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

Paul-Ehrlich-Institut

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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 September 2021

The Paul-Ehrlich-Institut (PEI) has 172,188 suspected cases of adverse events or vaccine-related complications logged in Germany to report. These cases have a temporal association with vaccinations against COVID-19 from 27 December 2020 (start of vaccination campaign) to 30 September 2021. The vaccines with which these cases are associated are the following: the mRNA vaccines Comirnaty (BioNTech Manufacturing GmbH) and Spikevax (MODERNA BIOTECH SPAIN, S.L.) and the vector vaccines Vaxzevria (AstraZeneca AB) and COVID-19 Vaccine Janssen. According to information from the Robert Koch-Institut, 107,888,714 vaccines were administered through 30 September 2021. Of those administered vaccines, 82,341,579 were Comirnaty, 9,668,138 were Spikevax, 12,692,700 were Vaxzevria, and 3,186,297 were COVID-19 Vaccine Janssen. 94,281 suspected cases were reported for the Comirnaty vaccine, 25,713 for Spikevax, 45,178 for Vaxzevria, and 6,243 for COVID-19 Vaccine Janssen. The COVID-19 vaccine was not specified in 773 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 for the market since 11 March 2021. Vaccinations with this vaccine began in Germany at the end of April 2021.

Booster vaccinations with mRNA vaccines began for certain groups in the summer of 2021.

The following section contains a summary of the reports of suspected cases of adverse events in Germany received by the Paul-Ehrlich-Institut from the beginning of the vaccination campaign until 30 September 2021.

2. Summary and conclusions

2.1. Myocarditis and pericarditis

Myocarditis and pericarditis belong to the list of known, very rare adverse events of the mRNA vaccines. Young men in particular, as well as male children and adolescents are affected by these adverse events after the second vaccination. Typically, the first symptoms appear within a few days of vaccination.[1-15] Myocarditis is an inflammation of the heart muscle, and pericarditis is an inflammation of the pericardium, the outer lining of the heart. In both cases, the inflammation is caused by the body’s own immune system, a reaction triggered by an infection or other cause. Published data shows that most 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.[1-15]

More than 92 million doses of the Comirnaty and Spikevax vaccines were administered in Germany through 30 September 2021. A total of 1,243 reports of suspected cases of myocarditis/pericarditis were received via spontaneous reporting through 30 September 2021. These reports were made independently of their causal link to vaccination. The reporting rate among boys and male adolescents from 12 to 17 years of age and young men under the age of 30 was the highest rate among these reports.

Data on spontaneous reports from Germany indicate that the risk after a Spikevax vaccine among young men and women could be greater than after a Comirnaty vaccine. Evidently, a higher risk of myocarditis among young men (< 30 years old) was also found in Canada[16] and in a meta-analysis of four vaccine register studies in Denmark, Finland, Norway, and Sweden. However, the analyses are currently not complete and are also not yet published. Additionally, the FDA (Food and Drug Administration), the US medicines authority, upon examination of four secure databases found no significant difference in the rate of occurrence of myocarditis between the two mRNA vaccines, although their estimations are uncertain due to wide confidence intervals and the heterogeneity of the study findings.[17]

2.2. Anaphylaxis

An anaphylactic reaction is a very rare complication observed in connection with all four authorised COVID-19 vaccines. The reporting rate of anaphylaxis (Brighton Collaboration BC Level 1-4)[18] in Germany as of 30 September 2021 was approximately six cases per one million first vaccinations for each of the two mRNA vaccines and approximately one to two cases per one million second vaccinations. The reporting rate of an anaphylactic reaction (Brighton Collaboration BC Level 1-4) for Vaxzevria in Germany is about the same as that of both mRNA vaccines. With two cases per one million vaccinations, the reporting rate is somewhat lower for COVID-19 Vaccine Janssen.

According to product information regarding the two mRNA vaccines and Vaxzevria, individuals who develop an anaphylactic reaction after the first vaccine dose should not receive a second. However, the results of retrospective studies[19, 20] indicate that individuals who suffered an immediate allergic reaction that included symptoms indicating an anaphylactic reaction can be safely vaccinated

again following a proper allergological diagnosis. This is because the patients generally don't show symptoms of a real (immunoglobulin E-mediated), immediate allergic reaction.

To assist doctors administering COVID-19 vaccines in dealing with patients with a positive history of allergic reactions, the Paul-Ehrlich-Institut has developed a flowchart with the Robert Koch-Institut and in close cooperation with Germany's associations of allergological experts. The flowchart presents possible steps to take following an anaphylactic reaction to the currently authorised COVID-19 mRNA vaccines, along with recommended courses of action if allergies are reported in the patient's medical history. This should contribute to a higher level of safety in the use of COVID-19 vaccines. The article with flowchart was published in Issue 1/2021 of the Pharmacovigilance Bulletin (www.pei.de/bulletin-sicherheit).

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 of 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.[21-27] This is a pattern that resembles "atypical" or "autoimmune" heparin-induced thrombocytopenia (aHIT).[28] According to early findings[29], 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 the second vaccination with Vaxzevria as it was after the first. 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).[30-32]

Individuals diagnosed with thrombocytopenia within three weeks of vaccination with Vaxzevria or COVID-19 Vaccine Janssen should be regularly examined for thromboses. Conversely, individuals in which a thrombosis has formed after vaccination should be immediately examined for thrombocytopenia. It is important to recognize that patients with thrombosis and normal levels of thrombocytes, or patients with thrombocytopenia without indications of thrombosis after vaccination could be in the early stages of TTS. For that reason, in these cases repeated TTS examinations are potentially necessary.

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, with one reported case per 100,000 (Vaxzevria) or 120,000 (COVID-19 Vaccine Janssen) vaccine doses.

2.5. Thrombocytopenia und 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.

In line with the referenced studies[33,34], several analyses completed by the Paul-Ehrlich-Institut in the past months have indicated evidence of a safety signal for thrombocytopenia after vaccination with Vaxzevria. The findings for COVID-19 Vaccine Janssen were not as clear. No verifiable safety signal for the two mRNA vaccines can be detected in the spontaneous reporting for Germany. During the meeting of the Pharmacovigilance Risk Assessment Committee (PRAC) at the European Medicines Agency (EMA) from 27-30 September 2021, the committee evaluated international reports of immune thrombocytopenia (ITP) that were reported after vaccination with Vaxzevria or COVID-19 Vaccine Janssen. The reported cases of ITP mostly occurred within four weeks of vaccination. The committee recommended an update for the product information of both vaccines to include ITP as an adverse event with unknown frequency. 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.

The Paul-Ehrlich-Institut will continue to intensively research and analyse suspected reports of thrombocytopenia or immune thrombocytopenia.

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.

At the last meeting of the PRAC, the committee evaluated rare cases of venous thromboembolism (VTE) after COVID-19 Vaccine Janssen. VTE had already been detected during the marketing authorization 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. Since that time, the PRAC has evaluated additional findings from the marketing authorisation clinical trial, as well as data from another large clinical trial. In the latter study, however, no increase in the number of venous thromboembolisms among vaccinated individuals was identified. Taking all data including international spontaneous reports into account, the PRAC came to the conclusion that there was a reasonable possibility that rare cases of VTE could be associated with vaccination with COVID-19 Vaccine Janssen.

An analysis of spontaneous reports from Germany of pulmonary embolisms did not indicate any signals for any of the four vaccines. Reports made to the Paul-Ehrlich-Institut of a venous sinus thrombosis without signs of thrombocytopenia after Vaxzevria were, in the time period running through 30 September 2021, higher than statistically expected. However, it cannot be ruled out that individual cases actually correspond to a case of TTS due to a lack of information regarding the number of thrombocytes. It is also possible that increased overall awareness of venous sinus thromboses after Vaxzevria led to a higher reporting rate. No safety signal for venous sinus thromboses was detected for Comirnaty, Spikevax, or COVID-19 Vaccine Janssen. The Paul-Ehrlich-Institut will continue to conduct

evaluations of reports of rare venous thromboses.

2.7. Booster vaccinations

Comirnaty has held an additional marketing authorisation as a booster vaccine (third dose) since 4 October 2021. According to the marketing authorisation, the third dose can be administered intramuscularly to individuals 18 years of age or older not less than six months after their second dose. Patients that are severely immunocompromised can be administered the third dose of Comirnaty or Spikevax (depending on the vaccine initially used) starting at 28 days after the second vaccination, according to the marketing authorisation. The German Standing Committee on Vaccination (Ständige Impfkommission, STIKO) has recommended a booster vaccination for certain groups based on age, risk level, and occupation. Analyses of the suspected cases of adverse events after booster vaccination reported through 30 September 2021 did not indicate any safety signals.

