Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel
Federal Institute for Vaccines and Biomedicines

Paul-Ehrlich-Institut

Langen, 7 September 2022

SAFETY REPORT

In the current safety report, the Paul-Ehrlich-Institut summarises the reports about suspected cases of adverse events and vaccination complications that it has received from the start of the vaccination campaign in Germany on 27 December 2020 through 30 June 2022.

Contents

1. Summary

- A total of 182,717,880 vaccinations against COVID-19 were carried out between 27 December 2020 and 30 June 2022. 73.7% of those vaccine doses were Comirnaty (BioNTech Manufacturing GmbH), 17.1% Spikevax (MODERNA BIOTECH SPAIN, S.L.), 7.0% Vaxzevria (AstraZeneca AB), 2.1% Jcovden (Janssen-Cilag International NV) and 0.1% Nuvaxovid (Novavax CZ, a.s.).
- In the same time period, the Paul-Ehrlich-Institut received 323,684 reports of suspected adverse events and vaccination complications.
- The reporting rate of suspected cases for all vaccines combined was 1.8 reports per 1,000 vaccine doses, for suspected cases of severe adverse events and vaccine complications the reporting rate was 0.3 reports per 1,000 vaccine doses.
- The reporting rate after booster vaccinations was lower for the two mRNA vaccines, Comirnaty and Spikevax, than after primary immunisation.
- Individual cases of myocarditis and/or pericarditis have been reported after Nuvaxovid, including a few cases from Germany.
- An evaluation of reports of chronic fatigue syndrome and Long COVID-like symptoms submitted to the Paul-Ehrlich-Institut and a comparison with international reports in the adverse reaction database at the European Medicines Agency (EMA) showed no risk signal up to the date of this evaluation.
- There was also no risk signal indicated following an evaluation of suspected case reports from Germany concerning various menstrual disorders in women of childbearing age and seizures after COVID-19 vaccines.

Note on future safety reports

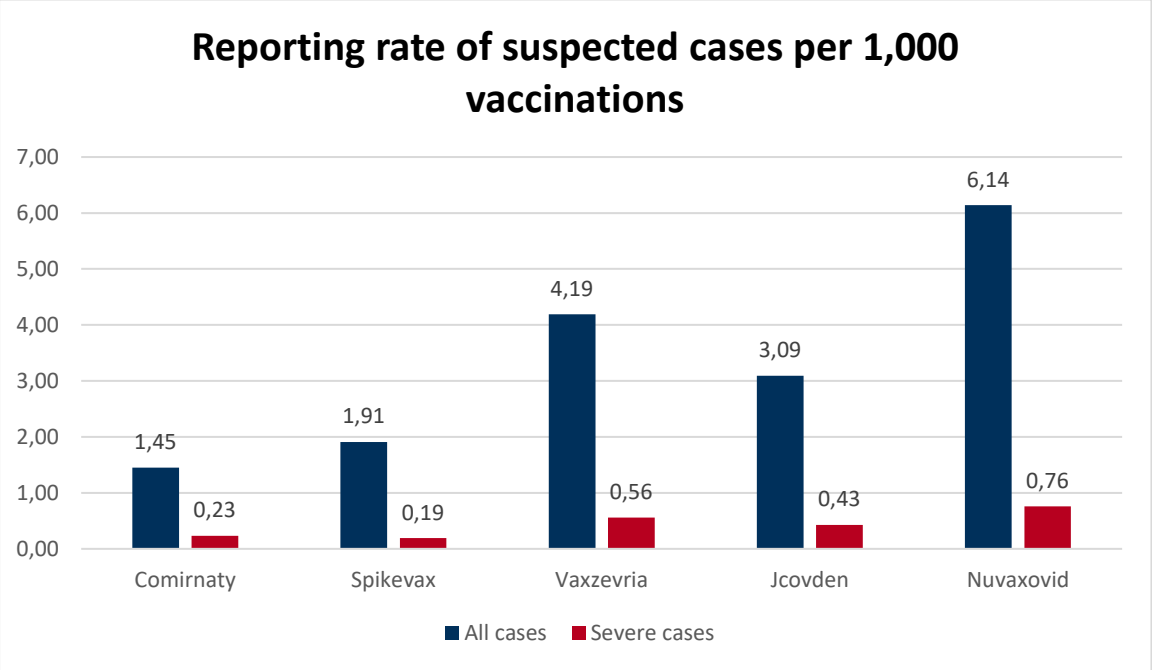
A large part of the population has now been vaccinated at least once. Currently, the number of reports of suspected adverse reactions and vaccine complications is decreasing due to the lower daily vaccination rate compared to other periods, such as the first quarter of 2022. This means that there is currently little change in the cumulative analysis of spontaneous reporting data for the COVID-19 vaccines available so far. Therefore, the format of future safety reports will be changed and the focus will henceforth be on booster vaccinations recommended by the Standing Committee on Vaccination (STIKO), new vaccines including the new variant vaccines and new possible risk signals.

2. Overview of suspected cases in Germany reported to the Paul-Ehrlich-Institut

2.1. Reporting rate of COVID-19 vaccines by vaccine dose

The Paul-Ehrlich-Institut received a total of 323,684 individual reports of suspected adverse events or vaccine complications through 30 June 2022. The majority of reports concerned Comirnaty with 196,465 (60.7%) of the reports, followed by Spikevax with 59,750 (18.5%) and Vaxzevria with 53,585 (16.6%) individual case reports. 11,567 (3.6%) individual case reports were received after Jcovden. Few adverse events have been reported for the vaccine Nuvaxovid (n = 796; 0.3%), therefore this reporting rate should continue to be interpreted with caution. No vaccine name was given in the report in 1,521 (0.5%) cases. The overall reporting rate and the reporting rate of suspected serious adverse events or vaccination complications following each vaccine is shown in Figure 1.

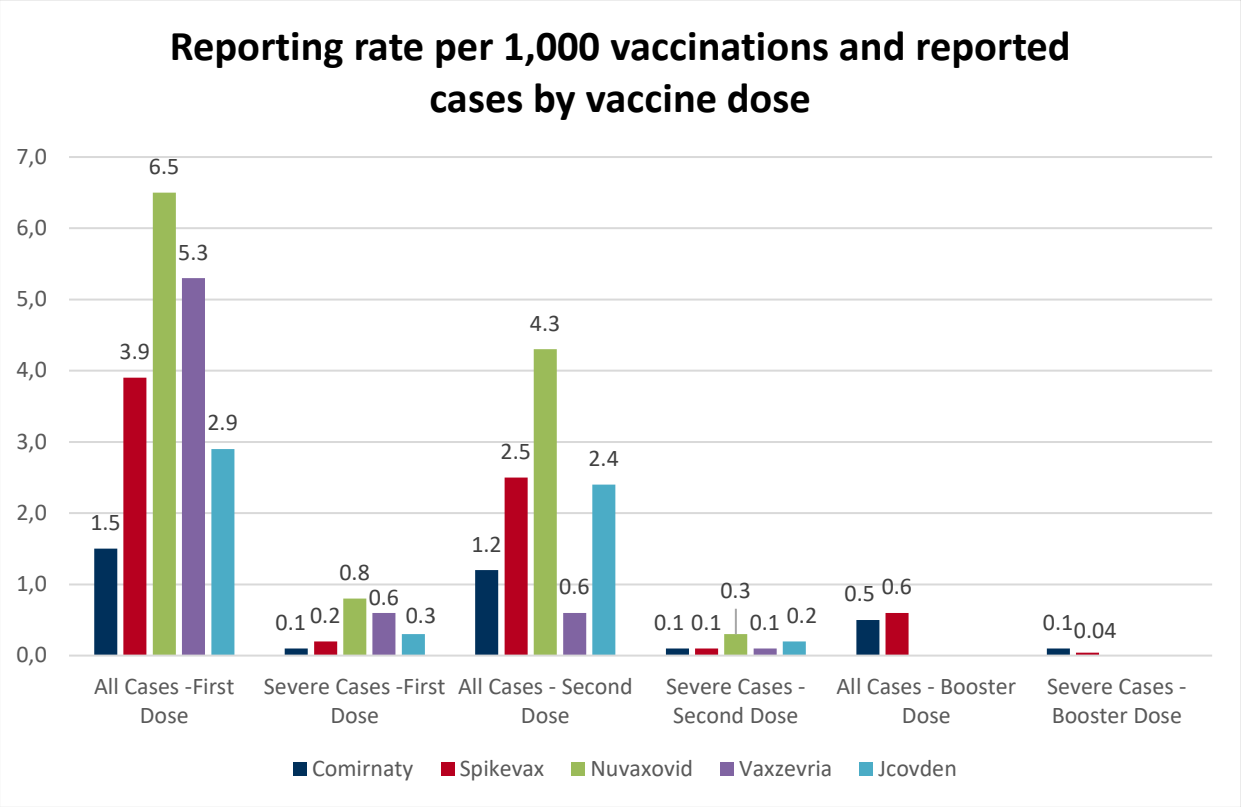
Figure 1: Overall reporting rates and reporting rates of suspected serious adverse events or vaccination complications per 1,000 vaccinations
(evaluation at case level)



The Paul-Ehrlich-Institut received a total of 681 individual case reports through 30 June 2022 for the fourth vaccination (n = 495 Comirnaty, n = 174 Spikevax, n = 1 Jcovden, n = 1 Vaxzevria and n = 10 without specifying the trade name) and 31 reports for the fifth vaccination (n = 17 Comirnaty, n = 7 Spikevax, n = 7 without specifying the trade name).

