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

Paul-Ehrlich-Institut

Langen, 23 December 2021

SAFETY REPORT

Suspected cases of adverse events and vaccine-related complications following vaccination against COVID-19 from 27 December 2020 (start of vaccination campaign) to 30 November 2021

The Paul-Ehrlich-Institut (PEI) reports suspected cases of adverse events or vaccine-related complications logged in Germany. These cases have a temporal association to vaccinations against COVID-19 from the beginning of the vaccination campaign on 27 December 2020 through 30 November 2021 with the mRNA vaccines Comirnaty (BioNTech Manufacturing GmbH) and Spikevax (MODERNA BIOTECH SPAIN, S.L.) and the vector vaccines Vaxzevria (AstraZeneca AB) und COVID-19 Vaccine Janssen. According to information from the Robert Koch-Institut (RKI), 123,347,849 vaccines were administered through 30 November 2021. Of those administered vaccines, 96,606,131 were Comirnaty, 10,576,131 were Spikevax, 12,703,030 were Vaxzevria, and 3,462,557 were COVID-19 Vaccine Janssen. 113,792 suspected cases were reported for the Comirnaty vaccine, 28,289 for Spikevax, 46,325 for Vaxzevria, and 7,758 for COVID-19 Vaccine Janssen. The COVID-19 vaccine was not specified in 810 of the suspected cases that were reported. The combined reporting rate for all vaccines was 1.6 reports per 1,000 vaccine doses. For severe reactions, the combined reporting rate was 0.2 reports per 1,000 vaccine doses.

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.

Contents

1. Introduction

Vaccination via effective, well tolerated COVID-19 vaccines is an effective measure to contain the Coronavirus pandemic and to protect oneself against COVID-19.

The mRNA vaccine Comirnaty (BioNTech) has been authorised for protection against COVID-19 in the European Union (EU), and therefore in Germany, since 22 December 2020. The COVID-19 vaccination campaign began in Germany and in other EU member states on 27 December 2020. Spikevax (Moderna), also an mRNA vaccine, was authorised in the EU on 6 January 2021. Vaccinations with this vaccine began in Germany in mid-January 2021. The adenovirus-based vector vaccine Vaxzevria (AstraZeneca) was authorised in the EU on 30 January 2021. Vaccinations with this vaccine began in Germany at the beginning of February 2021. COVID-19 Vaccine Janssen, also an adenovirus-based vector vaccine, has been authorised since 11 March 2021. Vaccinations with this vaccine began in Germany at the end of April 2021.

According to data from the RKI, 123,347,849 vaccinations with the four authorised COVID-19 vaccines named above were administered in Germany. For 11 months now the Paul-Ehrlich-Institut, together with its EU and international counterparts, has been continuously evaluating the safety profile of the COVID-19 vaccines. Worldwide data has shown that the vast majority of adverse events connected to vaccines available in Germany are temporary local and systemic reactions, as had been already observed in clinical trials before marketing authorisation. Tolerability of the mRNA vaccines among children and adolescents from 12 to 17 years of age is largely consistent with tolerability among young adults. Initial results from spontaneous reporting indicate a lower reporting rate of suspected cases of adverse events for booster vaccinations (third vaccinations) with Comirnaty or Spikevax than for the preceding vaccinations. According to current data, severe adverse events (summarised in the following sections) are very rare and do not alter the positive benefit-risk ratio of the vaccines.

2. Summary of very rare COVID-19 vaccine-related adverse events

2.1. Myocarditis and pericarditis

Myocarditis and pericarditis belong to the list of known, very rare adverse events associated with the mRNA vaccines. Data from many countries, including Germany, has shown an increased risk for young men after the second dose in particular[1-15], while a Danish study found a slightly higher risk among young women.[16] The first symptoms typically appear within a few days of vaccination. Published data consistently shows that the vast majority of patients suffering from myocarditis or pericarditis after vaccination with an mRNA vaccine respond well to treatment and rest and feel better quickly, although isolated cases of severe disease progression cannot be ruled out entirely.[1-16]

Preliminary data following the market launch in Germany indicates that the risk of myocarditis or pericarditis among young people after Spikevax, while rare, is possibly higher than after Comirnaty[15-17], which is why the Standing Committee on Vaccination (Ständige Impfkommission, STIKO) has recommended Comirnaty for people < 30 years old as a precaution.

2.2. Anaphylaxis

An anaphylactic reaction is a very rare, previously observed complication associated with all four authorised COVID-19 vaccines. The reporting rate of anaphylaxis (Brighton Collaboration BC Level 1-4)[18] in Germany as of 30 November 2021 was less than one case per 100,000 vaccinations. The rate is slightly higher among women than among men, and it is also higher for the first vaccination than for subsequent vaccinations. The results from initial retrospective studies[18,20] indicate that the anaphylactic reactions most probably cannot be attributed to Immunoglobulin E-mediated immediate allergic reactions and affected patients can in most cases be vaccinated again following allergological testing. A study in the US identified cases of pseudoallergy among patients with anaphylaxis after the first mRNA vaccination. This is a non-Immunoglobulin E-mediated reaction, which is called a complement activation-related pseudoallergy (CARPA).[21]

2.3. Thrombosis with thrombocytopenia syndrome (TTS)

A very rare, and in a few cases fatal, new syndrome has been reported as a serious adverse event associated with the Vaxzevria and COVID-19 Vaccine Janssen vector vaccines. The syndrome is characterised by venous and/or arterial thromboses in combination with a thrombocytopenia (thrombosis with thrombocytopenia syndrome, TTS). In such cases, the thromboses often appear in unusual locations, such as cerebral or mesenteric veins, or veins in the spleen or liver. High concentrations of antibodies against platelet factor 4 (anti-PF4 antibodies) were detected in several of the affected patients, as well as a high level of thrombocyte activation during clotting tests.[22-28] This is a pattern that resembles “atypical” or “autoimmune” heparin-induced thrombocytopenia (aHIT).[29] According to early findings[30], these cases appear to involve transient antibodies that, after 12 weeks or less, were in most cases no longer detectable in the patients who had developed TTS. This is also potentially the reason why TTS was much more rarely reported after a second vaccination with Vaxzevria as it was after a first vaccination. Early diagnosis and treatment of TTS is of extreme importance. Recommendations for treatment and therapy of the new syndrome have been published by various associations of experts in the field, including the German Society for Thrombosis and Haemostasis Research (GTH).[31-33]

2.4. Guillain-Barré Syndrome

It is possible, yet very rare, for individuals vaccinated with Vaxzevria or COVID-19 Vaccine Janssen to develop Guillain-Barré Syndrome (GBS). The reporting rate of GBS after vaccination with a vector vaccine was very low, equalling 0.88 (Vaxzevria) and 1.89 (COVID-19 Vaccine Janssen) reported cases per 100,000 vaccine doses.

2.5. Thrombocytopenia and immune thrombocytopenia (ITP)

Immune thrombocytopenia (ITP) is a disease in which the immune system erroneously attacks platelets, which are a type of blood cell necessary for normal blood clotting. A low platelet level (thrombocytopenia) can lead to abnormal bleeding and have severe health consequences.

Individual reports submitted post-authorisation and some reference data[34,35] indicate a correlation between vaccination with Vaxzevria or COVID-19 Vaccine Janssen and the occurrence of very rarely reported cases of ITP. The reported cases of ITP mostly occurred within four weeks of vaccination. If an individual has a history of ITP, the risk of a low platelet count should be considered before vaccination. After vaccination with one of these vaccines, observation of the platelet level is recommended.

2.6. Thrombosis

Multiple studies have examined the potential risk for thrombosis with COVID-19 vaccines (primarily Comirnaty and Vaxzevria).[14,33,35,36] However, the findings of the various studies were not consistent, making it difficult to draw a definitive conclusion with regards to the potential risk of thrombosis after COVID-19 vaccination. In the studies which also examined SARS-CoV-2 infections and risk of thromboses, the risk after viral infection was always higher than it was after vaccination. The Pharmacovigilance Risk Assessment Committee (PRAC) at the European Medicines Agency (EMA) noted the occurrence of rare cases of venous thromboembolisms (VTE) after COVID-19 Vaccine Janssen. VTE had already been detected during the marketing authorisation process as a signal that needed to be further assessed. This is because a higher percentage of VTE cases was identified in the vaccinated group than in the placebo group during the large clinical trial that led to the marketing authorisation of the vaccine. However, there was no indication of an increase in occurrences of venous thromboembolisms among vaccinated individuals in a subsequent large clinical trial.

Additionally, a safety signal was detected for very rare cases of venous sinus thromboses without thrombocytopenia after Vaxzevria. However, it cannot be ruled out that some cases actually correspond to cases of TTS due to a lack of information regarding the number of thrombocytes.

3. Reports of suspected cases and reporting rate of adverse events and vaccine-related complications

3.1. Overview

A total of 196,974 individual reports of suspected cases of adverse events or vaccine-related complications after vaccination with a COVID-19 vaccine in Germany were registered in the Paul-Ehrlich-Institut's database of adverse events through 30 November 2021. The reporting rate for all COVID-19 vaccinations was 1.6 suspected cases per 1,000 vaccine doses. For severe cases, the rate was 0.2 suspected cases (rounded off) per 1,000 vaccine doses. Table 1 shows the number of reported suspected cases of adverse events or vaccine-related complications after vaccination with a COVID-19 vaccine, as well as the respective reporting rates per 1,000 vaccinations in Germany from 27 December 2020 through 30 November 2021 for all of the COVID-19 vaccines used so far in Germany.

