

Title: Comparative assessment of allergic reactions to COVID-19 vaccines in Europe and the United States

To the Editor

Among the rare complications that may compromise vaccine acceptance are allergic reactions.¹⁻³ Recently we demonstrated that anaphylaxis rates associated with COVID-19 vaccines are within the range of those observed earlier with other vaccines, as indicated by passive reporting systems.⁴ Herein, we aimed to comparatively assess the incidence and potential underlying causes of the most common allergic reactions post COVID-19 vaccination in Europe and the United States (US). To our knowledge, such a comparison has not been performed before.

Allergic reactions data following COVID-19 vaccination reported from week 52/2020 to week 39/2021 were collected from EudraVigilance for the European Economic Area (EEA) and from Vaccine Adverse Event Reporting System (VAERS) for the US and analyzed for all licensed vaccines. These included mRNA-1273 (Moderna), BNT162b2 (Pfizer-BioNTech), AD26.COV2.S (Janssen/Johnson & Johnson), and the not yet licensed in the US ChAdOx1-S (Oxford/AstraZeneca). Incidence rates were calculated using the corresponding administered vaccine doses as denominators. Vaccine composition was examined to identify potential allergic triggers.

The most common allergic reactions after COVID-19 vaccination were anaphylactic reactions, with an overall incidence of 9.91/million doses (EEA: 13.69/million/US: 4.44/million, Fig.1). Anaphylactic shock followed, with much lower rates (overall incidence: 1.36/million, EEA: 2.01/million/US: 0.41/million). Other infrequently reported in the two databases allergic symptoms post vaccination included, among others, “anaphylactoid reactions” and “allergic edema”. Sampath *et al.* and Alhumaid *et al.* also reported a similar spectrum of allergic, and possibly non-allergic reactions post vaccination.^{2,5}

Higher anaphylactic reaction rates have been reported after the first than the second dose, especially when prior anaphylaxis was present, but that was not always the case.^{5,6}

The incidence of anaphylactic reactions reported in EudraVigilance varied considerably by vaccine and was 3- to 4-fold higher for BNT162b2 or mRNA-1273 compared to VAERS. AD26.COV2.S-associated anaphylaxis did not differ between databases. The very low incidence of anaphylactic shock also varied by vaccine, particularly as captured in EudraVigilance.

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Considering vaccine platforms, the incidence of anaphylactic reactions post adenovirus-vectored vaccination was higher compared to mRNA-based vaccines (EudraVigilance: 15.62/ vs. 13.36/million, VAERS: 6.79/ vs. 4.34/million doses). Anaphylactic shock incidence rates were also higher for vectored compared to mRNA vaccines (EudraVigilance: 3.14/ vs. 1.81/million, VAERS: 1.20/ vs. 0.38).

Detailed demographic data and outcomes of anaphylactic reaction and anaphylactic shock cases post-COVID-19 vaccination are presented in Tables S1 and S2, respectively. The vast majority of cases affected females (82% of anaphylactic reaction/75% of anaphylactic shock reports). The reasons why women have been implicated more frequently in hypersensitivity reactions throughout cohorts remain unknown.

With regard to age, different patterns are evident. In EudraVigilance, both types of anaphylaxis were more common among working age (18-64 years) and older individuals; in VAERS, anaphylactic reactions were more frequent among subjects aged 30-59 years (69%), while the very rare anaphylactic shock cases were distributed across age groups.

Regarding outcome, the vast majority of cases were resolved or resolving (90.0% of anaphylactic reaction/81.7% of anaphylactic shock cases as captured in EudraVigilance, Table S1). The disease course was complicated (life threatening or leading to permanent disability) in 25.5% of anaphylactic reaction and 31.3% of anaphylactic shock cases as captured in VAERS (Table S2). Fatalities from allergic reactions post COVID-19 vaccination were extremely rare and 2- to 6-fold higher for vectored than mRNA vaccines in both databases (Table 1).