2.8 Vaccination of pregnant patients

The STIKO recommended COVID-19 vaccinations with mRNA vaccines for pregnant patients in at least their second trimester and for breastfeeding patients on 10 September 2021. In light of this recommendation, the Paul-Ehrlich-Institut would like to call attention to its ongoing joint study with the Pharmacovigilance and Counselling Centre for Embryonic Toxicology at the Charité Hospital in Berlin. This prospective observational study examines the tolerability and safety of mRNA vaccines during pregnancy (www.embryotox.de). After the mother's vaccination, information on the course of her pregnancy and the newborn's condition is systematically recorded and evaluated for the study. The frequency of adverse events in the exposed study cohort is compared to that of a control cohort. The exposed cohort includes pregnant patients who were vaccinated with a COVID-19 vaccine during or shortly before pregnancy and then contacted the Pharmacovigilance and Counselling Centre for Embryonic Toxicology. In accordance with standardised procedure, medical history and demographic data are collected upon first contact with the centre. Data on the course and outcome of the pregnancy and on the newborn are collected during a subsequent follow-up. The recruiting of pregnant patients and the collection of data during the planned

study are integrated into the general counselling work of the institution. The first collection of data from exposed pregnant patients occurs in most cases during individual counselling on the phone. Further information on the study can be found at www.embryotox.de.

Since comparatively fewer vaccine doses were administered in September 2021 and the number of reports of suspected adverse events is continually decreasing, the Paul-Ehrlich-Institut will reduce the frequency of future safety reports to every two months. If in the interim there are safety-related findings, they will be prompty published on the Paul-Ehrlich-Institut's website.

3. COVID-19 vaccines

Table 1 shows the number of doses of each of the individual vaccines that were administered in Germany through 30 September 2021 based on information provided by the Robert Koch-Institut (RKI). According to the RKI, 53,682,694 individuals were fully vaccinated at that point in time.

Table 1: Number of administered doses of COVID-19 vaccines through 30 September 2021 (retroactive reporting possible by German federal states)

Vaccine	Total	1st dose	2nd dose	Booster
Comirnaty	82,341,579	39,739,132	41,864,164	738,283
Spikevax	9,668,138	4,460,412	5,177,336	30,390
Vaxzevria	12,692,700	9,237,104	3,455,596	**
COVID-19 Vaccine Janssen*	3,186,297	(3,185,598)	3,185,598	699
TOTAL	**107,888,714**	**53,436.648**	**53,682.694**	**769,372**

*The vaccination schedule for Janssen's COVID-19 vaccine includes only one dose, therefore those individuals vaccinated once with this vaccine count as fully vaccinated.

**The Robert Koch-Institut has indicated that any reported Vaxzevria booster vaccinations are considered implausible. In these cases, it is assumed that the vaccine used was incorrectly reported. These vaccinations are not included in the overview.

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

4.1. Overview

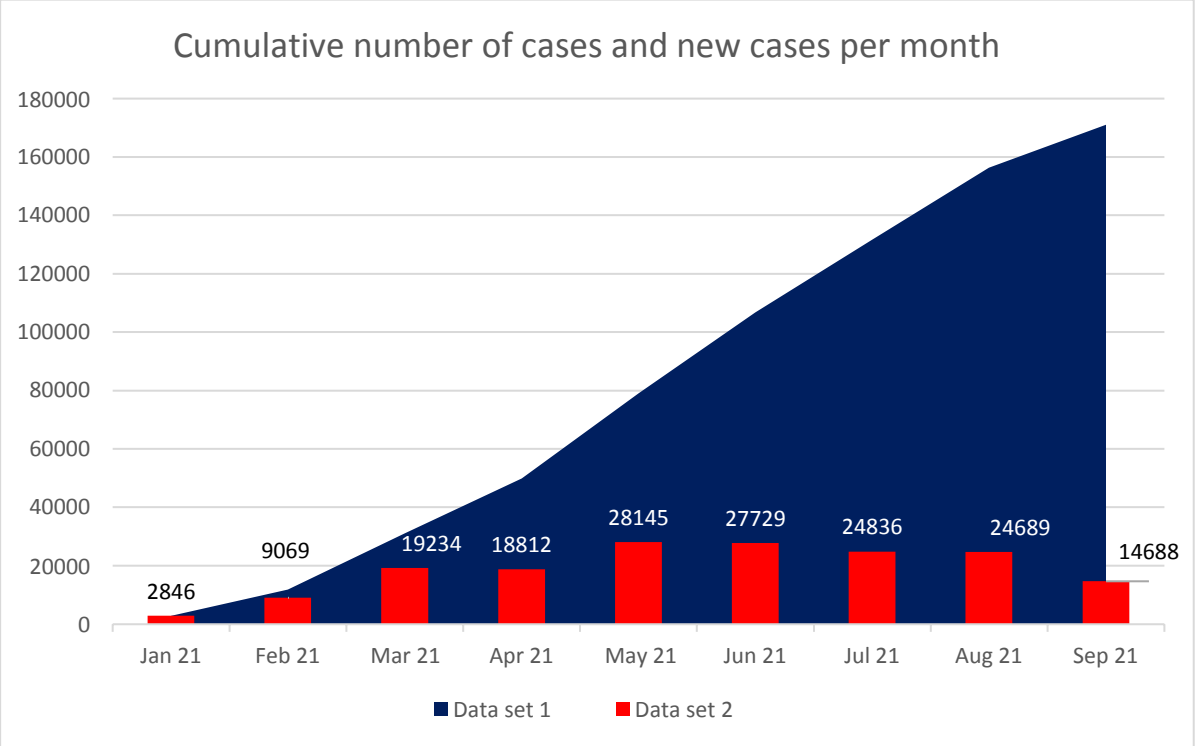
A total of 172,188 individual reports of suspected cases of adverse events or vaccine-related complications after vaccination with a COVID-19 vaccine in Germany were registered in the Paul-Ehrlich-Institut's database of adverse events through 30 September 2021. The reporting rate for all vaccinations with COVID-19 vaccines was 1.6 suspected cases per 1,000 vaccine doses. For severe cases, the rate was 0.2 suspected cases (rounded up) per 1,000 vaccine doses. Table 2 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 September 2021 for all of the COVID-19 vaccines used so far in Germany.

Table 2: 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 September 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	94,281	12,939 (13.7 %)	1.1	0.16
Spikevax	25,713	1,493 (5.8 %)	2.7	0.15
Vaxzevria	45,178	5,751 (12.7 %)	3.6	0.45
COVID-19 Vaccine Janssen	6,243	560 (9.0 %)	2.0	0.18
Vaccine unknown	773	311 (40.2 %)		
TOTAL	**172,188**	**21,054 (12.2 %)**	**1.6**	**0.2**

Figure 1 shows the number of suspected cases of adverse events reported to the Paul-Ehrlich-Institut, both cumulatively and per month.

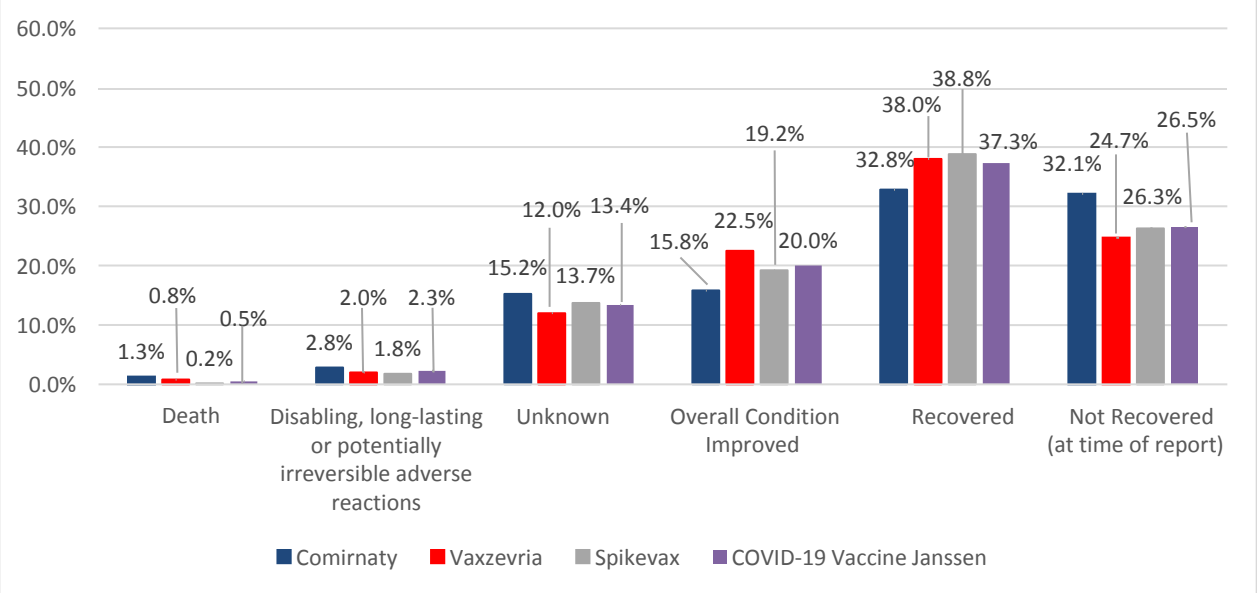
Figure 1: Reports of suspected cases of adverse events to the Paul-Ehrlich-Institut since 1 January 2021 (cumulative = blue curve and per month = red bars)



4.2. Outcome of reported reactions

Figure 2 shows the outcomes of the reported reactions per COVID-19 vaccine.