The reporting rate by vaccine and dose is shown in Figure 2. Information on booster doses (first and second booster vaccination) summarises the vaccinations with the respective vaccines that were given after the primary vaccination course.

Figure 2: Reporting rates of suspected adverse events and vaccination complications per 1,000 vaccinations by vaccine dose (evaluation at case level)



2.2. Reporting rates of commonly reported adverse events after COVID-19 vaccines

The most commonly reported transient local and systemic reactions were headache (0.37 per 1,000 vaccinations), fatigue (0.32 per 1,000 vaccinations), flu-like symptoms (0.26 per 1,000 vaccinations), pain at the injection site (0.25 per 1,000 vaccinations) and fever (0.24 per 1,000 vaccinations).

2.3. Reporting rates of Adverse Events of Special Interest (AESI)

The vaccine-related reporting rates of Adverse Events of Special Interest (AESI) are presented in Table 1, irrespective of time interval after vaccination, vaccination dose and the presence of a causal relationship. Chapter 4 of the report compares the number of cases reported for selected AESI in a given time interval after vaccination with the statistically random number of cases expected in a comparable population (observed versus expected analysis).

Table 1: Reporting rate of adverse events of special interest (AESI) per 100,000 vaccinations (rounded up or down). Evaluation based on the Medical Dictionary for Regulatory Activities, MedDRA, Preferred Terms, PT

AESI (reaction) absolute (n) and per 100,000 vaccinations (reporting rate, RR)	Comirnaty		Spikevax		Vaxzevria		Jcovden		Nuvaxovid	
	n	RR	n	RR	n	RR	n	RR	n	RR
Dyspnoea	9,218	6.83	2,524	8.08	1,515	11.84	481	12.83	46	35.5
Arrhythmia	6,546	4.85	1,669	5.35	730	5.71	265	7.07	26	20.06
Myocarditis*	2,128	1.58	576	1.84	85	0.66	49	1.31	4	3.09
Pulmonary embolism	1,324	0.98	309	0.99	505	3.95	99	2.64	2	1.54
Apoplexy	919	0.68	170	0.54	199	1.56	38	1.01	1	0.77
Syncope	834	0.62	177	0.57	337	2.63	64	1.71	7	5.4
Facial paralysis	787	0.58	128	0.41	99	0.77	42	1.12	1	0.77
Deep vein thrombosis	723	0.54	167	0.53	394	3.08	43	1.15		
Thrombosis	667	0.49	161	0.52	266	2.08	39	1.04	1	0.77
Respiratory disorder	465	0.34	91	0.29	418	3.27	14	0.37	2	1.54
Anaphylactic reaction	425	0.31	58	0.19	47	0.37	12	0.32	2	1.54
Myocardial infarction	416	0.31	86	0.28	78	0.61	23	0.61		
Thrombocytopenia	363	0.27	50	0.16	472	3.69	43	1.15	2	1.54
Pericarditis*	349	0.26	72	0.23	22	0.17	12	0.32	1	0.77
Seizure	334	0.25	41	0.13	86	0.67	19	0.51		
Loss of consciousness	288	0.21	54	0.17	126	0.98	16	0.43	1	0.77
Heart failure	258	0.19	41	0.13	38	0.3	11	0.29		
Guillain-Barré Syndrome	248	0.18	57	0.18	138	1.08	61	1.63	1	0.77
Acute myocardial infarction	230	0.17	47	0.15	56	0.44	13	0.35		
Cerebral venous sinus thrombosis	224	0.17	43	0.14	302	2.36	28	0.75		
Cerebral haemorrhage	219	0.16	32	0.1	115	0.9	17	0.45		
Acute hearing loss	184	0.14	45	0.14	66	0.52	2	0.05	2	1.54

(Continuation of Table 1)

AESI (reaction) absolute (n) and per 100,000 vaccinations (reporting rate, RR)	Comirnaty		Spikevax		Vaxzevria		Jcovden		Nuvaxovid	
	n	RR	n	RR	n	RR	n	RR	n	RR
Venous thrombosis	146	0.11	19	0.06	66	0.52	12	0.32		
Rheumatoid arthritis	144	0.11	35	0.11	22	0.17	5	0.13		
Anaphylactic shock	142	0.11	8	0.03	36	0.28	6	0.16		
Presyncope	139	0.1	19	0.06	43	0.34	14	0.37	2	1.54
Cardiac arrest	116	0.09	21	0.07	22	0.17	9	0.24		
Acute kidney damage	113	0.08	25	0.08	17	0.13	3	0.08		
Immune thrombocytopenia	107	0.08	16	0.05	146	1.14	23	0.61	1	0.77
Vasculitis	103	0.08	22	0.07	21	0.16	8	0.21		
Multiple sclerosis	98	0.07	12	0.04	15	0.12	2	0.05		
Myelitis	81	0.06	11	0.04	17	0.13	2	0.05		
Optic neuritis	79	0.06	14	0.04	31	0.24	10	0.27		
Encephalitis	65	0.05	19	0.06	32	0.25	5	0.13		
Embolism	54	0.04	7	0.02	19	0.15	1	0.03		
Multiple organ dysfunction syndrome	53	0.04	2	0.01	14	0.11	2	0.05		
Ischemic stroke	50	0.04	7	0.02	25	0.2	1	0.03		
Portal vein thrombosis	31	0.02	8	0.03	36	0.28	2	0.05		
Subarachnoid haemorrhage	22	0.02	6	0.02	14	0.11				
Thrombosis with thrombocytopenia syndrome (TTS)***	6	0	3	0.010	115	0.9	15	0.4		
Intracranial haemorrhage	6	0			24	0.19				
Hepatic vein thrombosis	2	0			14	0.11	1	0.03		

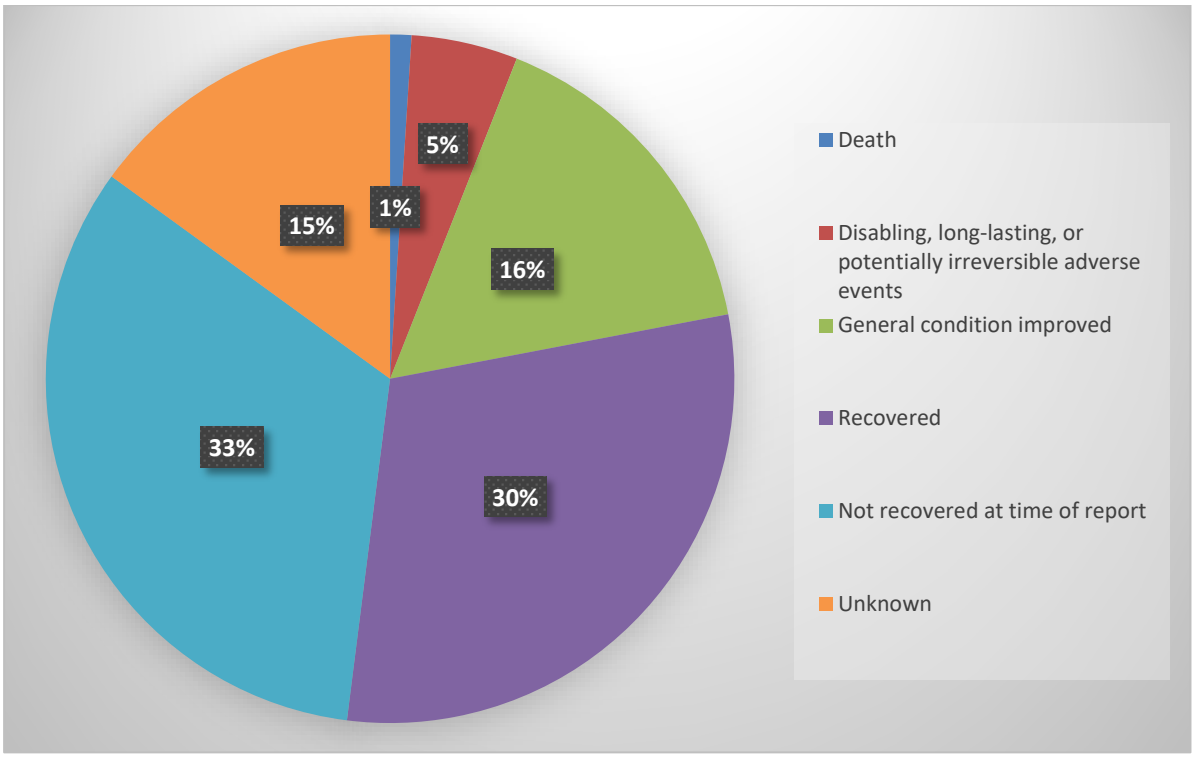
Reactions with a reporting frequency of < 1 reported adverse reaction per 2,000,000 doses of vaccine are presented with a decimal place as 0.0; *Myocarditis refers to cases of myocarditis with and without concomitant pericarditis; **Pericarditis refers to cases of isolated pericarditis; * **TTS: Only those cases that meet the case definition of a TTS according to CDC criteria were considered: thrombosis with unusual localisation plus platelet count < 150/ GL or thrombosis plus thrombocytopenia plus platelet factor 4 (PF)antibody positive

Due to the comparatively low number of vaccinations, the point estimators for Nuvaxovid should be viewed as uncertain.