Table 1: Number of reported suspected cases of adverse events or vaccine-related complications and reporting rates per 1,000 vaccinations after vaccination with a COVID-19 vaccine in Germany from 27 December 2020 through 30 November 2021

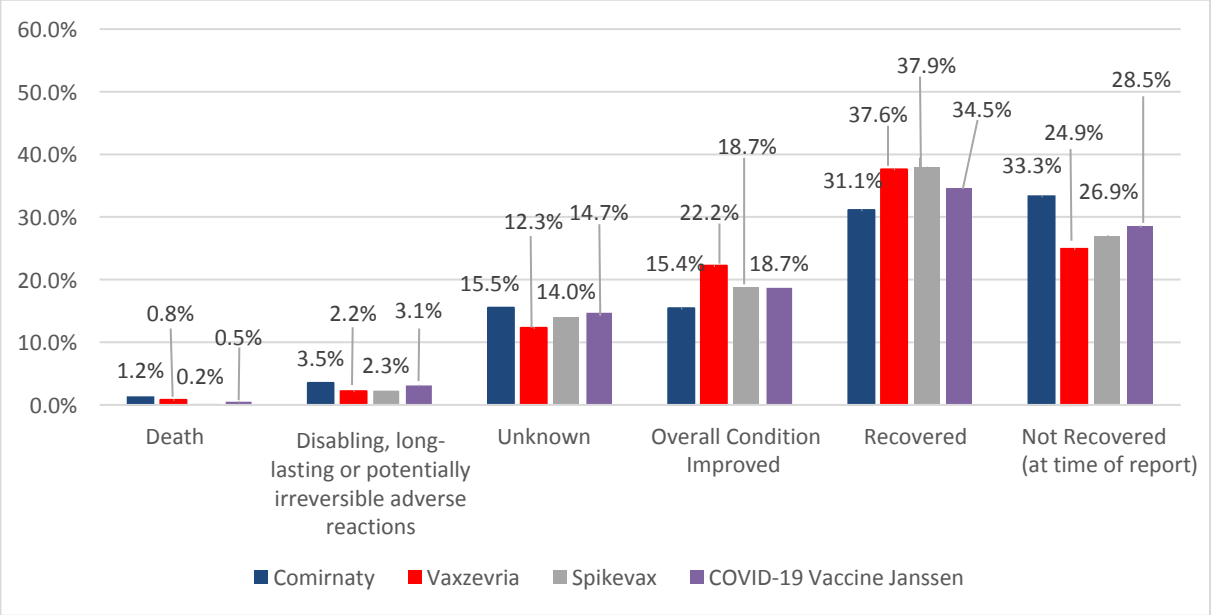
Vaccine	Total reports of suspected cases	Serious reports (% of total reports per vaccine)	Total reporting rate per 1,000 vaccinations	Serious reports per 1,000 vaccinations
Comirnaty	113,792	16,874 (14.8 %)	1.2	0.17
Spikevax	28,289	1,924 (6.8 %)	2.7	0.18
Vaxzevria	46,325	6,147 (13.3 %)	3.6	0.48
COVID-19 Vaccine Janssen	7,758	925 (11.9 %)	2.2	0.27
Vaccine unknown	810	326 (40.2 %)		
Total	**196,974**	**26,196 (13.3 %)**	**1.6**	**0.2**

As reporting rates are influenced by many factors, including age distribution of the vaccinated cohort and public awareness, a comparison of the total reporting rates of the different vaccines should be interpreted with caution.

3.2. Outcome of reported reactions

Figure 1 shows the outcomes of reported reactions for each of the COVID-19 vaccines.

Figure 1: Outcomes of reported reactions as a percentage of all reported events in connection with an individual vaccine, broken down by individual COVID-19 vaccine



Please note: Percentages were rounded up or down so that the sum of the percentages would equal 100%.

3.3. Reported cases of severe adverse reactions

Severe adverse reactions were reported in 26,196 of the suspected cases. Of these, 16,874 severe suspected cases emerged after vaccination with Comirnaty, 1,924 severe suspected cases after vaccination with Spikevax, 6,147 severe suspected cases after vaccination with Vaxzevria, und 925 severe suspected cases after vaccination with COVID-19 Vaccine Janssen. The name

of the vaccine was not provided in 326 suspected cases.

Fatal outcomes at varying points in time after vaccination (from 0 days to 289 days) were reported in 1,919 suspected case reports. In 78 of the cases, in which patients died from known vaccine risks such as thrombosis with thrombocytopenia syndrome (TTS), bleeding due to immune thrombocytopenia, or myocarditis at a logical temporal distance from vaccination, the Paul-Ehrlich-Institut evaluated a causal link with vaccination to be possible or probable.

Table 2: Number and reporting rate of deaths reported for each of the COVID-19 vaccines

Vaccine	Deaths	Reporting rate of deaths per 1,000 vaccinations
Comirnaty	1,427	0.02
Spikevax	80	0.01
Vaxzevria	307	0.02
COVID-19 Vaccine Janssen	52	0.02
Unknown vaccine	53	
Total	**1,919**	**0.02**

A comparison of the total number of reported deaths 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 four COVID-19 vaccines used so far in Germany. This comparison applies to booster vaccinations (table 3) and sudden, unexpected deaths (table 4). 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 timeframe of 30 days. This analysis did not indicate a safety signal for increased mortality for any of the four vaccines, as the Standardized Morbidity Ratio (SMR) was considerably under 1 (SMRs between 0.007-0.022; data not presented separately).

Table 3: Observed versus expected analysis of the deaths at varying time periods after vaccination against COVID-19 reported to the Paul-Ehrlich-Institut; cases included in which vaccination took place by 30 November 2021 and for which the time interval between vaccination and start of symptoms is known. According to data from the German Federal Statistical Office (extracted on 4 August 2021), there were 982,453 deaths in 2020 in Germany among 78,918,151 individuals aged 12 or older. The background incidence rate was 1,329.11 cases per 100,000 person years (Federal Statistical Office).

	Comirnaty		**Spikevax**		**Vaxzevria**		**COVID-19 Vaccine Janssen**	
Time interval between vaccination and start of symptoms	**Number of Cases**	**SMR 95 % CI**	**Number of Cases**	**SMR 95 % CI**	**Number of Cases**	**SMR 95 % CI**	**Number of Cases**	**SMR 95 % CI**
Total								
1 Day	122	0.035 (0.029-0.041)	9	0.023 (0.011-0.044)	18	0.039 (0.023-0.062)	2	0.016 (0.002-0.057)
2 Days	173	0.025 (0.021-0.028)	11	0.014 (0.007-0.026)	27	0.029 (0.019-0.042)	3	0.012 (0.002-0.035)
7 Days	363	0.015 (0.013-0.016)	19	0.007 (0.004-0.011)	63	0.019 (0.015-0.025)	7	0.008 (0.003-0.016)
14 Days	506	0.010 (0.009-0.011)	23	0.004 (0.003-0.006)	94	0.015 (0.012-0.018)	9	0.005 (0.002-0.010)
30 Days	618	0.0058 (0.0054-0.0063)	28	0.0024 (0.0016-0.0035)	117	0.008 (0.007-0.010)	11	0.003 (0.001-0.005)
42 Days	645	0.0044 (0.0040-0.0047)	30	0.0019 (0.0013-0.0026)	121	0.006 (0.005-0.007)	14	0.003 (0.001-0.004)
Booster Vaccination D3								
1 Day	11	0.031 (0.016-0.056)	1	0.0358 (0.0009-0.1992)			*	
2 Days	13	0.019 (0.010-0.032)	1	0.0179 (0.0005-0.0996)				
7 Days	27	0.011 (0.007-0.016)	1	0.0051 (0.0001-0.0285)				
14 Days	30	0.0061 (0.0041-0.0088)	1	0.0026 (0.00006-0.0142)				
30 Days	33	0.0031 (0.0022-0.0044)	3	0.0036 (0.0007-0.0105)				
42 Days	33	0.0022 (0.0015-0.0032)	3	0.0026 (0.0005-0.0075)				

Table 4: Observed versus expected analysis of unexplained deaths after vaccination against COVID-19; cases included in which vaccination took place by 30 November 2021 and for which the time interval between vaccination and start of symptoms is known, ICD-10 causes of death I46.1 + R96-R99, background incidence rate from cause-of-death statistics from the 2020 reporting year: 31,521 fatalities in the 10 years and older age group labelled with causes of death I46.1, R96-R99; population of the same age group in 2020: 75,440,349, incidence rate 41.78 cases per 100,000 person years; CI: confidence interval

	Comirnaty		Spikevax		Vaxzevria		COVID-19 Vaccine Janssen	
Time interval between vaccination and start of symptoms	**Number of cases**	**SMR 95 % CI**	**Number of cases**	**SMR 95 % CI**	**Number of cases**	**SMR 95 % CI**	**Number of cases**	**SMR 95 % CI**
Total								
1 Day	64	0.58 (0.45-0.74)	6	0.50 (0.18-1.08)	13	0.89 (0.48-1.53)	1	0.25 (0.01-1.42)
2 Days	89	0.40 (0.32-0.50)	7	0.30 (0.12-0.60)	16	0.55 (0.31-0.89)	2	0.25 (0.03-0.91)
7 Days	166	0.21 (0.18-0.25)	10	0.12 (0.06-0.22)	31	0.30 (0.21-0.43)	4	0.14 (0.04-0.37)
14 Days	224	0.14 (0.13-0.17)	12	0.07 (0.04-0.12)	42	0.21 (0.15-0.28)	5	0.09 (0.03-0.21)
30 Days	261	0.08 (0.07-0.09)	13	0.04 (0.02-0.06)	49	0.11 (0.08-0.15)	6	0.05 (0.02-0.11)
42 Days	271	0.06 (0.05-0.07)	13	0.03 (0.01-0.04)	49	0.08 (0.06-0.11)	7	0.04 (0.02-0.09)
Booster Vaccination								
1 Day	7	0.64 (0.26-1.31)	2	2.28 (0.28-8.22)	-	-	*	
2 Days	8	0.36 (0.16-0.72)	2	1.14 (0.14-4.11)	-	-		
7 Days	14	0.18 (0.10-0.31)	2	0.33 (0.04-1.17)	-	-		
14 Days	15	0.10 (0.05-0.16)	2	0.16 (0.02-0.59)	-	-		
30 Days	15	0.05 (0.03-0.08)	2	0.08 (0.01-0.27)	-	-		
42 Days	15	0.03 (0.02-0.08)	2	0.05 (0.01-0.20)	-	-		

4. Children and adolescents from 12 to 17 years old

Comirnaty has been authorised for vaccination of 12- to 15-year-olds since 31 May 2021 (Comirnaty had been previously approved from 16 years of age). Spikevax has been authorised for vaccination of 12- to 17-year-olds since 23 July 2021. Recently, an appropriate dosage form of Comirnaty (containing a third of the vaccine dose approved for 12+) has been authorised for the vaccination of children ages 5 to 11.

