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

Paul-Ehrlich-Institut

Langen, 7 February 2022

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 31 December 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 31 December 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 the Robert Koch Institute (RKI), 148,760,720 vaccinations were carried out through 31 December 2021, of which 110,533,639 were vaccinations with Comirnaty, 21,912,123 vaccinations with Spikevax, 12,738,494 vaccinations with Vaxzevria and 3,576,464 vaccinations with COVID-19 Vaccine Janssen. A total of 244,576 suspected adverse events were reported after Comirnaty, Spikevax, Vaxzevria and COVID-19 Vaccine Janssen. The combined reporting rate for all vaccines was 1.64 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 21 December 2020. The 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 29 January 2021. Vaccinations with this vaccine began in Germany at the beginning of February 2021. COVID-19 Vaccine Janssen (Johnson & Johnson) was authorised on 11 March 2021. This vaccine is also an adenovirus vector-based vector vaccine. Vaccinations with this vaccine began in Germany at the end of April 2021. Nuvaxovid was authorised for use in the EU on 20 December 2021. Nuvaxovid (NVX-CoV2373, Novavax CZ a.s.) is a protein-based vaccine. Vaccinations with this vaccine have not yet begun.

According to data from the RKI, 148,760,720 vaccinations with the four authorised COVID-19 vaccines named above were administered in Germany. For a year 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.

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

- The reporting rate of suspected adverse events after vaccination with the two mRNA vaccines predominantly in use in Germany through 31 December 2021 is 1.3 per 1,000 vaccinations for Comirnaty and 1.9 per 1,000 vaccinations for Spikevax. The overall reporting rate of case reports classified as serious was 0.2 and 0.1 per 1,000 vaccinations with Comirnaty or Spikevax, respectively.

- The evaluation of the reports that contained information on the vaccination dose numbers indicates a lower reporting rate for booster vaccination compared to primary immunisation.

- The suspected adverse events among children aged 5 to 11 years reported up to the cut-off date for the analysis mainly concern mild and temporary vaccination reactions.

- Myocarditis and pericarditis are serious, very rare risks connected to Comirnaty and Spikevax (less than one case per 10,000 people). Young men and male children and adolescents aged 12 to 17 years are particularly affected after the second dose.[1-18] The first symptoms typically appear within a few days of vaccination. The published data[1-18] indicates a predominantly mild disease progression, meaning that the majority of patients with myocarditis/pericarditis after vaccination with mRNA vaccines respond well to treatment and rest and recover quickly, even if in individual cases more severe and also fatal outcomes were observed.
  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 German Standing Committee on Vaccination (STIKO) recommends Comirnaty for people < 30 years as a precaution.
  Individual reports of myocarditis/pericarditis were reported to the Paul-Ehrlich-Institut following third mRNA vaccinations (booster vaccinations), whereby, as of 31 December 2021, the reporting rate of myocarditis/pericarditis after booster vaccination is lower than after primary immunisation. Young men aged 18 to 29 may be affected slightly more often than older people.

- Anaphylactic reactions (Brighton Collaboration BC Level 1-4)[19] are very rarely observed side effects of all four approved COVID-19 vaccines. The reporting rate of anaphylaxis among women, especially after first vaccination, is higher overall than among men, at around one case per 100,000 vaccinations. 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, most of the affected patients were able to be vaccinated again at low risk after allergological testing.

- The comparison of the number of cases reported to the Paul-Ehrlich-Institut of heart attacks or strokes occurring at 14, 30 and 42 days after vaccination with the number of heart attacks or strokes that would be statistically expected in the vaccinated population did not result in a safety signal for the four vaccines. This is due to the fact that the reported number of heart attacks and strokes was lower than the statistically expected value. The same applies to reports of pulmonary embolisms.

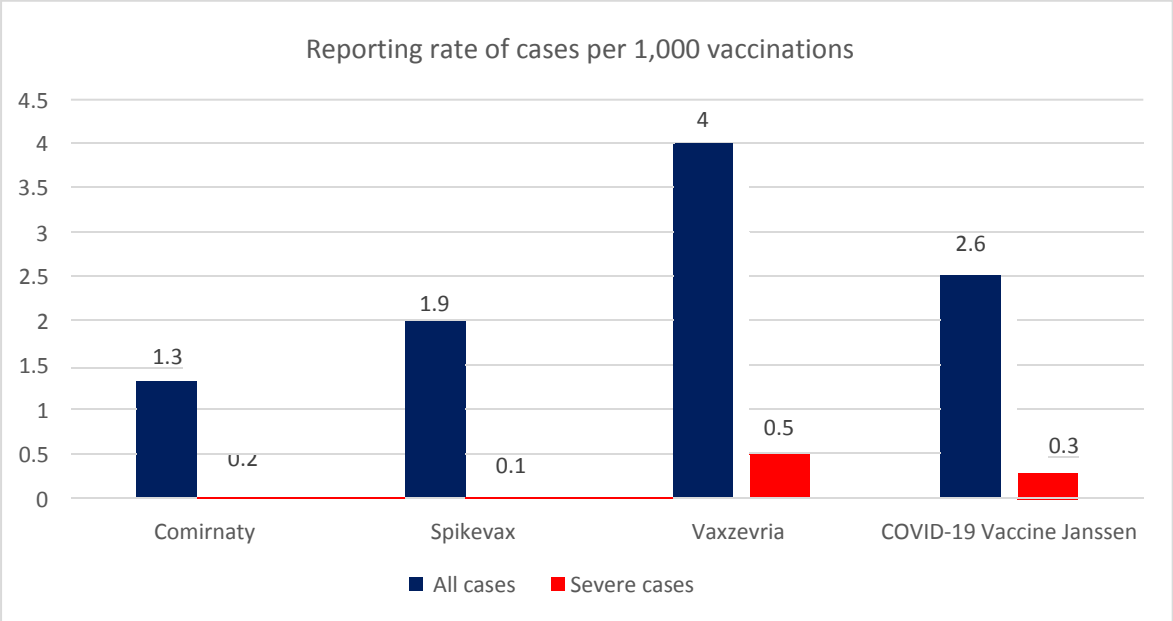
- As in previous evaluations, a safety signal was detected for very rare sinus vein thromboses (without simultaneous thrombocytopenia) after Vaxzevria, but not after the two mRNA vaccines. Sinus vein thrombosis is included as an adverse event in the product information for Vaxzevria. The Pharmacovigilance 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. A higher proportion of VTE cases were observed in the vaccinated group than in the placebo group in one of two major clinical trials.

3. Suspected case reports and reporting rate of adverse events and vaccine-related complications

3.1. Overview

As of 31 December 2021, a total of 244,576 individual case reports of suspected adverse events or vaccination complications after vaccination with COVID-19 vaccines in Germany were registered in the Paul-Ehrlich-Institut's database of adverse events, of which 141,894 suspected reports were based on Comirnaty, 41,193 on Spikevax, 51,130 on Vaxzevria, and 9,426 after COVID-19 Vaccine Janssen. In 933 case reports, the vaccine was not specified. Figure 1 shows the respective reporting rate for suspected adverse events or vaccination complications per 1,000 vaccinations in the period from 27 December 2020 to 31 December 2021 in Germany for the various COVID-19 vaccines used so far in this country.

Figure 1: Reporting rate of suspected adverse events or vaccination complications per 1,000 vaccinations after vaccination with the respective COVID-19 vaccines

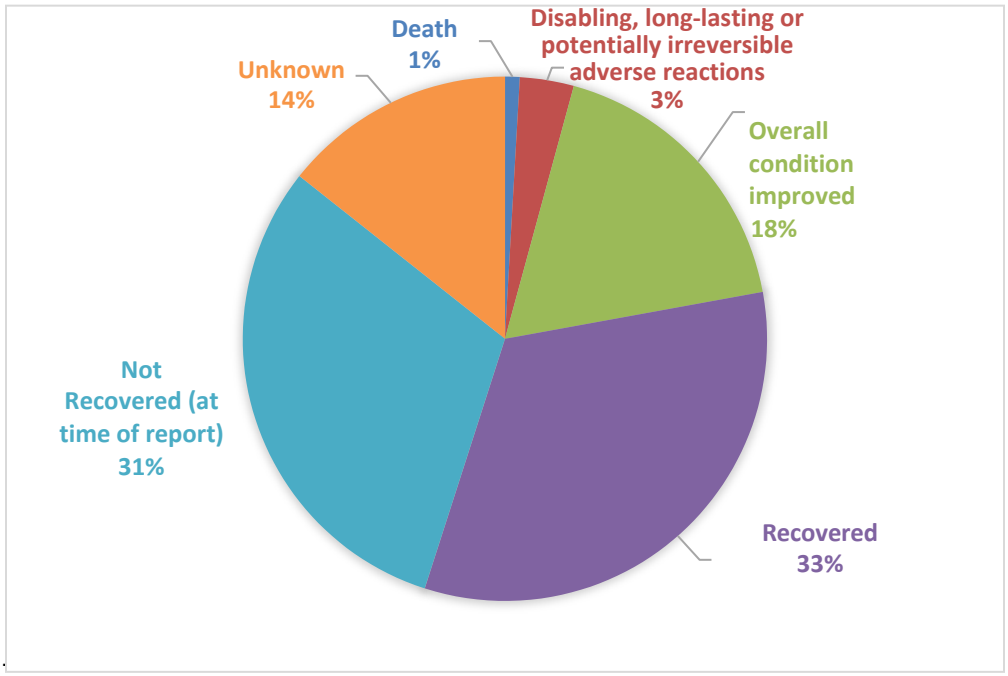


As reporting rates are influenced by many factors, including the age distribution of the vaccinated cohort and public awareness, a comparison of the total reporting rates of the different vaccines should be interpreted with caution.

3.2. Outcome of reported reactions

Figure 2 shows the outcome of suspected adverse events for the COVID-19 vaccines.

Figure 2: Outcome of the reported reactions as a percentage for the four COVID-19 vaccines used in Germany to date, presentation at case level



3.3. Reported severe adverse reactions

Serious adverse events were reported in 29,786 suspected cases. There were 19,444 suspected serious adverse events that occurred after vaccination with Comirnaty, 2,420 after vaccination with Spikevax, 6,541 after vaccination with Vaxzevria and 1,020 after vaccination with COVID-19 Vaccine

Janssen. The name of the vaccine was not provided in 361 suspected cases.

Fatal outcomes at varying points in time after vaccination (from 0 days to 234 days) were reported in 2,255 suspected case reports. In 85 of the cases in which patients died from known vaccination risks such as thrombosis with thrombocytopenia syndrome (TTS), bleeding due to immune thrombocytopenia, or myocarditis occurring within a logical time frame after vaccination, the Paul-Ehrlich-Institut evaluated a causal link with vaccination to be possible or probable.

