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

Paul-Ehrlich-Institut

Langen, 4 May 2022

SAFETY REPORT

In the current safety report, the Paul-Ehrlich-Institut summarises reports on suspected cases of adverse events and vaccination complications. These reports were received between 27 December 2020 (start of the vaccination campaign in Germany) and 31 March 2022.

Contents

1. Summary

- A total of 172,062,925 COVID-19 vaccinations were carried out in Germany between 27 December 2020 and 31 March 2022. 73.3% of vaccine doses were Comirnaty (BioNTech Manufacturing GmbH), 17.1% were Spikevax (MODERNA BIOTECH SPAIN, S.L.), 7.4% were Vaxzevria (AstraZeneca AB), 2.1% were COVID-19 Vaccine Janssen (now called Jcovden) and 0.1% were Nuvaxovid (Novavax CZ, a.s.).
- In the same time period, the Paul-Ehrlich-Institut received 296,233 reports of suspected adverse events.
- The overall reporting rate for all vaccines was 1.7 reports per 1,000 doses of vaccine. The reporting rate for serious adverse events was 0.2 reports per 1,000 doses of vaccine.
- The reporting rate after booster vaccinations with Comirnaty or Spikevax was lower than after primary immunisation.
- No new risk signal has been identified since the last safety report, which contained data through 31 December 2021.
- The Paul-Ehrlich-Institut will closely monitor and continue to investigate cases of myocarditis/pericarditis, thrombosis and immunologically mediated adverse events such as immune thrombocytopenia occurring after administration of the approved vaccines.

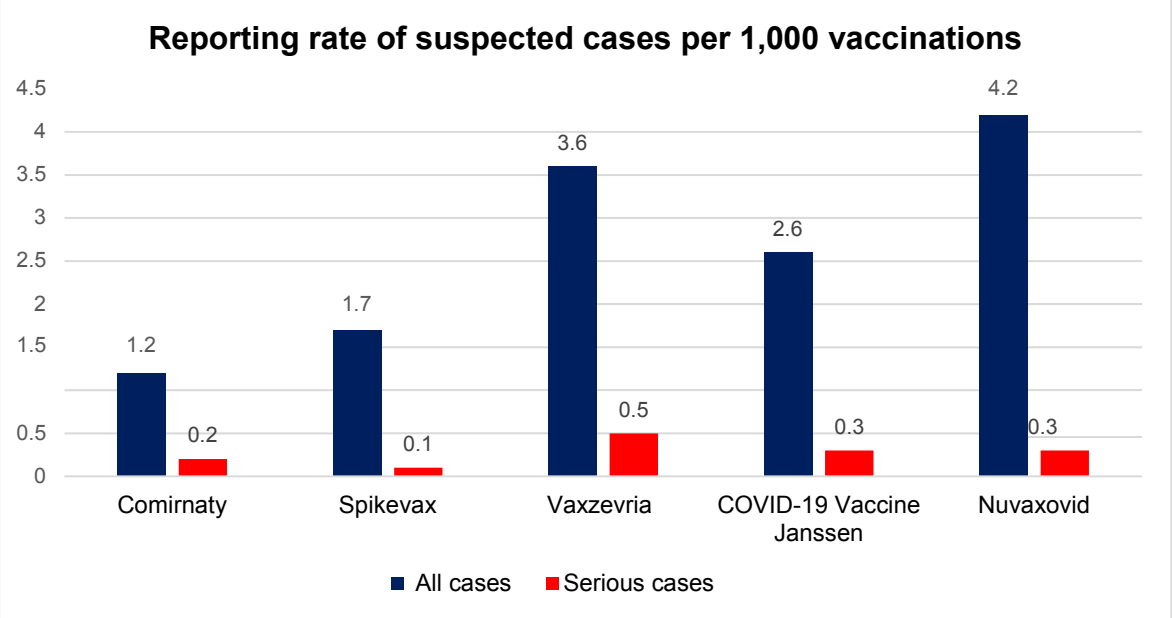
2. Overview of suspected cases in Germany reported to the Paul-Ehrlich-Institut

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

The reporting rate of suspected serious and non-serious adverse events following vaccination with the COVID-19 vaccines is shown in Figure 1.

