COVID-19 vaccination, as reported to EudraVigilance and the Vaccine Adverse Event Reporting System (VAERS) [7,8], and we compare them with those of other commonly administered vaccines.

2. Methods

The United States (US) VAERS is an early warning system managed by the US Centers for Disease Control and Prevention (CDC) and Food and Drug Administration (FDA) that records and analyzes possible adverse events post-vaccination [7]. EudraVigilance is the European Medicine Agency system for monitoring and analyzing suspected adverse reactions to medicines, including vaccines [8]. Healthcare professionals, patients, and others can report adverse events to VAERS and EudraVigilance. Both systems are passive reporting systems, and are therefore subject to misreporting biases. However, reported adverse events are subject to internal evaluation, including detection and merge of duplicated

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cases [7–9]. For VAERS we used the public database, which is coded using the MedDRA system. The Brighton Collaboration definitions are used only for cases for which additional follow-up, including collection of medical records, is done by CDC and FDA investigators.

Reported numbers of anaphylactic reaction and anaphylactic shock cases post COVID-19 vaccination that occurred from week 52/2020 (December 21 to 27, 2020) to week 31/2021 (August 2 to 8, 2021) were collected for all licensed COVID-19 vaccines from EudraVigilance and VAERS [7,8]. In particular, the following vaccines were studied: Spikevax (Moderna mRNA-1273 vaccine), Comirnaty (Pfizer-BioNTech mRNA BNT162b2 vaccine), and Janssen (Johnson & Johnson recombinant viral vector adenovirus vaccine), which are available in the US and Europe, and Vaxzevria (Oxford/Astra Zeneca ChAdOx1-S vaccine), which is licensed in Europe only. The corresponding total numbers of administered COVID-19 vaccine doses as of August 6 or 7, 2021 were retrieved from the European Centre for Disease Prevention and Control for Europe and from the CDC for the US [10,11]. These numbers were used as denominators to estimate anaphylaxis rates per 10⁶ doses for each vaccine. The mean anaphylaxis rate for these COVID-19 vaccines were calculated by summing all anaphylactic reaction and anaphylactic shock cases post COVID-19 vaccination reported to EudraVigilance and VAERS for all COVID-19 vaccines, and then dividing by the corresponding total number of administered doses [10,11]. We retrieved anaphylaxis rates for other licensed routine and travel vaccines as reported by Sampath et al. and McNeil et al. [6,12] and estimated the mean anaphylaxis rates and their ranges per vaccine. When only ranges of anaphylactic rates of other vaccines were available, we estimated the mean anaphylaxis rate and its standard deviation from the mean. The estimated mean anaphylaxis rate of COVID-19 vaccines was compared to the mean anaphylaxis rates of the other studied vaccines.

3. Results

From week 52/2020 through week 31/2021 a total of 349,790,000 doses of COVID-19 vaccines were administered in the US and 496,518,433 doses of COVID-19 vaccines in Europe [7,8]. Overall, 837,830,000 doses of COVID-19 vaccines have been delivered in the US and Europe during the study period, for which the vaccine name was known [7,8].

Table 1
Anaphylactic reaction and anaphylactic shock cases to licensed COVID-19 vaccines reported in EudraVigilance and VAERS, week 52/2020 through week 31/2021.

	COVID-19 vaccines	Administered doses (×10 ⁶) ¹	Anaphylactic reaction cases (N)	Anaphylactic shock cases (N)	Total anaphylaxis cases (N)	Fatal cases ² (N)
EudraVigilance ³	Spikevax ⁵	48.16	856	113	969	3
	Comirnaty ⁶	360.19	4259	581	4840	28
	Vaxzevria ⁷	67.72	1118	195	1313	10
	Janssen ⁸	12.29	79	27	106	2
Subtotal 1		488.36	6312	916	7228	43
VAERS ⁴	Spikevax ⁵	139.97	579	67	646	4
	Comirnaty ⁶	195.90	895	70	965	5
	Janssen ⁸	13.60	87	14	101	0
Subtotal 2		349.47	1561	151	1712	9
Total		837.83	7873	1067	8940	52
Rates per 10 ⁶ doses)			9.39	1.27	10.67	0.06

COVID-19: coronavirus disease 2019; VAERS: Vaccine Adverse Event Reporting System.