2.4. Outcome of reported suspected adverse events after COVID-19 vaccines

The overview of the outcome of suspected adverse events after all five COVID-19 vaccines used thus far in Germany as a percentage of the total number of suspected case reports is shown in Figure 3.

Figure 3: Outcome of suspected adverse event reports



In about one percent of the suspected case reports (n = 3,023 cases), death was reported at varying time intervals following COVID-19 vaccination. 120 cases were assessed by the Paul-Ehrlich-Institut to be consistent with a causal link to the administration of a COVID-19 vaccine (probable or possible causal relationship).

A comparison of the total number of reported suspected adverse events with a fatal outcome occurring between one day and six weeks after administration of COVID-19 vaccine with the number of deaths that would be statistically expected in the same time period (data from the Federal Statistical Office of Germany) did not indicate a safety signal for any of the five COVID-19 vaccines used so far in Germany. This conclusion is in line with the literature data[1]. No fatalities have been reported for the vaccine Nuvaxovid and therefore Nuvaxovid is not listed in the following tables.

Since the time between vaccination and first symptoms and/or time of death was not included in all reports, an additional analysis was carried out under the assumption that all deaths, even those occurring at an unknown or very long time after vaccination, occurred within a 30-day timeframe. Again, there was no safety signal for increased mortality for any of the five vaccines (data not presented separately).

Table 2: Observed versus expected analysis of the deaths reported to the Paul-Ehrlich-Institute at varying time intervals after vaccination against COVID-19 (up to 30 days after vaccination)

Included were cases that concerned a vaccination administered through 30 June 2022 and for which the time interval between vaccination and the onset of symptoms is known. Background incidence rate according to the Federal Statistical Office: 1,240.97 per 100,000 person years[1]

		Time between vaccination and onset of symptoms			
Total deaths		**1 Day**	**7 Days**	**14 Days**	**30 Days**
Comirnaty	Total cases	442	961	1,216	1,436
	SMR (95% CI)	0.096 (0.088-0.106)	0.030 (0.028-0.032)	0.019 (0.018-0.020)	0.0104 (0.0099-0.0110)
Spikevax	Total cases	61	115	137	154
	SMR (95% CI)	0.058 (0.044-0.074)	0.015 (0.013-0.019)	0.009 (0.008-0.011)	0.005 (0.004-0.006)
Vaxzevria	Total cases	59	135	185	236
	SMR (95% CI)	136 (0.103-0.175)	0.044 (0.037-0.053)	0.030 (0.026-0.035)	0.018 (0.016-0.021)
Jcovden	Total cases	14	26	35	39
	SMR (95% CI)	0.110 (0.060-0.184)	0.029 (0.019-0.043)	0.020 (0.014-0.027)	0.010 (0.007-0.014)
		Time between vaccination and onset of symptoms			
Deaths after booster vaccination		**1 Day**	**7 Days**	**14 Days**	**30 Days**
Comirnaty	Total cases	59	115	129	147
	SMR (95% CI)	0.047 (0.035-0.060)	0.013 (0.011-0.016)	0.007 (0.006-0.009)	0.004 (0.003-0.005)
Spikevax	Total cases	10	27	32	36
	SMR (95% CI)	0.015 (0.007-0.027)	0.006 (0.004-0.008)	0.003 (0.002-0.005)	0.0018 (0.0013-0.0025)
Vaxzevria	Total cases	0	0	0	1
	SMR (95% CI)	-	-	-	0.112 (0.003-0.626)
Jcovden	Total cases	0	0	0	1
	SMR (95% CI)	-	-	-	0.038 (0.001-0.214)

[1] Federal Statistical Office data (extracted on 19 January 2022): 982,792 deaths among those aged 5 years and older in 2020; population (age groups: 5 years and older in 2020): 79,195,618, CI: confidence interval

2.5. Adverse events among children and adolescents

Comirnaty is authorised from the age of 5 years and Spikevax from the age of 6 years. The Standing Committee on Vaccination (STIKO) recommends vaccination with Comirnaty for children and adolescents.

Since the start of the vaccination campaign on 27 December 2020, a total of 5,911 suspected adverse events have been reported to the Paul-Ehrlich-Institut, in which at least one adverse vaccination reaction was reported for children and adolescents after vaccination with COVID-19 vaccines.

Table 3: Suspected reports after COVID-19 vaccination of children and adolescents aged 5-17 years

	Children and adolescents 5 – 17 years	Adolescents 12 – 17 years	Children 5 – 11 years
Comirnaty	5,758	4,719	1,039
Spikevax	84	80	4
Vaxzevria	20	17	3
Jcovden	12	12	0
Nuvaxovid	0	0	0
COVID-19 vaccine unknown	37	31	6
Total	5,911	4,859	1,052

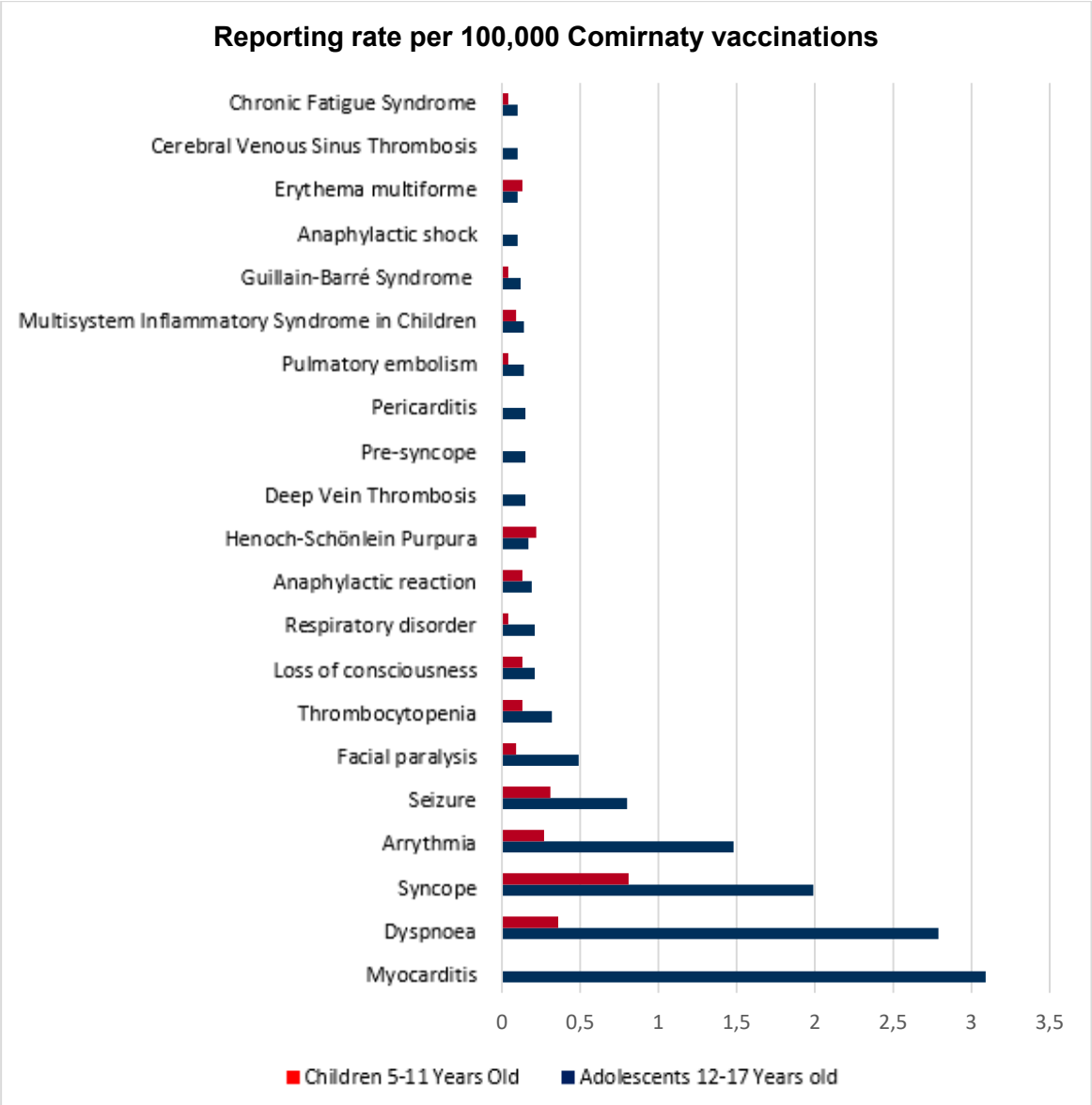
Furthermore, in 204 suspected cases following vaccination with a COVID-19 vaccine, children who were younger than 5 years of age at the time of vaccination were reported to have been vaccinated. Of these, 134 were children aged between 15 months and 4 years. The vaccine was not mentioned by name in a total of 37 suspected reports. A total of 70 suspected cases relate to infants whose mothers were vaccinated while the infants were still breastfeeding. These reports are not included in the following analysis. The Paul-Ehrlich-Institut supports a study by the Pharmacovigilance Centre for Embryonic Toxicology at the Charité Berlin on the safety of COVID-19 vaccination during pregnancy.

