// Suspected cases of side effects or vaccination complications after vaccination with the Omikron-adapted bivalent COVID-19 vaccines Comirnaty Original/Omicron BA.1, Comirnaty Original/Omicron BA.4-5, Spikevax bivalent/ Omicron BA.1 (until 31.10. reported in Germany in 2022

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The Paul-Ehrlich-Institut (PEI) reports 444 suspected cases of side effects or vaccination complications in temporal connection with booster vaccinations with the recently approved mRNA vaccine products Comirnaty Original/Omicron BA.1, Comirnaty Original/Omicron BA.4-5 (BioNTech Manufacturing GmbH) or Spikevax bivalent/Omicron BA.1 (COVID-19 Vaccine Moderna, MODERNA BIOTECH SPAIN, SL).

These bivalent Omicron-adapted COVID-19 vaccine products are hereinafter also referred to as bivalent vaccines. The vaccine Spikevax bivalent/BA.4-5 was approved on 10/20/2022. By the date of the evaluation on October 31, 2022, the Paul-Ehrlich-Institut had not received any reports of suspected side effects from this vaccine. According to the Robert Koch Institute (RKI), 1,907,923 vaccinations with the above-mentioned bivalent vaccines had been carried out by October 31, 2022.

The reporting rate for suspected side effects or vaccination complications after the bivalent COVID-19 vaccines was 0.23 per 1,000 vaccinations and for suspected serious side effects 0.03 per 1,000 vaccinations.

A total of 333,492 suspected cases of side effects and 50,833 suspected cases of serious side effects were reported to the Paul-Ehrlich-Institut after primary immunization plus booster vaccinations. The reporting rate was 1.78 per 1,000 vaccine doses for all individual reports and 0.27 per 1,000 vaccine doses for serious individual reports.

New safety signals were not detected after administration of the bivalent mRNA vaccines.

In the following, the Paul-Ehrlich-Institut summarizes reports of suspected cases of side effects with a focus on reports of suspected cases of side effects after the bivalent mRNA vaccines.

A NOTICE:

Information on the methodology can be found in the safety reports of the Paul Ehrlich Institute on its website (www.pei.de/Sicherheit-covid-19-impfstoffe).

OVERVIEW AND COMPARISON OF REPORT RATES MONOVALENT AND BIVALENT COVID-19 VACCINES

By October 31, 2022, the Paul Ehrlich Institute had received a total of 333,492 individual case reports on suspected cases of side effects or vaccination complications (adverse reactions) after vaccination with COVID-19 vaccines in Germany (primary immunization and booster vaccinations). The number of individual case reports per month peaked in December 2021 and has increased over the summer

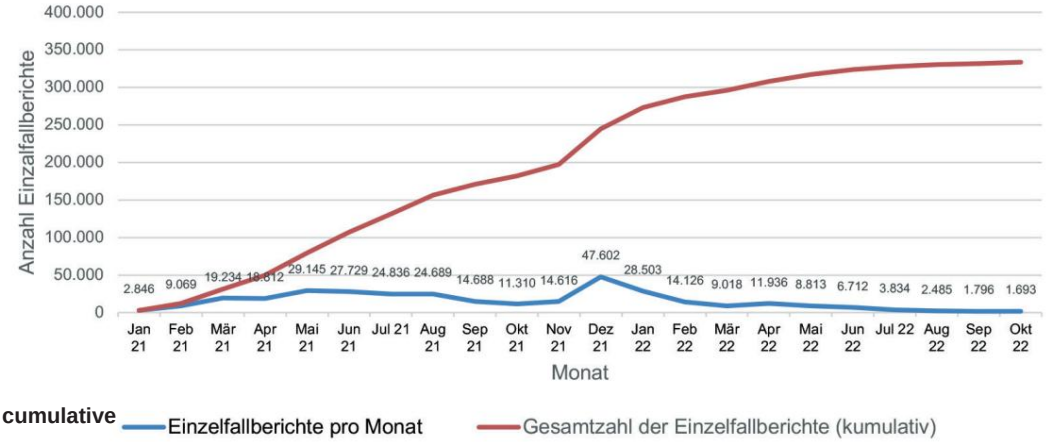

Figure 1: Number of suspected cases of side effects or vaccination complications per month and cumulative

months of 2022 (see Figure 1), which is approximately associated with the decrease in the number of vaccinations per month in Germany (https://impfdashboard.de/).

The number of individual case reports per vaccine product and the reporting rate per 1,000 vaccinations that the Paul Ehrlich Institute received from Germany by October 31, 2022 are shown in Table 1.

Table 1: Suspected cases of adverse reactions after vaccine and reporting rate per 1,000 vaccinations

vaccine product	Number Total reports of suspected cases	Reporting rate of suspected cases per 1,000 vaccinations in total	Number reports from Total suspected cases of serious side effects	Reporting rate per 1,000 vaccinations (major)
Comirnaty	202.963	1,47	34.315	0,25
Comirnaty Original/ Omicron*	424	0,23	42	0,02
Spikevax	61.642	1,95	6.584	0,2
Spikevax bivalent/ Omicron BA.*	20	0,43	6	0,08
Vaxzevria	54.053	4,2	7.343	0,57
Jcovden	11.857	3,16	1.715	0,45
Nuvaxovid	941	4,22	140	0,92
in total	**331.900**	**1,92**	**50.145**	**0,29**
Coronaimpfstoff n.b.	1.592		688	

The RKI summarizes the vaccination quotas for the bivalent mRNA vaccine products Comirnaty Original/BA.1 and Comirnaty Original/BA.4-5, which is why the number of suspected cases has also been summarized in Table 1; For the COVID-19 vaccine product Valneva, no reports of suspected side effects were submitted by the reporting date. nb=not known

The reporting rate for the bivalent mRNA vaccines seems to be significantly lower than for the monovalent vaccines (see Figure 2), although it should be noted that the follow-up time was significantly shorter than for the monovalent COVID-19 vaccines and suspected cases of Side effects are sometimes reported with a considerable delay. In addition, the bivalent vaccines are only approved as booster vaccines, ie presumably those people who have tolerated the previous vaccinations well can be vaccinated again. The Standing Vaccination Commission (STIKO) also recommends the second booster vaccination to a different collective than the basic immunization.