Table 1: Number and reporting rate of suspected adverse events with a fatal outcome

Vaccine	**Deaths**	**Reporting rate of deaths per 1,000 vaccinations**
Comirnaty	1,671	0.02
Spikevax	125	0.01
Vaxzevria	325	0.03
COVID-19 Vaccine Janssen	57	0.02
Vaccine unknown	77	
Total	**2,255**	**0.02**

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 indicated a safety signal for any of the four COVID-19 vaccines used so far in Germany. This comparison also applies to booster vaccinations and sudden, unexpected deaths (Tables 2 and 3). Since the time between vaccination and first symptoms and/or time of death was not included in all reports, an additional analysis was carried out under the assumption that all deaths, even those occurring at an unknown or very long time after vaccination, occurred within a 30-day timeframe. Again, there was no safety signal for increased mortality for any of the four vaccines, as the Standardized Morbidity Ratio (SMR) was well below one (SMRs between 0.006-0.033; data not presented separately).

A study in the US found no increased mortality among people vaccinated with the COVID-19 vaccines authorised there (product equivalents of Comirnaty, Spikevax, COVID-19 Vaccine Janssen).[23]

Table 2: Observed versus expected analysis of deaths at varying time intervals after vaccination against COVID-19 reported to the Paul-Ehrlich-Institut; cases included in which vaccination took place by 31 December 2021 and for which the time interval between vaccination and start of symptoms is known. Background incidence rate according to the Federal Statistical Office: 1,240.97 per 100,000 person years.[1]

	Comirnaty		Spikevax		Vaxzevria		COVID-19 Vaccine Janssen	
Time interval between vaccination and start of symptoms	Total cases	SMR 95% CI	Total cases	SMR 95% CI	Total cases	SMR 95% CI	Total cases	SMR 95% CI
Total Deaths								
1 Day	365	0.097 (0.087-0.108)	34	0.046 (0.032-0.064)	49	0.113 (0.084-0.150)	9	0.074 (0.034-0.141)
2 Days	464	0.062 (0.056-0.068)	43	0.029 (0.021-0.039)	69	0.080 (0.062-0.101)	10	0.041 (0.020-0.076)
7 Days	772	0.029 (0.027-0.032)	71	0.014 (0.011-0.017)	130	0.043 (0.036-0.051)	20	0.024 (0.014-0.036)
14 Days	981	0.019 (0.018-0.020)	82	0.008 (0.006-0.010)	173	0.029 (0.024-0.033)	26	0.015 (0.010-0.022)
30 Days	1147	0.0102 (0.0096-0.0108)	93	0.004 (0.003-0.005)	215	0.017 (0.014-0.019)	30	0.008 (0.006-0.012)
42 Days	1187	0.0075 (0.0071-0.0080)	94	0.003 (0.002-0.004)	219	0.012 (0.011-0.014)	35	0.007 (0.005-0.010)
Deaths after booster vaccination								
1 Day	45	0.066 (0.048-0.088)	8	0.021 (0.009-0.041)	-	-	*	
2 Days	56	0.041 (0.031-0.053)	10	0.013 (0.006-0.024)	-	-		
7 Days	89	0.019 (0.015-0.023)	17	0.006 (0.004-0.010)	-	-		
14 Days	97	0.010 (0.008-0.012)	18	0.003 (0.002-0.005)	-	-		
30 Days	107	0.005 (0.004-0.006)	18	0.0015 (0.0009-0.0024)	-	-		
42 Days	110	0.004 (0.003-0.005)	22	0.0013 (0.0008-0.0020)	-	-		

[1]Data from the Federal Statistical Office (extracted on 19 January 2022): 982,792 deaths among those aged 5 years and above in 2020; Population (age groups: 5 years old and above in 2020): 79,195,618. *One death was recorded after booster vaccination with COVID-19 Vaccine Janssen with a time period of 32 days between vaccination and start of symptoms reported, CI: confidence interval

Table 3: Observed versus expected analysis of unexplained deaths after vaccination against COVID-19; cases included in which vaccination took place by 31 December 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 according to the Federal Statistical Office 39.84/ 100,000 person years

	Comirnaty		Spikevax		Vaxzevria		COVID-19 Vaccine Janssen	
Time interval between vaccination and start of symptoms	Total cases	SMR 95% CI	Total cases	SMR 95% CI	Total cases	SMR 95% CI	Total cases	SMR 95% CI
ICD-10 causes of death I46.1, + R96-R99 total								
1 Day	102	0.85 (0.69-1.03)	11	0.46 (0.23-0.82)	15	1.08 (0.60-1.78)	1	0.26 (0.01-1.43)
2 Days	135	0.56 (0.47-0.66)	13	0.27 (0.14-0.47)	20	0.72 (0.44-1.11)	2	0.26 (0.03-0.93)
7 Days	227	0.27 (0.24-0.31)	24	0.14 (0.09-0.21)	34	0.35 (0.24-0.49)	4	0.15 (0.04-0.38)
14 Days	297	0.18 (0.16-0.20)	27	0.08 (0.05-0.12)	45	0.23 (0.17-0.31)	5	0.09 (0.03-0.21)
30 Days	344	0.10 (0.09-0.11)	28	0.04 (0.03-0.06)	54	0.13 (0.10-0.17)	6	0.05 (0.02-0.11)
42 Days	352	0.07 (0.06-0.08)	28	0.03 (0.02-0.04)	54	0.09 (0.07-0.12)	7	0.04 (0.02-0.09)
ICD-10 causes of death I46.1, + R96-R99 booster vaccination								
1 Day	16	0.73 (0.42-1.18)	3	0.24 (0.05-0.70)	-	-	*	
2 Days	20	0.45 (0.28-0.70)	3	0.12 (0.02-0.35)	-	-		
7 Days	34	0.22 (0.15-0.31)	7	0.08 (0.03-0.17)	-	-		
14 Days	37	0.12 (0.08-0.17)	8	0.05 (0.02-0.09)	-	-		
30 Days	40	0.06 (0.04-0.08)	8	0.02 (0.01-0.04)	-	-		
42 Days	40	0.04 (0.03-0.06)	8	0.02 (0.01-0.03)	-	-		

[1] Cause of death statistics for the reporting year 2020 (extracted on January 19, 2022): 31,552 deaths from ICD-10 causes of death I46.1, R96-R99, population (age groups: 5 years and older in 2020): 79,195,618. *no cases of unexplained deaths after booster vaccination with COVID-19 Vaccine Janssen CI: confidence interval

3.4. Reports of suspected cases after booster vaccination

A booster vaccination has been authorised for Comirnaty, Spikevax and COVID-19 Vaccine Janssen. The STIKO now recommends booster vaccination with an mRNA vaccine for all individuals aged 12 and over.

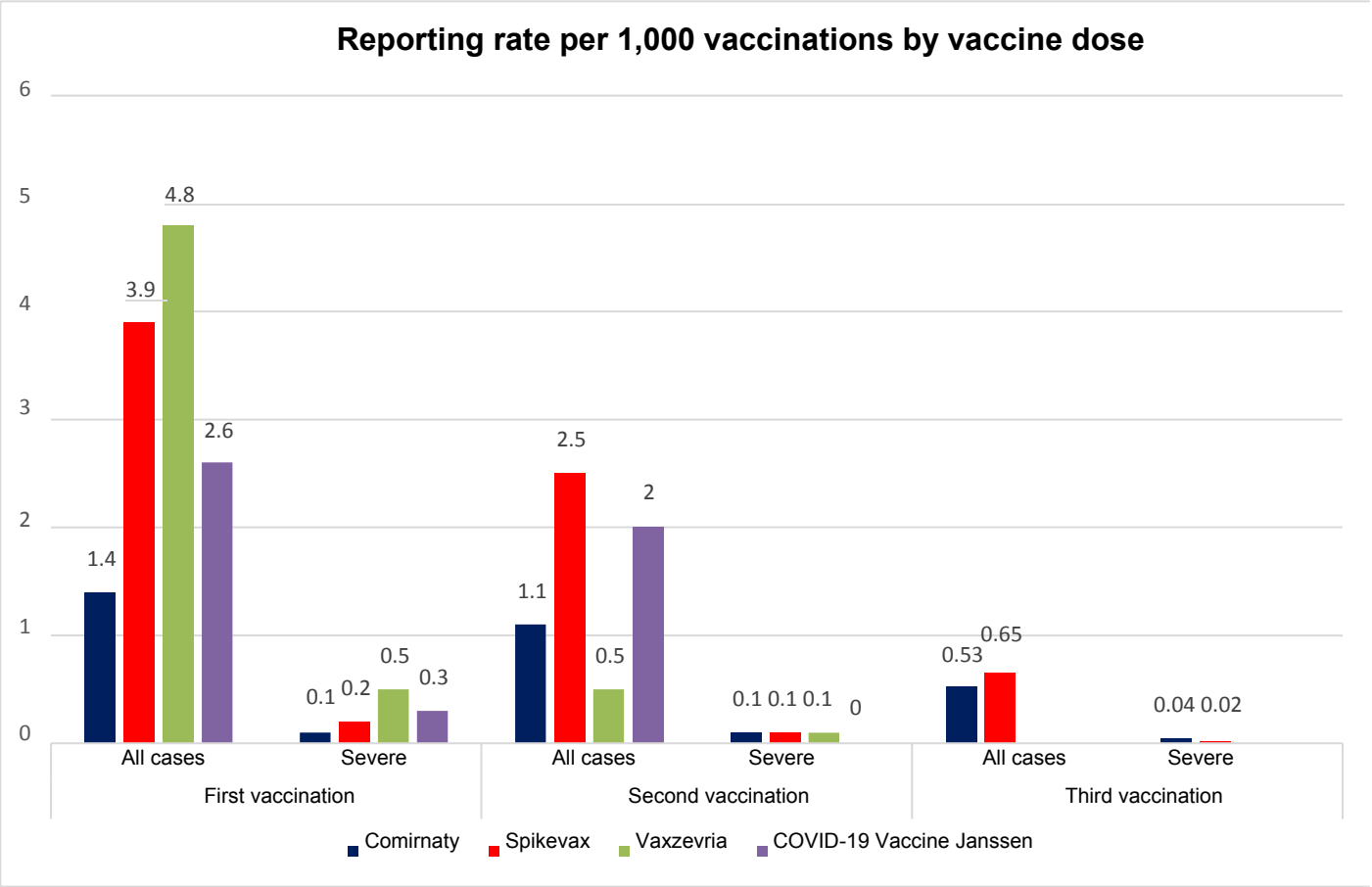
In this report, a report of a suspected adverse event or vaccination complication after booster vaccination is defined as a report providing information following

the third doses of the vaccines Comirnaty and Spikevax and the second dose for COVID-19 Vaccine Janssen. In some cases, heterologous vaccination schedules or the third dose of Vaxzevria were also reported.