2.5.1. Reports of suspected adverse events or vaccination complications after Comirnaty

The most commonly reported symptoms following vaccination with Comirnaty were: headache, 0.13 per 1,000 vaccinations; injection site pain, 0.10 per 1,000

vaccinations; fatigue, 0.09 per 1,000 vaccinations; and fever, 0.08 per 1,000 vaccinations. The reporting rate was lower among children aged 5 to 11 years than it was in adolescents aged 12 to 17 years.

Figure 4: Adverse Events of Special Interest (AESI) after Comirnaty in children and adolescents



3. Known adverse events of COVID-19 vaccines

An overview of the known adverse event profile of the individual COVID-19 vaccines is shown in Table 4. Adverse reactions (myocarditis/ pericarditis) are summarised in more detail below.

Table 4: Overview of (selected) adverse events/vaccination complications for authorised COVID-19 vaccines

Adverse event	Vaccine	Frequency	Note
Local and general reactions as an expression of the immune system's confrontation with the vaccine			
Local reactions	Comirnaty, Spikevax, Vaxzevria, Jcovden*, Nuvaxovid	Very common	Transient reactions shortly after vaccination, less frequent in the elderly
"COVID arm"	Spikevax > Comirnaty	Occasional	Delayed response ≥ 8 days, 100% blande
General reactions	Comirnaty, Spikevax, Vaxzevria, Jcovden, Nuvaxovid	Very common	mRNA vaccines, Nuvaxovid D2 > D1; Vaxzevria D1 > D2; less common in the elderly
Lymphadenopathy	Comirnaty, Spikevax, Vaxzevria, Jcovden, Nuvaxovid	Common Spikevax; uncommon Comirnaty	Comirnaty: more often after booster vaccination than after primary vaccination
Swelling of the vaccinated limb	Comirnaty	Unknown	
Hypersensitivity reactions			
Hypersensitivity reaction, angioedema, facial swelling	Comirnaty, Spikevax, Vaxzevria, Jcovden, Nuvaxovid	Occasional	Allergic reactions
Anaphylaxis	Comirnaty, Spikevax, Vaxzevria, Jcovden, Nuvaxovid	Very rare	Reporting frequency < 1/100,000 vaccinations; women > men, D1 > D2
Erythema multiforme	Comirnaty, Spikevax	Unknown	Individual cases after authorisation, blander course
Leukocytoclastic vasculitis	Jcovden	Unknown	Post-authorisation case reports
Other adverse events/vaccination complications			
Myocarditis/pericarditis	Comirnaty, Spikevax, Nuvaxovid*	Very rare	(see summary below)
Facial nerve paralysis	Comirnaty, Spikevax, Vaxzevria	Rare	mRNA vaccines: few cases in CT phase III; Vaxzevria: individual post-authorisation cases reported
TTS	Vaxzevria, Jcovden	Very rare	Similar aHIT, anti-PF4 antibodies; Vaxzevria D1 > D2
Cerebral venous thrombosis, venous sinus thrombosis	Vaxzevria	Very rare	Also reports of cases without concomitant thrombocytopenia
Venous thrombosis	Jcovden	Rare	More post-verum reports compared to placebo in 1 of 2 CT Phase III, individual post-authorisation cases reported
Guillain-Barré Syndrome	Vaxzevria, Jcovden	Very rare	Individual post-authorisation cases reported, molecular mimicry?
Transverse myelitis	Vaxzevria, Jcovden	Unknown	Individual post-authorisation cases reported
Immune thrombocytopenia	Vaxzevria, Jcovden	Unknown	Autoantibodies against platelets
Tinnitus	Jcovden	Rare	

Other adverse reactions/vaccination complications (continuation of Table 4)			
Facial swelling	Comirnaty, Spikevax	Unknown	For persons with dermatological fillers in their medical history
Relapse in capillary leak syndrome (CLS)	Spikevax	Unknown	Very few individual case reports in CLS patients, no deaths so far, apparently less frequent and less severe than relapse of the disease as a result of a SARS-CoV-2 infection
Capillary leak syndrome (CLS)	Vaxzevria, Jcovden	Unknown	Very rare reports of CLS, including in patients with known CLS; contraindication to known CLS
Paraesthesia, hypoaesthesia	Comirnaty, Spikevax, Nuvaxovid	Comirnaty: unknown; Spikevax: rare	Reported by a variety of vaccines, suspected to be transient stress-associated reactions
Increase in blood pressure	Nuvaxovid	Occasional	

Frequencies: very common ≥ 1/10, common ≥ 1/100 to < 1/10, uncommon ≥ 1/1,000 to < 1/100, rare ≥ 1/10,000 to < 1/1,000, very rare ≥ 1/10,000

D: dose; CT phase III: pre-marketing authorisation clinical trial; TTS: thrombosis with thrombocytopenia syndrome; aHIT: autoimmune heparin-induced thrombocytopenia; PL4: platelet factor 4

* Notice from the European Medicines Agency (EMA) dated 03.08.2022 concerning isolated cases of myocarditis/ pericarditis following Nuvaxovid (www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/safety-covid-19-vaccines)

The most significant, very rare serious adverse events of the two mRNA COVID-19 vaccines Comirnaty and Spikevax are myocarditis and/or pericarditis. Young men and male children and adolescents aged 12 to 17 years are particularly affected after the second dose.[2-22] Data from several countries that include Germany, along with data from a recently published summary of several studies on myocarditis and pericarditis, indicates that the risk of myocarditis/pericarditis in younger people is higher after Spikevax than after Comirnaty[20.22], which is why the Standing Committee on Vaccination (STIKO) recommends Comirnaty for persons younger than 30 years of age. The STIKO recommendation of COVID-19 vaccination of pregnant women with Comirnaty is not related to the adverse event of myocarditis/pericarditis described here.

The first symptoms typically appear within a few days of vaccination. The published data[2-22] indicates a primarily mild disease progression, meaning that the majority of patients with myocarditis and/or pericarditis after vaccination with mRNA vaccines respond well to treatment and rest and recover quickly from the initial symptoms, even if serious and also fatal courses were observed in individual cases. However, in a case series published in 2022 with 16 adolescent patients, radiological anomalies were still detected during follow-up examinations months after vaccination. However, the follow-up patients had an excellent clinical course.[23] It is important to further investigate potential long-term

effects of COVID-19 mRNA vaccination-related myocarditis/pericarditis. In this regard, the Paul-Ehrlich-Institute supports the paediatric myocarditis registry MYKKE.

A recent study from France published as a preprint suggests that the risk of myocarditis is still increased after booster vaccination (third dose) within seven days after mRNA vaccination in all age groups starting at the age of 12, although not to the same extent as after the second vaccination.[24] A study from England suggests that Comirnaty has a slightly increased risk of myocarditis after booster vaccination (the number of cases was too low to be assessed after Spikevax booster vaccination). The study also suggests that the risk of myocarditis after infection with SARS-CoV-2 was higher in unvaccinated individuals, perhaps with the exception of young men, than after vaccination. Vaccination also appears to provide some protection against myocarditis in vaccinated individuals who become infected with SARS-CoV-2 after vaccination. However, the study was carried out predominantly before the emergence of the Omicron variants (01.12.2020 to 15.12.2021).[25]
An increased risk of myocarditis and/or pericarditis following booster vaccination is already noted in the Spikevax SPC.