¹ Numbers of doses per COVID-19 vaccine were retrieved from [7,8].

² Anaphylaxis-associated fatal cases.

³ Data (up to August 7, 2021) retrieved from [8].

⁴ Data (up to August 6, 2021) retrieved from [7].

⁵ Spikevax: Moderna mRNA-1273 vaccine

⁶ Comirnaty: Pfizer-BioNTech mRNA BNT162b2 vaccine.

⁷ Vaxzevria: Oxford/Astra Zeneca ChAdOx1-S vaccine.

⁸ Janssen: Johnson & Johnson recombinant viral vector adenovirus vaccine.

Table 1 shows the numbers of administered COVID-19 vaccine doses and the numbers of anaphylactic reaction cases and anaphylactic shock cases per evaluated COVID-19 vaccine. In total there were 8940 notified anaphylactic cases reported to EudraVigilance and VAERS, including 7873 anaphylactic reactions cases and 1067 anaphylactic shock cases. The mean anaphylaxis rates per licensed COVID-19 vaccine were as follows: 8.58 per 10⁶ vaccine doses for Spikevax, 10.44 per 10⁶ vaccine doses for Comirnaty, 19.39 per 10⁶ vaccine doses for Vaxzevria, and 7.99 per 10⁶ vaccine doses for Janssen. The mean anaphylaxis rate of the four licensed COVID-19 vaccines overall was estimated at 10.67 per 10⁶ vaccine doses. Finally, there were 52 fatal anaphylaxis cases notified to VAERS and EudraVigilance, which corresponds to 0.06 fatal anaphylaxis cases per 10⁶ vaccine doses.

Fig. 1 shows the estimated anaphylaxis rates per studied vaccine in descending order. Rabies vaccine has by far the highest anaphylaxis rate among vaccines (70.77 anaphylaxis cases per 10⁶ doses), followed by tick-borne encephalitis vaccine, measles-mumps-rubella-varicella vaccine, and human papillomavirus vaccine (20, 19.8, and 13.65 anaphylaxis cases per 10⁶ vaccine doses, respectively) [6,12]. The estimated mean anaphylaxis rate of 10.67 among licensed COVID-19 vaccines rendered them fifth in this ranking, which is higher than the anaphylaxis rates of several routine or travel vaccines (Fig. 1) but within the range of mean anaphylaxis rates of most commonly administered vaccines (1 per 10⁶ vaccine doses to 10 per 10⁶ vaccine doses depending on the vaccine) [13].

4. Discussion

Post-licensure surveillance constitutes an essential element of safety procedures to promptly detect serious or life-threatening adverse events associated with vaccines, given that sample size is limited in phase 3 vaccine trials. Adverse event notification is imperative when emergency use authorization of vaccines is granted in the context of major public health threats such as the current pandemic [14]. The generated post-licensure safety data should be promptly communicated to vaccine policy makers and healthcare professionals in order to inform the general population and to increase vaccine confidence.

We studied post-COVID-19 vaccination anaphylaxis cases reported to VAERS and EudraVigilance from week 52/2020 through