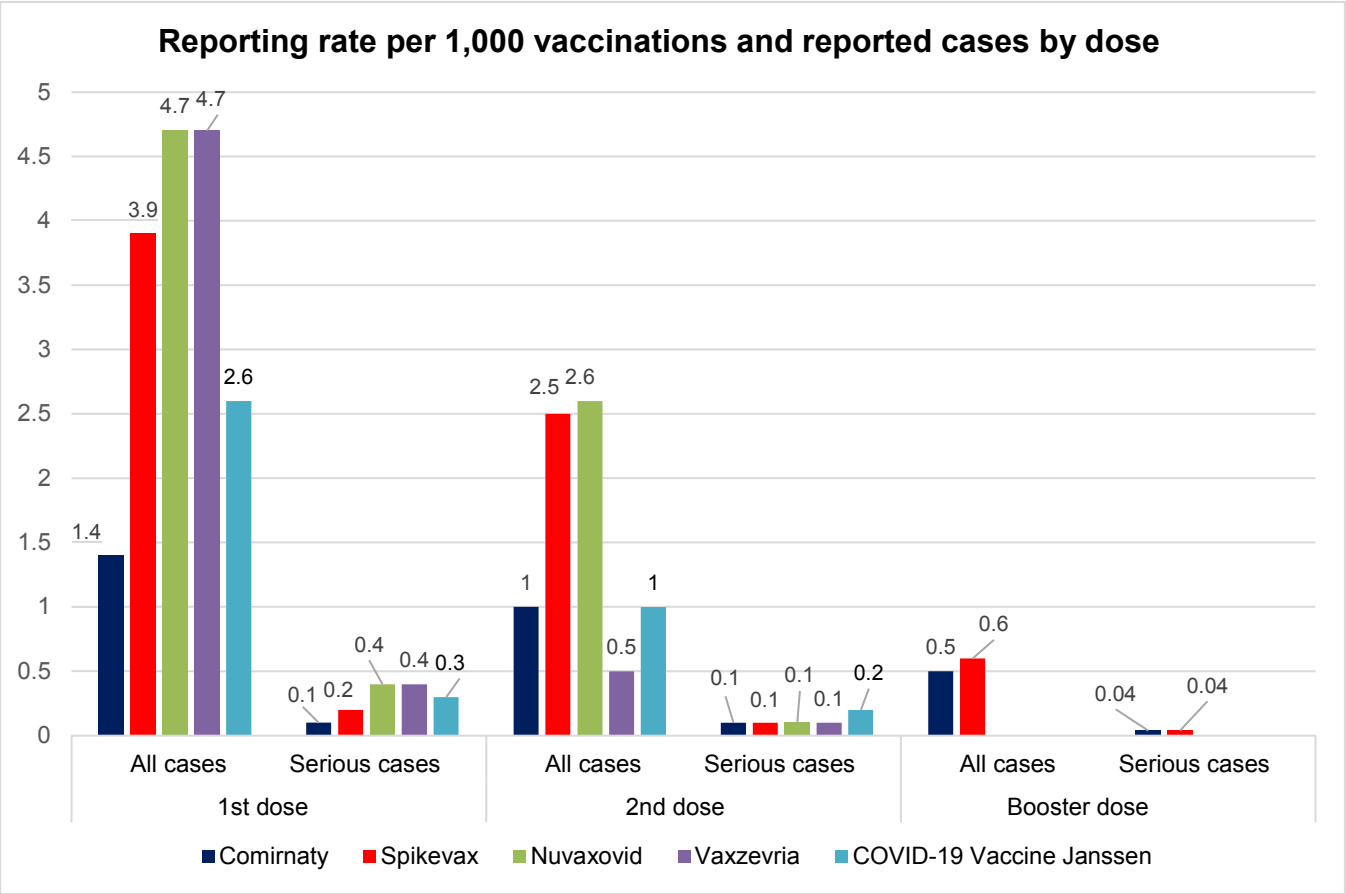
Few suspected reports have been received thus far for the vaccine Nuvaxovid (n = 390), therefore the reporting rate is currently still to be interpreted with caution.

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



The reporting rate by vaccine and dose is shown in Figure 2. The booster dose includes any vaccinations given after primary immunisation. In approximately 1,000 cases, no vaccine name was given.

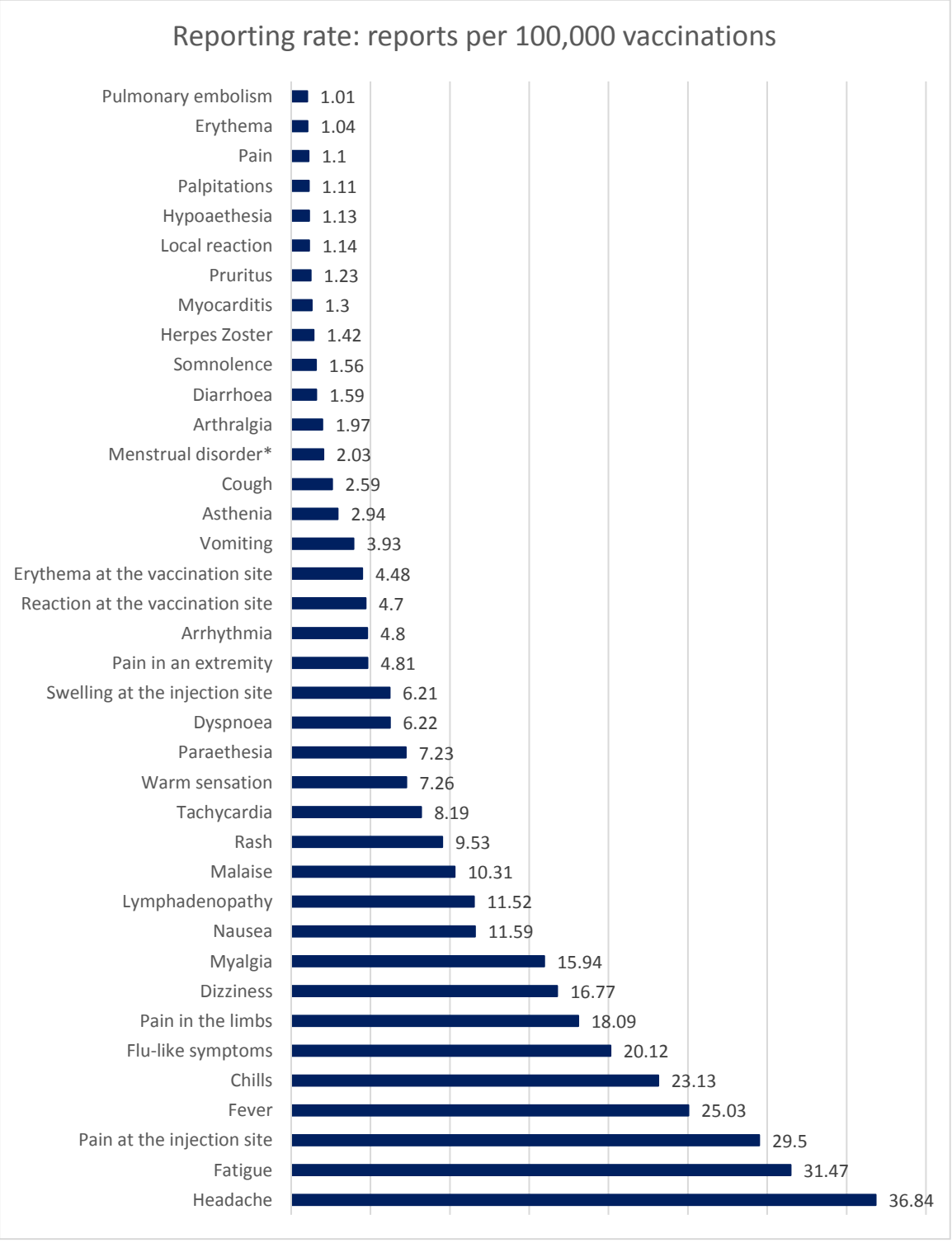
Figure 2: Reporting rates of suspected adverse events per 1,000 vaccinations by vaccine dose (evaluation at case level)



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

The overall reporting rate of the most frequently reported adverse events after COVID-19 vaccines (all suspected case reports for the five approved COVID-19 vaccines) is presented in the following figures. Temporary local and systemic reactions have been reported most frequently, as had already been observed in clinical trials before marketing authorisation.