A total of 2,777 suspected cases of adverse events concerning one or more child or adolescent vaccine reactions after COVID-19 vaccination have been reported to the Paul-Ehrlich-Institut since the beginning of the vaccination campaign on 27 December 2020. The Comirnaty vaccine was administered in 2,661 of the cases, and the Spikevax vaccine was administered in 62 of the cases. Even though as of 30 November 2021 (date of analysis of reports) only the two mRNA vaccines had been authorised for children and adolescents 12 years of age and older, there were 55 suspected cases reported to the Paul-Ehrlich-Institut in which an mRNA vaccine was administered to children < 12 years old, and 40 cases involving vector vaccines. The COVID-19 vaccine was not specified in 14 suspected case reports.

Based on an imputation of vaccine dose numbers (see Methodology), 0.62 suspected case reports (severe and non-severe reports) were reported per 1,000 vaccine doses. For Comirnaty, the vaccine most frequently administered in this age group, the reporting rate was 0.60 per 1,000 vaccine doses. Pain at the injection site, headache, fatigue, and fever were the most commonly reported adverse events (figure 2). Severe adverse reactions were described in 22.9% of the suspected case reports.

Figure 2: Reporting rate of common adverse reactions among children and adolescents per 1,000 Comirnaty vaccinations (multiple reactions per case may be reported)

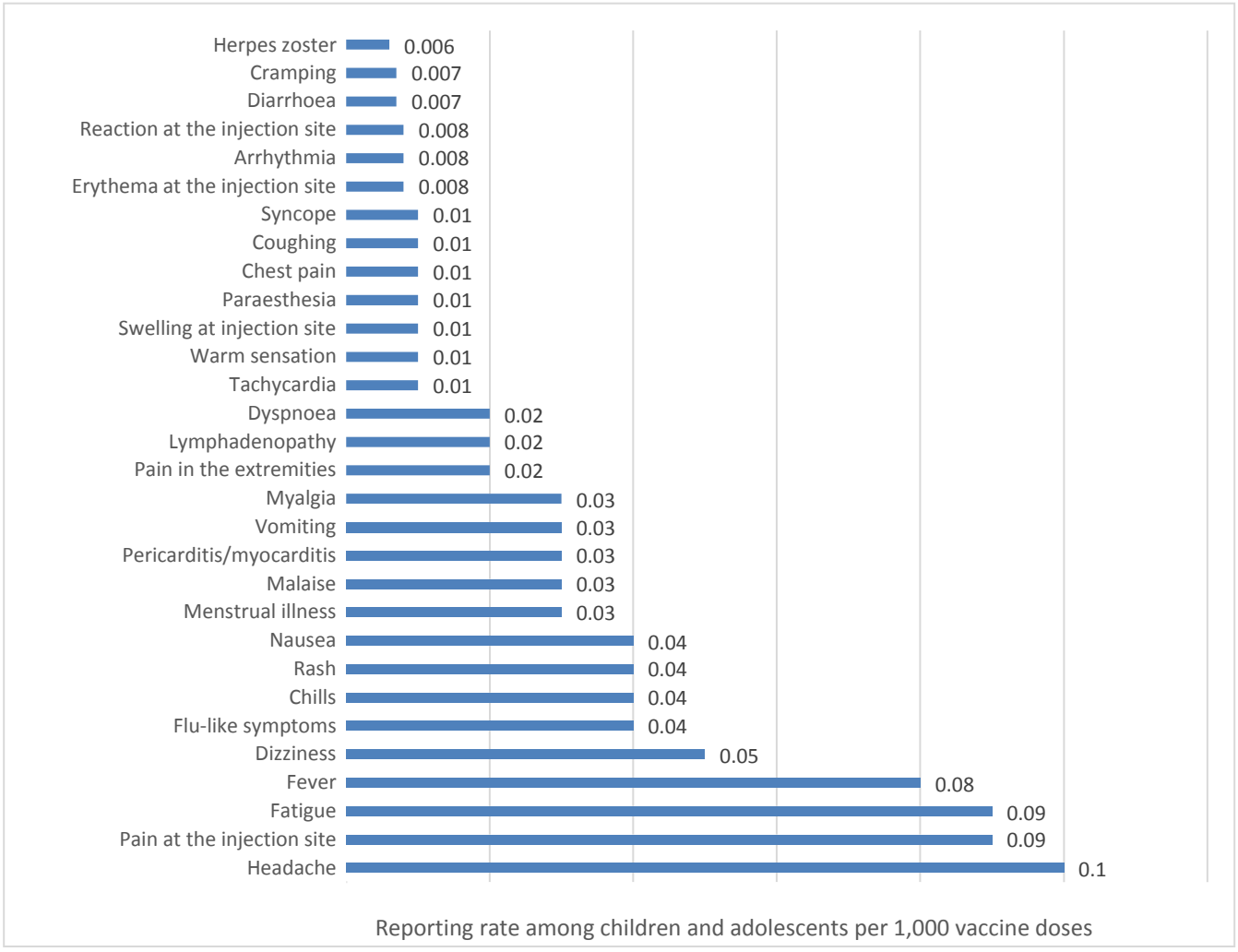
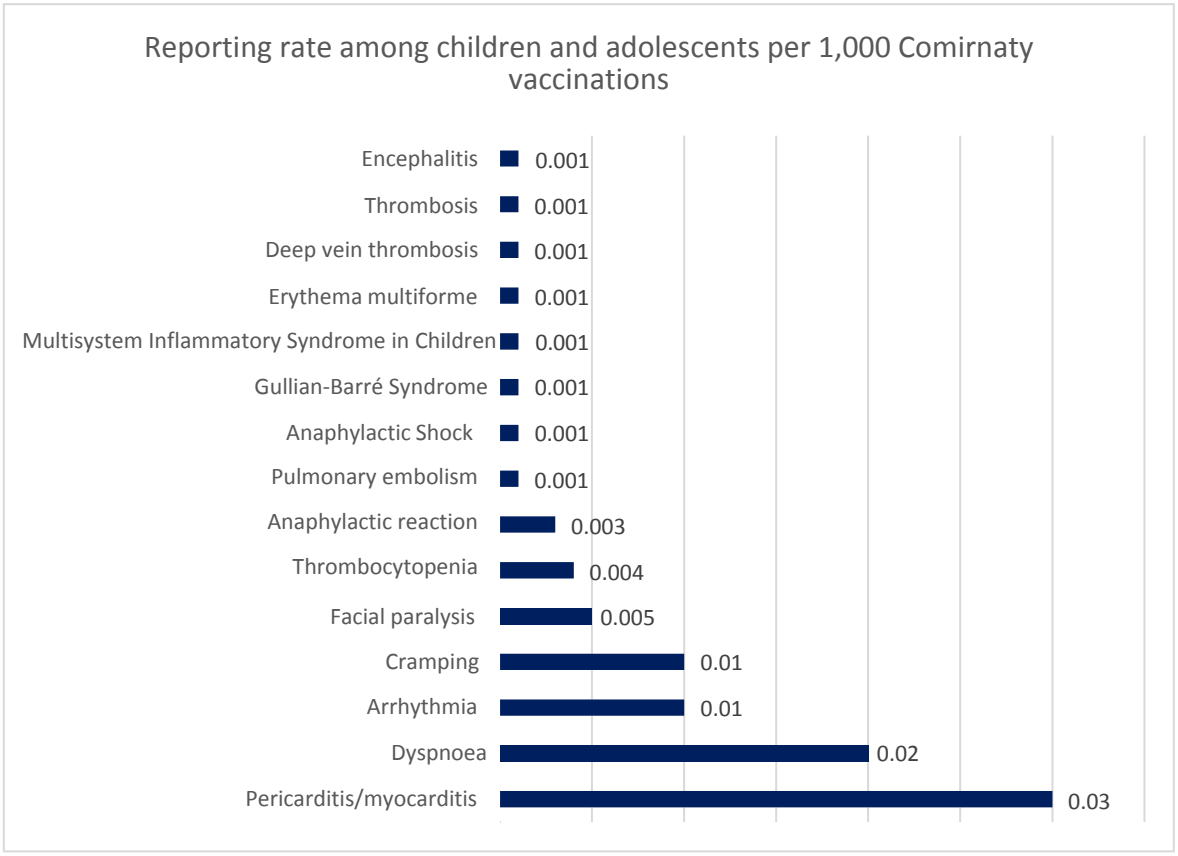


Figure 3 shows the reporting rate of Adverse Events of Special Interest (AESIs) reported more than twice. The rate is presented per 1,000 Comirnaty vaccinations. The most frequently reported of these AESIs were cases of myocarditis or pericarditis (see section 6.2, Myocarditis/pericarditis). An analysis of 18 reports of facial nerve paralysis within six weeks of Comirnaty vaccination showed that fewer cases were reported as would have been statistically expected in the age group (background incidence rate[38]). A safety signal was not identified.

Figure 3: Reports of adverse events of special interest reported more than once per 1,000 Comirnaty vaccines



There were reports on four adolescents (one male, three female, all 17 years old) filed reporting cases of paediatric inflammatory multiorgan syndrome (PIMS, also known as multisystem inflammatory syndrome in children or MIS-C) with a temporal association to the Comirnaty vaccination. The start of symptoms was reported as occurring between 20 and 78 days after the last vaccination. A previous SARS-CoV-2 infection was confirmed in three of the four cases. Important clinical information is missing for the fourth case, so the link to vaccination cannot be assessed. Multisystem inflammatory syndrome is a severe inflammatory disease affecting multiple parts of the body. It can cause symptoms such as fatigue, persistent high fever, diarrhoea, vomiting, stomach ache, headache, chest pain, and difficulty breathing. There have been some very rare reports of this syndrome resulting from a COVID-19 infection.

At the time of reporting, 55.4% of the vaccinated children and adolescents for whom adverse events were reported had seen an abatement or improvement of their adverse reactions. 30.1% were not yet fully recovered, and 13.9% had an unknown outcome. Six of the suspected case reports (one female and five male adolescents) reported deaths occurring in a time range of two days to five months after vaccination with Comirnaty. One death involved a female adolescent whose death five months after vaccination was linked to a congenital case of arrhythmia. No causal link to vaccination was found. In the case of one of the male adolescents, there was an especially severe underlying heart condition unrelated to the vaccine. Upon examination of the extensive medical findings, the Comirnaty vaccination does not appear to be the sole cause of death. A causal link with vaccination cannot be conclusively determined in the four other cases, but the symptoms and illness progression differ between them and there are no clinical similarities.