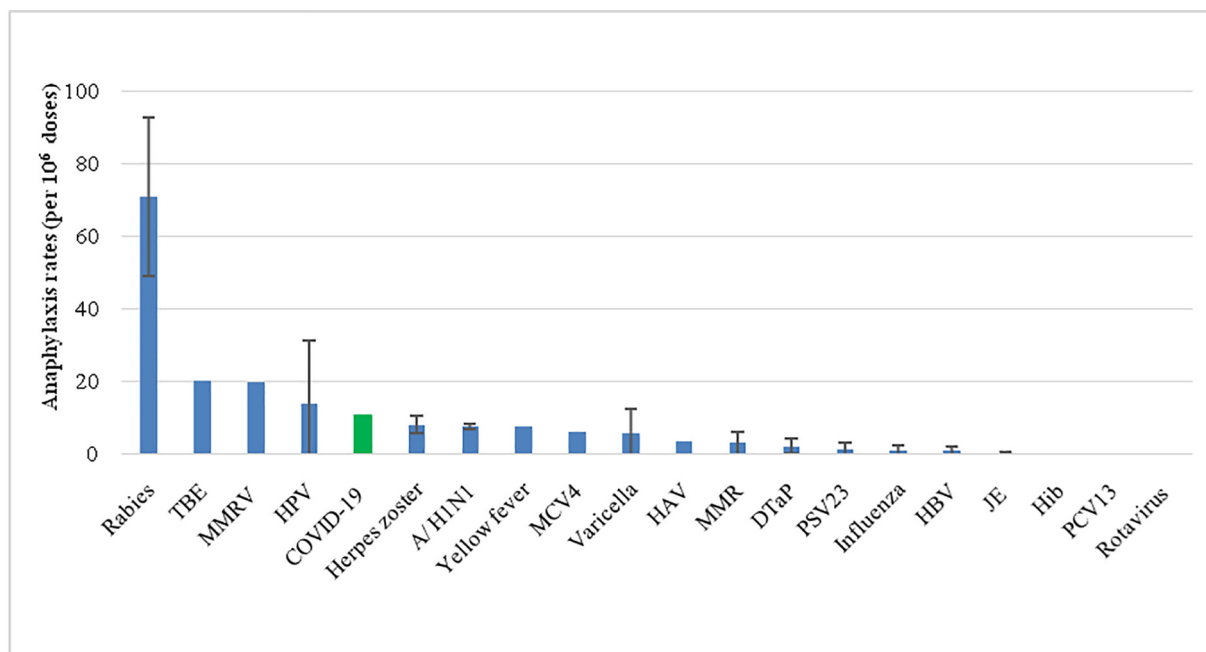


Fig. 1. Mean anaphylaxis rates associated with licensed COVID-19 vaccines* compared to other vaccines**. COVID-19: coronavirus disease 2019; TBE: tick-borne encephalitis; MMRV: measles-mumps-rubella-varicella; HPV: human papilloma virus; COVID-19: coronavirus disease 2019; A/H1N1: monovalent influenza pandemic A/H1N1; MCV4: tetraivalent meningococcus conjugate vaccine; HAV: hepatitis A virus; MMR: measles-mumps-rubella; DTaP: diphtheria tetanus acellular pertussis; PSV23: 23-valent pneumococcus polysaccharide vaccine; HBV: hepatitis B virus; JE: Japanese encephalitis; Hib: *Haemophilus influenzae*; PCV13: 13-valent pneumococcus conjugate vaccine *estimated from VAERS [7] and EudraVigilance [8] **retrieved from McNeil et al. [6] and Sampath et al. [12].

week 31/2021. During the eight-month study period more than 0.8 billion doses of COVID-19 vaccines were delivered in the US and Europe. To the best of our knowledge, no other vaccine has been administered in such large numbers within less than a year. Mass vaccination gave us the opportunity to study the safety profile of COVID-19 vaccines in a short time period, in contrast to other common vaccines introduced in the market under routine licensure procedures.