Figure 3: Frequently reported adverse events reported per 100,000 vaccinations. Adverse events with a reporting frequency ≥ 1 report per 100,000 doses of vaccine are shown. Note: Figures 1 and 2 show reports per 1,000 vaccinations, here reports per 100,000 vaccinations)



*Reporting rate for adolescents and women ≥ 12 years of age

2.3. Reporting rates of adverse events of special interest (AESI)

The vaccine-related reporting rates of Adverse Events of Special Interest (AESI) irrespective of time interval after vaccination and vaccination dose are shown in Table 1. Chapter 5 of the safety report compares the number of cases reported for selected AESI with the number of cases expected randomly in a given time interval 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)

AESI (reaction)	Comirnaty	Spikevax	Vaxzevria	Jcovden (COVID-19 Vaccine Janssen)
Dyspnoea	5.5	6.4	11 (1)	10.8
Arrhythmia	4.6	5	5.7	6.6
Myocarditis*	1.4	1.6	0.6	1.2
Pulmonary embolism	0.8	0.7	3.3	2
Apoplexy	0.6	0.4	1.5	0.9
Facial paralysis	0.5	0.4	0.7	0.9
Syncope	0.5	0.4	2.5	1.2
Thrombosis	0.4	0.4	1.9	0.8
Deep vein thrombosis	0.4	0.4	2.7	0.8
Respiratory disorder	0.3	0.3	3.3	0.4
Anaphylactic reaction	0.3	0.2	0.4	0.3
Myocardial infarction	0.3	0.2	0.6	0.6
Thrombocytopenia	0.3	0.1	3.2	0.7
Seizure	0.2	0.1	0.7	0.4
Pericarditis**	0.2	0.2	0.1	0.3
Loss of consciousness (syncope)	0.2	0.1	0.9	0.4
Heart failure	0.2	0.1	0.2	0.3
Cerebral haemorrhage	0.2	0.1	0.8	0.4
Guillain-Barré Syndrome	0.2	0.2	0.9	1.2
Acute myocardial infarction	0.2	0.1	0.4	0.3
Cerebral venous sinus thrombosis	0.1	0.1	2.0	0.6
Acute hearing loss	0.1	0.1	0.5	0.1
Relapsing-Remitting Multiple Sclerosis	0.1	0.1	0.1	0.1
Anaphylactic shock	0.1	0.0	0.3	0.2
Venous thrombosis	0.1	0.1	0.4	0.3

AESI (reaction)	Comirnaty	Spikevax	Vaxzevria	Jcovden (COVID-19 Vaccine Janssen)
Cardiac arrest	0.1	0.1	0.2	0.3
Rheumatoid arthritis	0.1	0.1	0.1	0.1
Presyncope	0.1	0.1	0.3	0.3
Acute kidney damage	0.1	0.1	0.1	0.1
Immune thrombocytopenia	0.1	0.0	0.8	0.4
Thrombosis with thrombocytopenia syndrome***	0.0	0.0	0.8	0.5

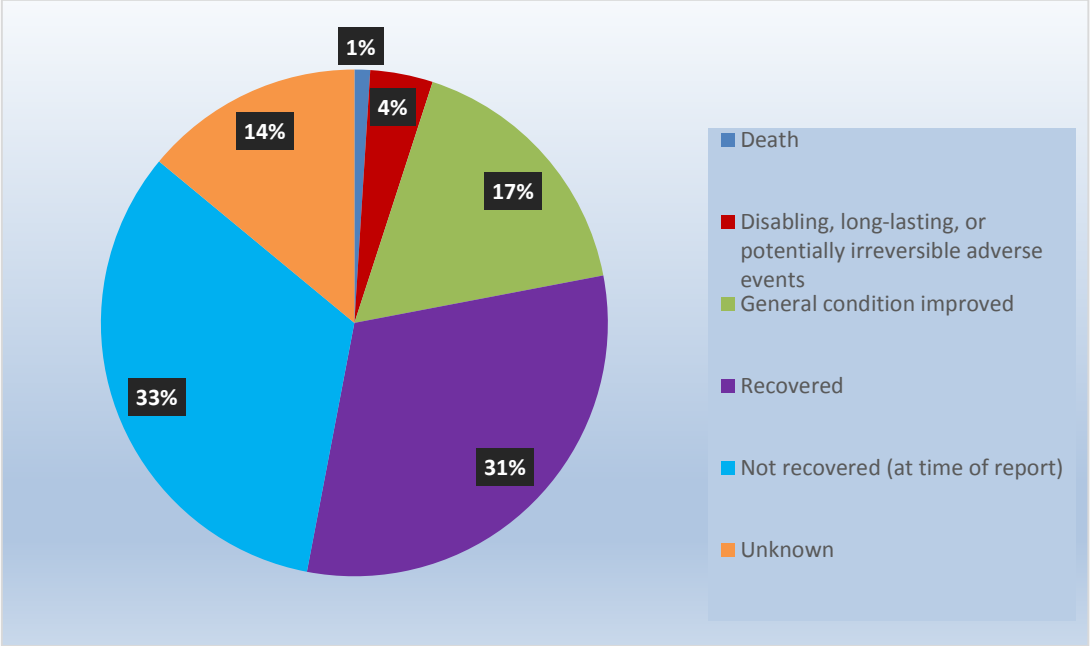
Reactions with a reporting frequency of < 1 reported adverse reactions per 2,000,000 vaccine doses are shown with a 0 after the decimal place. The 0 does not necessarily mean that there was no reports of that reaction.
*Myocarditis refers to cases of myocarditis with and without concomitant pericarditis; reported cases of myocarditis after Jcovden (COVID-19 Vaccine Janssen) n = 44 reports, time between vaccination and symptoms between 0-238 days; within 30 days after vaccination n = 22 (50%), of which 10 cases ≤ 30 years (exclusively men)
**Pericarditis refers to isolated cases of pericarditis
***TTS: Only those cases were considered which correspond to the case definition of TTS according to CDC criteria: thrombosis in an unusual location plus platelet count < 150 G/L or thrombosis plus thrombocytopenia plus positive for platelet factor 4 antibodies; there were n = 6 cases after Comirnaty and n = 2 after Spikevax.