Figure 2: Outcomes of the reported reactions as a percentage of all reported events in connection with an individual vaccine, broken down by individual COVID-19 vaccine

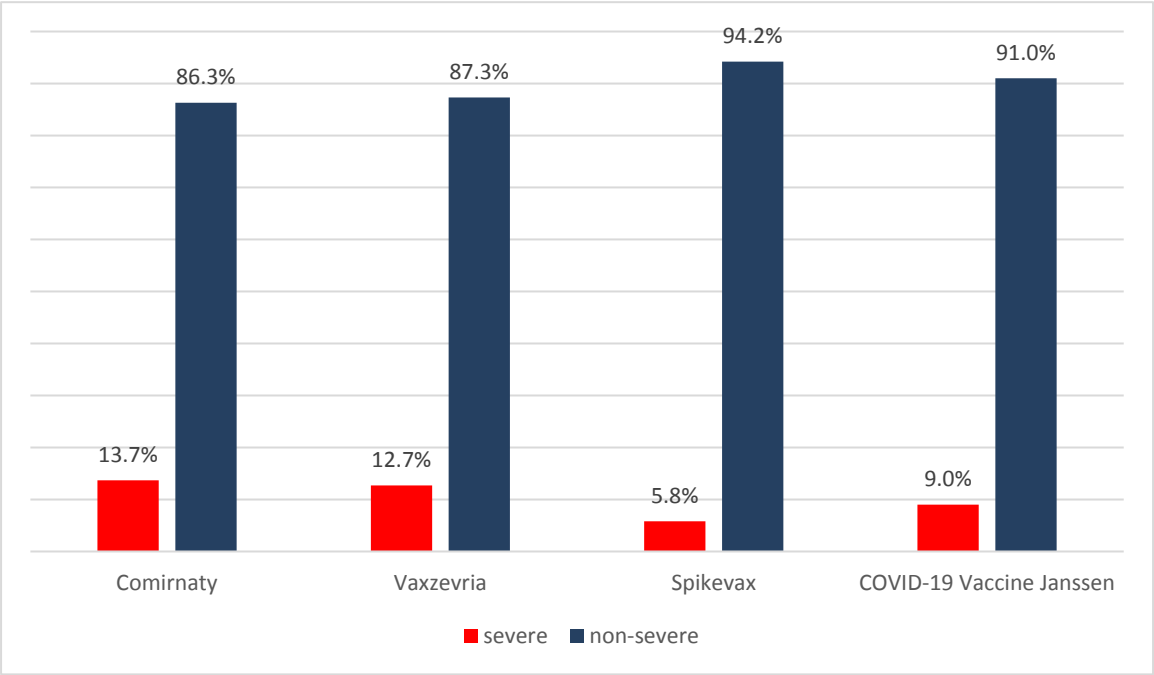


Please note: Percentages were rounded up or down so that the sum of the percentages shown may not equal 100%.

4.3. Severe adverse reactions

Severe adverse reactions were reported in 21,054 of the suspected cases. Of these, 12,939 severe suspected cases emerged after vaccination with Comirnaty, 1,493 severe suspected cases after vaccination with Spikevax, 5,751 severe suspected cases after vaccination with Vaxzevria, und 560 severe suspected cases after vaccination with COVID-19 Vaccine Janssen. The name of the vaccine was not provided in 311 suspected cases. Figure 3 shows the percentages of reports of severe and non-severe adverse events after vaccination with the different COVID-19 vaccines.

Figure 3: Percentages of severe and non-severe reported reactions per COVID-19 vaccine



Fatal outcomes at various points in time after vaccination were reported in 1,802 suspected case reports. An analysis of the data resulted in no major change to the evaluation from the previous safety report.

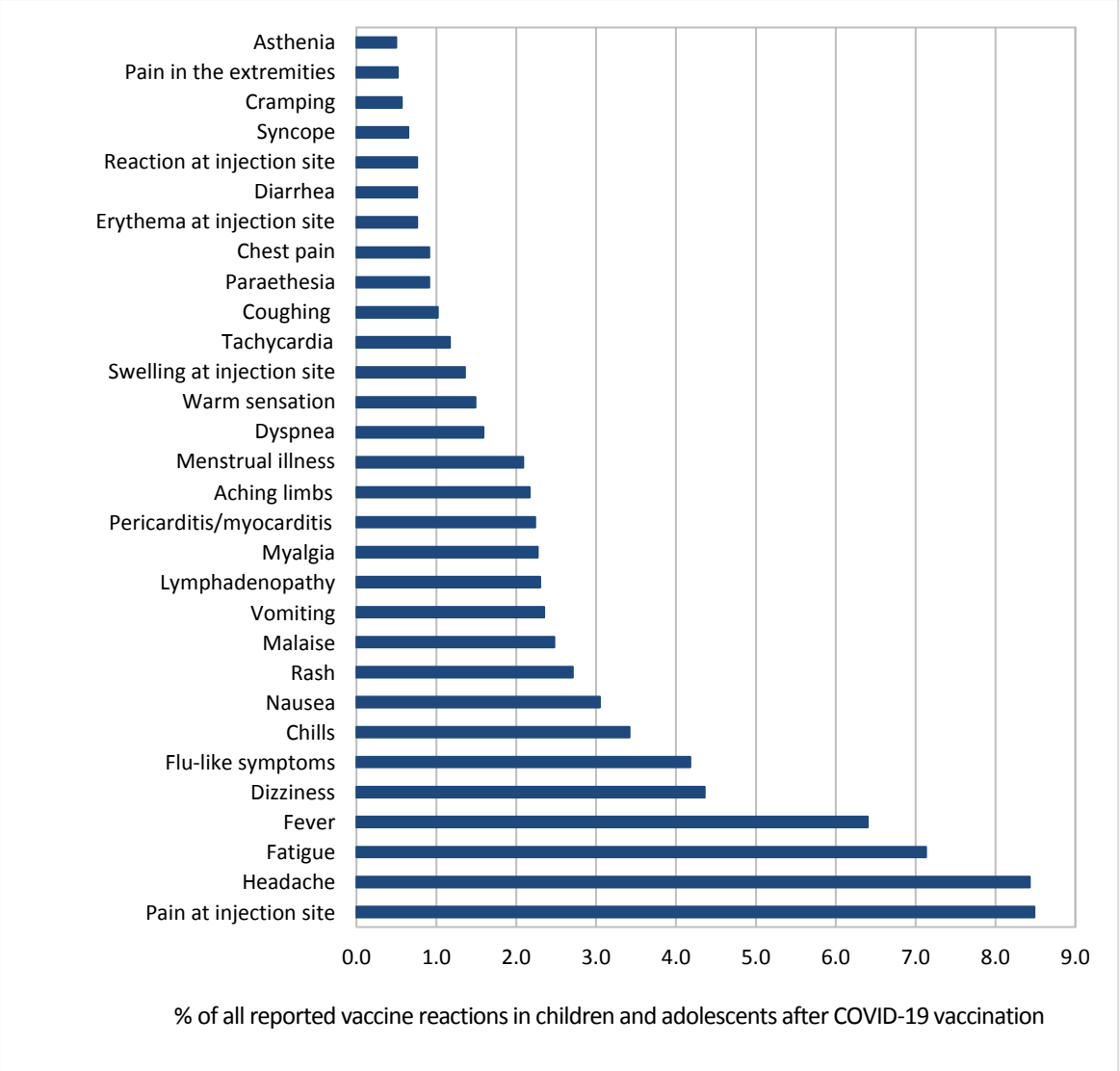
5. Children and adolescents from 12 to 17 years old

The German Standing Committee on Vaccination (Ständige Impfkommission, STIKO) recommended COVID-19 vaccination for all children and adolescents 12 years of age and older on 16 August 2021. This was an expansion of their original vaccine recommendation. Comirnaty and Spikevax received a marketing authorization from the European Commission for individuals 12 years of age and older.

5.1. Overview of suspected cases reported for children and adolescents

A total of 1,809 suspected cases of adverse events concerning one or more vaccine reactions in a child or adolescent after COVID-19 vaccination have been reported to the Paul-Ehrlich-Institut since the beginning of the vaccination campaign on 27 December 2021. Severe adverse reactions were described in 22.4% of the suspected case reports. The Comirnaty vaccine was administered in 1,744 of the cases, and the Spikevax vaccine was administered in 26 of the cases. In relation to the extrapolated vaccine doses (see Methodology in the appendix), that is 0.51 suspected case reports per 1,000 Comirnaty vaccine doses and 0.85 suspected case reports per 1,000 Spikevax vaccine doses. Pain at the injection site, headache, fatigue, and fever were the most commonly reported adverse events (figure 4). Additionally, 31 suspected cases connected to vector-based vaccines that do not have marketing authorisation for the vaccination of children were reported to the Paul-Ehrlich-Institut.