We estimated a mean anaphylaxis rate of 10.67 cases per 10⁶ COVID-19 vaccine doses, which differed by COVID-19 vaccine. This finding indicates that anaphylaxis is a rare adverse event following COVID-19 vaccination. Early studies found as low as 4.2 anaphylactic cases per 10⁶ doses of the two authorized for emergency use mRNA COVID-19 vaccines [15], a rate which was two to seven times higher for persons with a prior history of allergies and/or anaphylaxis, respectively [15]. In addition, an interim analysis of population-based safety surveillance data from Vaccine Safety Datalink found an incidence of 4.8 (95% confidence interval, 3.2–6.9) anaphylaxis cases per 10⁶ doses of Comirnaty vaccine and 5.15 (95% confidence interval, 3.3–7.6) anaphylaxis cases per 10⁶ doses of Spikevax vaccine [16]. Further studies are needed to elucidate the underlying mechanisms of these differences [17,5]. Compared with other routine and travel vaccines, the COVID-19 vaccines ranked fifth regarding post-vaccination anaphylaxis rates [12]. In the International Consensus Document on Allergic Reactions to Vaccines published under the auspices of the World Allergy Organization, American and European allergy and immunology scientific societies, it was reported that anaphylaxis rates for most commonly administered vaccines range from 1 per 10⁶ to 10 per 10⁶ depending on the vaccine [13]. The estimated mean anaphylaxis rate post-COVID-19 vaccination in the current study was within this range [13], despite the limitation that in a passive reporting system some cases could have been reported more than once and/or may not represent true cause and effect. The increased awareness of healthcare professionals regarding adverse events of COVID-19 vaccines in the context of emergency

use may partially account for the increased anaphylaxis rates compared with other commonly used vaccines [12], as well as the likelihood that highly allergic patient or those with prior anaphylaxis likely avoided receipt of a COVID-19 vaccine. However, even severe anaphylaxis can be promptly mitigated with appropriate preparation and medication, while most patients with a self-reported history of suspected drug or vaccine allergies can safely get vaccinated following careful risk-assessment, stratification, and in some cases desensitization [5,18]. It is important to establish background rates for adverse events to serve as reference in the assessment of COVID-19 vaccine safety [19]. Overall, there were 0.06 fatal anaphylaxis cases per 10⁶ COVID-19 vaccine doses, indicating an extremely rare event.

A clear strength of the current study is the use of data retrieved from the two largest reporting systems on vaccine-associated adverse events globally, namely VAERS and EudraVigilance. Nevertheless, both systems rely on passive reporting. While passive reporting systems can rapidly detect a potential safety problem and specifically rare adverse events, there is the limitation of potential reporting bias which could under- or over-estimate true anaphylaxis rates under the attention of mass media. However, in our opinion this was not the case the first eight months of COVID-19 vaccine administration and before licensure was granted by FDA and other regulatory authorities. Vaccine policy makers and healthcare professionals were highly sensitized about any possible COVID-19 vaccine-associated adverse event in a period of enhanced COVID-19 vaccine safety scrutiny, given the mass vaccination strategies implemented around the world. Furthermore, the sensitivity of VAERS for capturing anaphylaxis following vaccination is comparable to previous estimates for detecting important adverse events following vaccination [20]. Another limitation is the lack of a true denominator of vaccine doses administered in both reporting systems. Finally, passive reporting systems data generally cannot determine cause and effect. Another limitation is the fact that we compared to other vaccines that might be given for the most part to children while COVID-19 vaccines were given

mostly to adults. The fact that we estimated anaphylaxis rates based on data on COVID-19 vaccines retrieved from VAERS and EudraVigilance and we compared them with data on other vaccines retrieved from two recent reviews is also a possible limitation. In addition, there might be differences between the VAERS and EudraVigilance. Finally, AstraZeneca vaccine is not used in the US.

In conclusion, we studied a large number of anaphylaxis cases post-COVID-19 vaccination retrieved from the largest adverse events reporting systems of VAERS and EudraVigilance. We found that during the first eight months of emergency use authorization, COVID-19 vaccines had an anaphylaxis safety profile which was within the range of other commonly administered vaccines. The generated data should be communicated to healthcare professionals in order to reassure the general population about the safety profile of COVID-19 vaccines as a key public health measure to contain the COVID-19 pandemic and accelerate the return to normality.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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