There were vaccination complications described as disabling, long-lasting or potentially irreversible adverse events in the cases of nine adolescents (five male and four female) between the ages of 13 and 17 occurring in a time range from three days to eleven weeks after vaccination. A scar caused by the injection was reported in one case. A female adolescent was diagnosed with Hodgkin's lymphoma 40 days after Comirnaty vaccination. This case has no apparent link to the vaccination. Persistent diarrhoea lasting multiple months without a known cause was reported for a male adolescent. In five cases (two female and three male adolescents), diabetes mellitus type 1 was diagnosed after vaccination. With an incidence rate for diabetes mellitus type 1 of 24 per 100,000 children/adolescents per year, the number of reported cases after Comirnaty is significantly lower than expected and does not indicate a safety signal.[39] An additional report of a disabling, long-lasting or potentially irreversible side effect concerned a case of myocarditis.

According to the RKI, as of the report evaluation date 52.9% of adolescents ages 12 to 17 had been vaccinated at least once, and 46.4% had been fully vaccinated. Spontaneous reporting data showed that temporary and short-term local and general reactions were most frequently reported. Very rarely reported cases of myocarditis or pericarditis are considered serious adverse events related to mRNA vaccines. According to current data, the illness progression is mild in most cases. Symptoms completely disappear within a short time for the vast majority of affected patients.

The Paul-Ehrlich-Institut is carrying out a long-term trial in cooperation with the MYKKE Children's Myocarditis Registry to study the progression of myocarditis among children and adolescents after COVID-19 vaccination.

5. Reports of suspected cases after booster vaccination

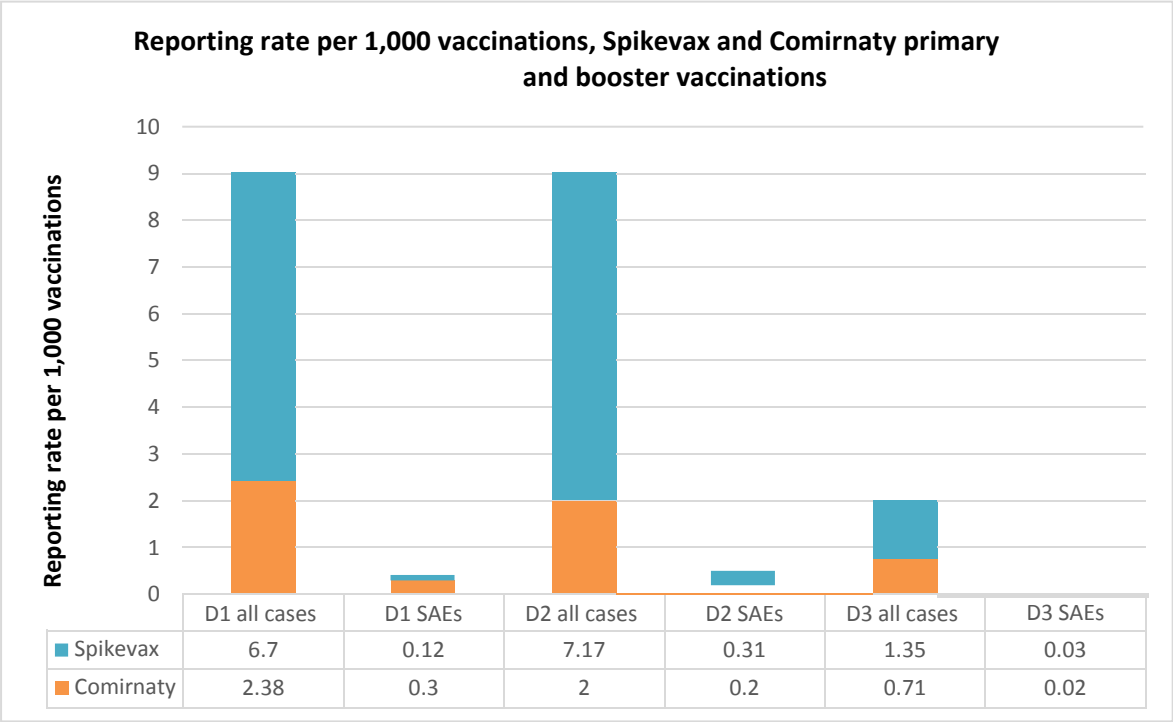
Booster vaccination with Comirnaty and Spikevax has been authorised for individuals 18 years of age or older as well as for severely immunocompromised individuals 12 years of age or older. The STIKO recommends a booster vaccination with an mRNA vaccine for everyone over the age of 18.

In order to be considered a suspected case report of an adverse event or vaccine-related complication after booster vaccination, reports must indicate that either the third vaccine dose of the Comirnaty, Spikevax, and Vaxzevria vaccines or the second dose of the COVID-19 Vaccine Janssen was administered. In some cases, heterologous vaccine schedules were also reported.

2,931 reports were made in connection with a Comirnaty booster vaccination, and 338 reports were made in connection with a Spikevax booster vaccination. A third vaccination with Vaxzevria was reported in one case, and the vaccine was unknown in eight cases. Severe reactions were reported in 268 reports, 244 cases after Comirnaty vaccines, 19 cases after Spikevax vaccination, and five cases in which the vaccine name was not provided.

A comparison of reporting rates after primary and booster vaccinations was completed, taking into consideration only the reports for which the vaccine dose number was known. This comparison shows that the reporting rate of suspected cases of adverse events per 1,000 vaccinations after a third dose of Comirnaty or Spikevax was significantly lower than the corresponding reporting rate after primary vaccination (figure 4). This was also demonstrated for the most commonly reported reactions by individual vaccine dose (figure 5). It should be noted, however, that older people, people in certain professions, and those who tolerated the first two vaccines well presumably comprised the majority of those who had received their booster by the report evaluation date. Additionally, the post-observation period is shorter for booster vaccinations as it is for primary vaccinations, so the current numbers should be viewed as preliminary.

Figure 4: Reporting rate per 1,000 vaccinations by vaccine dose: reporting rate of all reported cases and reporting rate of suspected serious adverse events (SAE)



	D1 all cases	D1 SAEs	D2 all cases	D2 SAEs	D3 all cases	D3 SAEs
Spikevax	6.7	0.12	7.17	0.31	1.35	0.03
Comirnaty	2.38	0.3	2	0.2	0.71	0.02

Evaluation at case level, a suspected case may involve multiple adverse events, D1: first dose, D2: second dose, D3: third dose, SAE: serious adverse event

Figure 5 a + b: Reporting rate per 1,000 vaccinations of the most frequently reported reactions after first, second, and third doses of Comirnaty (a) or Spikevax (b)

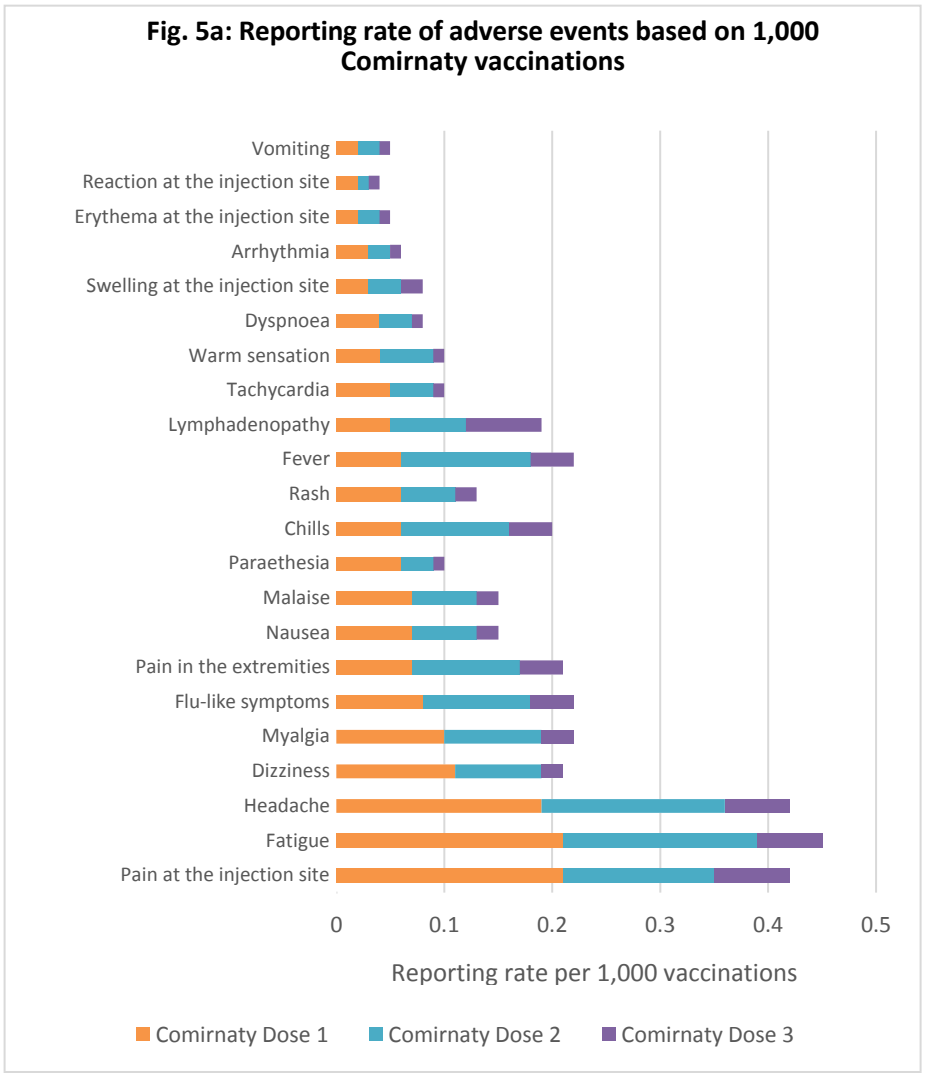
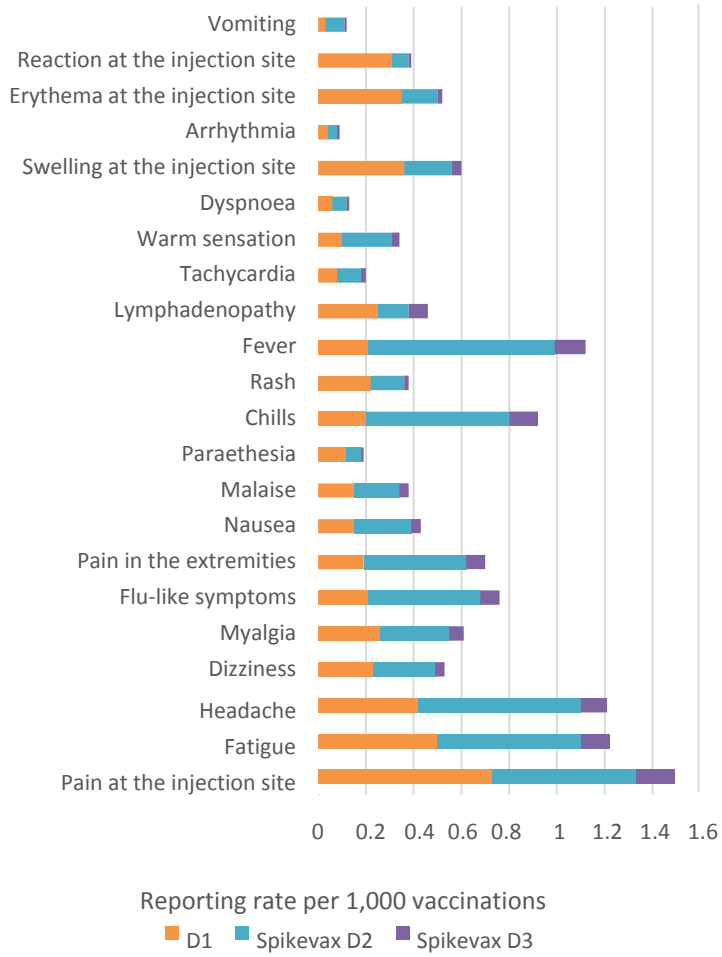