Figure 4: Frequently reported adverse reactions by percentage of all reported adverse reactions in children and adolescents after COVID-19 vaccination (multiple reactions per case can be reported)



5.2. Progression and outcome of reported reactions

At the time of reporting, 60% of the children and adolescents vaccinated had seen an abatement or improvement of their adverse reactions, 25.6% were not yet fully recovered, and 13.6% had an unknown outcome.

Five of the 1,809 suspected case reports resulted in death two to 24 days after vaccination with Comirnaty. One death involved a 16-year-old female adolescent whose death was connected with arrhythmia. Three deceased male adolescents were suffering from serious underlying conditions. Multiple organ failure, pulmonary haemorrhage, disseminated intravascular coagulation, septic shock, and fever were reported in the first case (male, 14 years), fever and circulatory collapse in the second case (male, 15 years), and a pulmonary embolism in the third case (male, 16 years). A causal link with vaccination cannot be assessed in these three cases, but the symptoms and illness progression differ between them and there are no clinical similarities. In the case of the death of a fourth male adolescent (12 years old), there is very limited and insufficient information regarding the progression of illness and circumstances surrounding the death.

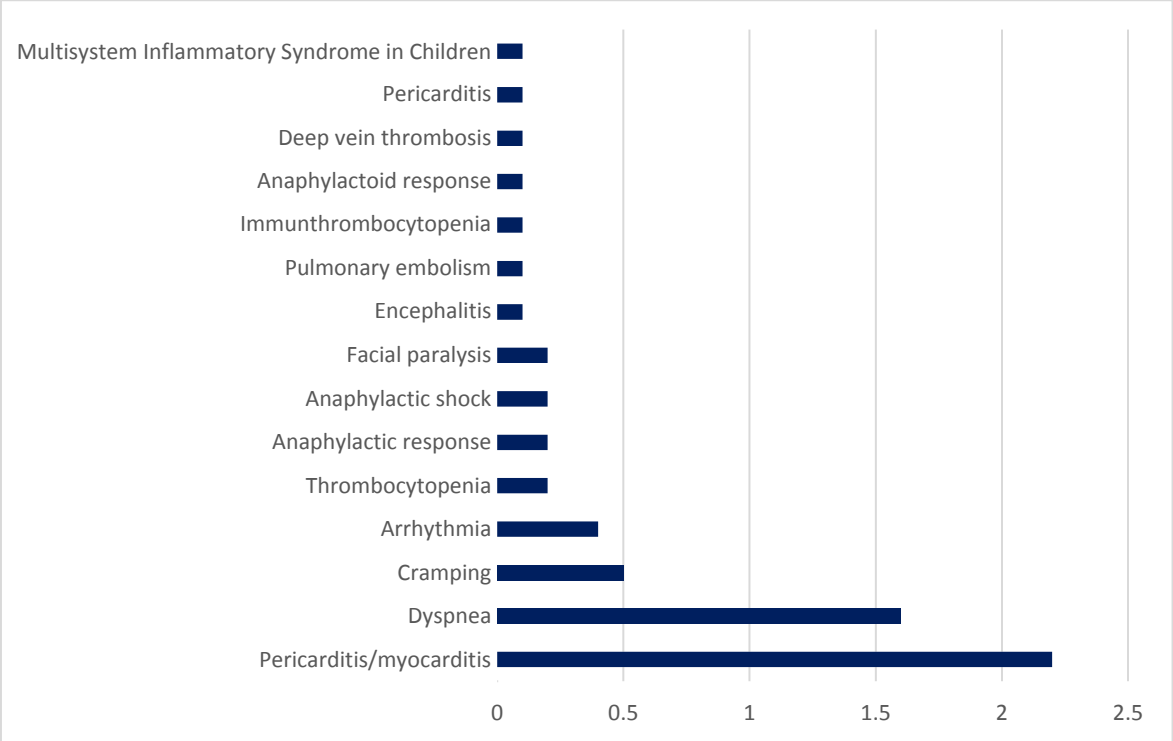
There were vaccination complications temporally associated with Comirnaty vaccination described as disabling, long-lasting or potentially irreversible adverse reactionsin the cases of nine adolescents (five male and four female) between the ages of 13 and 17. In one case (male, 16 years), a scar caused by the injection was reported. In another case (female, 16 years), a diagnosis of Hodgkin's lymphoma with a temporal association with the vaccine was coincidentally, but not causally, linked to vaccination. A 17-year-old adolescent developed a pulmonary embolism two months after vaccination with Comirnaty. The adolescent had known risk factors. Persistent diarrhoea lasting multiple months without a known cause was reported for a 16-year-old male adolescent. In five cases (two female and three male adolescents), diabetes mellitus type 1 was reported at intervals ranging from one day to one month after 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.[37]

5.3. Adverse Events of Special Interest (AESI)

Figure 5 shows the percentages of adverse events of special interest (AESI) that were reported more than once after vaccination with either of the two mRNA vaccines. The percentages are presented as a share of the total number of reported reactions. Similarly to the adult cases, the reported cases of myocarditis/pericarditis stand out in the figure. A total of 98 reports of myocarditis/pericarditis in children aged 12 to 17 were reported to the Paul-Ehrlich-Institut through 30 September 2021. These included two cases of myocarditis in two male adolescents after Spikevax and 96 cases of myocarditis/pericarditis after Comirnaty (8 girls and female adolescents, 85 boys

and male adolescents). No gender was provided in three of the reports. The majority of reports after Comirnaty concerned boys and male adolescents after their second vaccination (n=58). Taking the calculated vaccination rate into account (calculated with digital vaccination rate monitoring data [DIM] from the RKI and IQVIA data from registered doctors), the reporting rate totals one case of myocarditis/pericarditis per 13,812 second Comirnaty vaccinations among boys and male adolescents. After imputation (a method to fill in data in the data matrix that is missing from statistical surveys, see Methodology) of missing information on dose number and gender, the rate is one case per 12,188 second Comirnaty vaccinations. The reporting rate of myocarditis/pericarditis after a second dose of Comirnaty among female children and adolescents was significantly lower, with one report per approx. 210,000 to 250,000 second vaccinations (see section 7.1).

Figure 5: Reports of adverse events of special interest that were reported more than once; presented as percentage of all reported adverse events



Paediatric inflammatory multiorgan syndrome (PIMS, also known as multisystem inflammatory syndrome in children or MIS-C) was reported with a temporal association of about four weeks after Comirnaty vaccination in the cases of three adolescents (two male, one female). The Paul-Ehrlich-Institut currently does not have enough information on two of the three cases to be able to provide a final assessment. In the case of a 17-year-old female adolescent described in the last report and defined as Level 1 in the Brighton Collaboration Case definition criteria, further serological tests have confirmed the suspicion that the adolescent had most likely experienced a previous, asymptomatic SARS-CoV-2 infection. The adolescent has since recovered.

6. Reports of suspected cases after booster vaccination

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.

In total, 87 reports were made in connection with a Comirnaty booster vaccination. These reports involved 52 women and 33 men. The gender was not disclosed in two cases. The mean age was 75.6 years (12 to 92 years old; it is questionable whether the dose number was correctly indicated in the case of a 12-year-old male adolescent). Severe reactions were disclosed in 24 of the 87 reports. The reporting rate was 0.1 per 1,000 vaccinations. The severe reaction reporting rate was 0.03 per 1,000 vaccinations and is therefore significantly lower than the reporting rate after the total number of all vaccine doses (see 4.1).

Fatal outcomes occurring one to twelve days after vaccination were reported in 11 cases concerning three men and eight women with a mean age of 82.5 years (69-89 years old). One case involved a cerebral thrombosis at an unknown point in time after vaccination. In another case, a worsening of an underlying condition three days after vaccination was reported. The cause of death was unknown in the other cases. All 11 reports were missing important clinical information, making an assessment impossible.

Fourteen suspected cases were reported after booster vaccination with Spikevax. There were 11 women and three men affected. The individuals were between 23 and 89 years old. The mean age was 49.4 years. Three cases involved severe reactions: the sudden death of an 89-year-old individual with multiple risk factors, one pulmonary embolism, and a feverish reaction. The reporting rate was 0.5 per 1,000 booster vaccinations and 0.1 severe reactions per 1,000 booster vaccinations.

Four cases involving men from 18 to 80 years of age were reported after booster vaccination with COVID-19 Vaccine Janssen. Two cases were severe, both involving a report of myocarditis. There were no deaths reported.

According to data from the Robert Koch-Institut (RKI), there were no Vaxzevria booster vaccinations administered.