10,995 reports were received in connection with a booster vaccination with Comirnaty and 7,476 reports in connection with a booster vaccination with Spikevax. 893 cases after vaccination with Comirnaty and 230 cases after vaccination with Spikevax were classified as serious.

A comparison of the reporting rates after basic and booster vaccinations, taking into account the reports for which the vaccine dose was known, shows that the reporting rates of suspected adverse events related to 1,000 vaccinations after a third dose of Comirnaty or Spikevax are significantly lower than the corresponding reporting rates after primary vaccination (Figure 4). However, when comparing the reporting rate for primary and booster vaccinations, it must be taken into account that the observation period following booster vaccinations is shorter than after basic immunisations, so that the current figures are to be regarded as provisional. Additionally, the vaccine dose was not provided in all reports received by the Paul-Ehrlich-Institut.

Figure 4: Reporting rates of suspected adverse events per 1,000 vaccinations by vaccination dose (at case level)



4. Children and adolescents

Comirnaty has been authorised for individuals aged 16 and over since 21 December 2020. This authorisation was extended to children aged 12 to 15 on 31 May 2021. An authorised dosage form appropriate for vaccinating children aged 5 to 11 years has been available since 12 December 2021. Spikevax was authorised for 12 to 17-year-old children and adolescents on 23 July 2021, but this vaccine is currently not recommended by the STIKO for this age group.

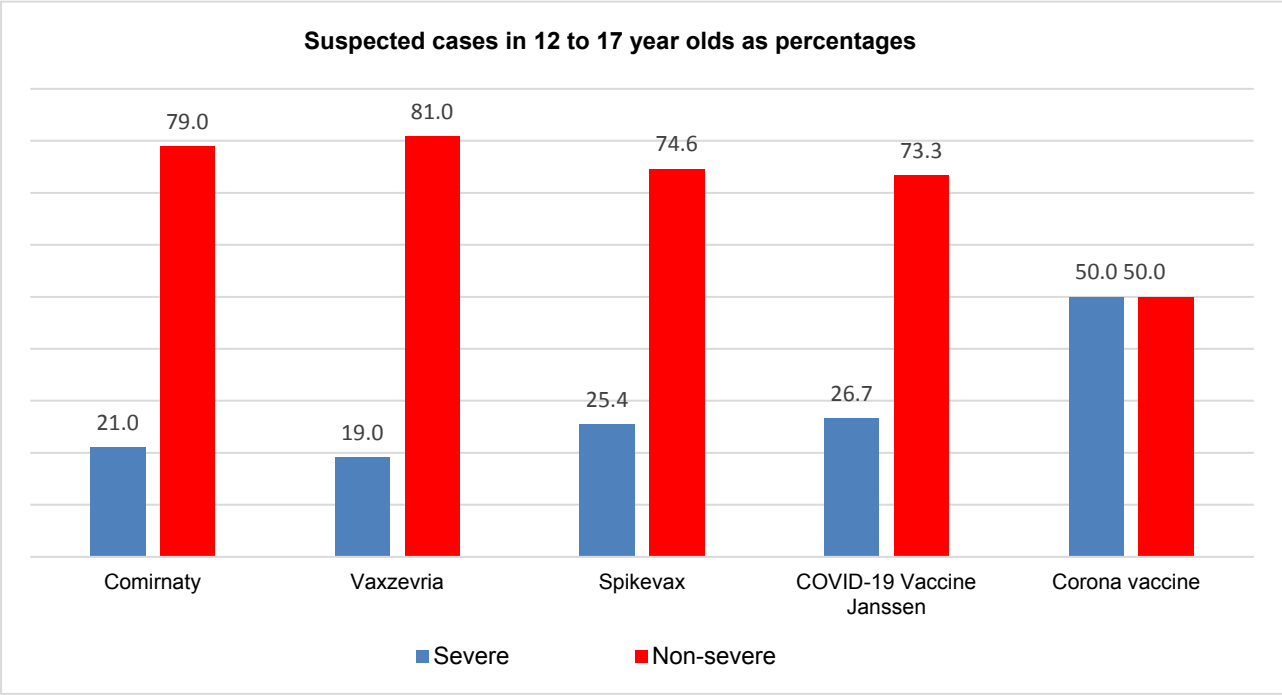
Since the start of the vaccination campaign on 27 December 2021, a total of 3,732 suspected adverse events have been reported to the Paul-Ehrlich-Institut in which at least one adverse vaccination reaction was reported for children and adolescents after vaccination with COVID-19 vaccines.

4.1. Children and adolescents from 12 to 17 years old

A total of 3,227 suspected cases of adverse events were reported for children and adolescents between 12 and 17 years old. Of these, 3,120 cases mentioned the vaccine Comirnaty and 59 cases Spikevax. Although only the two mRNA vaccines are currently authorised for children and adolescents aged 12 to 17, 21 suspected cases in which the vaccine Vaxzevria had been used were reported to the Paul-Ehrlich-Institut in this age group. COVID-19 Vaccine Janssen was administered in 15 cases. In 12 cases, the name of the COVID-19 vaccine was not provided.

The vast majority of the suspected adverse events for which the name of the COVID-19 vaccine was provided were defined as not severe (see Figure 5).

Figure 5: Percentage of severe and non-severe suspected case reports in 12 to 17 year olds according to the respective vaccines

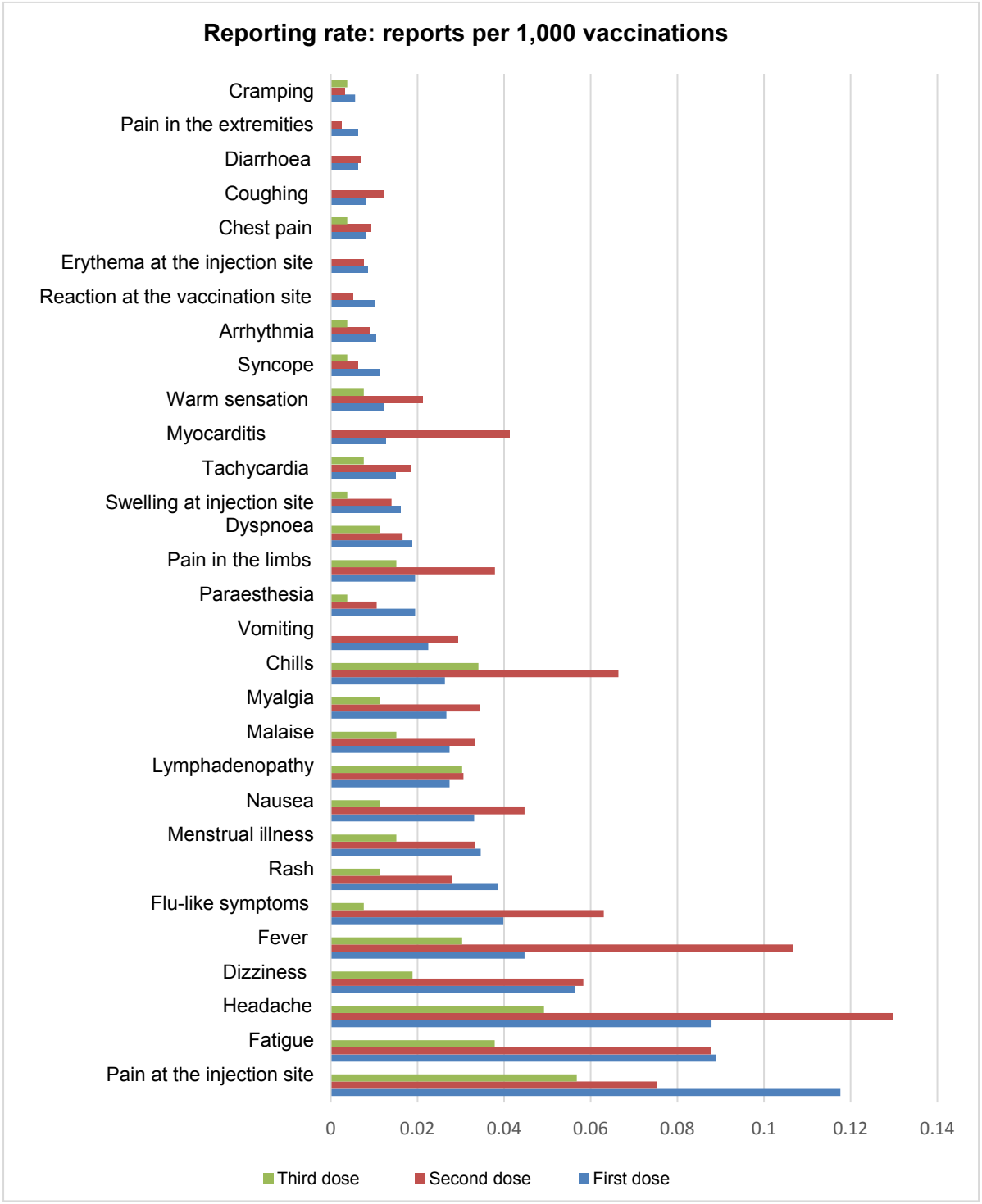


4.1.1. Children and adolescents from 12 to 17 years old after vaccination with Comirnaty

Based on an imputation of vaccine dose information (see Methodology), an overall reporting rate of 0.6 per 1,000 vaccine doses of Comirnaty can be calculated for the 3,120 suspected case reports. The reporting rate for severe reactions is 0.12 reports per 1,000 doses of Comirnaty vaccine, slightly lower than the reporting rate for adults.

Pain at the injection site, headache, fatigue, and fever were the most commonly reported adverse events (figure 5). The reporting rate of these reactions varies with the dose of the vaccine and appears to be lower after the booster dose than after the first two vaccine doses.

Figure 6: Rate of commonly reported adverse reactions per 1,000 vaccinations with Comirnaty by vaccine dose in children and adolescents (12 to 17 years) (several adverse reactions may be reported per case)



57.3 percent of those vaccinated were fully recovered or recovering at the time of reporting, 28 percent had not recovered at the time of reporting, and the outcome of 13.4 percent of children and adolescents was unknown. Eight of the 3,120 suspected case reports (0.26%) reported a fatal outcome occurring between two days and five months after vaccination with Comirnaty. One death concerned a female adolescent whose death died five months after vaccination was linked to a congenital case of arrhythmia. There was no causal link to vaccination. One adolescent died, presumably of myocarditis, shortly after vaccination with Comirnaty. The adolescent had a particularly severe underlying heart condition that was not related to vaccination. Upon examination of the extensive medical findings, the Comirnaty vaccination does not appear to be the sole cause of death. A causal link to the vaccination cannot be conclusively determined in four other cases, but the symptoms and illness progression differ between them and there are no clinical similarities. Two reports contain so little information that the clinical progression is completely unclear and cannot be assessed. Despite its efforts, the Paul-Ehrlich-Institut has not yet been able to obtain any additional information.