Suspected cases identified as AESI have been reported in temporal association with Nuvaxovid. These AESI are dyspnoea (reporting rate 20:100,000), arrhythmia (reporting rate 22:100,000) and presyncope (reporting rate 3:100,000). Due to the low number of reports and administrated doses of Nuvaxovid, the calculation should be considered preliminary.

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

The overview of the outcome of suspected adverse events after all five approved COVID-19 vaccines as a percentage of the total number of suspected case reports is shown in Figure 4.

Figure 4: Outcome of suspected adverse event reports



In about one percent of the suspected case reports (n = 2,810 cases), death was reported at varying time intervals to COVID-19 vaccination. 116 cases were assessed by the Paul-Ehrlich-Institut to be consistent with a causal link to the respective COVID-19 vaccination (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 COVID-19 vaccination 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 result agrees with literature data[1]. No fatalities have been reported for the vaccine Nuvaxovid and therefore Nuvaxovid is not listed in the following tables.
This also applies to booster vaccinations. 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, none of the five approved COVID-19 vaccines (data not presented separately) showed a risk signal for increased post-vaccination mortality.

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

Included were reported cases that connected to COVID-19 vaccination through 31 March 2022 and for which the time interval between vaccination and the onset of symptoms is known. According to the Federal Statistical Office, the background incidence is 1,240.97 deaths per 100,000 persons/year[1].

		Time between vaccination and onset of symptoms			
Total deaths		**1 Day**	**7 Days**	**14 Days**	**30 Days**
Comirnaty	Total cases	422	922	1165	1369
	SMR (95% CI)	0.098 (0.089-0.108)	0.031 (0.029-0.033)	0.019 (0.018-0.021)	0.011 (0.010-0.011)
Spikevax	Total cases	55	103	121	136
	SMR (95% CI)	0.055 (0.041-0.072)	0.015 (0.012-0.018)	0.009 (0.007-0.010)	0.0045 (0.0038-0.0054)
Vaxzevria	Total cases	57	131	180	230
	SMR (95% CI)	0.132 (0.100-0.170)	0.042 (0.036-0.051)	0.030 (0.025-0.034)	0.018 (0.015-0.020)
Jcovden (COVID-19 Vaccine Janssen)	Total cases	14	26	35	39
	SMR (95% CI)	0.114 (0.062-0.191)	0.030 (0.020-0.044)	0.020 (0.014-0.028)	0.011 (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	51	101	114	128
	SMR (95% CI)	0.049 (0.036-0.064)	0.014 (0.011-0.017)	0.008 (0.006-0.009)	0.004 (0.003-0.005)
Spikevax	Total cases	9	23	26	29
	SMR (95% CI)	0.015 (0.007-0.028)	0.005 (0.003-0.008)	0.003 (0.002-0.004)	0.0016 (0.0011-0.0023)
Vaxzevria	Total cases	-	-	-	-
	SMR (95% CI)	-	-	-	-
Jcovden (COVID-19 Vaccine Janssen)	Total cases	0	0	0	1
	SMR (95% CI)	-	-	-	1.66 (0.04-9.28)

[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
SMR: Standard Mortality Ratio (SMR) is the ratio between the number of deaths observed in a population over a given period of time and the number that would be expected over the same period of time if the study population had the same age-specific rates as the standard population.

2.5. Adverse events among children and adolescents

Comirnaty is authorised for children from the age of 5 years and Spikevax from the age of 6 years. The Standing Committee on Vaccination (STIKO) recommends Comirnaty as a COVID-19 vaccine for children and adolescents aged 12 to 17 years. In addition, the STIKO recommends COVID-19 vaccination with Comirnaty to children aged 5 to 11 years who are at an increased risk of a severe course of COVID-19 disease due to previous illnesses. The same applies to children and adolescents 5 years of age or older in who have relatives or other contact persons with a high risk of a severe COVID-19 course, who cannot be vaccinated themselves or for whom there is a reasonable suspicion of insufficient protection after vaccination. The COVID-19 vaccination can also be administered to 5 to 11-year-old children without previous illnesses at the individual request of children and parents or guardians after medical advice.

Since the start of the vaccination campaign on 27 December 2020, a total of 5,862 suspected adverse events have been reported to the Paul-Ehrlich-Institut, in which at least one adverse vaccination reaction was reported for a child or adolescent after vaccination with a COVID-19 vaccine.

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

	Children and adolescents 5 – 17 years	**Adolescents 12 – 17 years**	**Children 5 – 11 years**
Comirnaty	5,518	4,530	988
Spikevax	86	83	3
Vaxzevria	24	22	2
Jcovden (COVID-19 Vaccine Janssen)	16	16	0
Total	5,644	4,651	993

Furthermore, in 186 suspected cases, children who were younger than 5 years of age at the time of vaccination were vaccinated with a COVID-19 vaccine. Of these, 124 were children aged between 15 months and 4 years. In 32 suspected cases, the vaccine was not mentioned by name. A total of 61 suspected cases relate to infants whose mothers were vaccinated while the infants were still breastfeeding. In one case, it has been reported that a