In accordance with the literature referenced above, spontaneous reports from Germany of suspected myocarditis also indicate a safety signal in young adults aged 18 to 29 years (n = 52 men, n = 18 women) and male adolescents aged 12 to 17 years (n = 16) within seven days of booster vaccination (third vaccination) with Comirnaty. This is because the number of suspected cases reported seven days after vaccination is higher than statistically expected, taking the outpatient and inpatient data from the Institute for Applied Health Research Berlin (InGeF) from 2020 for the respective age groups into account as background incidences (myocarditis diagnosis ICD-10 code I40). No cases of myocarditis in a female adolescent aged 12 to 17 years was reported within seven days through 30 June 2022.
A safety signal for myocarditis after third vaccination was also observed for Spikevax for young men aged 18 to 29 years (n = 7 cases; n = 1 case among women). One case of myocarditis was reported each for the male 12 to 17 years age group and the female 18 to 29 years age group. An evaluation on the basis of a single report is not very meaningful. A short time interval of seven days was chosen for the comparison of the reported and statistically expected cases of myocarditis, because study data indicates that the plausible time interval of myocarditis after mRNA vaccination is very short. In addition, the high incidence of

low-symptomatic or asymptomatic SARS-CoV-2 infections increasingly leads to bias in the evaluations of spontaneous reports, even in vaccinated individuals, since the viral infection also causes myocarditis and in individual cases can be coincidentally temporally associated with a vaccination. This bias should be minimized in the evaluation with the use of a short, seven-day time interval.

A total of 1,935 suspected cases of myocarditis and pericarditis after Comirnaty and 566 suspected cases after Spikevax were reported to the Paul-Ehrlich-Institut in the period from 27 December 2020 to 30 June 2022. A total of 539 reports of suspected myocarditis/pericarditis have been reported following mRNA booster vaccinations, including five cases of myocarditis and/or pericarditis following second booster vaccinations. The latter concerns four cases after Comirnaty in two men and two women aged 32 to 57 years and one case after Spikevax in an 83-year-old man. In one case, the time interval between vaccination was not mentioned, in the other cases it was 1, 2, 4 and 12 days after vaccination.

In the observation period through 30 June 2022, no confirmed cases of myocarditis in children aged 5 to 11 years were reported to the Paul-Ehrlich-Institut.

The Pharmacovigilance Risk Assessment Committee (PRAC) at the European Medicines Agency (EMA) established on 3 August 2022 that cases of myocarditis and/or pericarditis may occur after Nuvaxovid. This conclusion is based on individual suspected case reports (EMA Safety Update 3 August 2022), five of which came from Germany. Two of the reports from the Paul-Ehrlich-Institut are considered to be possibly or probably related to vaccination. In a third report from Germany, no connection with vaccination has been identified and two further reports cannot be assessed, since essential information is missing or the suspected diagnosis could not be confirmed in a cardiological examination.

4. Observed versus expected (OE) analysis of selected adverse events

The Paul-Ehrlich-Institut analyses suspected adverse event reports in order to identify any potential safety signals. In addition to case-by-case assessments, the Paul-Ehrlich-Institut regularly carries out observed-versus-expected analyses (see Chapter 6.3 for details). A standardised morbidity ratio (SMR) with a lower 95% confidence interval ≥ 1 indicates a safety signal, but this must be further analysed via additional investigations, since the comparison of spontaneous reports with the known incidences from other studies is considered exploratory due to various methodological limitations. There is no significant difference from the previous safety report.

Table 5: Observed versus expected analysis of selected adverse reactions; all reports with age and known time interval between vaccination and first symptoms were included

		Time between vaccination and onset of symptoms			
		7 Days	**14 Days**	**30 Days**	**42 Days**
Apoplexy (ischaemic) ≥18 years Incidence 1641 cases per 100,000 person-years					
Comirnaty	Total cases	605	844	1,071	1,164
	SMR (95% CI)	0.15 (0.14-0.17)	0.111 (0.100-0.115)	0.064 (0.060-0.068)	0.049 (0.047-0.052)
Spikevax	Total cases	96	137	175	187
	SMR (95% CI)	0.10 (0.08-0.12)	0.07 (0.06-0.08)	0.042 (0.036-0.048)	0.032 (0.027-0.037)
Vaxzevria	Total cases	124	185	251	268
	SMR (95% CI)	0.31 (0.26-0.37)	0.23 (0.20-0.27)	0.15 (0.13-0.16)	0.11 (0.10-0.13)
Jcovden	Total cases	23	33	45	46
	SMR (95% CI)	0.20 (0.12-0.29)	0.14 (0.10-0.20)	0.09 (0.07-0.12)	0.07 (0.05-0.09)
Nuvaxovid	Total cases	1	1	1	1
	SMR (95% CI)	0.25 (0.01-1.37)	0.12 (0.003-0.685)	0.057 (0.001-0.320)	0.041 (0.001-0.228)

Continuation of Table 5: Observed versus expected analysis of selected adverse reactions; all reports with age and known time interval between vaccination and first symptoms were included

		Time between vaccination and onset of symptoms			
		7 Days	**14 Days**	**30 Days**	**42 Days**
Myocardial infarction ≥18 years Incidence 334.7 [2] cases per 100,000 person-years					
Comirnaty	Total cases	258	335	423	455
	SMR (95% CI)	0.032 (0.028-0.036)	0.021 (0.019-0.023)	0.012 (0.011-0.014)	0.0095 (0.0086-0.0104)
Spikevax	Total cases	64	82	98	105
	SMR (95% CI)	0.032 (0.025-0.041)	0.021 (0.016-0.025)	0.011 (0.009-0.014)	0.0088 (0.0072-0.0106)
Vaxzevria	Total cases	48	73	94	102
	SMR (95% CI)	0.059 (0.043-0.078)	0.044 (0.035-0.056)	0.027 (0.022-0.033)	0.021 (0.017-0.025)
Jcovden	Total cases	9	15	20	23
	SMR (95% CI)	0.038 (0.017-0.071)	0.031 (0.018-0.052)	0.019 (0.012-0.030)	0.016 (0.010-0.024)
Nuvaxovid	Total cases	0	0	0	0
	SMR (95% CI)	-	-	-	-
Pulmonary embolism ≥18 years Incidence 81 (72–90) [3] cases per 100,000 person-years					
Comirnaty	Total cases	416	598	819	886
	SMR (95% CI)	0.21 (0.19-0.24)	0.15 (0.14-0.17)	0.099 (0.092-0.106)	0.076 (0.071-0.081)
Spikevax	Total cases	108	154	209	223
	SMR (95% CI)	0.22 (0.18-0.27)	0.16 (0.14-0.19)	0.101 (0.088-0.115)	0.077 (0.067-0.088)
Vaxzevria	Total cases	124	232	320	360
	SMR (95% CI)	0.62 (0.52-0.74)	0.58 (0.51-0.66)	0.38 (0.34-0.42)	0.30 (0.27-0.34)
Jcovden	Total cases	22	43	56	64
	SMR (95% CI)	0.38 (0.24-0.57)	0.37 (0.27-0.50)	0.23 (0.17-0.29)	0.18 (0.14-0.23)
Nuvaxovid	Total cases	0	0	1	1
	SMR (95% CI)	-	-	0.116 (0.003-0.647)	0.083 (0.002-0.462)

Continuation of Table 5: Observed versus expected analysis of selected adverse reactions; all reports with age and known time interval between vaccination and first symptoms were included

		Time between vaccination and onset of symptoms			
		7 Days	**14 Days**	**30 Days**	**42 Days**
Sinus/cerebral vein thrombosis ≥ 18 years: Incidence 1.9 (1.4-2.3)[4] cases per 100,000 person-years					
Comirnaty	Total cases	65	101	154	170
	SMR (95% CI)	1.43 (1.10-1.82)	1.11 (0.90-1.35)	0.79 (0.67-0.92)	0.62 (0.53-0.72)
Spikevax	Total cases	10	16	28	30
	SMR (95% CI)	0.88 (0.42-1.62)	0.70 (0.40-1.14)	0.58 (0.38-0.83)	0.44 (0.30-0.63)
Vaxzevria	Total cases	48	95	124	131
	SMR (95% CI)	10.31 (7.60-13.67)	10.20 (8.25-12.47)	6.21 (5.17-7.41)	4.69 (3.92-5.56)
Jcovden	Total cases	3	6	11	12
	SMR (95% CI)	2.20 (0.45-6.44)	2.20 (0.81-4.80)	1.89 (0.94-3.37)	1.47 (0.76-2.57)
Nuvaxovid	Total cases	0	0	0	0
	SMR (95% CI)	-	-	-	-
Immune thrombocytopenia ≥ 18 years Incidence 3.8 (3.6-4.1)[5] cases per 100,000 person-years*					
Comirnaty	Total cases	141	221	296	337
	SMR (95% CI)	1.55 (1.30-1.83)	1.21 (1.06-1.39)	0.76 (0.67-0.85)	0.62 (0.55-0.69)
Spikevax	Total cases	24	38	54	57
	SMR (95% CI)	1.06 (0.68-1.57)	0.84 (0.59-1.15)	0.56 (0.42-0.72)	0.42 (0.32-0.54)
Vaxzevria	Total cases	123	285	404	424
	SMR (95% CI)	13.21 (10.98-15.76)	15.30 (13.58-17.18)	10.12 (9.16-11.16)	7.59 (6.88-8.35)
Jcovden	Total cases	8	37	52	56
	SMR (95% CI)	2.94 (1.27-5.79)	6.79 (4.78-9.37)	4.46 (3.33-5.84)	3.43 (2.59-4.45)
Nuvaxovid	Total cases	0	1	2	3
	SMR (95% CI)	-	5.31 (0.13-29.57)	4.95 (0.60-17.89)	5.31 (1.09-15.51)
Immune thrombocytopenia <18 Incidence 4.2 (3.7-4.7)[5] cases per 100,000 person-years*					
Comirnaty	Total cases	12	17	18	18
	SMR (95% CI)	1.49 (0.77-2.60)	1.06 (0.62-1.69)	0.52 (0.31-0.82)	0.37 (0.22-0.59)