7. Adverse Events of Special Interest (AESI)

The Paul-Ehrlich-Institut evaluates Adverse Events of Special Interest (AESI). Selected events to which particular focus was paid are described in the following sections.

7.1. Myocarditis and/or pericarditis

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 outer lining of the heart. Men between the ages of 20 and 50 appear to have the highest risk for pericarditis.

7.1.1. Reports of myocarditis/pericarditis after mRNA vaccine

Tables 3 and 4 below show the reported cases of myocarditis and pericarditis after Comirnaty and Spikevax. Cases involving a heterologous vaccine schedule in which Comirnaty was administered after previous vaccination with another COVID-19 vaccine (such as Vaxzevria) are detailed separately.

Table 3: Reports of myocarditis/pericarditis after Comirnaty by age, gender, and vaccine dose number

Comirnaty									
	Total	**Men**				**Women**			
Age (Years)		**D1**	**D2**	**D NS**	**Heterol. Sched.**	**D1**	**D2**	**D NS**	**Heterol. Sched.**
12-17	96	17	58	10	0	4	3	1	0
18-29	296	40	154	42	3	12	25	13	2
30-39	154	28	48	19	1	16	22	19	1
40-49	114	15	37	4	2	14	28	9	2
50-59	121	14	28	11	5	16	26	19	1
60-69	44	7	13	2	2	7	9	3	0
70-79	37	6	12	4	1	4	9	1	0
80+	15	2	3	2	0	1	5	2	0
NG	53	19	13	2	0	12	2	1	0
Total	930	148	366	96	14	86	129	68	6

D1: Dose 1; D2: Dose 2; D NS: dose not specified; Heterol. Sched.: heterologous vaccine schedule; the 930 total reports are calculated from 913 reports plus 17 reports with no gender provided; TTO (time to onset): 5 days median, 12.6 days average (range of 0 to 180 days).

Table 4: Reports of myocarditis/pericarditis after Spikevax by age, gender, and vaccine dose number

Spikevax									
	Total	Men				Women			
Age (Years)		D1	D2	D NS	Heterol. Sched.	D1	D2	D NS	Heterol. Sched.
12-17	2	0	2	0	0	0	0	0	0
18-29	136	8	79	20	2	2	23	2	0
30-39	51	4	31	6	0	2	4	3	1
40-49	22	3	10	3	0	0	5	1	0
50-59	19	0	10	0	0	3	4	2	0
60-69	2	1	1	0	0	0	0	0	0
70-79	4	0	2	0	0	0	2	0	0
80+	1	1	0	0	0	0	0	0	0
NG	1	0	1	0	0	0	0	0	0
Total	238	17	136	29	2	7	38	8	1

D1: Dose 1; D2: Dose 2; D NS: dose not specified; Heterol. Sched.: heterologous vaccine schedule; the 241 total reports are calculated from 238 reports plus 3 reports with no gender provided; TTO (time to onset): 3 days median, 7 days average (range of 0 to 124 days).

7.1.2. Reporting rates of myocarditis/pericarditis after mRNA vaccine

Table 5 shows the reporting rates for men and women by age group, which takes into account the digital vaccination rate monitoring data (DIM) from the Robert Koch-Institut and data from an analysis of a representative number of registered doctors who are administrating vaccines. A sensitivity analysis took a potential underestimation of the vaccine rate among adults into account, which produced similar results with slightly lower estimates. This analysis is not included in this report.

The vaccine dose number was unknown for some of the reports of myocarditis/pericarditis with temporal association with a COVID-19 vaccination at the time of evaluation. Additionally, the calculation of rates of vaccination with heterologous vaccine schedules stratified by age and gender

is subject to a high level of uncertainty. For this reason, no reporting rate was calculated on the basis of the first and second vaccine doses, with the exception of the data provided for children and adolescents (see section 2.7).

Table 5: Reporting rate of myocarditis/pericarditis after Comirnaty and Spikevax based on 100,000 vaccine doses by gender and age group. The sensitivity analysis took a potential underestimation of the vaccination rate into account.

	Comirnaty		**Spikevax**	
	Reporting rate per 100,000 vaccinations		**Reporting rate per 100,000 vaccinations**	
Age group (years)	**Men**	**Women**	**Men**	**Women**
12-17	4.81	0.49	11.41 [1]	-
18-29	4.68	0.97	11.71	2.95
30-39	1.88	1.11	4.67	1.12
40-49	1.12	0.93	2.13	0.80
50-59	0.71	0.77	0.99	0.91
60-69	0.38	0.29	0.31	-
70-79	0.47	0.25	0.50	0.45
89+	0.18	0.13	0.47	-
Total	1.57	0.65	3.78	1.09

[1] based on reports with n=2, therefore subject to a high level of uncertainty

As described in the product information of both mRNA vaccines, myocarditis/pericarditis was reported more frequently among boys, male adolescents, and young men under the age of 30 than any other age group or women. Furthermore, the data indicates a higher reporting rate among young men in particular (also, although somewhat less pronounced, among young women) after Spikevax in comparison to Comirnaty.

7.1.3. Observed versus expected analysis of reports of suspected cases of myocarditis after mRNA vaccine

In addition to calculating the reporting rate, the Paul-Ehrlich-Institut carried out an observed versus expected analysis on reports of myocarditis. The background incidence rates were calculated using diagnoses in inpatient and outpatient care from 2020 in Germany for women and men in the following age groups: 12-17, 18-29, 30-59 and 60+ years (analysis completed by the Institute for Applied Health Research [InGeF], internal communication). The number of reports of myocarditis (diagnoses I41, I40, I51.4, I01.2 or I09.0) in the previously named age groups within 21 days of vaccination with Comirnaty or Spikevax was compared with the statistically expected number of reports of myocarditis among the vaccinated group. Since the Paul-Ehrlich-Institut also received reports that did not provide information on the time interval between vaccination and first appearance of myocarditis symptoms, an imputation of these reports was carried out.

In the 12- to 17-years-old age group, 74 cases of myocarditis were reported among boys and male adolescents within 21 days of Comirnaty vaccination (imputation 74.9 days), while 10.88 cases among the exposed group in the same time interval would have been statistically expected (SMR without imputation 6.80; 95% confidence interval [CI] 5.41-8.63, SMR with imputation 6.88; 95% CI 5.41-8.63). Among males aged 18-29, 191 cases (imputation 205.3 cases) were reported, while only 111.82 cases of myocarditis would have been statistically expected (SMR without imputation 1.714; 95% CI 1.47-1.97, SMR with imputation 1.84; 95% CI 1.59-2.11). For girls, female adolescents, and women, as well as men in the 30 to 59 and 60+ years-old age groups, the number of reports was close to or under the expected value. Based on this data, there was no indication of a safety signal for the last groups mentioned.

Two cases of myocarditis among male adolescents were reported for Spikevax. Under the circumstances detailed above, 0.11 cases would have been statistically expected among the vaccinated group in a 21-day timeframe. Due to the low number of vaccinations and reported cases, an analysis is not possible at this time. At the time of evaluation, 90 cases of myocarditis that occurred within 21 days (imputation 94.6 cases) among young men aged 18-29 were cumulatively reported. In contrast, 20.28 cases would have been statistically expected (SMR without imputation 4.44; 95% CI 3.57-5.46, SMR with imputation 4.67; 95% CI 3.77-5.71). There were no cases reported among girls and female adolescents (expected value 0.06). There were 21 cases of myocarditis within 21 days of vaccination reported among young women in the 18- to 29-years-old age group (imputation 23.5 cases) with an expected value of 9.30. Therefore a safety signal is also indicated here (SMR without imputation 2.26; 95% CI 1.40-3.45, SMR with

imputation 2.53; 95% CI 1.61-3.78). This safety signal should continue to be observed. In the other age groups, the number of reported cases of myocarditis among men and women corresponded to or was lower than the expected value.

An observed versus expected analysis can indicate the presence of safety signals. It is not a suitable instrument for determining the existence of a causal link or quantifying risk, so results are to be interpreted with caution.