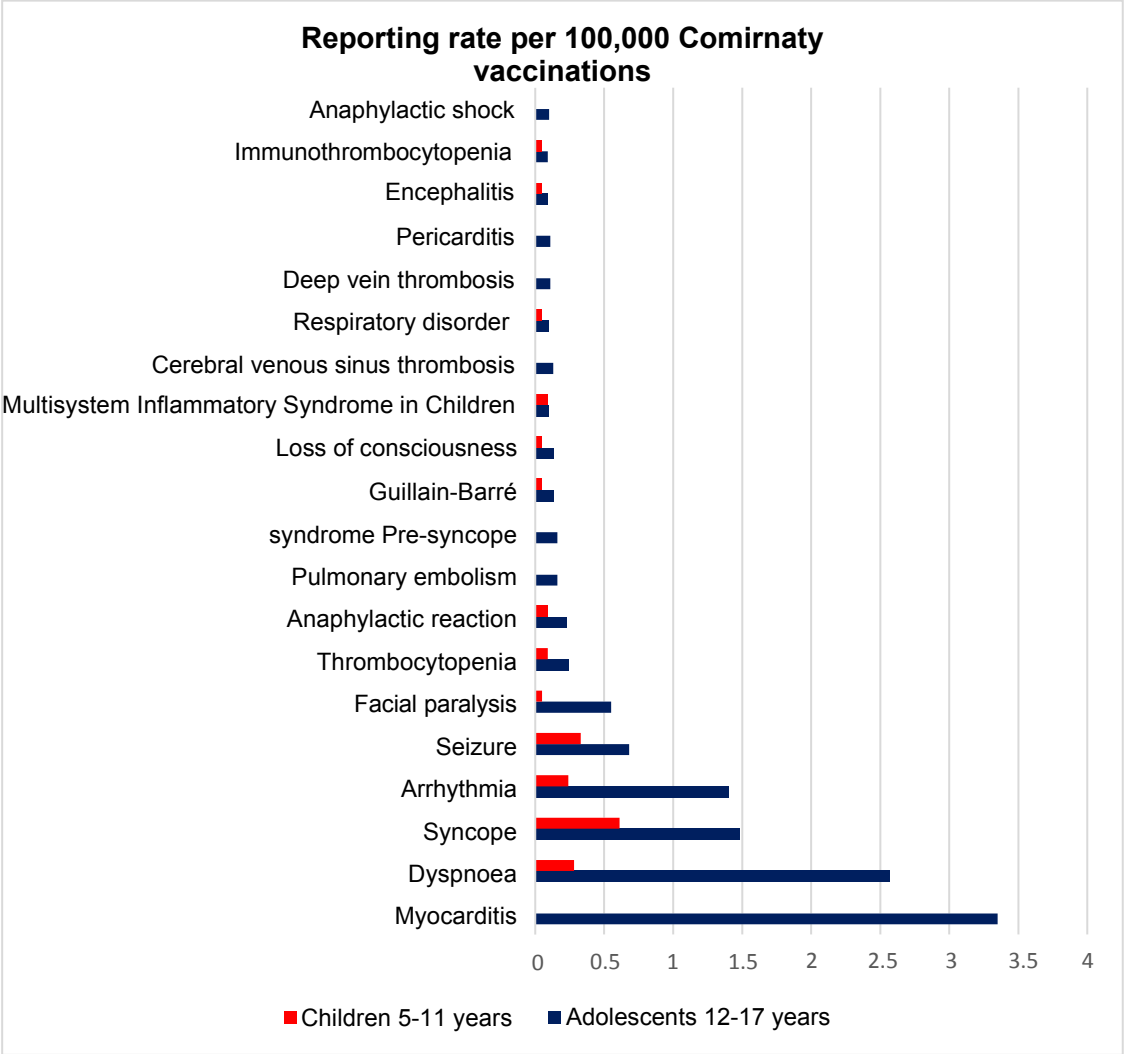
baby given birth to by a vaccinated woman died on the day of birth. Upon investigation, it was determined that placental detachment with significant hematoma formation was responsible for the newborn's complications.

Table 4: Comirnaty adverse events among children and adolescents aged 5-11 years and 12-17 years with a total reporting rate of more than 1 per 100,000 doses of vaccine

Reported reaction	Children and adolescents 5 – 17 years	Adolescents 12 – 17 years	Children 5 – 11 years
Headache	12.4	13.6	8.2
Pain at the injection site	10.3	9.6	9.5
Fatigue	9.3	10.1	6.0
Fever	8.5	8.7	6.8
Dizziness	6.0	7.1	2.1
Menstrual illness*	5.8	7.5	0
Flu-like symptoms	5.1	6.0	2.1
Rash	4.5	4.1	5.4
Chills	4.5	5.4	1.4
Nausea	4.3	4.6	3.2
Lymphadenopathy	4.2	4.6	2.8
Vomiting	3.6	3.1	5.1
Malaise	3.2	3.6	1.7
Myalgia	3.0	3.6	1.0
Pain in the limbs	2.9	3.4	1.1
Myocarditis*	2.6	3.4	0.0
Pain at the injection site	2.1	1.0	5.6
Dyspnoea	2.1	2.6	0.3
Tachycardia	2.0	2.4	0.6
Paraesthesia	1.5	1.8	0.4
Warm sensation	1.5	1.9	0.1
Chest pain	1.4	1.7	0.4
Swelling at injection site	1.4	1.5	0.8
Syncope	1.3	1.5	0.6
Arrhythmia	1.1	1.4	0.2
Erythema at the injection site	1.0	0.9	0.9
Diarrhoea	1.0	0.9	1.2
Pain in the extremities	0.9	0.9	1.2
Cough	0.9	1.0	0.3
Reaction at the vaccination site	0.8	0.8	0.9
Herpes Zoster	0.8	0.9	0.4
Urticaria	0.7	0.7	0.9
Abdominal pain	0.7	0.5	1.2

* Calculation of the reporting rate of menstrual illness based on the vaccinations of female persons of the respective age group

Figure 5: Adverse events of special interest (AESI) after Comirnaty vaccination in children and adolescents



3. Known adverse events of COVID-19 vaccines

3.1. Overview

An overview of the known adverse event profile of the individual vaccines is shown in Table 5. Suspected cases of adverse events are summarised in more detail to relevant risks in the following section.