[1]Sedova Pet al.: Incidence of Stroke and Ischemic Stroke Subtypes: A Community-Based Study in Brno, Czech Republic. Cerebrovasc Dis. 2021;50(1):54-61. Incidence adjusted for the 2010 European standard population

[2]Keller Ket al.: Sex-specific differences regarding seasonal variations of incidence and mortality in patients with myocardial infarction in Germany, Int J Cardiol . 2019 Jul 15;287:132-138

[3]Dellucet al.: Current incidence of venous thromboembolism and comparison with 1998: a community-based study in Western France, Thromb Haemost 2016; 116: 967-974
[4]Jacob et al.: Incidence of cerebral venous sinus thrombosis in adults in Germany – a retrospective study using health claims data; (2021), doi 10.21203/rs.3.rs-428469/v2
[5]Schoonen et al.: Epidemiology of immune thrombocytopenic purpura in the General Practice Research Database. Br J Haematol. 2009;145(2):235-244

*Included were all reports of thrombocytopenia/immune thrombocytopenia, including those with possible alternative causes, concomitant SARS-CoV-2 infection and worsening of pre-existing immune thrombocytopenia. The majority of the reports were BC level 4, so that the diagnostic safety could not be conclusively assessed.

There were no safety signals identified in the observed versus expected analysis for apoplexy (stroke), myocardial infarction and pulmonary embolism in any of the authorised COVID-19 vaccines. The number of reports of sinus/cerebral vein thrombosis after Vaxzevria was significantly higher than the expected value at the defined time intervals, but not for the other four vaccines.

The analysis indicates a risk signal for immune thrombocytopenia (ITP)/ thrombocytopenia (low platelet counts with the risk of bleeding if the levels fall very low) in adults following Vaxzevria and Jcovden. Immune thrombocytopenia is an adverse event listed in the product information of both vaccines. For Comirnaty, the SMR is significantly increased in adults in the time window of up to 14 days after vaccination, but not at intervals of 30 or 42 days after vaccination. Further analyses, which are not presented separately here, showed that the effect can be observed especially in the age group of 18-64 years. Limitations must be considered when interpreting these calculations, especially in the case of slightly increased SMR (> 1), such as in the case of Comirnaty. This is why the Paul-Ehrlich-Institut evaluated cases of thrombocytopenia and immune thrombocytopenia together, since there was no clear distinction between the two terms in the reports. It was not possible to identify thrombocytopenia originating from other causes (e.g. tumour diseases, infections including SARS-CoV-2 infection or taking certain medications) due to a lack of information. Since in most cases no prior platelet counts were included or communicated, it was also not possible to distinguish reliably between existing, possibly hitherto unknown and newly developed thrombocytopenia. There were no age-stratified incidences from Germany available to the Paul-Ehrlich-Institut, so the Institute used published background incidences from Great Britain, which seemed appropriate overall. Nevertheless, very different incidences of ITP have been published in the literature from other countries, including significantly higher incidences, on the basis of which the signal would disappear in the time window of up to 14 days after Comirnaty vaccination.

It is important to note that in non-interventional studies in Scotland and Israel, which are more scientifically informative than the observed versus expected analysis, no increased risk of ITP or thrombocytopenia after Comirnaty was found.[13, 26] In this respect, a valid safety signal for thrombocytopenia/ ITP after Comirnaty cannot currently be assumed to exist.

5. Additional analysis

5.1. Menstrual disorders analysis

In conjunction with the ongoing evaluation procedure [27] by the PRAC for the two mRNA vaccines, Comirnaty and Spikevax, the Paul-Ehrlich-Institut carried out a new evaluation of menstrual disorders after COVID-19 vaccination. Through 30 June 2022, the Paul-Ehrlich-Institut received 20,795 suspected reports from women aged 12 to 49 years, in which at least one menstrual disorder was reported as an adverse event. The Paul-Ehrlich-Institut calculated that more than 38 million vaccinations were administered in this age group during the same period. The following MedDRA codes were used for the research in the Paul-Ehrlich-Institut's adverse event database: menstrual disease (Preferred Term, PT, 10027372), menstrual symptoms (PT 10056344), absence of menstruation (PT 10000326), irregular menstruation (PT 10027339), intermittent bleeding (PT 100022559), delayed menstruation (PT 100027336), severe menstrual bleeding (PT 10085423), polymenorrhea (PT 10036086), dysmenorrhea (PT 10013935), oligomenorrhea (PT 10030295), hypomenorrhea (PT 10021033) and amenorrhea (PT 10001928).

Healthcare professionals (e.g. doctors/pharmacists, health authority staff, the Drug Commission of the German Medical Association) provided 5.5% (1,135) of the individual case reports and 94.5% (19,660) of the reports came from the women or relatives concerned. The median age of women affected is 33 years (median 32 years).

Of the 20,795 suspected reports, 3,857 (18.5%) suspected reports (median age of the women affected is 32.3 years, median 32 years) did not include a valid date of vaccination or a valid date of first occurrence of symptoms, so that it was not possible to assess whether and how many regular cycles occurred between vaccination and first symptoms. In the cases containing all relevant data, the time between the occurrence of menstrual disorders and the COVID-19 vaccination was very variable (minimum: day of vaccination, maximum: 373 days after vaccination). In 399 cases (1.9% of the reports), the gap between the symptoms

and vaccination was so great that at least one normal cycle (25-35 days) must have occurred between vaccination and symptoms, and therefore a connection with the vaccination is considered questionable. In eleven suspected cases, the name of the vaccine was not mentioned. The number of suspected reports corresponds to a reporting rate of 0.54 per 1,000 vaccinations in women aged 12 to 49 years.

Table 6: Number and frequency of reports per 100,000 vaccinations of reported cycle disorders in adolescent women and women aged 12 to 49 years (more than 1 adverse reaction possible per case).

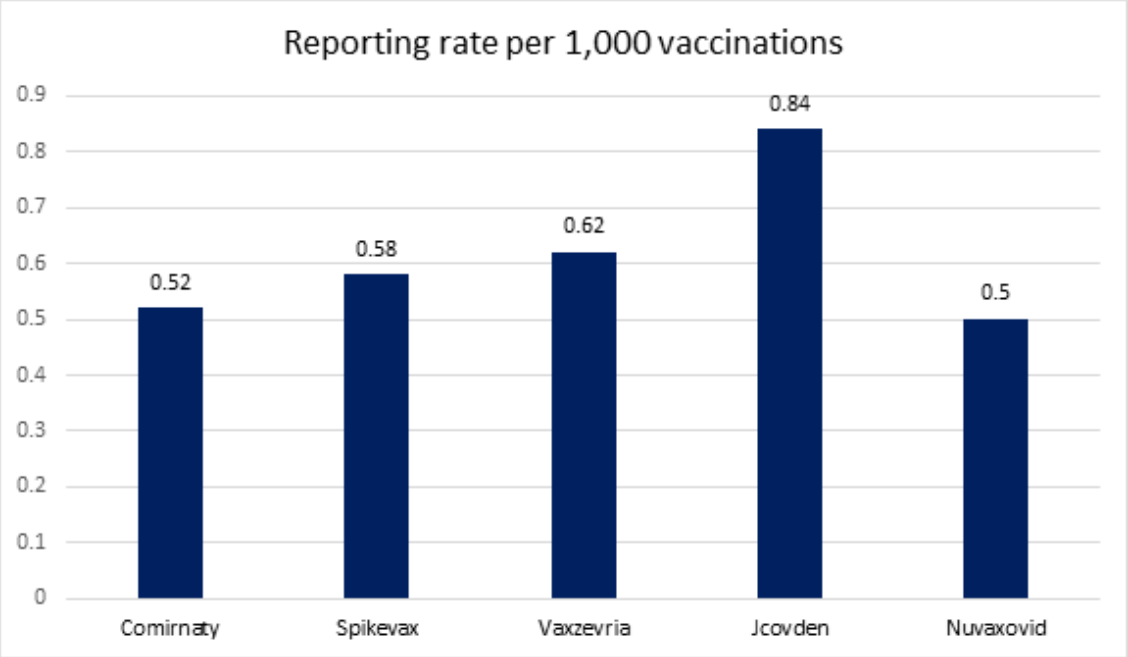
Reported Menstrual Disorder	Number of reactions	Reporting rate per 100,000
Menstrual illness	6,981	18.12
Severe menstrual bleeding	5,977	15.51
Amenorrhea	3,890	10.1
Polymenorrhea	3,583	9.3
Dysmenorrhea	2,729	7.08
Irregular menstruation	2,140	5.55
Intermittent bleeding	2,000	5.19
Oligomenorrhea	1,894	4.92
Delayed menstruation	1,220	3.17
Menstrual discomfort	923	2.4
Hypomenorrhea	434	1.13
Menometrorrhagia	22	0.06

In addition to menstrual disorders, other adverse events have also been mentioned in many reports. Fatigue (n = 1,853 adverse reactions), headache (1,663 reactions), injection site pain (1,571 reactions), flu-like illness (n = 928 reactions), fever (n = 853 reactions) and chills (n = 803 reactions) were the most commonly reported.