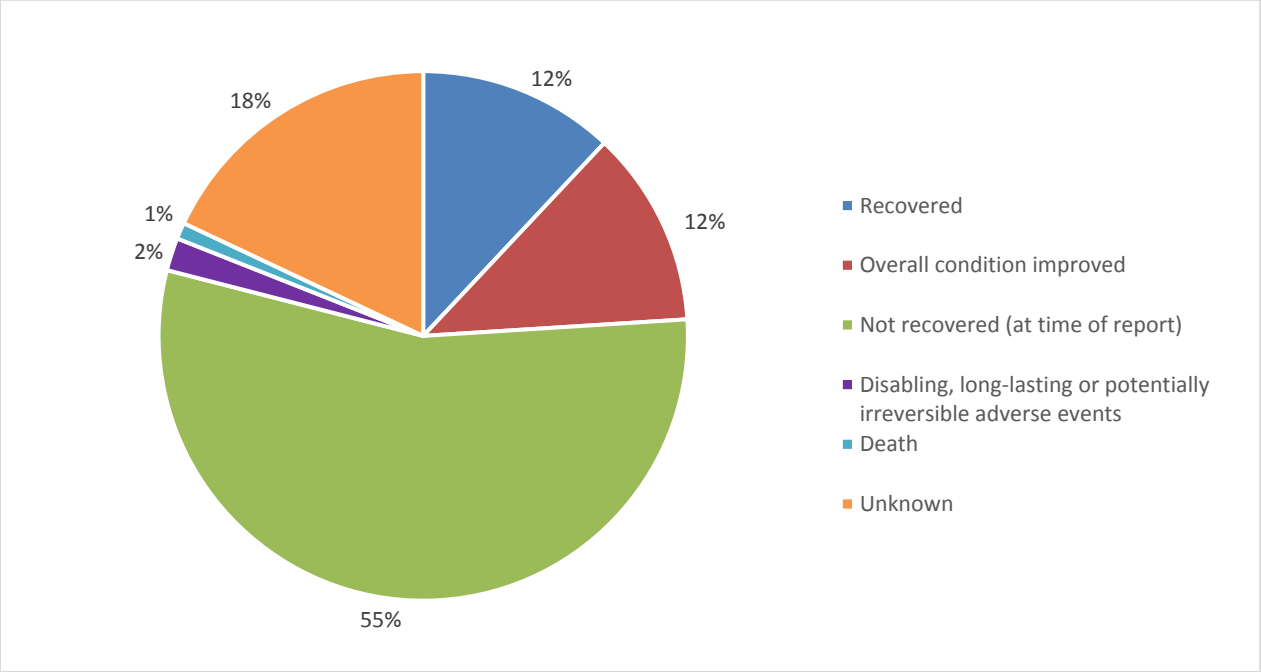
7.1.4. Reports of myocarditis/pericarditis after adenoviral vector vaccine

Gender was not provided in 61 cases of myocarditis reported in temporal association with the Vaxzevria vaccine and in 27 cases after COVID-19 Vaccine Janssen. The reports did not indicate a safety signal.

7.1.5. Outcome of reports of myocarditis/pericarditis

Figure 6 shows the outcomes of adverse reactions in the cases where myocarditis/pericarditis was reported after receiving one of the four COVID-19 vaccines. In the majority of reports, the final outcome of the reactions at the time of reporting was not yet conclusively assessable.

Figure 6: Outcome of reports of myocarditis/pericarditis after receiving COVID-19 vaccine



Nine deaths with a temporal association with COVID-19 vaccination and myocarditis/pericarditis were reported: six men and three women between the ages of 35 and 84. Five of the reports, involving three women and two men with a mean age of 70 (58-84 years), were related to Comirnaty. One of these cases, in which myocarditis was verified histologically, was seen by the reporting doctor as correlating to the vaccination. Further information regarding the four other cases is missing, which means a conclusive evaluation is not currently possible. The cases of myocarditis in two men after Spikevax were determined not to be the cause of death. In both cases, it is likely that other diseases not associated with vaccination caused death. One fatal outcome each was reported after Vaxzevria and COVID-19 Vaccine Janssen vaccinations. There is still additional information missing in both cases.

Additionally, there were three cases reported in which clear evidence of myocarditis was found during the course of an autopsy (see safety report from the Paul-Ehrlich-Institut from 20 August 2021). The pseudonymised autopsy reports have not been made available to the Paul-Ehrlich-Institut.

7.2. Anaphylactic reactions

Through 30 September 2021, there were 417 reports of anaphylactic reactions that the Paul-Ehrlich-Institut evaluated as corresponding to Brighton Collaboration[16] (BC) Levels 1-4 (see table 6). 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.

Table 6: Number of reported cases of anaphylaxis by vaccine and dose number

Vaccine	**Comirnaty**			**Spikevax**			**Vaxzevria**		**Janssen**	**Total**
Dose	**1**	**2**	**NS**	**1**	**2**	**NS**	**1**	**2**	**1**	
BC Level 1	80	28	1	8	2	0	27	1	0	147
BC Level 2	56	24	4	2	1	0	13	1	3	104
BC Level 3	7	1	0	1	1	0	0	0	0	10
Total BC Levels 1-3	143	53	5	11	4	0	40	2	3	261
BC Level 4	86	24	8	17	0	3	14	0	4	154
Total BC Levels 1-4	229	77	13	28	4	3	54	2	7	417 1)

NS: not specified
1) There was an additional anaphylaxis BC level 1 reported without information on the COVID-19 vaccine

7.3. 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, 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), paralysis of the

eye muscles, and loss or weakening of muscular reflexes.

There were a total of 255 cases of GBS/MFS reported to the Paul-Ehrlich-Institut. Of those, two cases after Vaxzevria, three after Comirnaty, and one after Moderna had a fatal outcome. Seventeen patients (n=8 Vaxzevria, n=7 Comirnaty, n=1 Spikevax, n=1 Janssen) needed to be treated in intensive care units, some receiving invasive ventilation.

Table 7: Age distribution of reported cases of GBS/MFS after COVID-19 vaccination

Reported GBS/MFS cases after vaccination				
Age group	**Comirnaty**	**Spikevax**	**Vaxzevria**	**Janssen**
up to 19 years	1	0	0	0
20-29 years	9	0	4	2
30-39 years	16	0	9	2
40-49 years	11	2	16	7
50-59 years	19	1	36	11
60-69 years	19	3	24	11
70-79 years	16	2	13	0
80+ years	8	3	2	2
No information	4	0	2	0
Total	103	11	106	35
Average age (years)	54.9	67	55.4	54.2
Reporting rate per 100,000 vaccine doses	0.13	0.11	0.84	1.10

Table 8: Number of reported GBS/MFS cases after vaccination according to Brighton Collaboration[38] case definition

	Comirnaty	Spikevax	Vaxzevria	Janssen	Total
BC Level 1	16	2	37	16	71
BC Level 2	11	2	11	0	24
BC Level 3	4	0	4	2	10
Total BC Levels 1-3	31	4	52	18	105
BC Level 4	72	7	54	17	150
Total BC Levels 1-4	103	11	106	35	255

GBS is a known adverse event of both adenoviral vector vaccines and is listed accordingly in the product information of both vaccines. The reporting rate of GBS for both mRNA vaccines is significantly lower (table 7) than what would have been statistically expected.

7.4. Thrombosis with thrombocytopenia

A total of 189 cases of thrombosis with concurrent thrombocytopenia was reported for Vaxzevria. 109 women and 79 men were affected. Gender was not reported in one case. Five patients reported thrombosis with thrombocytopenia after the second vaccination. The time interval between a second vaccination with Vaxzevria and the start of the reaction was between one and five days in those cases. The total reporting rate for men and women in all age groups was 1.49 suspected cases per 100,000 vaccine doses. The reporting rate corresponding to the second vaccine was significantly lower, with a reporting rate of 0.14 per 100,000 vaccine doses. The highest reporting rates were among women aged 40-49 (3.87 per 100,000 vaccine doses) and among men aged 30-39 (3.86 per 100,000 vaccine doses). Table 9 shows the number of reports per age group among women and men, as well as the number of reports that conform to the case definition of TTS according to the Centres of Disease Control and Prevention (CDC) in the US, which reads: thrombosis in an unusual location with concurrent thrombocytopenia with or without evidence of anti-PF4 antibodies, or thrombosis in a common location with thrombocytopenia and evidence of anti-PF4 antibodies.

A total of 20 cases were reported after vaccination with COVID-19 Vaccine Janssen. Five women (one possible duplicate report) and 14 men were affected. Gender was not provided in one case (table 9). In one instance, the individual had previously received a Vaxzevria vaccination.

Table 9: Number of reports and reporting rate of thrombosis with thrombocytopenia after Vaxzevria and COVID-19 Vaccine Janssen among women and men by age group

Age (years)	Vaxzevria				COVID-19 Vaccine Janssen			
	Women		Men		Women		Men	
	Cases (deaths)	Meets CDC case definition	Cases (deaths)	Meets CDC case definition	Cases (deaths)	Meets CDC case definition	Cases (deaths)	Meets CDC case definition
18-29	12 (0)	11	15 (1)	15			1 (1)	0
30-39	11 (1)	10	23 (4)	18	1 (0)	0	6 (1)	4
40-49	24 (6)	19	9 (2)[1]	7	2 (2)[3]	2	3 (0)	3
50-59	19 (1)	13	5 (0)	3	1 (0)	1	2 (0)	1
60-69	28 (4)	20	18 (3)[2]	11	1 (0)	1		
70-79	10 (1)	2	6 (1)[1]	1				
80+	4 (1)	1	1	1				
Unknown	1 (0)	0	2	1			2 (0)	0
Total	109 (14)	76	79 (11)	57	5 (2)	4	14 (2)	8
Reporting rate per 100,000 vaccinations	1.78		1.2		0.45		0.67	
Sensitivity analysis: Reporting rate per 100,000 vaccinations	1.65		1.12		0.42		0.63	

1: Includes two cases of TTS after the second vaccination, 2: one case of TTS after the second vaccination, 3: Two reports of TTS resulting in death are possibly due to duplicate reporting; in one case gender was not reported

A total of 33 cases of thrombosis with thrombocytopenia after Comirnaty affecting 17 women and 16 men between the ages of 27 and 99 were reported to the Paul-Ehrlich-Institut. Information on the number of thrombocytes was missing in most cases. Five reports after Spikevax describe cases of thrombosis and thrombocytopenia. None of the reports shared information on evidence of anti-PF4 antibodies. The data that is available to the Paul-Ehrlich-Institut does not indicate an association between the reports of thrombosis with thrombocytopenia and either of the two mRNA vaccines.