Fig. 5b: Reporting rate of adverse events based on 1,000 Spikevax vaccinations



Current data indicates a favourable safety profile for the third dose of Comirnaty and Spikevax.

6. Very rare COVID-19 vaccine risks

6.1. Anaphylactic reactions

Anaphylactic reactions are known, very rare adverse events associated with the four authorised COVID-19 vaccines that have been used so far in Germany.

There were 452 reports of anaphylactic reactions made through 30 November 2021 that were evaluated by the Paul-Ehrlich-Institut on the basis of their diagnostic certainty as defined by the internationally accepted Brighton Collaboration (BC)[18] levels 1-4. Level 1 is the highest grade of diagnostic certainty, levels 2 and 3 are lower grades, and level 4 indicates a report of a suspicion of anaphylaxis with incomplete information regarding the clinical symptoms.

The reporting rate of anaphylaxis at BC levels 1-4 is less than one case/100,000 vaccinations and is therefore very low. The rate after first vaccination is higher than after the subsequent vaccinations, and it is higher among women than among men (table 5).

Table 5: Number of anaphylaxis reports (BC levels 1-4) after COVID-19 vaccine and reporting rates per 100,000 vaccinations total and among women

	Comirnaty		**Spikevax**		**Vaxzevria**		**COVID-19 Vaccine Janssen**	
	BC 1-3	BC 1-4	BC 1-3	BC 1-4	BC 1-3	BC 1-4	BC 1-3	BC 1-4
Dose 1	147	240	12	30	40	55	3	7
Dose 2	53	79	2	3	2	2	-	-
Dose 3	0	2	-	1	-	-	-.	-.
NS	5	19	-	3	-	2	-	-
Heterologous Vaccine Schedule	2	3	2	2	-.	-	-	-
Total number	207	343	16	39	42	59	3	7
Total reporting rate (women)		0.36 (0.61)		0.37 (0.55)		0.46 (0.87)		0.20
Reporting rate D1 (women)		0.57 (0.93)		0.66 (0.87)		0.60 (1.13)		0.20 (0.17)*

Reporting rate per 100,000 vaccinations, D: vaccine dose, NS: dose not specified, 4 cases with no information on vaccine used, *based on 2 reports, therefore not a reliable point estimate

6.2. Myocarditis and/or pericarditis

Myocarditis and pericarditis are very rare adverse events following the mRNA vaccines Comirnaty and Spikevax. Myocarditis is an inflammation of the heart muscle, which can manifest itself as chest pain, heart palpitations, arrhythmia, and even heart failure. This condition can affect children and adolescents and is more common among young men than young women. Pericarditis is an inflammation of the pericardium, which is the outer lining of the heart. Men between the ages of 20 and 50 appear to have the highest risk for pericarditis. Myopericarditis is a combination of myocarditis and pericarditis.

6.2.1. Overview

Tables 6 and 7 show the reported cases of myocarditis and/or pericarditis after Comirnaty and Spikevax. Cases involving a heterologous vaccine schedule in which Comirnaty was administered after Vaxzevria vaccination are detailed separately. The majority of reports for both vaccines involved men in the 18-29 age group.

For the most part, these reports for Comirnaty and Spikevax concerned cases of myocarditis or myopericarditis. Isolated cases of pericarditis were reported in 12.4% of the Comirnaty cases and 6.69% of the Spikevax cases. Three reports detailed symptoms that first occurred 10, 14, and 21 days before the second dose. In one of these cases, the symptoms got worse after the second vaccination. In the other two cases the symptoms improved, despite the patients being vaccinated again.

Table 6: Reports of myocarditis and pericarditis after Comirnaty by age, gender, and vaccine dose

	Total[1]	Men					Women				
Age (years)		**D1**	**D2**	**D3**	**D NS**	***Het. Sch.***	**D1**	**D2**	**D3**	**D NS**	***Het. Sch.***
12-17	139	24	82	0	18	*0*	7	7	0	1	*0*
18-29	386	57	199	1	65	*6*	15	33	0	16	*1*
30-39	215	31	70	1	26	*4*	25	35	2	25	*1*
40-49	144	16	41	1	10	*3*	14	46	2	14	*2*
50-59	166	13	45	0	23	*5*	27	37	0	21	*2*
60-69	66	8	22	1	5	*4*	12	14	0	4	*1*
70-79	47	6	14	0	5	*1*	4	15	0	3	*0*
80+	22	2	3	4	3	*0*	1	6	1	2	*0*
NS	60	18	16	1	7	*0*	10	5	0	3	*0*
Total	**1245**	**175**	**492**	**9**	**162**	*23*	**115**	**198**	**5**	**89**	*7*

D1: Dose 1; D2: Dose 2; NS: not specified; Het. Sch.: heterologous vaccine schedule (included in D2 and/or D3); Time in days from vaccination to reaction (time to onset, TTO): median 5 days, average 13.8 days (range 0 to 194 days). [1] Reports missing gender information with or without age information were included in the total

Table 7: Reports of myocarditis and pericarditis after Spikevax by age, gender, and vaccine dose

	Total[1]	Men					Women				
Age (years)		**D1**	**D2**	**D3**	**D NS**	***Het. Sch.***	**D1**	**D2**	**D3**	**D NG**	***Het. Sch.***
12-17	3	1	2	0	0	*0*	0	0	0	0	*0*
18-29	169	13	97	1	28	*2*	2	25	0	3	*0*
30-39	68	3	37	0	11	*1*	3	9	0	5	*1*
40-49	28	3	12	1	4	*0*	1	6	0	1	*0*
50-59	24	1	13	0	1	*0*	3	4	0	2	*0*
60-69	7	2	4	0	0	*0*	0	0	0	1	*0*
70-79	5	0	2	0	0	*0*	0	3	0	0	*1*
80+	1	1	0	0	0	*0*	0	0	0	0	*0*
NS	4	1	3	0	0	*0*	0	0	0	0	*0*
Total	**309**	**25**	**170**	**2**	**44**	*3*	**9**	**47**	**0**	**12**	*2*

D1: Dose 1; D2: Dose 2; NS: not specified; Het. Sch.: heterologous vaccine schedule (included in D2 and/or D3); Time in days from vaccination to reaction (time to onset, TTO): median 3 days, average 9.5 days (range 0 to 174 days). [1] Reports missing gender information with or without age information were included in the total

6.2.2. Time between vaccination and first symptoms

The length of time between mRNA vaccination and first symptoms of myocarditis or pericarditis is shown to peak a few days after vaccination (figures 6 and 7). A causal link between vaccination and myocarditis or pericarditis is doubtful when the time period is very long. This conclusion is drawn from current data and is in accordance with scientific literature.

Figure 6: Time in days between vaccination with Comirnaty and appearance of myocarditis/pericarditis (all reports with time period information) after the first, second, and third vaccinations (D1-3)