There were vaccination complications described as disabling, long-lasting or potentially irreversible adverse events in the cases of ten adolescents aged 13 to 17 years occurring in a time range from three days to eleven weeks after vaccination (0.32% of all case reports). A scar caused by the injection was reported in one case. In another case, Hodgkin's lymphoma was diagnosed 40 days after Comirnaty vaccination. This case has no causal link to vaccination. Diabetes mellitus type 1 was diagnosed in five cases (two female and three male adolescents) between 3 and 26 days after the Comirnaty vaccination. With an incidence rate for diabetes mellitus among children and adolescents 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.[24] Diarrhoea lasting several months was reported for a male adolescent, the cause of which remained unclear.
An additional report of a disabling, long-lasting or potentially irreversible side effect concerned a case of myocarditis, which was assessed as possibly related to vaccination. A pulmonary embolism that occurred four days after Comirnaty vaccination was reported for a female adolescent. The reports of pulmonary embolisms after COVID-19 vaccination do not indicate a safety signal.

The reporting rate of adverse events of special interest after Comirnaty vaccination reported twice or more per 1,000 vaccinations is shown in Figure 6. Similarly to the adult cases, the reported cases of myocarditis/pericarditis stand out in the figure. The Paul-Ehrlich-Institut received 147 reports of myocarditis/pericarditis in children and adolescents aged 12 to 17 years through 31 December 2021.132 male and 15 female adolescents were affected. In male children and adolescents, the reactions occurred after the second vaccination in 90 cases and after the first vaccination in 24 cases. No information on the vaccination dose was given in 18 reports. There were seven cases of adverse events after both the first and second doses among female children and adolescents (see Table 6). The vaccine dose was not reported in one case. The imputed reporting rate of myocarditis/pericarditis, taking into account missing information on the vaccine dose, was 5.1 cases per 100,000 vaccine doses in male children and adolescents and 0.6 cases per 100,000 vaccine doses in female children and adolescents. The imputed reporting rate among male children and adolescents after the second vaccination was higher at 8.6 per 100,000 vaccine doses than after the first vaccination, at 2.0 per 100,000 vaccine doses. The reporting rate among male children and adolescents aged 12 to 17 years after the second vaccination dose is thus of a comparable order of magnitude to the risk estimate for 12 to 15 year old boys after the second Comirnaty vaccination in Israel.[18] For female children and adolescents, the imputed reporting rates of 0.6 and 0.7 were about equal following the first and second vaccinations with Comirnaty. Overall, the reporting rate of myocarditis/pericarditis among 12 to 17-year-old children and adolescents remained at about the same level as in the analysis through 30 November 2021. The outcome of disease was described as recovered or improving in the majority of cases (40.2% and 17.9%, respectively). In 28 percent of the cases, the adverse events had not completely subsided at the time of reporting, and in 13.3 percent of the reports, the outcome of the myocarditis/pericarditis was not known. One patient died and a disabling, long-lasting or potentially irreversible adverse event was reported in another patient. No cases of myocarditis/pericarditis were reported via spontaneous reporting after the third vaccination through 31 December 2021 (see also Chapter 5.2.1).

A total of six cases of Guillain-Barré Syndrome (GBS) in the 12 to 17 year age group were reported. GBS is a rarity in children and adolescents, with an incidence of 0.75(0.60–0.92) per 100,000 patient years for 10 to 19 year olds.[25] All six GBS cases occurred within 42 days. In the observed-versus-expected

(OvE) analysis, the SMR, at 1.32, was not significantly increased (95% CI 0.48 – 2.87). Even if no safety signal can be justified at the moment, the Paul-Ehrlich-Institut will continue to actively follow-up on any future reports.

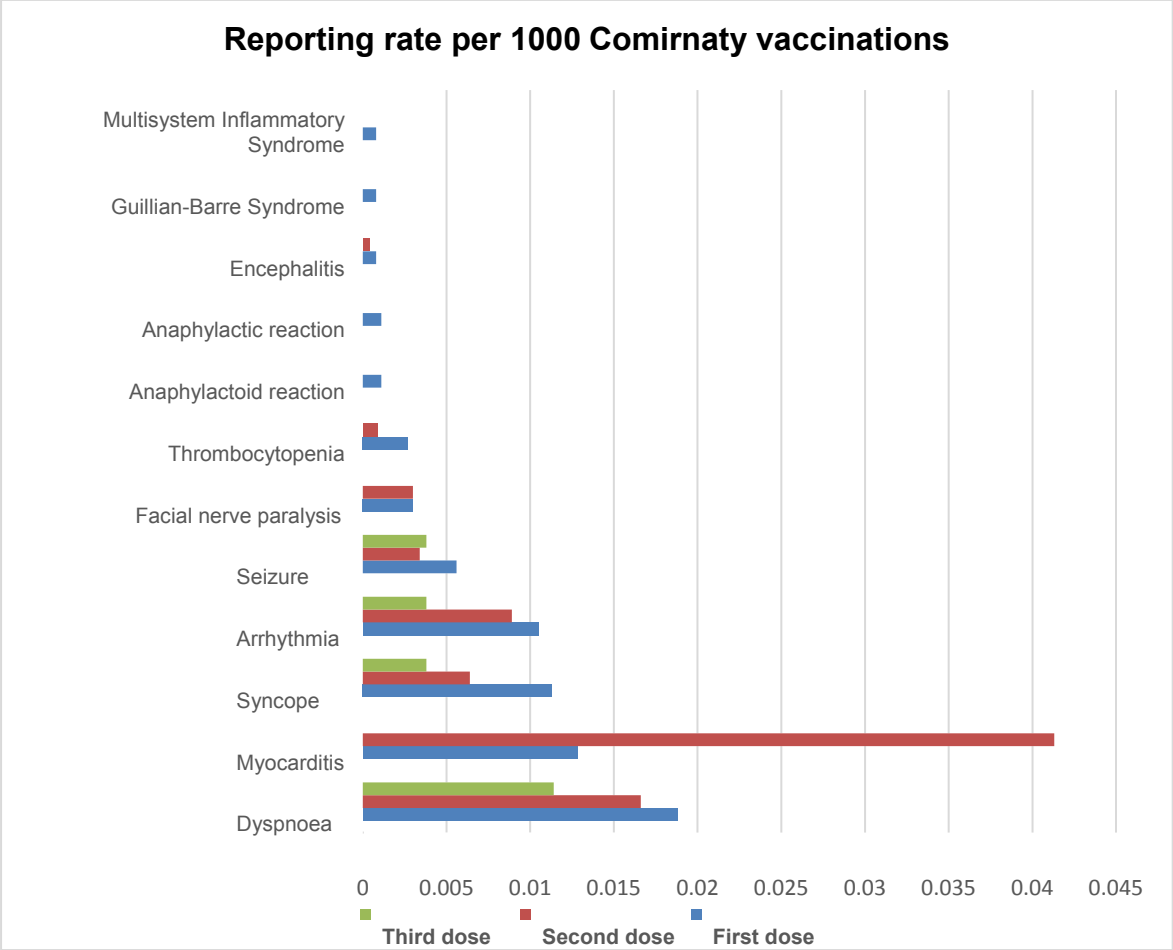
A total of 22 reports concerned cases of facial paralysis within six weeks of vaccination. There is no safety signal indicated, as more cases of facial nerve paralysis would have been statistically expected in the group of vaccinated adolescents aged 12 to 17 years based on the published incidence rate (expected value 92.83 cases, SMR 0.15-0.36).

Thrombocytopenia was reported in 17 reports, in some cases in the context of other coinciding underlying conditions.

Six cases were coded as encephalitis, including one case with encephalopathy without clinical diagnosis of encephalitis, one case of paediatric multiorgan inflammatory syndrome (MIS-C, PIMS) with encephalitis manifested in the organs (see below), three cases of encephalitis 3 to 30 days after vaccination, and one case of acute disseminated encephalomyelitis (ADEM). The six cases do not show a uniform clinical pattern, so a causal link with vaccination cannot be determined.

Paediatric inflammatory multisystem syndrome (PIMS, also known as multisystem inflammatory syndrome in children, MIS-C) was reported with a temporal link to vaccination in four adolescents. The onset of symptoms occurred between 20 and 78 days after the last vaccination. A SARS-CoV-2 infection, which is known to be a cause of MIS-C, was listed in the medical histories of three adolescents.

Figure 6: Reporting rate of adverse events of special interest per 1,000 Comirnaty vaccinations that were reported more than once



4.2. Children under 12 years old

A total of 505 suspected adverse events were reported to the Paul-Ehrlich-Institut in which the child was younger than 12 years old at the time of COVID-19 vaccination. 498 cases were after Comirnaty, four after Spikevax, two after Vaxzevria and one case after COVID-19 Vaccine Janssen. Of the 505 suspected adverse reactions reported after vaccination of children under 12 years of age with Comirnaty, a total of 103 suspected adverse events reported an age of less than 5 years at the time of vaccination. Twenty of those 103 cases involved breastfed infants, for which adverse events have been reported with a