The anaphylactic reactions and anaphylactic shock cases reported to EudraVigilance compared to VAERS indicated significant differences to exist between reporting systems, vaccine platforms and manufacturers. Conceivably, the reported variability may reflect population differences in the degree of sensitization to ingredients prior to vaccination as well as differences in the prevalence of atopy, which has been linked to anaphylactic incidents post vaccination.^{2, 9} Differences in implementation between the two reporting systems could also contribute to the observed differences between databases.

The cause(s) that may trigger allergic reactions after vaccination remain elusive.² Potential contributing factors include: i) components of the final pharmaceutical product (i.e., the active ingredient and excipients); ii) impurities or “related materials” unintentionally present in the final formula;¹ iii) the packaging material, especially the rubber stopper.² Cross-reactivity has been reported upon exposure between two of the main excipients of mRNA and vectored vaccines

(polyethylene glycol 2000 and polysorbate 80, respectively).¹⁰ If true, should we anticipate increased anaphylaxis rates following first time or booster vaccination with vaccines of different platforms according to the so-called heterologous vaccination (mix-and-match) approach?

A potential limitation of the study may be the likely underreporting of allergic reactions, including anaphylaxis that generally holds for passive surveillance systems; nonetheless, this may not hold for COVID-19 vaccines that have been under scrutiny by regulators and under the watchful eyes of healthcare professionals and the public since the beginning of their deployment. Other potential limitations, also related to passive reporting systems, entail possible reporting errors (e.g. duplicate or incomplete records), as well as the fact that recorded events only show temporal and not cause-effect relationships. In addition, the terminology used for the categorization of anaphylaxis post vaccination possibly introduces mechanistical explanations that may not be accurate. Nevertheless, for anaphylaxis and Guillain-Barré syndrome, the sensitivity of VAERS was found to be comparable to previous estimates for detecting important adverse events following vaccination.¹¹

Our pragmatic analysis is based on imperfect, but real-world data of two of the world's largest and most reliable vaccine adverse event spontaneous reporting systems (EudraVigilance and VAERS). Our estimated rates from VAERS for anaphylactic reactions [4.34 for mRNA vaccines (5.41 for mRNA-1273 and 4.42 for BNT162b2) cases per million vaccinations] are in agreement with those reported largely in individuals with a history of allergy, by the Centers for Disease Control and Prevention (CDC), which were also based on passive spontaneous reporting methods (2.5 – 11.1 per million vaccinations).⁶ We found higher corresponding rates in EudraVigilance (13.36 per million vaccinations for mRNA vaccines overall), and more elevated for mRNA-1273 rather than BNT162b2 (20.39 vs. 12.36 per million vaccinations, respectively). Blumenthal *et al.* found larger incidence rates of confirmed anaphylaxis to mRNA vaccines using either the Brighton Criteria,⁷ or the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria⁸ (2.47 per 10000 vaccinations).⁹ Interestingly, this study also reported more frequently detecting acute allergic reactions with the Moderna rather than the Pfizer-BioNTech vaccine (2.20% [95% CI, 2.06%-2.35%] vs. 1.95% [95% CI, 1.79%- 2.13%]; $P = .03$).⁹

Relevant investigations in the literature report contradictory results, concluding on higher anaphylaxis incidence for mRNA-1273⁹ or BNT162b2.⁵ These results emphasize the influence of the chosen datasets on the final conclusion.

Our study revealed differences in anaphylaxis rates as captured in two of the world's largest pharmacovigilance databases between Europe and the US, as well as between vaccines and vaccine platforms. Understanding the reasons behind true differences could lead to the further optimization of COVID-19 vaccines.

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CONFLICT OF INTEREST

Dr. Poland is the chair of a Safety Evaluation Committee for novel investigational vaccine trials being conducted by Merck Research Laboratories. Dr. Poland provides consultative advice on vaccine development to Merck & Co., Medicago, GlaxoSmithKline, Sanofi Pasteur, Johnson & Johnson/Janssen Global Services LLC, Emergent Biosolutions, Dynavax, Genentech, Eli Lilly and Company, Kentucky Bioprocessing, Bavarian Nordic, AstraZeneca, Exelixis, Regeneron, Janssen, Vyriad, Moderna, and Genevant Sciences, Inc.

These activities have been reviewed by the Mayo Clinic Conflict of Interest Review Board and are conducted in compliance with Mayo Clinic Conflict of Interest policies.