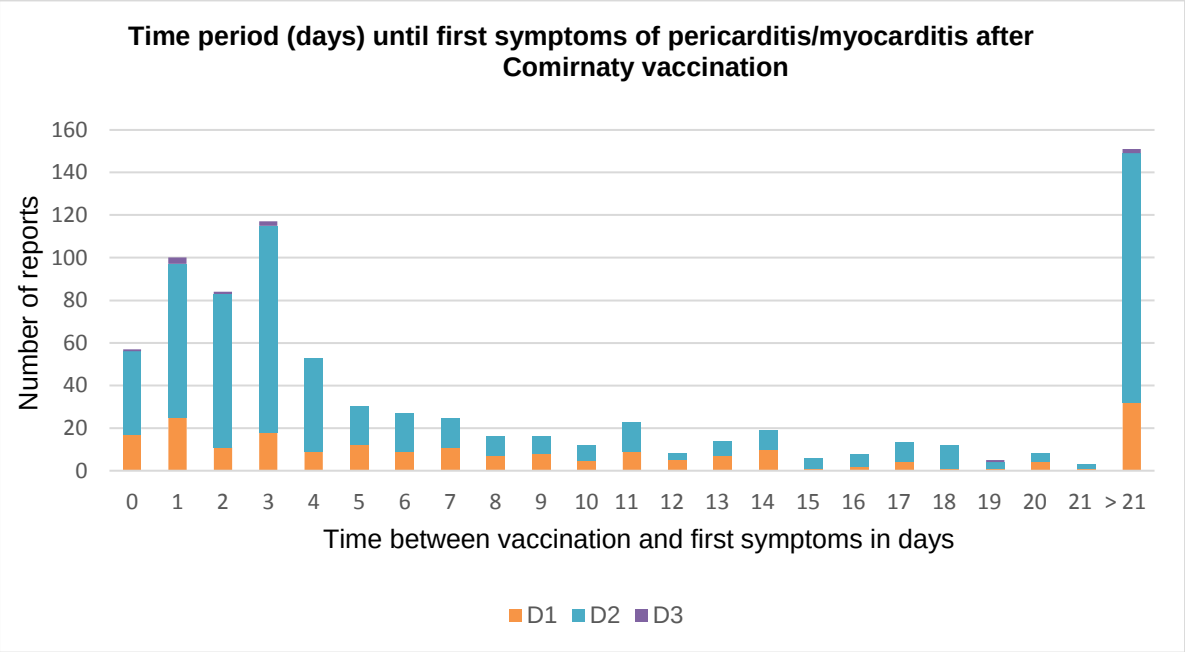
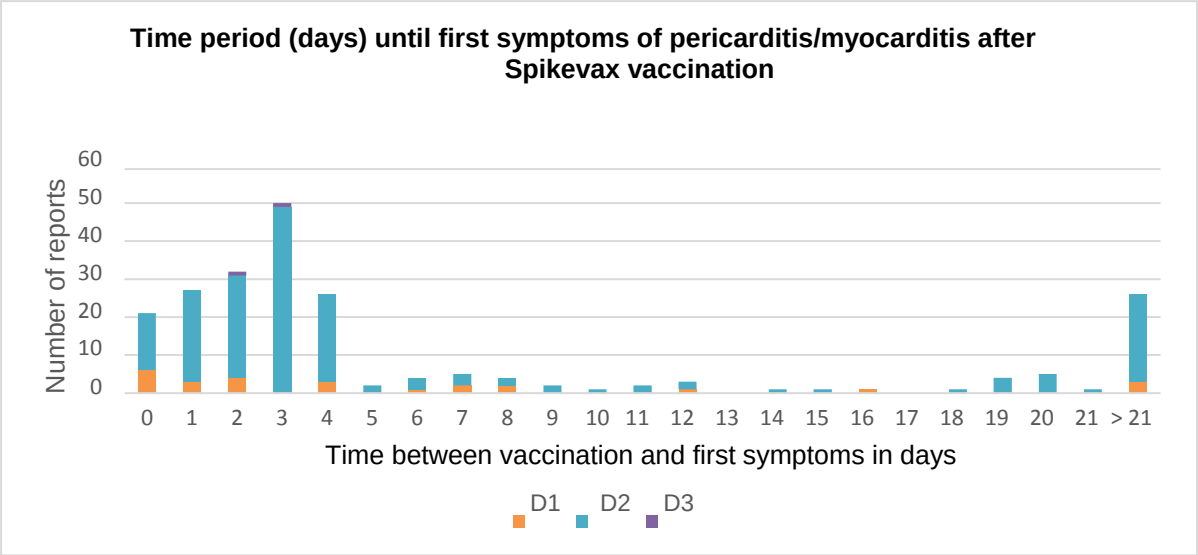


Figure 7: Time in days between vaccination with Spikevax and appearance of myocarditis/pericarditis (all reports with time period information) after the first, second, and third vaccinations (D1-3)



6.2.3 Reporting rate (imputation of missing information on dose)

The reporting rate of myocarditis and pericarditis after Comirnaty is highest among male adolescents and young men (18-29 years) after the second vaccination, with 8.97 and 8.68 cases per 100,000 vaccine doses, respectively (imputation of missing dose information, see methodology for explanation). In comparison, the reporting rate for female adolescents and young women in the same age group after Comirnaty is significantly lower, with 0.76 and 1.53 cases per 100,000 vaccine doses, respectively.

The reporting rate for Spikevax was highest among young men (18-29 years) after the second dose, with 25.60 cases per 100,000 vaccinations. Due to the low case number (n=3), a calculation of the reporting rate for 12- to 17-year-old children and adolescents was not useful for an evaluation. The reporting rate of myocarditis/pericarditis among young women (18-29 years) after second vaccination was 5.77 cases per 100,000 vaccine doses. There were no cases reported after the first dose among female adolescents.

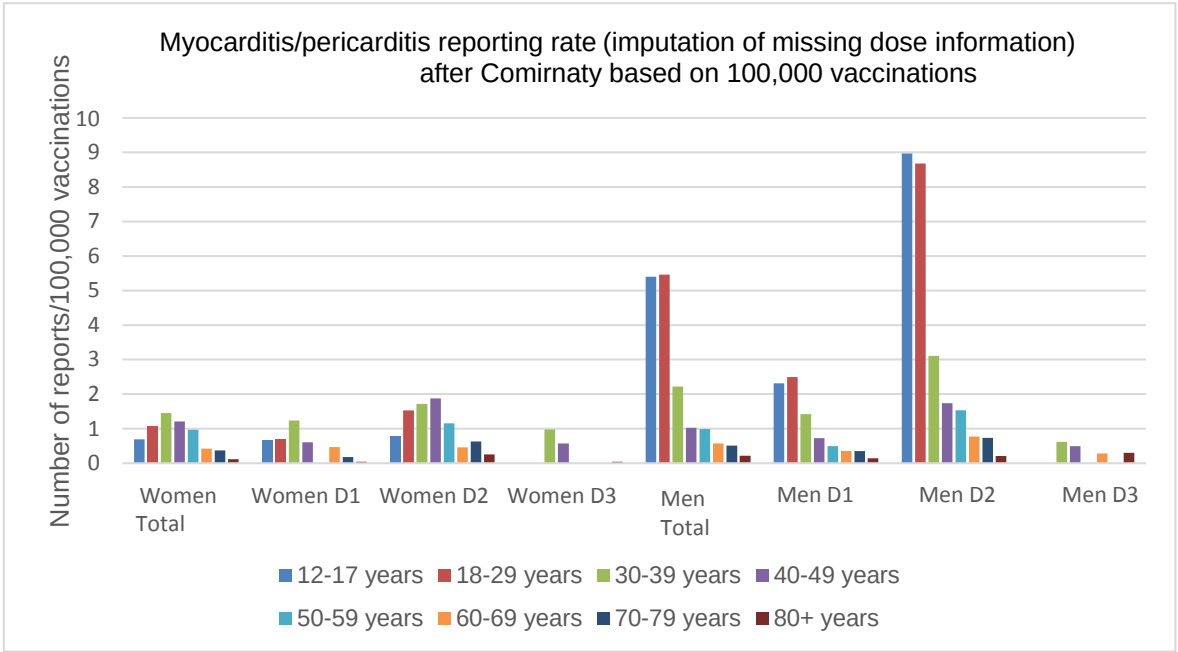
The reporting rate decreases as age increases among both genders for both vaccines. This results in a total reporting rate for all age groups and all Comirnaty vaccinations of 0.79 cases per 100,000 vaccinations among women and

1.50 cases per 100,000 vaccinations among men. For Spikevax the total reporting rate is 1.28 cases per 100,000 vaccinations among women and 4.60 cases per 100,000 vaccinations among men. The higher total reporting rate after Spikevax is primarily due to a higher reporting rate among young adults. The STIKO recommends vaccination with Comirnaty for the < 30 age group as a precaution.

6.2.4. Myocarditis/pericarditis and booster vaccination

To date there have been very few reports of myocarditis/pericarditis submitted after a third mRNA vaccination (booster vaccination). The current reporting rates of myocarditis/pericarditis are significantly lower than those after the first or second vaccination. Figure 8 shows the reporting rates in comparison to primary vaccination for the example of Comirnaty. As there were only two cases reported for Spikevax after booster vaccination, it is not practical to present the data separately.

Figure 8: Reporting rate of myocarditis/pericarditis by age, gender, and first, second, third vaccine dose (D1-D3) of Comirnaty based on 100,000 vaccinations (imputation of missing dose information)



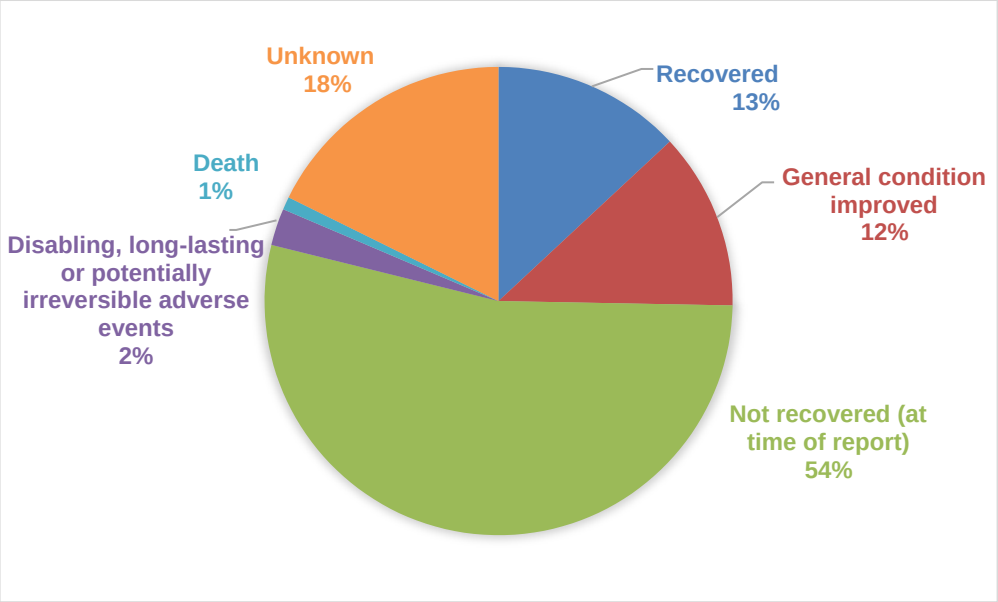
6.2.5. Myocarditis and pericarditis after adenovirus-based vector vaccines

There were 69 cases of myocarditis/pericarditis reported with a temporal association to the Vaxzevria vaccine (17.39% isolated pericarditis) and 35 cases after COVID-19 Vaccine Janssen (17.14% isolated pericarditis).

6.2.6 Outcome of adverse reactions

Figure 9 shows the outcomes of reported cases of myocarditis/pericarditis after receiving one of the four COVID-19 vaccines used in Germany.