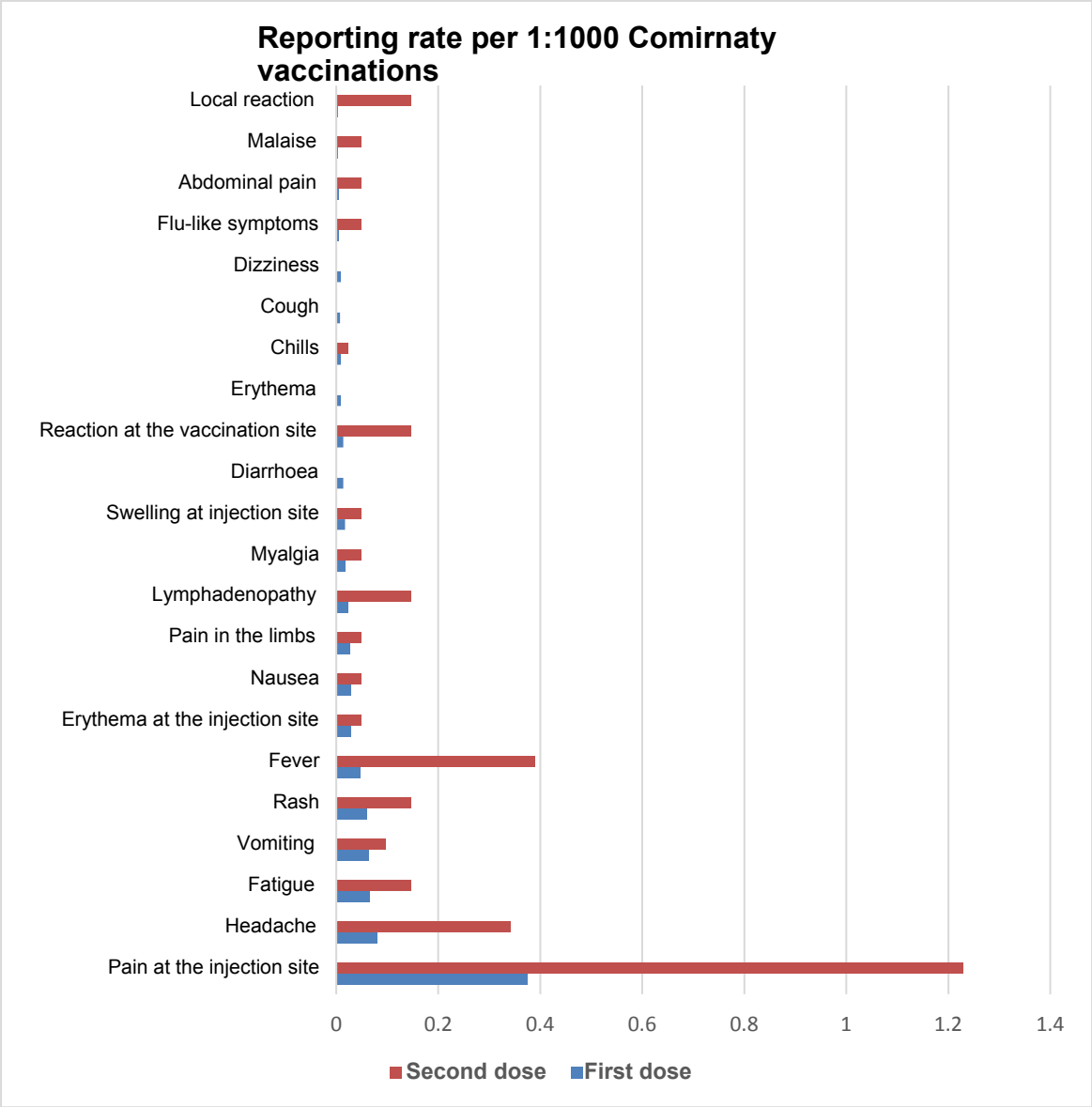
temporal link to the mothers' vaccination. All reported adverse events in the 103 suspected cases among children under 5 years of age were classified as non-severe.

In the 5 to 11 years age group, 398 suspected adverse events after vaccination with Comirnaty were reported. Five reports described adverse events that were classified as severe based on the definition of the Medicinal Products Act or on the European Medicines Agency's requirements (adverse event of special interest automatically classified as severe). These are diabetes mellitus type 1, immune thrombocytopenia, vomiting and fever, fever and syncope. A reporting rate of 1.14 serious cases per 100,000 vaccinations with Comirnaty can be calculated from these reports.

Most of the reported suspected cases (n= 306) concerned vaccination reactions after the first Comirnaty vaccination. Three children were vaccinated with vaccines that are not approved for this age group. The vaccine name was not included in another report. Figure 7 shows the reported adverse events as the reporting rate per 1,000 Comirnaty vaccinations.

In 76.4 percent of the cases, the children had fully recovered at the time of the report, and in 9.8 percent of the reports, an improvement in their general condition was reported. At the time of reporting, 8.6 percent of the children experiencing adverse events had not recovered, and the outcome of the case is unknown in 5.6 percent. No disabling, long-lasting or potentially irreversible adverse events or deaths were reported (percentages rounded).

Figure 7: Adverse event reporting rate in children aged 5-11 years per 1,000 Comirnaty vaccinations (several adverse events can be reported in one case, analysis at event level)



5. Very rare COVID-19 vaccine risks

5.1. Anaphylactic reactions

Anaphylactic reactions are a well-known, very rare adverse event linked to the four COVID-19 vaccines used in Germany to date. 489 reports of an anaphylactic reaction were reported through 31 December 2021. These were evaluated by the Paul-Ehrlich-Institut on the basis of their diagnostic certainty as defined by the internationally accepted Brighton Collaboration (BC)[19] 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 for the four vaccines combined is very rare at less than one case per 100,000 vaccinations. The rate is higher after the first vaccination than after subsequent vaccinations and higher among women than among men (Table 5).

Table 5: Number of reports of anaphylaxis (BC levels 1-4) by COVID-19 vaccine and reporting rates per 100,000 vaccinations in total and for 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	161	266	13	34	43	59	4	8
Dose 2	55	85	2	3	2	2	-	1
Dose 3	-	5	-	1	-	-	-	-
NS	5	14	-	3	-	-	-	-
Heterologous vaccination schedule	5	6	2	2	-	-	-	-
Total number	226	376	17	43	45	61	4	9
Total reporting rate women		0.34 (0.52)		20 (0.28)		0.48 (0.90)		0.25 (0.32)
Reporting rate D1 women		0.61 (0.97)		0.69 (1.08)		0.64 (1.20)		0.22 (0.16)*

Reporting rates per 100,000 vaccinations, D: vaccination dose, NS: dose not specified, 53 cases with no information on the vaccine, *based on 2 reports, therefore not a reliable point estimate

5.2. 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 among 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.

5.2.1. Overview

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

Reports of myocarditis/pericarditis after Comirnaty by age, gender, and vaccine dose number

	Total[1]	**Men**					**Women**				
Age (years)		**D1**	**D2**	**D3**	**D NS**	***Het. Sch.***	**D1**	**D2**	**D3**	**D NS**	***Het. Sch.***
12-15	44	5	26	0	7	0	3	3	0	0	0
16-17	103	19	64	0	11	2	4	4	0	1	0
18-29	467	74	224	9	67	8	23	41	5	17	3
30-39	257	39	85	5	29	5	30	39	5	24	1
40-49	191	25	53	5	13	3	20	54	4	13	4
50-59	202	20	55	4	20	4	30	41	7	23	4
60-69	92	9	28	3	5	5	15	22	3	5	2
70-79	55	6	20	0	4	1	5	15	0	3	0
80+	23	2	4	4	4	4	1	5	1	2	0
NS	77	23	16	2	8	2	13	9	0	3	0
Total	1511	222	575	32	168	34	144	233	25	91	14

D1: dose 1; D2: dose 2; D3: dose 3; NS: not specified; Het. sch.: heterologous vaccination schedule (included in D2 and/or D3); Time in days from vaccination to adverse event (time to onset, TTO): median 5, mean 14.7 (range 0 to 198). 1028 reactions (100%) occurred within 28 days of vaccination, 66% within the first week, 17% within the second week, 13% within the third week and 5% within the fourth week. Gender was specified to be male in about 66% of the reports, female in 32%, and was not specified in 2%. [1Reports] missing gender information (n = 21) with or without age information were included in the total.

Reports of myocarditis/pericarditis after Spikevax by age, gender, and vaccine dose number

	Total[1]	Men					Women				
Age (years)		**D1**	**D2**	**D3**	**D NS**	***Het. Sch.***	**D1**	**D2**	**D3**	**D NS**	***Het. Sch.***
16-17	5	1	2	0	2	0	0	0	0	0	0
18-29	186	17	100	4	30	2	4	25	1	3	0
30-39	86	5	41	6	12	0	5	10	1	4	1
40-49	41	3	15	4	5	1	2	8	1	3	0
50-59	38	2	16	3	1	1	3	8	1	3	0
60-69	9	2	5	1	0	0	0	0	0	1	0
70-79	7	0	2	0	0	0	1	3	1	0	1
80+	3	1	1	0	0	0	0	1	0	0	0
NS	6	1	3	0	0	0	0	1	0	0	0
Total	381	32	185	18	50	4	15	56	5	14	2

D1: dose 1; D2: dose 2; D3: dose 3; NS: not specified; Het. Sch.: heterologous vaccination schedule (included in D2 and/or D3); Time in days from vaccination to adverse event (time to onset, TTO): median 3, mean 12.6 (range 0 to 225). 292 reactions (100%) occurred within 28 days of vaccination, 78% within the first week, 10% within the second week, 9% within the third week and 3% within the fourth week. Gender was specified to be male in about 75% of the reports, female in 24%, and was not specified in 1%. [1]Reports missing gender information (n = 6) with or without age information were included in the total.

5.2.2. Time between vaccination and first symptoms

The length of time between mRNA vaccination and first symptoms of myocarditis/pericarditis is shown to peak a few days after vaccination (Figures 8 and 9). 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 8: Time in days between vaccination with Comirnaty and occurrence of myocarditis/pericarditis (all reports with time period information) after the first, second and third vaccinations (D1-D3)