Dr. Poland holds patents related to vaccinia, influenza, and measles peptide vaccines. Dr. Poland has received grant funding from ICW Ventures for preclinical studies on a peptide-based COVID-19 vaccine. This research has been reviewed by the Mayo Clinic Conflict of Interest Review Board and was conducted in compliance with Mayo Clinic Conflict of Interest policies.

SH, CA, VL, HM, EA, and AT declare no conflict of interest in relation to this work.

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AUTHOR CONTRIBUTIONS

SH and CA designed the study, acquired the data and wrote the manuscript. SH, CA, VL and HM contributed to data analysis and interpretation. CA, VL, HM, EA, GP, AT revised the manuscript critically for important intellectual content. All authors approved the final version of the manuscript.

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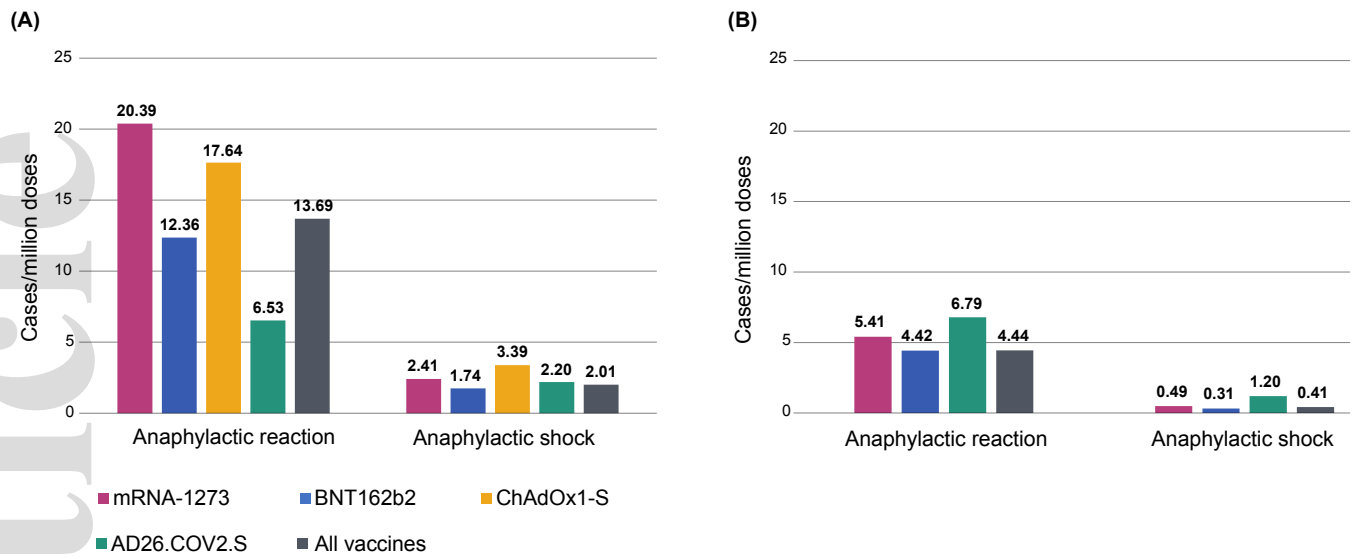
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Table 1. Fatalities incidence related to anaphylactic reaction, anaphylactic shock and their sum post COVID-19 vaccination with licensed vaccines reported in EudraVigilance for the European Economic Area and in VAERS for the United States from week 52, 2020 through week 39/2021 by vaccine platform.

Platform Database	Fatalities/100 million administered vaccine doses					
	Anaphylactic reaction		Anaphylactic shock		Sum	
	mRNA	Vector	mRNA	Vector	mRNA	Vector
EudraVigilance	5.15	10.70	1.85	10.70	7.01	21.41
VAERS	1.85	6.66	0.79	0	2.64	6.66

FIGURE LEGENDS

Figure 1. Incidence of anaphylactic reaction and anaphylactic shock post-COVID-19 vaccination for licensed vaccines reported in EudraVigilance (**a**) and VAERS (**b**) databases from week 52, 2020 to week 39, 2021. Rates were estimated by normalizing the number of reported cases to administered vaccine doses (and expressed per million doses).