Table 10: Number of reports and reporting rate of thrombosis with thrombocytopenia after Comirnaty and Spikevax among women and men and according to age group

Age (years)	Comirnaty				Spikevax			
	Women		Men		Women		Men	
	Cases (deaths)	Meets CDC case definition	Cases (deaths)	Meets CDC case definition	Cases (deaths)	Meets CDC case definition	Cases (deaths)	Meets CDC case definition
18-29	1 (0)	1	2 (0)	1	2 (0)	0		
30-39	0		1 (0)	0				
40-49	2 (0)	0	2 (0)[2,3]	0				
50-59	1 (0)	0	3 (0)	0				
60-69	3 (0)[1]	0	3 (0)[4]	1	1 (0)	0	1 (0)	1
70-79	3 (1)	0	1 (1)	0	1 (0)	0		
80+	7 (3)[2]	0	3 (0)[5]	1				
Unknown								
Total	17 (4)	1	15 (1)	3	4 (0)	0	1	1
Reporting rate per 100,000 vaccinations	0.04		0.04		0.08		0.02	
Sensitivity analysis: Reporting rate per 100,000 vaccinations	0.04		0.04		0.08		0.02	

1 negative HIT diagnosis, 2 Vaccine Induced Thrombosis Thrombocytopenia Syndrome (VITT) ruled out, 3 antiphospholipid syndrome, 4 pre-existing ITP, 5 negative HIPA

7.5. Observed versus expected analysis (OE) of additional selected AESI

The number of reports of pulmonary embolisms, venous sinus thromboses, and cases of thrombocytopenia, including immune thrombocytopenia (ITP), after receiving a vaccination were evaluated in comparison to the number of illnesses that would be expected based on the general population incidence rate independent from vaccination.

7.5.1. Thrombocytopenia / immune thrombocytopenia (ITP)

In the following tables, OE analyses of reports of thrombocytopenia or ITP (with no thrombosis reported) after the four authorised COVID-19 vaccines are presented. The analysis found that there were more suspected cases of thrombocytopenia or ITP after Vaxzevria than would be statistically expected. The Standardized Morbidity Ratio (SMR) for COVID-19 Vaccine Janssen is indeed > 1, however, the cases were low in terms of absolute numbers and the 95% confidence interval includes 1 (table 11).

ITP is named as a possible adverse event in section 4.8 of the product information for Vaxzevria und COVID-19 Vaccine Janssen, the two adenoviral vector vaccines.

Table 11: Standardized Morbidity Ratio (SMR) for suspected case reports of a thrombocytopenia or immune thrombocytopenia (ITP); analysis with case numbers and vaccinations through 30 September 2021; cases for which the time interval between vaccination and start of symptoms is known are included; SMR for thrombocytopenia/ ITP was calculated based on reports indicating a concurrent thrombocytopenia.

	Background incidence rate (cases per 100,000 person years + 95% confidence interval)	Time interval between vaccination and start of symptoms in days	Number of cases Comirnaty	SMR 95% CI Comirnaty	Number of cases Spikevax	SMR 95% CI Spikevax	Number of cases Vaxzevria	SMR 95% CI Vaxzevria	Number of cases COVID-19 Vaccine Janssen	SMR 95% CI COVID-19 Vaccine Janssen
Total ≥18 years	3.8 (3.6-4.1)	14	107	0.93 (0.76-1.12)	13	0.93 (0.49-1.58)	114	6.17 (5.09-7.41)	8	1.73 (0.75-3.40)
		30	151	0.61 (0.52-0.72)	19	0.63 (0.38-0.99)	168	4.24 (3.63-4.94)	12	1.21 (0.62-2.11)
		42	166	0.48 (0.41-0.56)	19	0.45 (0.27-0.70)	178	3.21 (2.76-3.72)	13	0.94 (0.50-1.60)
Male ≥18 years	3.1 (2.7-3.4)	14	46	1.05 (0.77-1.39)	6	1.05 (0.39-2.29)	41	5.25 (3.77-7.13)	4	1.62 (0.44-4.14)
		30	63	0.67 (0.51-0.85)	7	0.57 (0.23-1.18)	71	4.25 (3.32-5.35)	5	0.94 (0.31-2.20)
		42	70	0.53 (0.41-0.67)	7	0.41 (0.16-0.84)	75	3.20 (2.52-4.01)	6	0.81 (0.30-1.76)
Female ≥18 years	4.6 (4.2-5.0)	14	61	0.83 (0.63-1.06)	6	0.70 (0.26-1.53)	73	6.77 (5.31-8.51)	4	2.07 (0.56-5.29)
		30	87	0.55 (0.44-0.68)	11	0.60 (0.30-1.08)	97	4.20 (3.40-5.12)	7	1.69 (0.68-3.48)
		42	95	0.43 (0.35-0.52)	11	0.43 (0.21-0.77)	103	3.18 (2.60-3.86)	7	1.21 (0.48-2.48)

The case numbers for Spikevax are low enough to make a further age-specific and gender-specific analysis impractical. This kind of analysis was completed for reports after vaccination with Comirnaty (table 12). Even though the SMR is 1 for some age groups, the result in all evaluations is not significant and therefore no safety signal is indicated.

Table 12: Observed versus expected analysis of thrombocytopenia without thrombosis after Comirnaty; cases in which the individual was vaccinated by or on 30 September 2021 and for which the time interval between vaccination and start of symptoms is known are included.

Age group	Background incidence rate (cases per 100,000 person years + 95% confidence interval)[1]	Time interval between vaccination and start of symptoms in days	Total Comirnaty cases	SMR 95% CI Comirnaty total
<18 years	4.2 (3.7-4.7)	14	8	1.46 (0.63-2.88)
		30	8	0.68 (0.29-1.34)
		42	8	0.49 (0.21-0.96)
18–64 years	2.9 (2.7-3.2)	14	73	1.25 (0.98-1.57)
		30	100	0.80 (0.65-0.97)
		42	106	0.61 (0.50-0.73)
65–100 years	7.4 (6.6-8.1)	14	34	0.45 (0.31-0.63)
		30	51	0.32 (0.24-0.42)
		42	60	0.27 (0.20-0.34)
≥18 years	3.8 (3.6-4.1)	14	107	0.93 (0.76-1.12)
		30	151	0.61 (0.52-0.72)
		42	166	0.48 (0.41-0.56)
<18 years, male	4.7 (3.9-5.5)	14	5	1.57 (0.51-3.66)
		30	5	0.73 (0.24-1.71)
		42	5	0.52 (0.17-1.22)
18–64 years, male	2.2 (1.7-2.3)	14	29	1.35 (0.90-1.94)
		30	41	0.89 (0.64-1.21)
		42	43	0.67 (0.48-0.90)
65–100 years, male	7.8 (6.6-9.0)	14	17	0.49 (0.29-0.79)
		30	22	0.30 (0.19-0.45)
		42	27	0.26 (0.17-0.38)

Age group	Background incidence rate (cases per 100,000 person years + 95% confidence interval)[1]	Time interval between vaccination and start of symptoms in days	Total Comirnaty cases	SMR 95% CI Comirnaty total
≥18 years male	3.1 (2.7-3.4)	14	46	1.05 (0.77-1.39)
		30	63	0.67 (0.51-0.85)
		42	70	0.53 (0.41-0.67)
<18 years, female	3.7 (3.0-4.4)	14	3	1.29 (0.27-3.77)
		30	3	0.60 (0.12-1.76)
		42	3	0.43 (0.09-1.26)
18–64 years, female	3.8 (3.4-4.2)	14	44	1.12 (0.81-1.50)
		30	59	0.70 (0.53-0.90)
		42	63	0.54 (0.41-0.68)
65–100 years, female	7.1 (6.1-8.0)	14	17	0.42 (0.24-0.67)
		30	28	0.32 (0.21-0.46)
		42	32	0.26 (0.18-0.37)
≥18 years, female	4.6 (4.2-5.0)	14	61	0.83 (0.63-1.06)
		30	87	0.55 (0.44-0.68)
		42	95	0.43 (0.35-0.52)

[1]Schoonen et al. Epidemiology of immune thrombocytopenic purpura in the General Practice Research Database. British Journal of Haematology, 145, 235–24

7.5.2. Pulmonary embolism

Table 13 shows the comparison of the reporting rate of pulmonary embolisms with the number of pulmonary embolisms that would be statistically expected among the vaccinated population in the time interval of 14 to 30 days. In order to evaluate the vaccines' thrombotic potential, which is a known, very rare complication associated with the adenoviral vector vaccines that isn't based on the development of anti-PF4 antibodies, only reports of a pulmonary embolism without concurrent thrombocytopenia were taken into consideration. According to these calculations, there was no safety signal indicated for any of the four COVID-19 vaccines, as the SMR is clearly under 1.