The reporting rate of the various reported menstrual disorders in adolescents and women aged 12 to 49 years varies between 0.5 and 0.84 per 1,000 vaccinations, based on the individual vaccines, and appears to be rather low when one considers that a large proportion of women of childbearing potential have been

vaccinated. The frequency of menstrual disorders such as severe and excessively long menstrual periods is stated in the literature to be about 9-10 cases per 1,000 person years. These incidences presumably represent an under-reporting, since not all affected women contact their doctor because of temporary menstrual disorders.[28.29]

Figure 5: Reporting rate of menstrual disorders per 1,000 vaccinations by different vaccines



The reporting rate of menstrual disorders refers to the number of suspected cases reported in adolescents and women aged 12 to 49 years and the vaccination rate in female vaccinated individuals in the same age group. Menstrual disorders are very common and can result from a variety of underlying medical conditions, including stress and fatigue. The majority of suspected case reports to the Paul-Ehrlich-Institut lack important clinical information, e.g. information on the pre-vaccination cycle, information on underlying diseases and differential diagnoses, so that it cannot be deduced from the reports whether or not the reported menstrual disorders are attributable to vaccination.

Several studies have looked at cycle disorders after COVID-19 vaccination. These studies show inconsistent results and usually serious methodological weaknesses,

so that a causal connection with the COVID-19 vaccination based on the studies cannot currently be proven from the perspective of the Paul-Ehrlich-Institut.[30-38]

At its June 2022 meeting, the PRAC found no association between mRNA COVID-19 vaccines and the absence of menstruation (amenorrhea: absence of bleeding over a period of 90 days or more) based on the available data.[27] The committee continues to investigate whether mRNA vaccines may temporarily cause severe menstrual bleeding. However, spontaneous reporting data from Germany does not currently provide a safety signal here.

5.2. Suspected reports of long-term symptoms after COVID-19 vaccination – "Post Vac"

In recent months, the Paul-Ehrlich-Institut has received an increasing number of reports of symptoms occurring at different time intervals following COVID-19 vaccination. These symptoms have been referred to as Long COVID-like chronic fatigue syndrome (CFS/ME), postural tachycardia syndrome (POTS), or “Post Vac” syndrome. "Post Vac" is not an established term for a disease. The term appears to refer to many symptoms that are also associated with Long COVID. However, important clinical information is often lacking and diagnostic safety can often not be assessed.

A search of the Paul-Ehrlich-Institut's adverse event database (containing reports from Germany) was carried out on 6 July 2022. The following MedDRA Preferred Terms (PTs) were evaluated: Chronic Fatigue Syndrome (CFS, PT 10008874), Post Vaccination Syndrome (PT 10036242), Postural Orthostatic Tachycardia Syndrome (POTS, PT 10063080) and Post-Acute COVID-19 Syndrome (PT 10085503). The search provided a cumulative total of 472 events in connection with a vaccination against COVID-19. 42 case reports contained more than one of the PTs mentioned above. The majority of reports related to Comirnaty, the vaccine most commonly used in Germany (Table 7). The Paul-Ehrlich-Institut received the majority of the reports from the affected patients.

Table 7: Reports of suspected adverse events coded as CFS, Post Vac, POTS, and Post-COVID-19 after COVID-19 vaccines up until 6 July 2022

		CFS[1]	Post Vac	POTS[2]	Post-COVID-19	
					Worsening of Condition[3]	New Occurrence[4]
Number of reports		273	36	48	35	80
Number of reports by medical professionals, state/health authorities, pharmaceutical commissions (%)		110 (40%)	13 (36%)	14 (29%)	8 (23%)	20 (25%)
Median age in years (range)		43 (8–87)	44 (15–83)	36 (14–60)	49 (25–65)	47 (14–85)
Age	< 18 years	8	2	3	0	3
	between the ages of 18 and 60	240	31	45	33	65
	> 60 years	21	2	0	2	9
	Unknown	4	1	0	0	3
Gender	female	200	29	35	29	55
	male	68	7	12	6	24
	unknown	5	0	1	0	1
Vaccine	Comirnaty	194	27	39	31	59
	Spikevax	47	2	3	4	7
	Vaxzevria	24	5	5	0	11
	Jcovden	5	1	1	0	2
	Nuvaxovid	1	0	0	0	0
	Unknown	2	1	0	0	1

[1] The overview does not include 11 cases that describe worsening of pre-existing CFS.
[2] The overview does not include 5 cases that describe worsening of pre-existing POT.
[3] Worsening of pre-existing post-COVID disease was reported after COVID-19 vaccination.
[4] Development of post-COVID disease was reported after vaccination. 20 reports are also included with wording that is not clear as to whether the post-COVID disease occurred after an infection or if the symptoms appeared only after vaccination.

The Paul-Ehrlich-Institut carried out a comparative cumulative evaluation of international suspected case reports in the EMA's adverse reaction database (EudraVigilance) up until 30 June 2022. The search included reports with at least one of the above-mentioned codes (CFS, Post Vac, POTS, Post-Acute COVID-19 Syndrome). The evaluation showed that 54.6% of the reports from the European Economic Area and 34.8% of international reports with the above codes in the EudraVigilance database come from Germany. However, since Germany did not carry out 55% of vaccinations in the European Economic Area (EEA), it can be assumed that there is a disproportionate amount of reporting in Germany. A reporting bias for Germany cannot be excluded.

Some individual reports contain findings of allegedly elevated autoantibodies. Whether these are pathological (functional) autoantibodies is also often questionable on the basis of the detection methods used and a lack of preliminary findings.

At present, in view of the spontaneous reports, no safety signal can be detected in the international context for persistent symptoms associated with fatigue after COVID-19 vaccination. Nevertheless, the Paul-Ehrlich-Institut will closely monitor reports and attempt to investigate the topic in the context of further studies.

An analysis of publicly available, aggregated hospital discharge diagnoses (InEK – Institute for the Hospital Reimbursement System, InEK data browser, analyses conducted in August 2022) revealed an increase in the number of cases for the main diagnosis of chronic fatigue syndrome (CFS; ICD-10 code G93.3) from 1,407 cases in 2019 and 1,115 cases in 2020 to 2,221 cases in 2021 and 1,303 cases in 2022 (up to and including May). An infection with SARS-CoV-2 probably plays a role in the increase (secondary diagnosis: "Post-COVID-19 condition, not further specified", ICD-10 codes U07.4 and U09.9). Among the ICD-10 codes U07.4 and U09.9 as secondary diagnoses for CFS as the main diagnosis, there are 0 cases in 2019, 19 cases in 2020, 703 cases in 2021 and 536 cases by May 2022. A further secondary diagnosis for the years 2021 and 2022 is the ICD-10 code U12.9 "Adverse reactions to the use of COVID-19 vaccines, not further specified". These were 15 cases in 2021 and 19 cases in 2022 up to and including May. Although it is unclear whether the secondary diagnosis U12.9 in the affected patients refers to the main diagnosis or is independent thereof, the number of hospital cases with the main diagnosis CFS in which a side effect was coded after vaccination (U12.9) appears to be rather low.

The aggregated data of the hospital discharge diagnoses should be interpreted with caution, as pseudonymised individual data is not available. In addition, hospital diagnoses represent only a part of the German health system’s data.

It is also of interest that, according to the results of studies from the United Kingdom (UK) and Italy, COVID-19 vaccines also appear to protect against Long COVID. [38,39]

5.3. Seizures

Seizures in connection with vaccinations are among the adverse events of special interest (Adverse Event of Special Interest, AESI), which are generally (by

convention) classified as serious events after vaccination for the reporting and monitoring of the safety of vaccines, even if the formal criteria as defined in the Medicinal Products Act are not met.

A total of 1,169 suspected cases of seizures were reported to the Paul-Ehrlich-Institut after vaccination with a COVID-19 vaccine through 30 June 2022. In 146 of these cases, another pre-existing condition was probably the cause of the seizure, including sinus/cerebral vein thrombosis, cerebral infarction or encephalitis.