Figure 9: Outcome of reports of myocarditis/pericarditis after COVID-19 vaccination



There were 15 deaths reported with a temporal association to COVID-19 vaccination: eight after Comirnaty, five after Spikevax, and one each after Vaxzevria and COVID-19 Vaccine Janssen. In three cases (two Comirnaty after second vaccination, one Vaxzevria after first vaccination), the link to vaccination was evaluated as possible based on the autopsy report. For all of the other cases, the Paul-Ehrlich-Institut does not see a causal link to the vaccination based on

currently available data. This evaluation resulted from either a higher probability of an alternative cause of death upon overall assessment of all the information or missing important clinical information.

6.3. Thrombosis with thrombocytopenia syndrome

A very rare, and in a few cases fatal, new syndrome has been reported as a serious adverse event of the Vaxzevria and COVID-19 Vaccine Janssen vector vaccines. The syndrome is characterised by venous and/or arterial thromboses in combination with thrombocytopenia (thrombosis with thrombocytopenia syndrome, TTS). In such cases, the thromboses often appear in unusual locations, such as cerebral or mesenteric veins, or veins in the spleen or liver. High concentrations of antibodies against platelet factor 4 (anti-PF4 antibodies) were detected in several of the affected patients, as well as a high level of thrombocyte activation during clotting tests.

As thrombosis with concurrent thrombocytopenia can be a symptom of multiple illnesses, various case definitions for this new syndrome have been published. The Centers of Disease Control and Prevention (CDC) in the US have developed a pragmatic case definition, which the Paul-Ehrlich-Institut also uses. According to this definition, a case of TTS is indicated by thromboses occurring in an unusual location (e.g., sinus veins) with concurrent thrombocytopenia (< 150 G/L), or by thrombosis in a common location (e.g., pulmonary embolism) with evidence of antibodies against platelet factor 4 (anti-PF4 antibodies).

Table 8 shows the reported cases of thrombosis with concurrent thrombocytopenia after COVID-19 vaccination.

Table 8: Thrombosis with thrombocytopenia after each of the COVID-19 vaccines

	Number of reports of thrombosis with thrombocytopenia	Fulfills CDS TTS criteria	Positive for anti-PF4 antibodies	Reporting rate of thrombosis with thrombocytopenia per 100,000 vaccinations
Comirnaty	36	4	0	0.037
Spikevax	5	1	0	0.047
Vaxzevria	200 [1,2]	137	90	1.574 (D2: 0.260 [3])
COVID-19 Vaccine Janssen	24	13	6	0.693

[1] One case negative for anti-PF4 antibodies, [2] one case negative for anti-PF4 antibodies, and negative HIPA and PIPA tests, [3] nine reports of TTS after second Vaxzevria vaccination, five of which fulfil the CDC criteria.

A total of 31 people died due to thrombosis with thrombocytopenia after vaccination with Vaxzevria and seven after vaccination with COVID-19 Vaccine Janssen. Based on the information currently available, 29 of the 38 reports of a fatal outcome of thrombosis with thrombocytopenia fulfilled the CDC criteria.

Four people died due to thrombosis with thrombocytopenia after vaccination with Comirnaty. One patient died after vaccination with Spikevax. The CDC criteria were not fulfilled in any of the fatal outcomes reported after mRNA vaccination. Anti-PF4 antibodies were not documented in any of the cases.

6.4. Guillain-Barré Syndrome (GBS)

GBS is an acute inflammation of the peripheral nervous system and the nerve roots (polyradikuloneuritis). In most cases, the symptoms eventually recede. However, some patients experience symptoms for an extended period of time. Neurological residual symptoms, disabling, long-lasting or potentially irreversible adverse events, or death can also occur. Miller-Fisher Syndrome (MFS) is a rare variant of GBS and is characterized by ataxia (disruption of motor coordination), paralysis of the eye muscles, and loss or weakening of muscular reflexes.

A total of 314 cases of GBS/MFS were reported to the Paul-Ehrlich-Institut (see table 9 for age distribution; see table 10 for BC levels[40] evaluation). There were two fatal cases after Vaxzevria, five after Comirnaty, and one after Moderna. Twenty-four patients (n=8 Vaxzevria, n=13 Comirnaty, n=1 Spikevax, n=2 Janssen) needed to be treated in intensive care units, some receiving invasive ventilation. Five cases of GBS were reported after booster vaccination with Comirnaty. The affected patients (4 men, 1 woman) were between 51 and 88 years old.

Table 9: Age distribution of reported GBS/MFS cases after COVID-19 vaccination and reporting rate per 100,000 vaccinations

Age in years	Comirnaty		Spikevax		Vaxzevria		COVID-19 Vaccine Janssen	
	Total GBS/MFS cases	GBS/MFS cases within 42 days	Total GBS/MFS cases	GBS/MFS cases within 42 days	Total GBS/MFS cases	GBS/MFS cases within 42 days	Total GBS/MFS cases	GBS/MFS cases within 42 days
12-17	4	3	0	0	0	0	0	0
18-29	11	9	0	0	4	3	4	2
30-39	21	18	1	1	10	9	4	4
40-49	15	12	2	1	16	16	8	5
50-59	24	20	3	1	37	30	16	14
60-69	27	22	3	3	26	24	11	11
70-79	16	13	2	2	15	13	1	0
80+	14	10	3	3	2	2	2	2
Unknown	8	2	0	0	2	1	2	1
Booster	5	4	0		0		0	
Total	140	109	14	11	112	98	48	39
Reporting rate/100,000 vaccinations	0.145		0.132		0.882		1.387	

Note: A time period of up to 42 days after vaccination is considered biologically plausible

Table 10: Number of reported GBS/MFS cases by vaccine in accordance with the Brighton Collaboration (BC) case definition

	Comirnaty	Spikevax	Vaxzevria	COVID-19 Vaccine Janssen	Total
BC level 1	**23**	**4**	**40**	**19**	**85**
BC level 2	**12**	**3**	**11**	**2**	**28**
BC level 3	**4**	**0**	**6**	**2**	**11**
Total BC levels 1-3	**39**	**7**	**57**	**23**	**124**
BC level 4	**101**	**7**	**55**	**25**	**190**
Total BC levels 1-4	**140**	**14**	**112**	**48**	**314**

GBS is a known adverse event associated with both adenoviral vector vaccines and is listed accordingly in the product information of these vaccines. A connection to the mRNA vaccine has not been established up to this point.

6.5. Thrombocytopenia/immune thrombocytopenia

Post-marketing authorisation reports indicate a connection between immune thrombocytopenia and vaccination with Vaxzevria and COVID-19 Vaccine Janssen. Table 11 shows an overview of the reports of thrombocytopenia/ immune thrombocytopenia with and without haemorrhages after the currently available COVID-19 vaccines. Petechiae were the most common haemorrhages. A few patients died due to a brain haemorrhage.

Table 11: Overview of suspected cases of thrombocytopenia/immune thrombocytopenia after COVID-19 vaccination by age group and total reporting rate per 100,000 vaccinations (Avg: average)

Age in years	Comirnaty		Spikevax		Vaxzevria		COVID-19 Vaccine Janssen	
	Total cases	Total cases with haemorrhages (deaths)	Total cases	Total cases with haemorrhages (deaths)	Total cases	Total cases with haemorrhages (deaths)	Total cases	Total cases with haemorrhages (deaths)
12-17	15	5						
18-29	29	2	3		23	2	3	
30-39	41	6	3	1	30	8 (1)	3	2
40-49	29	6	1		31	11	3	2
50-59	37	11 (1)	8	2	62	19 (2)	7	5 (1)
60-69	51	11	5	1	72	23 (2)	4	2
70-79	41	9 (1)	5	1	36	13 (1)	2	
80 +	49	14 (2)	2	1	7	4		
Unknown	22	10	1		8	1	1	1
Total	314[1]	74	28[2]	6	269	81	23	12
Women	166	42 (4)	15	5	153	46 (4)	9	2
Men	147	32	11	1	116	35 (2)	14	10 (1)
Avg age (years)	53.8		56		55		45	
Reporting rate	0.33		0.27		2.12		0.66	

[1] One Comirnaty case did not include information on the patient's gender
[2] Two Spikevax cases did not include information on the patient's gender

An observed versus expected analysis of the reports of thrombocytopenia/ immune thrombocytopenia within 30 days of vaccination, which was completed using a background incidence rate calculated in England[41], indicated that more cases were reported within 30 days of vaccination with Vaxzevria as would have been expected based on the background incidence rate (SMR 3.8; 95 % CI 3.6-4.1). A slightly high but not significant estimator was calculated for COVID-19 Vaccine Janssen (SMR 1.19; 95 % CI 0.71-1.88). There was no safety signal for either of the mRNA vaccines (Comirnaty SMR 0.68, 95 % CI 0.59-0.78; Spikevax SMR 0.73, 95 % CI 0.47-1.09).

7. Additional analyses

Table 12 shows additional observed versus expected analyses. The total reports of pulmonary embolisms, myocardial infarctions, transverse myelitis, and herpes

zoster (HZ) after 14, 30, and 42 days were lower than would be statistically expected. There was a safety signal indicated for cerebral venous sinus thromboses (CVST) without concurrent thrombocytopenia for Vaxzevria. Venous sinus thrombosis was recently added as an adverse event in the Vaxzevria product information. However, it cannot be ruled out that individual cases actually correspond to cases of TTS and that the number of thrombocytes was not included in the report. It is also possible that increased overall awareness of venous sinus thromboses after Vaxzevria could have led to a higher reporting rate.