Table 5: Tabulated overview of (selected) adverse events/vaccination complications according to approved 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, COVID-19 Vaccine Janssen, Nuvaxovid	Very common	Transient reactions shortly after vaccination, less frequent in the elderly
Delayed increased local reaction at the vaccination site "COVID arm"	Spikevax > Comirnaty	Occasional	Delayed response ≥ 8 days, 100% mild
General reactions	Comirnaty, Spikevax, Vaxzevria, COVID-19 Vaccine Janssen, Nuvaxovid Nuvaxovid	Very common	mRNA vaccines, Nuvaxovid D2 > D1; Vaxzevria D1 > D2; less common in the elderly
Lymphadenopathy	Comirnaty, Spikevax, Vaxzevria, COVID-19 Vaccine Janssen, Nuvaxovid	Common Spikevax; uncommon Comirnaty, Vaxzevria, Nuvaxovid; rarely Janssen	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, COVID-19 Vaccine Janssen, Nuvaxovid Nuvaxovid	Occasional	Allergic reactions
Anaphylaxis	Comirnaty, Spikevax, Vaxzevria, COVID-19 Vaccine Janssen	Very rare	Reporting frequency < 1/100,000 vaccinations Women > Men, D1 > D2; presumably mostly no IgE-mediated reaction, possibly IgG against PEG
Erythema multiforme	Comirnaty, Spikevax	Unknown	Individual cases after authorisation, blander course
Leukocytoclastic vasculitis	COVID-19 Vaccine Janssen	Unknown	Post-authorisation case reports
Other adverse events/vaccination complications			
Myocarditis/pericarditis	Comirnaty, Spikevax	Very rare	More frequently in young men after D2, less frequently after D3, mainly rapidly resolving symptoms; fatalities described in individual cases
Facial nerve paralysis	Comirnaty, Spikevax, Vaxzevria	Rare	mRNA vaccines: few cases in CT phase III; Vaxzevria: individual post-authorisation cases reported

TTS	COVID-19 Vaccine Janssen	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	COVID-19 Vaccine Janssen	Rare	More post-verum reports compared to placebo in 1 of 2 CT Phase III, individual post-authorisation cases reported
Guillain-Barré Syndrome	COVID-19 Vaccine Janssen	Very rare	Individual post-authorisation cases reported, molecular mimicry?
Transverse myelitis	COVID-19 Vaccine Janssen	Unknown	Individual post-authorisation cases reported
Immune thrombocytopenia	COVID-19 Vaccine Janssen	Unknown	Autoantibodies against platelets
Tinnitus	COVID-19 Vaccine Janssen	Rare	
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, appears to be rarer and less severe as relapse of the disease resulting from a SARS-CoV-2 infection
Capillary leak syndrome (CLS)	COVID-19 Vaccine Janssen	Unknown	Very rare reports of CLS, including in patients with known CLS; contraindication to known CLS
Paraesthesia, hypoaesthesia	Comirnaty, Spikevax	Comirnaty: unknown; Spikevax: rare	Reported after various vaccines; it is suspected that they are 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

*Jcovden (COVID-19 Vaccine Janssen); D: dose; peg: polyethylene glycol; CT phase III: clinical trial prior to approval; TTS: thrombosis with thrombocytopenia syndrome; aHIT: autoimmune heparin-induced thrombocytopenia; PL4: platelet factor 4

3.2. Myocarditis/pericarditis and mRNA vaccines

A total of 2,026 suspected cases of myocarditis and pericarditis after Comirnaty and 532 suspected cases after Spikevax were reported to the Paul-Ehrlich-Institut in the period from 27 December 2020 to 31 March 2022. This corresponds to a reporting rate of 1.6 suspected cases per 100,000 doses of Comirnaty and 1.8 suspected cases per 100,000 doses of Spikevax.

Myocarditis/pericarditis is a very rare side effect of Comirnaty and Spikevax. Young men and male children and adolescents aged 12 to 17 years are particularly affected after the second dose.[2-19] The first symptoms typically appear within a few days of vaccination. The published data [2-19] indicate a predominantly mild course, i.e. the majority of patients with myocarditis/pericarditis after vaccination with mRNA vaccines respond well to treatment and rest and recover quickly,

even if severe courses and also fatalities were observed in individual cases.

Data from several countries, including Germany, indicate that the risk of myocarditis/pericarditis in younger people is higher after Spikevax than after Comirnaty, which is why the Standing Committee on Vaccination (STIKO) recommends Comirnaty for people < 30 years as a precaution.

A total of 153 reports of myocarditis/pericarditis were reported to the Paul-Ehrlich-Institut after mRNA booster vaccination, whereby as of 31 March 2022 the reporting rate of myocarditis/pericarditis after booster vaccination is lower with 0.3 cases per 100,000 doses of vaccination than after primary immunisation.

In the observation period through 31 March 2022, no confirmed cases of myocarditis in children aged 5 to 11 years were reported to the Paul-Ehrlich-Institut. In two cases, additional information is currently being obtained, since the clinical description is not sufficient to confirm the initial suspected diagnosis of myocarditis. Based on currently available information, the clinical findings do not meet the Brighton Collaboration case definition of myocarditis.[21]

3.3. Anaphylactic reactions

Anaphylactic reactions (Brighton Collaboration BC-Level 1-4) [22] are very rarely observed adverse events of the COVID-19 vaccines Comirnaty, Spikevax, Vaxzevria and Jcovden (COVID-19 Vaccine Janssen), see also Table 5. The reporting rate of anaphylaxis after mRNA vaccination in female patients is higher than in male patients and higher than in subsequent vaccinations, in particular after the first dose with 0.98 reports per 100,000 vaccinations for Comirnaty and 1.07 per 100,000 vaccinations for Spikevax. The results of initial retrospective studies [20-22] indicate that the majority of anaphylactic reactions most probably cannot be attributed to immediate immunoglobulin E-mediated allergic reactions. In the studies, affected patients were mostly vaccinated again at low risk after allergological testing.