“Comparative assessment of allergic reactions to COVID-19 vaccines in Europe and the United States” by Hatziantoniou *et al.*

Materials and Methods

The data source for VAERS was the public use database where data are coded using the MedDRA system. Typically, the Brighton Collaboration criteria regarding anaphylaxis are applied only in cases for which additional follow-up is done by CDC and FDA investigators.¹ The total numbers of administered COVID-19 vaccine doses as of October 2, 2021, were retrieved from the European Centre for Disease Prevention and Control (ECDC) for the EEA and from the publicly available domain “our world in data” for the US.^{2,3}

Results

Other infrequent reports related to post vaccination allergic reactions included anaphylactoid reactions, allergic edema, allergic reactions to excipients, and multiple allergies. This study focused on the analysis of anaphylactic reactions and anaphylactic shock cases following COVID-19 vaccination.

As of October 2, 2021, anaphylactic reaction cases post-COVID-19 vaccination recorded in EudraVigilance and VAERS amounted to 7,798 and 1,745, respectively, for a total of 9,543 cases (Tables S1a and S2a). Anaphylactic shock cases post-COVID-19 vaccination recorded in EudraVigilance and VAERS amounted to 1,144 and 163, correspondingly, for a total of 1,307 cases (Tables S1b and S2b). Administered vaccine doses for licensed mRNA and vectored vaccines for which the manufacturer was known were 569,431,130 in the EEA and 393,360,144 in the US for a total of 962,791,274 doses of vaccine.

The composition of each vaccine is described in the summary of product characteristics of the European Public Assessment Report (EPAR).⁴⁻⁷

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Table S1a. Description of anaphylactic reaction cases post COVID-19 vaccination reported in EudraVigilance from week 52, 2020 to week 39, 2021[†].

Vaccine	mRNA-1273				BNT162b2				ChAdOx1-S				AD26.COV2.S			
N[‡]	60,480,227				424,876,685				68,764,151				15,310,067			
Age group \ Sex	♀	♂	NS	Total	♀	♂	NS	Total	♀	♂	NS	Total	♀	♂	NS	Total
Not specified (NS)	42	6	4	52	246	33	45	324	100	10	18	128	5	0	2	7
0-1 month	0	0	0	0	1	0	0	1	1	0	0	1	0	0	0	0
2 months - 2 years	1	0	0	1	0	2	1	3	1	0	0	1	0	0	0	0
3-11 years	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
12-17 years	1	4	0	5	45	27	1	73	0	1	0	1	0	0	0	0
18-64 years	820	234	4	1058	3661	537	32	4230	806	131	27	964	40	48	1	89
65-85 years	86	27	0	113	386	113	4	503	89	22	3	114	3	1	0	4
> 85 years	3	1	0	4	95	23	0	118	3	1	0	4	0	0	0	0
Total	953	272	8	1233	4434	735	83	5252	1000	165	48	1213	48	49	3	100
Outcome	Number of individual cases															
Fatal	1				24				7				2			
Not recovered/Not resolved	98				265				111				8			
Recovered/Resolved	579				2994				505				48			
Recovered/ resolved with sequelae	6				63				23				1			
Recovering/Resolving	132				1092				259				12			
Unknown	417				814				308				29			

Table S1b. Description of anaphylactic shock cases post COVID-19 vaccination reported in EudraVigilance from week 52, 2020 to week 39, 2021[†].