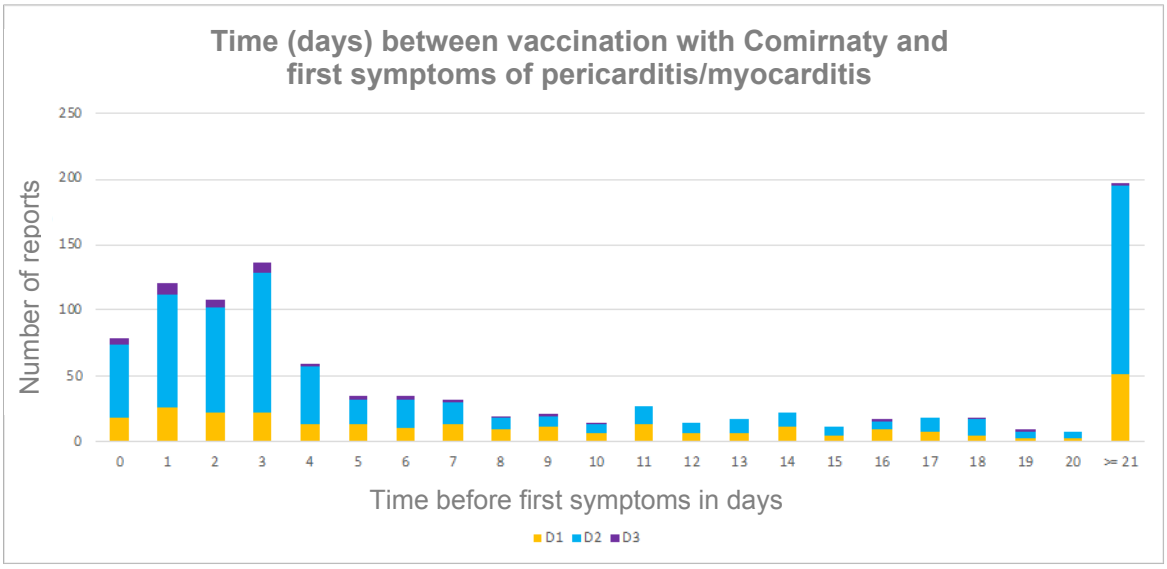
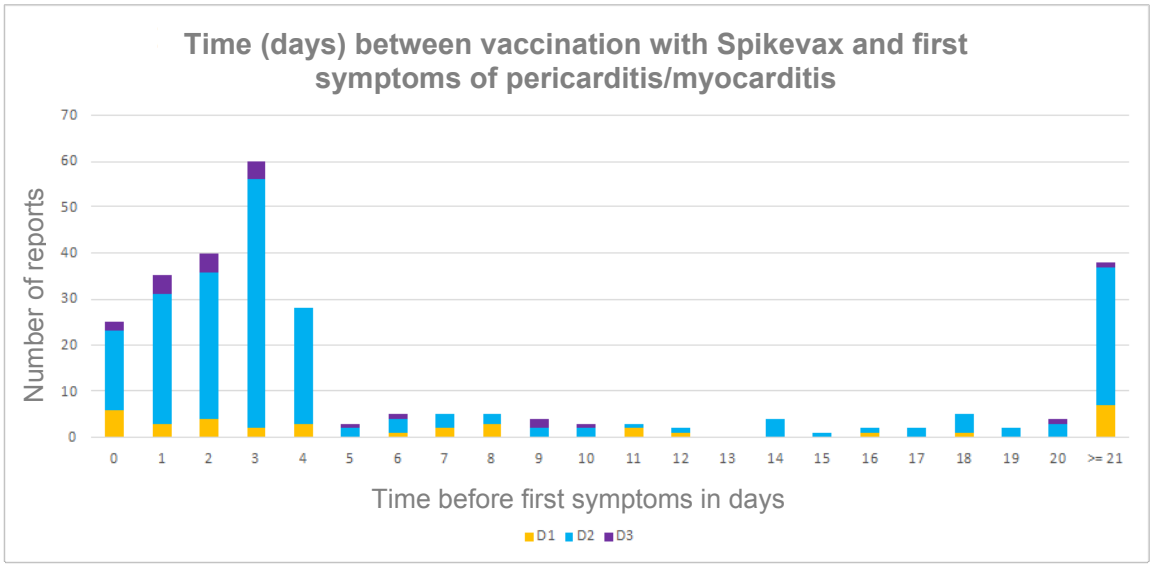


Figure 9: Time in days between vaccination with Spikevax and occurrence of myocarditis/pericarditis (all reports with time period information) after the first, second and third vaccinations (D1-D3)



5.2.3. Myocarditis/pericarditis after booster vaccination

The Paul-Ehrlich-Institut has received an increasing number of reports of myocarditis/pericarditis in adults that are missing information and/or occur at implausible, long periods of time after the first or second mRNA vaccination (> 30 days).
Therefore, a calculation of a reporting rate only makes sense for the third vaccination and for children and adolescents.

The overall reporting rate for the mRNA vaccines after the third vaccination is 0.38 (Comirnaty) and 0.34 (Spikevax) per 100,000 vaccine doses. The reporting rate is highest for both vaccines among young males aged 18 to 29 (1.11 and 2.98 per 100,000 doses of Comirnaty or Spikevax). The reporting rate in young men aged 18 to 29 years should be interpreted with caution, since only four cases of myocarditis after Spikevax have been reported in this age group. The overall reporting rate for myocarditis/pericarditis among vaccinated women is 0.21 and 0.08 per 100,000 vaccine doses for Comirnaty and Spikevax, respectively. Based on just five cases, the reporting rate is highest among women aged 30 to 39 after vaccination with Comirnaty, at 0.86 per 100,000 vaccine doses. Only a few cases have been reported among women after vaccination with Spikevax. Age stratification is therefore not useful for evaluation.

Overall, the reporting rate of myocarditis/pericarditis after booster vaccination for reports through 31 December 2021 seems to be lower than after primary immunisation (see safety report through 30 November 2021 to compare). This is also consistent with data from the UK's Medicines and Healthcare products Regulatory Agency (MHRA) (January 2022). However, in the case of data from Germany, the shorter post-observation period after booster vaccination compared to vaccination as part of primary immunisation must be taken into account, and additional data should be considered.

5.2.4. Myocarditis/pericarditis after adenovirus-based vector vaccines

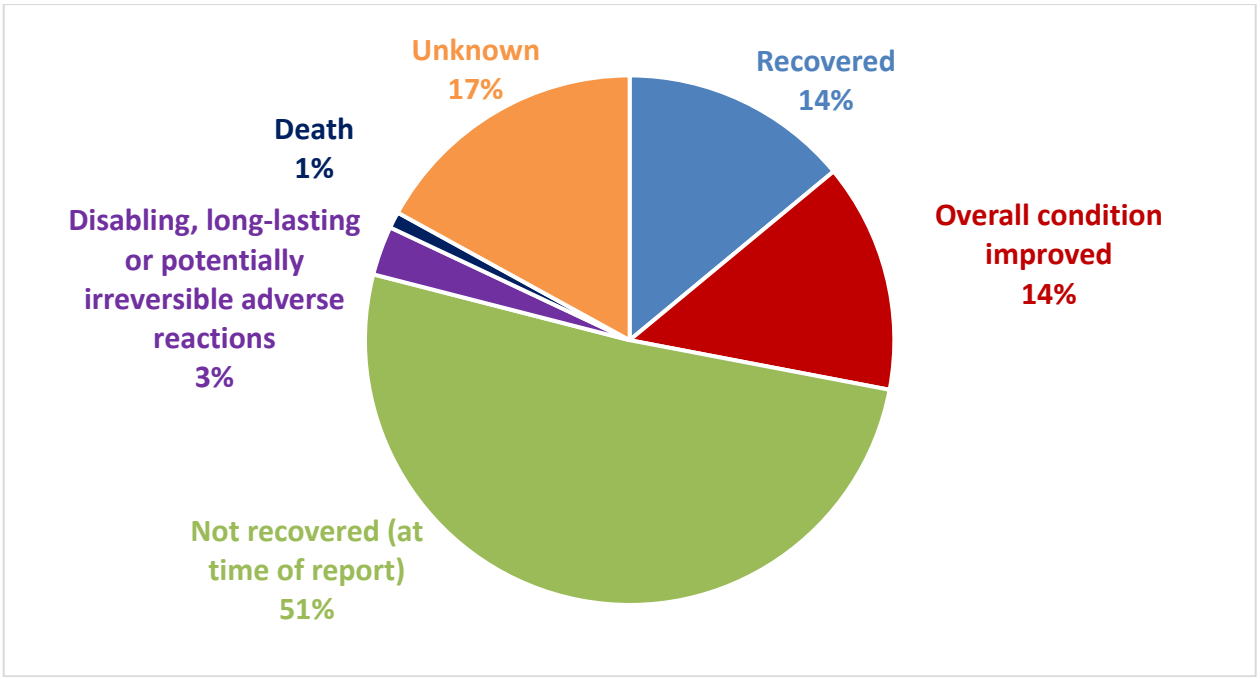
Seventy-nine cases of myocarditis/pericarditis have been reported with a temporal association to the Vaxzevria vaccine: 44 men and 35 women. The median age was 45 years. Forty cases were reported after COVID-19 Vaccine Janssen: 33 men and 7 women. Twelve reports described cases of myocarditis in men aged 18 to 29 years within 21 days of vaccination. An observed-versus-expected analysis considering the background incidence rate of myocarditis of 38.59 cases per

100,000 person years (Institute for Applied Health Research [InGef] database 2020, 18-29 age group, internal communication) yielded no safety signal (SMR 1.01).

5.2.5. Outcome of adverse events

The outcome of the reported cases of myocarditis/pericarditis after administration of one of the four COVID-19 vaccines used in Germany is shown in Figure 10.

Figure 10: Outcome of reports of myocarditis/pericarditis after receiving COVID-19 vaccine



Eighteen deaths from myocarditis/pericarditis temporally associated to COVID-19 vaccination were reported: seven related to Comirnaty vaccination, seven related to Spikevax, three related to Vaxzevria and one related to COVID-19 Vaccine Janssen. In five cases (three Comirnaty, one Vaxzevria and one COVD-19 Vaccine Janssen) the connection with the vaccination was evaluated to be possible by the Paul-Ehrlich-Institut based on the autopsy report. For all of the

other cases, the Paul-Ehrlich-Institut does not observe a causal link to vaccination based on currently available data. This evaluation results from either a higher probability of an alternative cause of death upon overall assessment of all the information or missing important clinical information.

5.3. Thrombosis with thrombocytopenia syndrome (TTS)

A very rare, and in a few cases fatal, new syndrome has been reported as a severe 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 in cerebral or mesenteric veins, or in 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.[26-32] This is a pattern that resembles "atypical" or "autoimmune" heparin-induced thrombocytopenia (aHIT).[33] According to early findings [34], 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).[35-37]

As thromboses with simultaneous thrombocytopenia can be a symptom of other diseases, 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 that is also used by the Paul-Ehrlich-Institut. According to this definition, a case of TTS is indicated by thromboses occurring in unusual locations (e.g. sinus veins) with simultaneous thrombocytopenia (<150 G/L) or by thrombosis in a common location (e.g. pulmonary embolism) plus detection of antibodies against platelet factor 4 (anti-PF4 antibodies).

Table 11 shows the reported cases of thrombosis with concurrent thrombocytopenia after COVID-19 vaccination.

Table 11: Thrombosis with thrombocytopenia after each of the COVID-19 vaccines

	Number of reports of thrombosis with thrombocytopenia	Fulfils CDC TTS criteria	Positive for anti-PF4 antibodies	Reporting rate of thrombosis with thrombocytopenia per 100,000 vaccinations
Comirnaty	41	6	0	0.037
Spikevax	5	1	0	0.023
Vaxzevria	205 [1,2]	142	83	1.609 (D2: 0.202 [3])
COVID-19 Vaccine Janssen	27	18	9	0.755

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

A total of 34 people died due to thrombosis with thrombocytopenia after Vaxzevria and nine people after vaccination with COVID-19 Vaccine Janssen. Based on the information currently available, 35 of the 43 reports of fatal thrombosis with thrombocytopenia met the CDC criteria for TTS.