Table 12: Observed versus expected analysis of selected adverse events

			Comirnaty		Spikevax		Vaxzevria		COVID-19 Vaccine Janssen	
AESI	Incidence cases per 100,000 PY	Time between vaccination and start of symptoms	Number of cases	SMR 95% CI	Number of cases	SMR 95% CI	Number of cases	SMR 95% CI	Number of cases	SMR 95% CI
Pulmonary embolism ≥18 years	81 [1]	14	381	0.13 (0.12-0.15)	60	0.18 (0.14-0.24)	174	0.44 (0.39-0.51)	28	0.26 (0.17-0.38)
		30	521	0.085 (0.078-0.093)	81	0.12 (0.09-0.14)	238	0.28 (0.25-0.32)	38	0.17 (0.12-0.23)
		42	570	0.066 (0.061-0.072)	84	0.086 (0.068-0.11)	273	0.23 (0.20-0.26)	43	0.13 (0.10-0.18)
Myocardial infarction	334.7 [2]	14	205	0.017 (0.014-0.019)	22	0.017 (0.010-0.025)	65	0.040 (0.031-0.051)	9	0.020 (0.009-0.038)
		30	259	0.010 (0.009-0.011)	28	0.010 (0.006-0.014)	84	0.024 (0.019-0.030)	14	0.015 (0.008-0.025)
		42	276	.0074 (0.0066-0.0084	29	0.007 (0.005-0.0010)	87	0.018 (0.014-0.022)	16	0.012 (0.007-0.019)
CSVT ≥18 years	1.9 [3]	14	68	1.01 (0.79-1.28)	6	0.78 (0.29-1.7)	73	7.89 (6.19-9.93)	3	1.19 (0.25-3.48)
		30	104	0.72 (0.59-0.88)	12	0.73 (0.38-1.28)	97	4.9 (3.97-5.97)	7	1.30 (0.52-2.67)
		42	113	0.56 (0.46-0.67)	12	0.52 (0.27-0.91)	106	3.82 (3.13-4.62)	7	0.93 (0.37-1.91)
Transverse myelitis	0.97 [4]	14	4*	0.11 (0.03-0.29)	0	-	0	-	0	-
		30	7*	0.09 (0.04-0.19)	0	-	4	0.40 (0.11-1.01)	2	0.72 (0.09-2.62)
		42	7*	0.06 (0.03-0.13)	0	-	5	0.35 (0.11-0.82)	2	0.52 (0.06-1.87)
HZ total	575 [6]	14	818	0.038 (0.036-0.041)	177	0.075 (0.065-0.087)	172	0.061 (0.052-0.071)	13	0.017 (0.009-0.029)
		30	1109	0.024 (0.023-0.026)	149	0.030 (0.025-0.035)	236	0.039 (0.034-0.044)	19	0.012 (0.007-0.018)
		42	1203	0.019 (0.018-0.020)	156	0.022 (0.019-0.026)	256	0.030 (0.027-0.034)	21	0.009 (0.006-0.014)
HZ 12-17 years	318 [5]	14	16	0.029 (0.017-0.048)	1	0.19 (0.01-1.04)	0	-	0	-
		30	23	0.020 (0.013-0.030)	1	0.09 (0.002-0.48)	0	-	0	-
		42	25	0.015 (0.010-0.023)	1	0.06 (0.002-0.35)	0	-	0	-

SMR: Standardized Morbidity Ratio

[1]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

[2]Keller K 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]Jacob et 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]Williame et al. (2021) Incidence Rates of Autoimmune Diseases in European Healthcare Databases: A Contribution of the ADVANCE Project. Drug Safety 44:383–395, https://doi,org/10,1007/s40264-020-01031-1, EUROPE, Overall

[6]Utsch et al. (2013) Epidemiology and cost of herpes zoster and postherpetic neuralgia in Germany. Eur J Health Econ. 2013 Dec;14(6):1015-26. doi: 10.1007/s10198-012-0452-1

7.1. Hepatitis/autoimmune hepatitis

Some cases of hepatitis or immune hepatitis with a temporal association to the administration of a COVID-19 vaccine were reported in the referenced literature, including a case after a Spikevax vaccination in England with positive re-exposure.[42-48] Table 13 shows an evaluation of the reported cases of hepatitis or autoimmune hepatitis following vaccination with the vaccines available in Germany. The Paul-Ehrlich-Institut will continue to monitor hepatitis and autoimmune hepatitis in temporal association with the COVID-19 vaccines.

Table 13: Reports of hepatitis/autoimmune hepatitis with temporal association to COVID-19 vaccination

	Number (n) of hepatitis cases (including n reports of autoimmune hepatitis)							
	Comiranty		**Spikevax**		**Vaxzevria**		**COVID-19 Vaccine Janssen**	
Age group	Men	Women	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
12-17 years	1							
18-29 years	1					1		
30-39 years	1	2 (1)		2 (2)		1	1	
40-49 years	2	2 (1)	1		2		1 (1)	
50-59 years	4 (2)	8 (3)			1	2		
60-69 years	4	3 (2)			1	3 (1)		
70-79 years	1	4 (1)	1 (1)					
80+ years	1	1		1	1			
Unknown	1	2 (1)				1		
Total	16 (2)	22(9)	2 (1)	3 (2)	5	8 (1)	2 (1)	0
TTO (Days) Min, Max	10 (0-33 D)	16 (0-41 D)	5 D, 22 D	0 D, 42 D, unk.	9 (1-19 D)	13 (9-25 D)	0.3 D	
Vaccine dose	D1: n=4 D2: n=8 Unk: n=4	D1: n=3 D2: n=14 D3: n=1 Unk: 4	D1: n=1 D2: n=2	D1: n=2 Unk: n=1	D1: n=3 Unk :n=2	D1: n=1 D2: n= 2 Unk: n=10	D1: 2	-
Reporting rate of all age groups, men and women	0.4 / 1 Mill. vaccinations		0.5 / 1 Mill. vaccinations		1.0 / 1 Mill. vaccinations		0.6 / 1 Mill. vaccinations	

TTO (time to onset): time interval between vaccination and first symptoms, Min: Minimum, Max: Maximum, T: days, D1: first vaccine dose, D2: second vaccine dose, D3: third vaccine dose, 1 Mill.: 1 million; unk: unknown

8. SafeVac 2.0 survey

A total of 725,541 people with at least one vaccine dose had registered for the survey taken via the SafeVac 2.0 app as of 30 November 2021. The app is intended to monitor the safety of COVID-19 vaccines. The number of participants is equal to 1.2% of vaccinated individuals based on the total of 59,407,188 first vaccinations as of 30 November 2021. Severe reactions were reported in 2,827 reports (39%).

The most commonly reported adverse events were temporary pain at the injection site, fatigue, headache, malaise, muscle pain, dizziness, swelling at the injection site, chills, fever, and joint pain.

As of 30 November 2021, 20,005 users had submitted data on booster vaccinations. These reports described only non-severe reactions. The most commonly reported adverse events after booster vaccination were temporary pain at the injection site, fatigue, headache, muscle pain, malaise, fever, swelling at the injection site, dizziness, joint pain, and chills.

There are now also 835 adolescents between the ages of 12 and 17 registered for the app.

9. Appendix

9.1. Methodology

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.

A suspected case report can include multiple adverse reactions, such as fever plus headache plus pain at the injection site.

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 to a certain extent.

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 report, regardless of the causal link to the vaccination.

The Paul-Ehrlich-Institut focuses on specific topics in each safety report in order to provide an overview. Due to rounding up or down, the sum of percentages in some charts and in the text may not add up to 100.

Reports of adverse events after vaccination with a COVID-19 vaccine are received by the Paul-Ehrlich-Institut via the local public health departments in accordance with the German Infection Protection Act (Infektionsschutzgesetz, IfSG). Physicians are legally obligated to notify their local 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 local 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, the marketing authorisation holders via the European Medicines Agency's (EMA) Eudravigilance database, as well as directly from doctors and vaccinated individuals or their family members. Reports are submitted by mail, email, telephone, or online via either the Paul-Ehrlich-Institut's reporting portal (www.nebenwirkungen.bund.de) or the EMA's EudraVigilance database. Reports on one particular suspected case may therefore be submitted by multiple sources, which can lead to an increase in the number of reports. Duplicate reports (reports on the same case from multiple sources) are merged by the Paul-Ehrlich-Institut into one case that contains all of the information on the report from the different sources. Identification of duplicate reports is not always possible due to their requisite pseudonomised nature. Additionally, the Paul-Ehrlich-Institut receives further information on previous reports on an ongoing basis. This means that numbers and evaluations contained in each of the safety reports may be altered, and that these changes may not necessarily be due to an increase in reports as the vaccination rate progresses over time.

Suspected case reports in which anaphylaxis or GBS is reported or in which characteristic symptoms are described that indicate an anaphylactic reaction or GBS are evaluated at the Paul-Ehrlich-Institut in accordance with the internationally-accepted Brighton Collaboration case definition[18, 40] with regards to diagnostic certainty. In some cases, this is performed after receiving specific additional information. Level 1 is the highest grade of diagnostic certainty and levels 2 and 3 are lower grades. Reports of anaphylactic reactions and/or GBS that do not correspond to levels 1-3 are considered to correspond to level 4 of diagnostic certainty if the information on clinical symptoms is not yet complete.

In the context of identifying possible new signals, the Paul-Ehrlich-Institut carries out observed versus expected (OE) analyses[49] 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, then the Paul-Ehrlich-Institut presumes the presence of a safety signal that should be examined further with additional studies. [50] An OE < 1 indicates that fewer studies were collected than was expected (marked green). It is important to note that an OE analysis can indicate a safety signal, however, this type of analysis is not suited for confirming the presence of risk. OE calculations included reports until 30 November 2021 for which the time interval between vaccination and the first symptoms (time to onset, TTO) is known.

The background incidence rate for myocarditis was determined on the basis of patient data in the Institute for Applied Health Research (InGef) database. Data from patients with at least one inpatient or outpatient diagnosis of myocarditis I41, I40, I51.4, I01.2 or I09.0 was used. The resulting estimators are lower if the determination of the background incidence rate is limited to patient data in the InGef database regarding patients with at least one inpatient or outpatient diagnosis of myocarditis I40. If these estimators are used for the OE analysis, it results in a higher SMR. It is also important to take the potential for annual fluctuations in age-specific or gender-specific incidence rates into account. The incidence rate from 2020, during the pandemic, was chosen because SARS-CoV-2 infections were also linked to myocarditis.

The following aspects pose limitations for an observed versus expected analysis: variance in the information on background incidence rates in the original source literature, 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. Additionally, age stratification can only be carried out when relevant reference data on background incidence rate in individual age groups is available. 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 November 2021 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.

The imputation method was used to fill in missing details and include them in the respective calculations. For example, when information on the vaccine dose number was missing, it was assumed that the proportion of first to second doses

contained in the reports missing information on the dose number matches the proportion in reports containing this information.

The Paul-Ehrlich-Institut is conducting a survey on the tolerability of the COVID-19 vaccines with the SafeVac 2.0 App. Vaccinated individuals who volunteer to participate are surveyed multiple times over a period of three or four weeks after each vaccination on the safety of COVID-19 vaccines. They are surveyed again at six and twelve months after the last vaccination in regards to the level of protection they received. The survey has now been expanded to include the booster dose and to allow for participation of adolescents from 12 to 17 years of age with the authorisation of a parent or guardian. This survey is taking place as part of an observational study over a twelve month period.

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