Of the remaining 1,023 events, 741 were reported after Comirnaty vaccination and 131 after Spikevax vaccination. This corresponds to a reporting rate of 0.5 cases per 100,000 Comirnaty vaccinations and 0.4 cases per 100,000 Spikevax vaccinations. 113 reports were made after vaccination with Vaxzevria and 38 reports after vaccination with Jcovden. This corresponds to a reporting rate of 0.9 cases per 100,000 Vaxzevria vaccinations and 1 case per 100,000 Jcovden vaccinations.

Of the reported events, 576 were women, 431 were men, and gender was unknown for 16 events. The median age of the subjects was 43 years (range 2 to 107 years). 269 events had documented pre-vaccination epilepsy, 463 events concerned an individual's first seizure, and 291 events had no information.

397 of the reported seizures occurred after the 1st dose, 304 after the 2nd dose, 111 after the 3rd dose and three after the 4th dose. The vaccination dose was unknown in 208 cases. The number of reports after the time to onset (TTO) interval is shown in Table 8.

Table 8: Overview of suspected reports of seizures by vaccine and time interval between vaccination and occurrence of the seizure

	Comirnaty	Spikevax	Vaxzevria	Jcovden
Number of TTO ≤ 7 days	428	91	82	28
Number of TTO ≤ 14 days	520	101	96	30
Number of TTO ≤ 30 days	595	113	101	34
Number of TTO ≤ 42 days	622	118	104	35
Reporting rate per 100,000 vaccinations	0.5	0.4	0.9	1.0

TTO: time to onset

Observed versus expected analyses taking into account published background incidences (Safety Platform for Emergency Vaccines, ACCESS) did not reveal a safety signal for any of the authorised COVID-19 vaccines within different time intervals between 7 and 42 days after vaccination.

This finding coincides with a publication [40] which also did not detect an increased risk of seizures in connection with vaccinations against COVID-19. Studies in patients with known epilepsy indicated a low seizure rate and good tolerability of the vaccines.[40,41]

6. Methodology

The reporting of suspected cases of adverse events and vaccine-related complications is a central pillar of assessments of vaccine safety because it enables the rapid detection of new safety signals. It should still be noted here that the reported adverse reactions are chronologically, but not necessarily causally, linked to vaccination. The reporting of such reactions with a questionable link to vaccination is expressly welcomed. However, this also means that not all reported reactions are actually adverse events. The Paul-Ehrlich-Institut summarises all submitted reports in its safety reports, regardless of the causal link to the vaccination.

6.1. Reporting obligations and reporting channels for suspected adverse events and vaccination complications

Reports of adverse events after vaccination with a COVID-19 vaccine are received by the Paul-Ehrlich-Institut via the public health departments of the German federal states in accordance with the German Infection Protection Act (Infektionsschutzgesetz, IfSG). Physicians are legally obligated to notify their competent public health department of any vaccine-related complications affecting a patient's health if the complications go beyond the typical level of a vaccine reaction and are not obviously the result of other causes. The competent public health department then immediately sends the report in pseudonymised form (meaning without the patient's name or address) to the Paul-Ehrlich-Institut. The Paul-Ehrlich-Institut also receives reports from the Medicines Commissions of the Federal Union of German Associations of Pharmacists and of the German Medical Association, as pharmacists and doctors have a professional obligation to report suspected adverse events. According to the Medicinal Products Act, marketing

authorisation holders are obliged to report to EudraVigilance, the European suspected adverse events database. Reports from Germany are sent from there to the Paul-Ehrlich-Institut.

In addition, medical specialists and vaccinated persons or their relatives can report directly to the Paul-Ehrlich-Institut. Reports are submitted by mail, email, telephone, or online via the Paul-Ehrlich-Institut's reporting portal (www.nebenwirkungen.bund.de) . The Paul-Ehrlich-Institut merges reports on the same case together into one case.

According to the Medicinal Products Act, the Paul-Ehrlich-Institut is obliged to report suspected cases of side effects at certain intervals electronically in an internationally standardized format and pseudonymised to the joint EudraVigilance database at the European Medicines Agency, to which every regulatory authority in the EU has access.

6.2. Notes on the safety report

The Paul-Ehrlich-Institut always presents reports on suspected cases of vaccine-related complications and adverse events cumulatively. Here it should be noted that if additional information on a suspected case is received, changes could be made to areas such as the reported reactions, the level of severity, or the final outcome, all of which will be taken into consideration in the most current evaluation. This could result in numerous changes made in regards to previous reports. This can also lead to a reduction in the total number if, for example, reported reactions have not been confirmed by further investigations.

The identification of duplicate messages (messages from different sources) is not always possible to carry out reliably due to the necessary pseudonymization. In case of doubt, if there are no clear indications of a duplicate report, two reports from different sources will not be merged into one report.

A suspected case report can include multiple adverse reactions, such as fever plus headache plus pain at the injection site. Evaluations are carried out both at case level (one patient) and at reaction level (several adverse events can be reported in one patient report). Due to rounding up or down, the sum of percentages in some charts and in the text may not add up to 100.

A differentiation in the suspected case reports in regards to the receipt of the first or second vaccination is generally not possible, as this specific information is

missing in some cases. Comparisons between vaccine doses always refer to the cases for which this information is available.

For reasons of clarity, the Paul-Ehrlich-Institut does not present all the evaluations of the Paul-Ehrlich-Institut in each safety report, but focuses on identified potential vaccination risks.

6.3. Signal detection based on suspected case reports

In the context of identifying possible new signals, the Paul-Ehrlich-Institut carries out observed versus expected (OE) analyses on an ongoing basis. In these, the frequency of the adverse events reported after vaccination to the Paul-Ehrlich-Institut is compared to the statistically expected frequencies in a comparable (non-vaccinated) population, taking variation in time intervals into consideration. If there is a significantly higher number of suspected case reports for an adverse event after vaccination than would be statistically expected in a comparable population, the Paul-Ehrlich-Institut assumes the presence of a safety signal (standardised morbidity or mortality ratio, SMR > 1 and lower 95% confidence interval ≥ 1). It should be noted that an observed versus expected analysis may indicate a safety signal, but it is not suitable for confirming risk. The risk should then be further investigated, if necessary, by additional studies.[44] An SMR < 1 indicates that fewer suspected case reports were recorded than expected. The observed versus expected calculation includes suspected case reports up to the day of evaluation with a known time interval between vaccination and first symptoms (time to onset, TTO).

The following aspects pose limitations for an observed versus expected analysis: variance in the information on background incidence rates in the original sources, lack of information regarding both the time interval between vaccination and start of symptoms as well as the exposure level, reporting delays, and somewhat shorter observation times post-vaccination for the last dose administered. In addition, age stratifications can only be carried out to the extent that data from the literature on the background incidence is available for individual age groups. Therefore, the individual analyses also differ in regards to the age groups presented.

The total number of administered doses of the individual COVID-19 vaccines was based on digital vaccine monitoring data (DIM) and data from registered doctors. The Robert Koch-Institut (RKI) was kind enough to provide this data to the Paul-Ehrlich-Institut. The Paul-Ehrlich-Institut was provided with a stratification of the

DIM data on doses administered through 30 June 2022 by vaccine, age group, and gender. Data from the RKI aggregated by vaccine and dose was used for the data on doses administered by registered doctors. Since the data from registered doctors did not include any information on age or gender of the vaccinated individuals, IQVIA data from a representative group of registered doctors was used to determine the age and gender distribution by vaccine. This distribution was projected onto the aggregated data stratified by vaccine, which the RKI had obtained from registered doctors. A potential underestimation of the vaccination rate, which was indicated by the RKI, was not taken into account in the evaluations.

6.4. Definitions

According to section 4 of the Medicinal Products Act (Arzneimittelgesetz, AMG), adverse events are harmful and unintended reactions to the medicine.

Serious adverse events are adverse events that are fatal or life-threatening, require hospitalisation or the prolongation of existing hospitalisation, or lead to persistent or significant disability, incapacity, congenital anomalies or birth defects. In addition, all adverse events of particular interest after COVID-19 vaccinations are classified as "serious", regardless of the legal definition of "serious" in the AMG. In this respect, a direct comparison of reports with those of other vaccines is not possible. In addition, adverse events of special interest as defined in the European Union are always defined as serious by agreement of the authorities in the EU, even if the formal criteria of the Medicinal Products Act are not met.

The suspicion of damage to health beyond the usual extent of a vaccination reaction (vaccination complication) according to section 6 of the Infection Protection Act refers to symptoms occurring after a vaccination, which could be causally related to the vaccination and go beyond one of the following vaccination reactions. These are, for example, short-term, temporary, local and general reactions or symptoms of a 'vaccine disease' that can be interpreted in the same sense.

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Note

Please note: this is a translation of the original German report. In the event of inconsistencies between the German and English versions, the German version will prevail.

7. Literature

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