4. Signals

4.1. Signal procedure of the Pharmacovigilance Risk Assessment Committee (PRAC) at the European Medicines Agency

At its meeting in February 2022, the Pharmacovigilance Risk Assessment Committee (PRAC) at the European Medicines Agency (EMA) decided to further investigate the occurrence of severe menstrual bleeding or amenorrhea (absence of menstrual bleeding) after vaccination with Comirnaty or Spikevax on the basis of spontaneous reports and literature data. Menstrual disorders are very common and can results from a wide range of underlying diseases as well as from stress and fatigue (https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk- assessment-committee-prac-7-10-february-2022).

4.2. Observed versus expected analyses (OE analyses) of selected adverse events

The Paul-Ehrlich-Institut analyses suspicious activity reports received with regard to new risk signals. In addition to the case-by-case assessment, the Paul-Ehrlich-Institut regularly carries out observed versus expected analyses (see Chapter 6.3). A Standardized Mobility Ratio (SMR) with a 95% confidence interval (CI) ≥ 1 indicates a safety signal, which still must be investigated further, as the comparison of spontaneous reports with known incidences is of an explorative nature due to various methodological limitations. As none of the reactions listed in the tables below have been reported for Nuvaxovid, the vaccine is not listed separately.

Table 6: Observed versus expected analysis (OE analysis) of selected adverse events occurring in a time interval of 7, 14, 30 or 42 days.
All reports with a known time interval of first symptoms after vaccination were included.

		Time between vaccination and onset of symptoms			
		7 Days	**14 Days**	**30 Days**	**42 Days**
Apoplexy (ischaemic) ≥18 years Incidence 164[1] cases per 100,000 person-years					
Comirnaty	Total cases	562	778	981	1061
	SMR (95% CI)	0.15 (0.14-0.17)	0.111 (0.099-0.114)	0.062 (0.058-0.066)	0.048 (0.045-0.051)
Spikevax	Total cases	77	111	139	145
	SMR (95% CI)	0.08 (0.07-0.10)	0.06 (0.05-0.07)	0.035 (0.030-0.041)	0.026 (0.022-0.031)
Vaxzevria	Total cases	120	182	244	259
	SMR (95% CI)	0.30 (0.25-0.36)	0.23 (0.20-0.26)	0.142 (0.125-0.161)	0.108 (0.095-0.122)
Jcovden (COVID-19 Vaccine Janssen)	Total cases	20	28	38	39
	SMR (95% CI)	0.18 (0.11-0.27)	0.12 (0.08-0.18)	0.078 (0.055-0.107)	0.057 (0.041-0.078)
Myocardial infarction ≥18 years Incidence 334.7[2] cases per 100,000 person-years					
Comirnaty	Total cases	192	284	364	393
	SMR (95% CI)	0.026 (0.022-0.029)	0.019 (0.017-0.021)	0.011 (0.010-0.013)	0.009 (0.008-0.010)
Spikevax	Total cases	45	63	76	81
	SMR (95% CI)	0.024 (0.017-0.032)	0.017 (0.013-0.021)	0.009 (0.007-0.012)	0.007 (0.006-0.009)
Vaxzevria	Total cases	42	63	83	93
	SMR (95% CI)	0.051 (0.037-0.069)	0.039 (0.030-0.049)	0.024 (0.019-0.029)	0.019 (0.015-0.023)
Jcovden (COVID-19 Vaccine Janssen)	Total cases	6	11	16	19
	SMR (95% CI)	0.026 (0.009 - 0.056)	**0.024 (0.012 - 0.042)**	**0.016 (0.009 - 0.026)**	0.014 (0.008 - 0.021)
Pulmonary embolism ≥18 years Incidence 81 (72–90)[3] cases per 100,000 cases per 100,000 person-years					
Comirnaty	Total cases	295	463	643	710
	SMR (95% CI)	0.16 (0.14-0.18)	0.139 (0.12-0.14)	0.083 (0.076-0.089)	0.065 (0.060-0.070)
Spikevax	Total cases	79	117	154	161
	SMR (95% CI)	0.17 (0.14-0.22)	0.13 (0.11-0.15)	0.08 (0.07-0.09)	0.06 (0.05-0.07)
Vaxzevria	Total cases	89	180	261	288
	SMR (95% CI)	0.45 (0.365-0.555)	0.45 (0.39-0.53)	0.31 (0.27-0.35)	0.24 (0.22-0.27)
Jcovden (COVID-19 Vaccine Janssen)	Total cases	13	24	40	46
	SMR (95% CI)	0.23 (0.12-0.40)	0.21 (0.14-0.32)	0.17 (0.12-0.23)	0.14 (0.10-0.18)
Sinus/cerebral vein thrombosis ≥ 18 years 1.9 (1.4-2.3)[4] cases per 100,000 person-years					
Comirnaty	Total cases	58	91	140	151
	SMR (95% CI)	1.36 (1.03-1.76)	1.07 (0.86-1.31)	0.77 (0.65-0.91)	0.59 (0.50-0.69)

Spikevax	Total cases	7	11	22	23
	SMR (95% CI)	0.65 (0.26-1.35)	0.51 (0.26-0.92)	0.48 (0.30-0.73)	0.36 (0.23-0.54)
Vaxzevria	Total cases	47	94	122	130
	SMR (95% CI)	10.13 (7.44-13.46)	10.13 (8.18-12.39)	6.13 (5.09-7.32)	4.67 (3.90-5.54)
Jcovden (COVID-19 Vaccine Janssen)	Total cases	2	5	10	10
	SMR (95% CI)	1.52 (0.18-5.48)	1.90 (0.62-4.43)	1.77 (0.85-3.26)	1.26 (0.61-2.33)
Immune thrombocytopenia ≥ 18 years Incidence 3.8 (3.6-4.1) [5] cases per 100,000 person-years					
Comirnaty	Total cases	135	216	292	325
	SMR (95% CI)	1.58 (1.33-1.88)	1.27 (1.10-1.45)	0.80 (0.71-0.90)	0.64 (0.57-0.71)
Spikevax	Total cases	22	30	41	41
	SMR (95% CI)	1.03 (0.64-1.56)	0.70 (0.47-1.00)	0.45 (0.32-0.61)	0.32 (0.23-0.43)
Vaxzevria	Total cases	94	259	379	398
	SMR (95% CI)	10.13 (8.18-12.39)	13.95 (12.30-15.76)	9.53 (8.59-10.53)	7.15 (6.46-7.88)
Jcovden (COVID-19 Vaccine Janssen)	Total cases	8	33	48	49
	SMR (95% CI)	3.03 (1.31-5.80)	6.26 (4.31-8.79)	4.25 (3.135-5.63)	3.10 (2.29-4.10)
Immune thrombocytopenia <18 Incidence 4.2 (3.7-4.7) [5] cases per 100,000 person-years					
Comirnaty	Total cases	8	20	20	20
	SMR (95% CI)	1.08 (0.47-2.14)	1.36 (0.83-2.09)	0.63 (0.39-0.98)	0.45 (0.28-0.70)