Table 13: Observed versus expected analysis of pulmonary embolisms
Standardized Morbidity Ratio (SMR), analysis on reports of a pulmonary embolism; case numbers until 30 September 2021 and vaccinations through 30 September 2021; cases for which the time interval between vaccination and start of symptoms is known are included; SMR for pulmonary embolisms was calculated based on reports without thrombosis.

Incidence rate (cases of pulmonary embolism per 100,000 person years + 95% CI)	Time interval between vaccination and start of symptoms in days	Total Comirnaty cases	SMR 95% CI Comirnaty	Total Spikevax cases	SMR 95% CI Spikevax	Total Vaxzevria cases	SMR 95 % CI Vaxzevria	Total cases COVID-19 Vaccine Janssen	SMR 95% CI COVID-19 Vaccine Janssen
81 (72–90)[1]	14	339	0.13 (0.12-0.15)	51	0.17 (0.13-0.22)	160	0.41 (0.35-0.47)	23	0.23 (0.15-0.35)
	30	471	0.12 (0.11-0.13)	69	0.15 (0.12-0.19)	227	0.38 (0.31-0.44)	32	0.22 (0.15-0.30)

[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; CI: confidence interval

7.5.3. Venous Sinus Thrombosis

In addition to the comparably frequently occurring pulmonary embolisms, an observed versus expected analysis of rarer venous sinus thromboses was completed. Exclusively cases of venous sinus thrombosis without concurrent thrombocytopenia were taken into consideration (table 14). A clear safety signal was indicated for Vaxzevria (SMR > 1). However, it cannot be ruled out that some reports involved cases with a concurrent thrombocytopenia that was not included in the report. These cases would therefore correspond to TTS (see 6.4). It must also be taken into consideration that the reporting rate of venous sinus thrombosis, especially for Vaxzevria, could be higher due to increased awareness and diagnostics (evaluation of headaches with temporal association with vaccination).

Case numbers were low and estimations uncertain for Spikevax and COVID-19 Vaccine Janssen. The reporting rate of venous sinus thrombosis for women within 14 days of Comirnaty vaccination was slightly high, with an SMR of 1.11, but was not significantly higher than the expected value (n = 36,9). Additional age stratification showed that this calculation was primarily based on 8 reports of venous sinus thrombosis among young women (18-29 years, table 15), while there was no increased SMR indicated among men of the same age. It cannot be presently ruled out that the awareness of venous sinus thrombosis among young women after COVID-19 vaccination could have led to distortion of the reporting rate. The Paul-Ehrlich-Institut will continue to monitor and track venous sinus thromboses after COVID-19 vaccination.

Table 14: Observed versus expected analysis of venous sinus thrombosis without thrombocytopenia among adults; cases regarding individuals vaccinated through 30 September 2021 and with known age and time interval between vaccination and start of symptoms are included.

	Background incidence rate (cases per 100,000 person years + 95% confidence interval)	Time interval between vaccination and start of symptoms in days	Number of cases Comirnaty	SMR 95% CI Comirnaty	Number of cases Spikevax	SMR 95% CI Spikevax	Number of cases Vaxzevria	SMR 95% CI Vaxzevria	Number of cases COVID-19 Vaccine Janssen	SMR 95% CI COVID-19 Vaccine Janssen
Total ≥18 years	1.9 (1.4-2.3)[1]	14	53	0.92 (0.69-1.21)	6	0.86 (0.31-1.86)	63	6.82 (5.24-8.72)	3	1.30 (0.27-3.79)
		30	83	0.67 (0.54-0.84)	11	0.73 (0.37-1.31)	81	4.09 (3.25-5.09)	6	1.21 (0.44-2.63)
		42	90	0.52 (0.42-0.64)	11	0.52 (0.26-0.93)	88	3.18 (2.55-3.91)	6	0.86 (0.32-1.88)
Male ≥18 years	1.4 (0.8-2.0)[1]	14	11	0.55 (0.28-0.99)	4	1.55 (0.42-3.97)	21	5.96 (3.69-9.11)	1	0.89 (0.02-4.99)
		30	26	0.61 (0.40-0.89)	7	1.27 (0.51-2.61)	29	3.84 (2.57-5.51)	1	0.42 (0.01-2.33)
		42	29	0.49 (0.33-0.70)	7	0.91 (0.36-1.87)	33	3.12 (2.15-4.38)	1	0.30 (0.01-1.66)
Female ≥18 years	2.3 (1.5-3.0)[1]	14	41	1.11 (0.80-1.51)	2	0.47 (0.06-1.70)	42	7.79 (5.61-10.53)	2	2.07 (0.25-7.46)
		30	54	0.68 (0.51-0.89)	4	0.44 (0.12-1.12)	52	4.50 (3.36-5.90)	5	2.41 (0.78-5.63)
		42	58	0.52 (0.40-0.68)	4	0.31 (0.09-0.80)	55	3.40 (2.56-4.43)	5	1.72 (0.56-4.02)

[1]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

Table 15: Observed versus expected analysis of venous sinus thrombosis without thrombocytopenia after Comirnaty; cases regarding individuals vaccinated through 30 September 2021 and with known age and time interval between vaccination and start of symptoms are included.

Age group	Base incidence rate (cases per 100,000 person years + 95% confidence interval)[1]	Time interval between vaccination and start of symptoms in days	Total Comirnaty cases	SMR 95% CI Comirnaty total
18-29 years male	0.8 (0.0-1.9)	14	1	0.65 (0.02-3.61)
		30	3	0.91 (0.19-2.65)
		42	3	0.65 (0.13-1.89)
≥30 years male	1.6 (0.9-2.2)	14	10	0.51 (0.24-0.94)
		30	23	0.55 (0.35-0.82)
		42	26	0.44 (0.29-0.65)
≥18 years total male	1.4 (0.8-2.0)	14	11	0.55 (0.28-0.99)
		30	26	0.61 (0.40-0.89)
		42	29	0.49 (0.33-0.70)
18-29 years female	2.6 (0.5-4.7)	14	8	1.56 (0.67-3.07)
		30	11	1.00 (0.50-1.79)
		42	11	0.71 (0.36-1.28)
≥30 years female	2.2 (1.4-3.0)	14	33	1.06 (0.73-1.50)
		30	43	0.65 (0.47-0.87)
		42	47	0.51 (0.37-0.67)
≥18 years total female	2.3 (1.5-3.0)	14	41	1.11 (0.80-1.51)
		30	54	0.68 (0.51-0.89)
		42	58	0.52 (0.40-0.68)

[1]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

8. SafeVac 2.0 survey

A total of 712,341 people with at least one vaccine dose had registered for the survey taken via the SafeVac 2.0 app as of 30 September 2021. The app is meant to monitor the safety of COVID-19 vaccines. The number of participants is equal to 1.3% of vaccinated individuals based on the total of 56,622,246 first vaccinations as of 30 September 2021. Severe reactions were reported in 2,632 reports (37%).

The most common 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.

9. Appendix

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.

9.1. 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 chronologically, but not necessarily causally, linked to vaccination. Due to rounding up or down, the sum of percentages in some charts and in the text may not add up to 100.

The Paul-Ehrlich-Institut focuses on specific topics in each safety report. It is not possible to include all evaluations that the Paul-Ehrlich-Institut makes within a month due to space limitations.

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, 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.

The Paul-Ehrlich-Institut collects all submitted reports, regardless of the causal link to the vaccination. It is important to set the reporting threshold at a low level in order to identify potential new safety signals as soon as possible. As a result, reports that are purely chronologically and not causally linked to a vaccine are significant (link to WHO manual: https://web.archive.org/web/20181019084617/http://gvsi-aefi-tools.org/new). The Paul-Ehrlich-Institut seeks out additional information on a large number of reports.

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[18, 38] case definition 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[39] 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[40]. 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 September 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. 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 September 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. Sensitivity analyses took a potential underestimation of the vaccination rate into account, which was indicated by a comparison between the vaccination rate officially provided by the RKI and the results of the COVIMO study[41].

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 (first or second) 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 adults 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. This survey is taking place as part of an observational study over a twelve month period. [42]

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