Vaccine	mRNA-1273				BNT162b2				ChAdOx1-S				AD26.COV2.S			
N[‡]	60,480,227				424,876,685				68,764,151				15,310,067			
Age group \ Sex	♀	♂	NS	Total	♀	♂	NS	Total	♀	♂	NS	Total	♀	♂	NS	Total
Not specified (NS)	4	1	2	7	35	8	5	48	20	1	3	24	1	1	2	4
0-1 month	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2 months - 2 years	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3-11 years	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
12-17 years	0	1	0	1	9	11	1	21	0	0	0	0	0	0	0	0
18-64 years	87	21	2	110	439	127	8	574	146	34	5	185	15	10	0	25
65-85 years	18	6	0	24	52	23	1	76	18	6	0	24	1	1	0	2
> 85 years	2	1	0	3	13	3	0	16	0	0	0	0	0	0	0	0
Total	111	30	4	145	548	172	15	735	184	41	8	233	17	12	2	31
Outcome	Number of individual cases															
Fatal	2				7				7				2			
Not recovered/Not resolved	20				55				23				3			
Recovered/Resolved	64				378				79				10			
Recovered/ resolved with sequelae	2				27				11				0			
Recovering/Resolving	11				113				51				5			
Unknown	46				155				62				11			

[†] Data (up to Oct 2, 2021) summarized from: European Medicines Agency. EudraVigilance-European database of suspected adverse drug reaction reports. Available at: <https://www.adrreports.eu>.

[‡] The total number of COVID-19 vaccine doses administered in Europe was 580,051,991 as of October 2, 2021, of which 10,620,861 were of other/unknown manufacturer. Available at: <https://vaccinetracker.ecdc.europa.eu>.

Table S2a. Description of anaphylactic reaction cases post COVID-19 vaccination reported in VAERS from week 52, 2020 to week 39, 2021.

Vaccine	mRNA-1273				BNT162b2				AD26.COV2.S			
N[†]	151,622,624				226,714,560				15,022,960			
Age group \ Sex	♀	♂	Unknown	Total	♀	♂	Unknown	Total	♀	♂	Unknown	Total
Unknown	38	7	15	60	58	8	29	95	5	0	15	20
6-17 years	0	1	0	1	33	18	0	51	0	0	0	0
18-29 years	60	16	0	76	102	15	1	118	6	7	0	13
30-39 years	102	23	1	126	151	26	2	179	15	5	0	20
40-49 years	122	13	0	135	181	24	1	206	16	3	0	19
50-59 years	104	18	0	122	160	18	0	178	12	3	1	16
60-64 years	38	9	0	47	56	12	0	68	5	1	0	6
65-79 years	49	17	0	66	72	19	2	93	5	2	0	7
>80 years	6	2	0	8	8	6	0	14	1		0	1
TOTAL	519	106	16	641	821	146	35	1002	65	21	16	102
Outcome[‡]												
Fatal	1	0	1	2	1	1	3	5	0	0	1	1
Complicated course	95	24	2	121	143	146	22	311	9	4	0	13

Table S2b. Description of anaphylactic shock cases post COVID-19 vaccination reported in VAERS from week 52, 2020 to week 39, 2021.

Vaccine	mRNA-1273				BNT162b2				AD26.COV2.S			
N[†]	151,622,624				226,714,560				15,022,960			
Age group \ Sex	♀	♂	Unknown	Total	♀	♂	Unknown	Total	♀	♂	Unknown	Total
Unknown	6	1	3	10	6	2	0	8	1	0	2	3
6-17 years	0	0	0	0	3	1	0	4	1	0	0	1
18-29 years	7	4	0	11	3	2	0	5	2	0	0	2
30-39 years	8	1	0	9	9	1	0	10	4	0	0	4
40-49 years	13	4	1	18	12	3	0	15	4	1	0	5
50-59 years	9	2	0	11	12	5	0	17	3	0	0	3
60-64 years	2	0	0	2	2	1	0	3	0	0	0	0
65-79 years	8	4	0	12	5	2	0	7	0	0	0	0
>80 years	1	1	0	2	1	0	0	1	0	0	0	0
TOTAL	54	17	4	75	53	17	0	70	15	1	2	18
Outcome[‡]												
Fatal	1	0	1	2	1	0	0	1	0	0	0	0
Complicated course	17	5	0	22	18	6	0	24	5	0	0	5

†The total number of COVID-19 vaccine doses administered in the US was 393,360,144 as of October 1, 2021, of which 320,000 were of unspecified manufacturer. Available at: <https://ourworldindata.org>.

‡ Only severe outcome categories are included for clarity. Data for complete entries summarized from: Vaccine Adverse Event Reporting System. Available at: <https://vaers.hhs.gov/data.html>