[1]Sedova P et al. (2021) Incidence of Stroke and Ischemic Stroke Subtypes: A Community-Based Study in Brno, Czech Republic. Cerebrovasc Dis. 2021;50(1):54-61. doi: 10.1159/000512180. Incidence adjusted for the 2010 European standard population
[2]KellerK et al. (2019) Sex-specific differences regarding seasonal variations of incidence and mortality in patients with myocardial infarction in Germany, International journal of cardiology 287: 132-138
[3]Delluc et al. (2016) Current incidence of venous thromboembolism and comparison with 1998: a community-based study in Western France, Thromb Haemost 2016; 116: 967-974,
[4]Jacobet al. (2021) Incidence of cerebral venous sinus thrombosis in adults in Germany – a retrospective study using health claims data, doi 10.21203/rs.3.rs-428469/v2.https://www.researchsquare.com/article/rs-428469/v2
[5]Schoonenet al. (2009) Epidemiology of immune thrombocytopenic purpura in the General Practice Research Database. British Journal of Haematology. 145:235-244
SMR: Standardized Morbidity Ratio

For apoplexy (stroke), myocardial infarction and pulmonary embolism, none of the approved vaccines showed a risk signal in the OE analysis. 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 fir immune thrombocytopenia (ITP)/ thrombocytopenia (low platelet counts with the risk of bleeding if the levels fall very low) in adults following Vaxzevria and Jcovden (COVID-19 Vaccine Janssen). Immune thrombocytopenia is an adverse event listed in the product information of both vaccines. For Comirnaty,

the SMR is significantly increased in the time period of up to 14 days in adults, 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 taken into account when interpreting these calculations, which limit the meaningfulness 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 distinguish between primary ITP (unknown cause) and secondary ITP (caused by diseases such as tumours, infections including SARS-CoV-2 infection or taking certain medicines) due to a lack of information. Since in most cases there was no prior value of the number of platelets present or the number wasn't communicated, it was not possible to distinguish reliably between possibly hitherto unknown but already existing and newly developed thrombocytopenia. The Paul-Ehrlich-Institut did not have any age-stratified incidences from Germany available, so the Institute used published background incidences from Great Britain, which seemed suitable overall. Nevertheless, very different incidences of an 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 up to 14 days after Comirnaty vaccination.[26]

It is important to note that in non-interventional studies in Scotland and Israel, which are more scientifically informative than the OE analysis, no increased risk of ITP or thrombocytopenia after Comirnaty was found.[13, 27] In this respect, a valid signal of thrombocytopenia/ ITP according to Comirnaty cannot currently be assumed to exist.

5. New: Nuvaxovid

Since the end of February, a total of 390 suspected cases of adverse events were reported to the Paul-Ehrlich-Institut through 31.03.2022. Fatigue (n = 92), headache (n = 90), pain at the injection site (n = 61) and other flu-like symptoms and general reactions mentioned in the product information were reported most frequently. In addition, paraesthesia (n = 21), hypoaesthesia (n = 5) and loss of feeling (n = 1) were reported. Three suspected case reports related to herpes zoster, including one

case of herpes zoster opticus. One suspected case report describes a case of facial paralysis.

Based on the comparatively low number of reports of suspected adverse events, no new risk signal was detected.

Paraesthesia refers to an unpleasant, but primarily non-painful sensation in which the body is triggered by inadequate stimuli. Paraesthesia has also been reported after immunisation with other vaccines, including COVID-19 vaccines. The cause is unknown.

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 events 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) . Identical reports received from multiple sources are merged into one case by the Paul-Ehrlich-Insititut

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 EudraVigilance database at the European Medicines Agency, to which every medicines 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 number of reports, if reported reactions were not confirmed by further investigations, for example.

The identification of duplicate reports is not always possible due to the necessary pseudonymisation. In case of doubt, if there are no clear indications of a double 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

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 vaccine dose is generally not possible, as this specific information is missing to a certain extent. 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[28] 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 the reporting rate for an adverse event after vaccination is significantly higher than would be statistically expected in a comparable population, the Paul-Ehrlich-Institut assumes a risk signal is present (SMR of the lower 95%CI ≥ 1). It should be noted that the OE analysis can indicate a safety signal. However, it is not suitable for confirming a risk. This should then be further investigated, if necessary, by additional studies.[29] An OE < 1 indicates that fewer reports were recorded than expected. OE calculations included reports received up until the evaluation day for which the time interval between vaccination and the first symptoms (time to onset, TTO) is known.

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 rate is available in 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 31 March 2022 by vaccine, age group, and gender. Data from the RKI aggregated by vaccine 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 noxious and unintended reactions to the medicinal product.

According to the AMG, **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 vaccination are classified as "serious", regardless of the legal definition of "serious" in the AMG. In this respect, a direct comparison with the reports on other vaccines is not possible.

The suspicion of damage to health beyond the usual extent of a vaccination reaction (synonym: vaccination complication) according to section 6 of the Infection Protection Act is a symptom occurring after vaccination, which could be causally related to the vaccination and goes beyond the usual vaccination reactions. These are, for example, short-term, transient local and general reactions or similar symptoms of a 'vaccine disease'.

In the text, the terms adverse event and vaccination complication are combined and referred to as *adverse events*.

Note: The Paul-Ehrlich-Institut would like to thank all those reporting suspected adverse events. They contribute to the rapid detection and reduction of risk signals.

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.

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