Nine people died as a result of thrombosis with thrombocytopenia after vaccination with Comirnaty. One patient died after Spikevax. The CDC criteria were met in a report describing a fatal outcome after vaccination with Comirnaty. It was a venous sinus thrombosis without evidence of anti-PF4 antibodies. In no cases following an mRNA vaccine were anti-PF4 antibodies detected.

Since the vaccination rates for the adenovirus vector-based vaccines have not increased significantly in the last few months of the vaccination campaign and no indication of a risk signal of TTS has been identified thus far for the mRNA vaccines, the Paul-Ehrlich-Institut will only present analyses of TTS in future safety reports if the risk assessment has changed.

5.4. Guillain-Barré Syndrome (GBS)

GBS is an acute inflammation of the peripheral nervous system and the nerve roots (polyradikuloneuritis). The symptoms eventually recede in most cases. Neurological residual symptoms, long-lasting or potentially irreversible damage, or death can also occur. Miller-Fisher Syndrome (MFS) is a rare variant of GBS and is characterized by ataxia (disruption of motor coordination), eye muscle paralysis, and loss or weakening of muscular reflexes.

A total of 354 cases of GBS/MFS were reported to the Paul-Ehrlich-Institut (see Table 9 for age distribution; see table 10 for assessment according to BC levels [38]). There were two fatal cases after Vaxzevria cases, six after Comirnaty, and one after Moderna. Twenty-eight patients (n=11 Vaxzevria, n=14 Comirnaty, n=1 Spikevax, n=2 Janssen) needed to be treated in intensive care units, some receiving invasive ventilation. Fourteen cases of GBS after the third vaccination (n=11 Comirnaty, n=3 Spikevax) were reported in connection with booster vaccination. The affected patients (9 men, 5 women) were between 22 and 88 years old.

Table 9: Age distribution of reported GBS/MFS cases (BC 1-4) 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	6	6	0	0	0	0	0	0
18-29	15	12	0	0	4	3	4	2
30-39	27	22	1	1	11	10	4	4
40-49	17	14	2	1	16	16	8	5
50-59	31	24	4	2	38	30	17	15
60-69	30	23	4	4	27	25	11	11
70-79	18	13	4	4	18	14	1	0
80+	15	11	3	3	2	2	2	2
Unknown	9	3	0	0	2	1	3	1
Total	168	128	18	15	118	101	50	40
Booster	11	9	3	3	0	0	0	0

	Comirnaty		Spikevax		Vaxzevria		COVID-19 Vaccine Janssen	
Reporting rate / 100,000 vaccinations	0.152		0.082		0.923		1.398	

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

Table 10: Number of reported GBS/MFS cases after COVID-19 vaccination according to the case definition of Brighton Collaboration (BC) levels 1-3

	Comirnaty	Vaxzevria	Spikevax	COVID-19 Vaccine Janssen	Total
BC level 1	25	41	4	19	89
BC level 2	13	11	3	2	29
BC level 3	4	6	0	2	12
Total BC levels 1-3	42	58	7	23	130

GBS is a known adverse event associated with both of the adenovirus vector-based COVID-19 vaccines and is listed accordingly as such in the product information of these vaccines. A connection to the mRNA vaccines has not been established as of yet.

5.5. Thrombocytopenia/immune thrombocytopenia

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.

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 vaccination with the currently available COVID-19 vaccines. Petechiae were the most common haemorrhages. A few patients died due to brain haemorrhages.

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

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)
5-11	1							
12-17	17	8						
18-29	34	6	3		25	3	5	1
30-39	49	8	4	2	32	8 (1)	4	3
40-49	36	7	1		33	11 (1)	4	2
50-59	48	14 (2)	9	2	64	17 (2)	7	5 (1)
60-69	63	9	5	1	77	25 (1)	4	1
70-79	49	10 (1)	5	1	44	15 (1)	2	1
80+	56	15 (2)	2	1	8	4		
Unknown	26	11	1		11	1	1	
Total	379	88	30	7	294	84	27	13
Women	204	48 (5)	17	6	163	46 (4)	12	3
Men	173	40	11	1	131	38 (2)	15	10 (1)
Booster vaccination	14	5						
Mean age (years)	53.6		55		55		45	
Total reporting rate Cases per 100,000 vaccinations	0.34		0.14		2.31		0.75	
Booster reporting rate cases per 100,000 vaccinations	0.07							

[1]Gender was not specified in two cases connected to Comirnaty.

6. Additional analyses

6.1. Observed versus expected analyses

Table 12 shows additional observed versus expected analyses. The total number of reports of certain arterial and venous thromboses such as myocardial infarctions, strokes, and pulmonary embolisms that occurred 14, 30, or 42 days after vaccination was 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 should also be noted that increased overall awareness of venous sinus thromboses after Vaxzevria could have led to a higher reporting rate.

Thrombocytopenia/immune thrombocytopenia is a known adverse event connected to vector vaccines. This is also reflected in the rates of reports made to the Paul-Ehrlich-Institut.

Reports of transverse myelitis in Germany do not indicate a safety signal for any of the four vaccines. Transverse myelitis (TM) is a rare acute neurological condition in which parts of the spinal cord become inflamed. TM is associated with a number of viruses such as herpes and influenza. As a precaution, the PRAC recommended including TM in the product information based on a small number of individual cases reported worldwide, due to the severe nature of this adverse event.

Table 12: Observed versus expected analysis of selected adverse events, including all reports for which the time period between vaccination and first symptoms is known

Incidence rate (cases per 100,000 person years + 95% confidence interval)	Time between vaccination and start of symptoms	Comirnaty		Spikevax		Vaxzevria		COVID-19 Vaccine Janssen	
		Total cases	SMR 95% CI	Total cases	SMR 95% CI	Total cases	SMR 95% CI	Total cases	SMR 95% CI
Apoplexy (ischemic)									
164[1]	14 Days	621	0.089 (0.082-0.097)	63	0.046 (0.035-0.059)	177	0.221 (0.190-0.256)	28	0.125 (0.083-0.180)
	30 Days	769	0.052 (0.048-0.055)	78	0.026 (0.021-0.033)	236	0.138 (0.121-0.156)	38	0.079 (0.056-0.108)
	42 Days	829	0.040 (0.037-0.043)	84	0.020 (0.016-0.025)	250	0.104 (0.092-0.118)	39	0.058 (0.041-0.079)
Myocardial infarction									
334.7[2]	14 Days	236	0.017 (0.015-0.019)	37	0.013 (0.009-0.018)	70	0.043 (0.033-0.054)	12	0.026 (0.014-0.046)
	30 Days	300	0.010 (0.009-0.011)	45	0.007 (0.005-0.010)	89	0.025 (0.020-0.031)	18	0.018 (0.011-0.029)
	42 Days	319	0.0075 (0.0067-0.0084)	46	0.005 (0.004-0.007)	93	0.019 (0.015-0.023)	20	0.015 (0.009-0.022)
Pulmonary embolism ≥18 years									
81 (72-90)[3]	14 Days	456	0.140 (0.128-0.154)	77	0.113 (0.090-0.142)	183	0.463 (0.398-0.535)	32	0.29 (0.20-0.41)
	30 Days	625	0.090 (0.083-0.097)	103	0.071 (0.058-0.086)	260	0.307 (0.271-0.347)	46	0.194 (0.142-0.258)
	42 Days	681	0.070 (0.065-0.075)	106	0.052 (0.043-0.063)	300	0.253 (0.225-0.283)	52	0.156 (0.117-0.205)
Venous sinus thrombosis ≥18 years									
1.9 (1.4-2.3)[4]	14 Days	74	0.97 (0.76-1.22)	7	0.44 (0.18-0.91)	87	9.38 (7.51-11.57)	3	1.15 (0.24-3.37)
	30 Days	110	0.67 (0.55-0.81)	17	0.50 (0.29-0.80)	113	5.69 (4.69-6.84)	8	1.44 (0.62-2.83)
	42 Days	118	0.52 (0.43-0.62)	17	0.36 (0.21-0.57)	122	4.39 (3.64-5.24)	8	1.03 (0.44-2.02)
Thrombocytopenia/ ITP ≥18 years									
3.8 (3.6-4.1)[5]	14 Days	167	1.09 (0.93-1.27)	18	0.57 (0.33-0.89)	129	6.96 (5.81-8.27)	13	2.50 (1.33-4.28)
	30 Days	242	0.74 (0.65-0.84)	27	0.40 (0.26-0.58)	197	4.96 (4.29-5.70)	22	1.98 (1.24-2.99)
	42 Days	264	0.58 (0.51-0.65)	27	0.28 (0.19-0.41)	211	3.79 (3.30-4.34)	22	1.41 (0.88-2.14)
Transverse myelitis									
0.97 (0.92–1.01)[6]	14 Days	5	0.122 (0.040-0.284)	0	-	1	0.211 (0.005-1.176)	0	-

Incidence rate (cases per 100,000 person years + 95% confidence interval)	Time between vaccination and start of symptoms	Comirnaty		Spikevax		Vaxzevria		COVID-19 Vaccine Janssen	
		Total cases	SMR 95% CI	Total cases	SMR 95% CI	Total cases	SMR 95% CI	Total cases	SMR 95% CI
	30 Days	8	0.091 (0.039-0.179)	0	-	4	0.394 (0.107-1.009)	2	0.702 (0.085-2.535)
	42 Days	8	0.065 (0.028-0.128)	0	-	5	0.352 (0.114-0.821)	2	0.501 (0.061-1.811)

[1]SedovaP 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,
4Jacobet 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
5Schoonenet al. (2009) Epidemiology of immune thrombocytopenic purpura in the General Practice Research Database. British Journal of Haematology. 145:235-244
6Williameet 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

6.2. Vasculitis

In December 2021, the PRAC recommended that cutaneous small vessel vasculitis be included in the product information as a possible adverse event after vaccination with COVID-19 Vaccine Janssen. The recommendation of the PRAC was based on a few individual case reports (EMA, 9 December 2021, COVID-19 vaccine safety update COVID-19 Vaccine Janssen).

Cutaneous small vessel vasculitis is an inflammation of the blood vessels in the skin and can cause bruising. It can be caused by infections as well as by reactions to a wide variety of medicines. In most cases, symptoms resolve with symptomatic treatment.

The assessment of the PRAC prompted the Paul-Ehrlich-Institut to carry out a more in-depth analysis of all reports of vasculitis. It should be noted that vasculitis is a generic term for a group of pathophysiologically different, very rare vascular inflammations and diseases.[39,40] Inflammation of the vascular wall can lead to reduced blood flow to the affected organs and to organ damage.

Vasculitides are classified according to various criteria. One criterion is the size of the vessels, i.e. whether the disease affects primarily large (aorta and its

branches), medium (major organ arteries) or small vessels (parenchymal arteries, arterioles, capillaries and venules). Furthermore, the vasculitides are differentiated according to structural and functional aspects.[40] It is noteworthy that different types of vasculitis exhibit age tropism, e.g. Kawasaki disease in children and giant cell arteritis in people older than 50 years. In 2012, the Chapel Hill Consensus Conference published a classification for vasculitis nomenclature for the different disease names and entities.[40]

The Paul-Ehrlich-Institut has grouped reports of vasculitis with varying temporal associations to COVID-19 vaccination according to the reported reactions in line with the Chapel Hill classification, although in most cases there was missing clinical information, which prevented an assessment of the respective diagnostic certainty (Table 13).

Table 13: Overview of the reports of a wide variety of diseases that were reported under the generic term vasculitis

Number of reports	Comirnaty	Spikevax	Vaxzevria	COVID-19 Vaccine Janssen
Reported reaction conforms to Chapel Hill nomenclature	83 (53.55%)	11 (42.31%)	25 (53.19%)	5 (55.56%)
Number of leukocytoclastic vasculitis cases included in row above	20	3	3	2
Vasculitis without further specification	52 (33.55%)	12 (46.15%)	18 (38.30%)	4 (44.44%)
Other*	20 (12.90%)	3 (11.54%)	4 (10.64%)	-
Total	155	26	47	9
Total vasculitis reporting rate (cases/ 100,000 vaccinations)	0.140	0.119	0.369	0.252

* Not assigned to any Chapel Hill classification based on reported information; Percentages rounded up or down

Overall, a wide range of different types of vasculitis were reported, which often could not be assigned according to the Chapel Hill classification, so it remains unclear which form of vasculitis was reported in those cases. A few cases of leukocytoclastic vasculitis affecting the small blood vessels in the skin have been reported. In most cases, however, the result of a skin biopsy, which would confirm the diagnosis, was not communicated. In view of the low reporting rate and often missing clinical information, no safety signal can be derived on the basis of the spontaneous reports from Germany.

7. Appendix

7.1. Methodology

The reporting of suspected cases of adverse events and vaccine-related complications is a central pillar of assessments of vaccine safety because it enables the rapid detection of new safety signals. It should still be noted here that the reported adverse reactions are temporally, 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.

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

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

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

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 and pseudonymised format to the joint EudraVigilance database at the European Medicines Agency, to which every regulatory authority in the EU has access.

7.1.2. 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 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.

As explained above, reports of a suspected case can come from various reporting sources, which is desirable overall in order to increase 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. 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 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 administration of the first or second vaccination 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.

7.1.3. 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[41] 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.[42] An OE < 1 indicates that fewer studies were collected than was expected (marked green). It should be noted that the OvE analysis can indicate a safety signal. However, it is not suitable for confirming a risk. OE calculations included reports through 31 December 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 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 go as far

as data from the literature on the background 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 31 December 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.

8. References

1. Kim HW et al .: Patients with acute myocarditis following mRNA COVID-19 vaccination. JAMA Cardiol 2021 Oct 1; 6 (10): 1196-1201

2. Montgomery J et al .: Myocarditis following immunization with mRNA COVID-19 vaccines in members of the US military. JAMA Cardiol 2021 Oct 1;6(10):1202-1206

3. Marshall M et al.: Symptomatic acute myocarditis in seven adolescents following Pfizer-BioNTech COVID-19 vaccination. Pediatrics (2021) 148 (3): e2021052478

4. Rosner CM et al .: Myocarditis temporally associated with COVID-19 vaccination. Circulation. Circulation 2021 Aug 10; 144 (6): 502-505

5. Mouch SA et al.: Myocarditis following COVID-19 mRNA vaccination. Vaccine 2021: 39 (29): 3790-3793

6. Larson KF et al .: Myocarditis after BNT162b2 and mRNA-1273 vaccination. Circulation 2021 Aug 10; 144 (6): 506-508

7. Home AM et al .: COVID-19 Vaccine Safety in Adolescents Agend 12-17 years-United States, December 14, 2020 - July 16, 2021. MMWR Morb Mortal Wkly Rep 2021 Aug 6; 70 (31): 1053-1058

8. Gargano JW et al .: Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices - United States, June 2021. MMWR Morb Mortal Wkly Rep 2021 Jul 9; 70 (27): 977-982

9. Arola A et al .: Ocurrence and Features of Childhood Myocarditis: A Nationalwide Study in Finland. J Am Heart Assoc. 2017; 6: e005306. DOI: 10.1161 / JAHA.116.005306

10. Dionne A et al.: Association of Myocarditis with BNT162b2 Messanger RNA COVID-19 Vaccine in a case series of children, JAMA Cardiol 2021 Dec 1;6(12):1446-1450

11. Surveillance of myocarditis (inflammation of the heart muscle) cases between December 2020 and May 2021. News release. Israeli Ministry of Health; June 6, 2021. Accessed June 22, 2021

12. Barda N et al.: Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. N Engl J Med 2021 Sep 16; 385 (12): 1078-1090

13. Witberg G et al .: Myocarditis after Covid-19 Vaccination in a Large Health Care Organization. N Engl J Med 2021 Dec 2; 385 (23): 2132-2139

14. Mevorach D et al.: Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Israel. N Engl J Med 2021 Dec 2;385(23):2140-2149

15. Buchan SA et al .: Epidemiology of myocarditis and pericarditis following mRNA vaccines in Ontario, Canada: by vaccine product, schedule and interval. MedRxiv. preprint. www.medrxiv.org/content/10.1101/2021.12.02.21267156v1. (12/17/2021.) doi:10.1101/2021.12.02.21267156

16. Klein N: Myocarditis Analyzes in the Vaccine Safety Datalink: Rapid Cycle Analyzes and “Head-to-Head” Product Comparisons. Presentation at the Advisory Committee on Immunization Practices (ACIP) October 20, 2021. www.cdc.gov/vaccines/acip/meetings/slides-2021-10-20-21.html. (Access December 16, 2021

17. Patone M et al.: Risk of myocarditis following sequential COVID-19 vaccinations by age and sex, MedRxiv. Preprint, doi: https://doi.org/10.1101/2021.12.23.21268276 (visited 01/25/2022)

18. Mevorach D et al.: Myocarditis after BNT162b2 Vaccination in Israeli Adolescents. January 26, 2022, at NEJM.org. https://www.nejm.org/doi/full/10.1056/NEJMc2116999

19. Rüggeberg JU et al .: Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. SMR 2007 Aug 1;25(31):5675-5684

20. Krantz MS et al.: Safety Evaluation of the Second Dose of Messenger RNA COVID-19 Vaccines in Patients With Immediate Reactions to the First Dose. JAMA Intern Med 2021 Nov 1;181(11):1530-1533

21. Rasmussen TH et al.: Patients with suspected allergic reactions to COVID-19 vaccines can be safely revaccinated after diagnostic work-up. Clin Transl Allergy 2021 Jul;11(5):e12044

22. Warren CM et al.: Assessment of Allergic and Anaphylactic Reactions to mRNA COVID-19 Vaccines With Confirmatory Testing in a US Regional Health System. JAMA Network Open. 2021;4(9):e2125524

23. Xu S et al.: COVID-19 Vaccination and Non–COVID-19 Mortality Risk — Seven Integrated Health Care Organizations, United States, December 14, 2020–July 31, 2021 , MMWR / October 29, 2021 / Vol. 70 / no. 43

24. Stahl-Pehe A, Rosenbauer J: Inzidenz und Prävalenz des Typ-1-Diabetes in Deutschland. Der Diabetologe 3/2019. https://www.springermedizin.de/typ-1-diabetes/inzidenz-und-praevalenz-des-typ-1-diabetes-in-deutschland/16396102

25. Sejvar JJ et al.: Population incidence of Guillain-Barré syndrome: a systematic review and meta-analysis. Neuroepidemiology 2011;36(2):123-133

26. Eichinger S et al.: Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. N Engl J Med 2021 Jul 15;385(3):e11

27. Schultz NH et al.: Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. N Engl J Med 2021 Jun 3;384(22):2124-2130

28. Scully M et al.: Pathologic antibodies to platelet factor 4 after ChAdOx1 nCoV-19 vaccination. N Engl J Med 2021 Jun 10;384(23):2202-2211

29. Tiede A et al.: Prothrombotic immune thrombocytopenia after COVID-19 vaccine. Blood. 2021. Blood 2021 Jul 29;138(4):350-353

30. Wolf M et al.: Thrombocytopenie and intracranial venous sinus thrombosis after COVID-19 vaccine AstraZeneca. J Clin Med 2021 Apr 9;10(8):1599

31. Muir KL et al.: Thrombotic thrombocytopenia after Ad26.COV2.S vaccination. N Engl J Med 2021 May 20;384(20):1964-1965

32. Pavord S et al.: Clinical Features of Vaccine-Induced Immune Thrombocytopenia and Thrombosis.N Engl J Med 2021 Oct 28;385(18):1680-1689

33. Greinacher A et al.: Autoimmune heparin-induced thrombocytopenia, J Thromb Haemost, 2017 Nov;15(11):2099-2114

34. Schönborn L et al.: Decline in Pathogenic Antibodies over Time in VITT. N Engl J Med 2021 Nov 4;385(19):1815-1816

35. GTH: Aktualisierte Stellungnahme der GTH zur Impfung mit dem AstraZeneca COVID-19 Vakzin, Stand 22 .

36. British Society for Haematology: Guidance produced by Expert Haematology Panel (EMP) focussed on Vaccine induced Thrombosis and Thrombocytopenia (VITT), https://b-s-h.org.uk/about-us/news/guidance-produced-by-the-expert-haematology-panel-ehp-focussed-on-vaccine-induced-thrombosis-and-thrombocytopenia-vitt/

37. American Society of Hematology: Thrombosis with Thrombocytopenia Syndrome. https://www.hematology.org/covid-19/vaccine-induced-immune-thrombotic-thrombocytopenia

38. Sejvar JJ et al.: Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 2011; 29: 599- 612

39. Watts RA et al.: Global epidemiology of vasculitis, Nat Rev Rheumatol. 2022 Jan;18(1):22-34

40. Jennette JC et al.: 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides, Arthritis Rheum. 2013 Jan;65(1):1-11

41. Mahaux O et al.: Pharmacoepidemiological considerations in observed-to-expected analyses for vaccines. Pharmacoepidemiol Drug Saf 2016 Feb;25(2):215-22250. Guideline in good vigilance practices (GVP) Vaccines for prophylaxis against infectious diseases EMA/488220/2012 Corr*

42. Guideline in good vigilance practices (GVP) Vaccines for prophylaxis against infectious diseases EMA/488220/2012 Corr*