For Spikevax bivalent/Omicron BA.1, only 20 individual case reports were reported at the time of the analysis. Due to the small number, the calculated reporting rate is to be regarded as uncertain. For the COVID-19 vaccines Valneva and Spikevax bivalent/Omicron BA.4-5, no reports of suspected side effects were submitted by the reporting date.

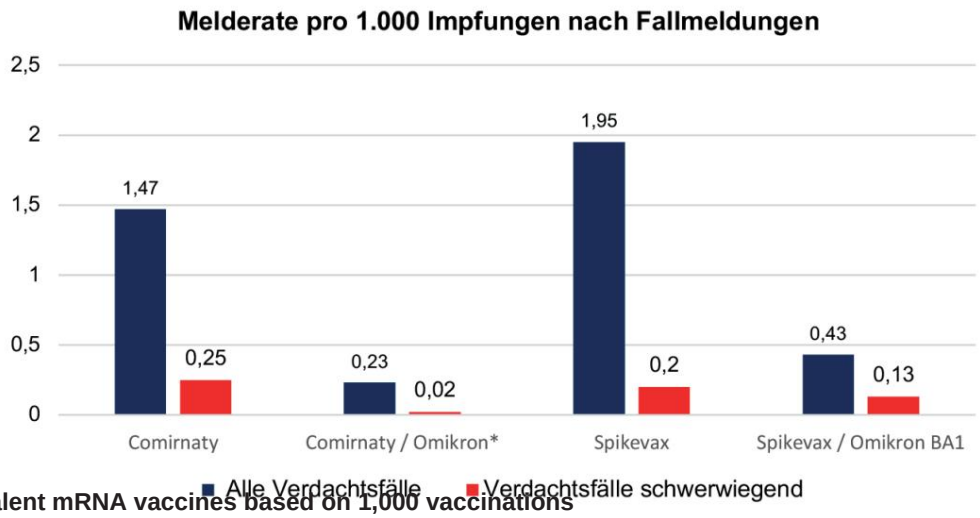

Figure 2: Comparison of the reporting rates of suspected cases of side effects or vaccination complications after bivalent versus the corresponding monovalent mRNA vaccines based on 1,000 vaccinations

*The RKI summarizes the vaccination rates for the bivalent mRNA vaccines Comirnaty Original/BA.1 and Comirnaty Original/BA.4-5, which is why the number of suspected cases has also been summarized here.

The mean age of the affected persons in the reported suspected cases of bivalent mRNA vaccines was 49 years (median 53 years). The gender distribution of the single case reports of suspected adverse reactions indicates a clear female predominance for all COVID-19 vaccines except Jcovden vaccine, which cannot be explained by the gender-stratified vaccination rates (see Table 2). In an analysis of the individual case reports about the suspicion of a serious side effect by a healthcare professional (health care professional, HCP, mostly doctor) after vaccination with Comirnaty, the COVID-19 vaccine most commonly used in Germany, the difference is much smaller out of. Serious suspected cases of side effects after vaccination with Comirnaty affected 57.49 percent women and 41.12 percent men. In the case of serious suspected cases reported by an HCP to the Paul Ehrlich Institute, 53.23 percent were women and 45.82 percent were men (the gender was not specified for the other reports). This indicates that the imbalance in the reports of suspected cases in women and men is mainly due to reports of suspected cases of non-serious side effects by the vaccinated persons (or by relatives).

Table 2: Number of reports up to October 31, 2022 by gender about suspected side effects/ vaccination complications after COVID-19 vaccine administration

	Number of reports male	Number of reports female	Number of reports kA
Comirnaty	55.232 (28,52%)	13.6235 (70,36%)	2.169 (1,12%)
Comirnaty Original/ Omicron BA.4-5	103 (31,31%)	225 (68,39%)	1 (0,30%)
Comirnaty Original/ Omicron BA.1	28 (31,11%)	62 (68,89%)	0
Spikevax	17.725 (29,33%)	42.098 (69,66%)	608 (1,00%)
Spikevax bivalent/ Omicron BA.1	9 (45,00%)	11 (55,00%)	0
Jcovden	5.421 (47,28%)	5.916 (51,6%)	129 (1,13%)
Nuvaxovid	245 (26,41%)	676 (72,85%)	7 (0,75%)
Vaxzevria	16.083 (30,80%)	35.655 (68,28%)	478 (0,92%)

Percentages do not always add up to 100 percent.

Note: The differences in the numbers from Table 1 result from cases without information on age and gender.

OUTCOME OF SUSPECTED CASES REPORTED AFTER DUAL VACCINATION COVID-19 VACCINES

At the time of reporting, the reported adverse reactions had completely subsided in 114 suspected cases, and the general condition had improved in 71 cases. In 137 cases, the state of health had not yet recovered at the time the report was made, and in 114 cases the outcome of at least one adverse reaction was unknown. Two deaths were reported to the Paul Ehrlich Institute by October 31, 2022. Two elderly people (ÿ80 years) with multiple, severe previous illnesses were affected, who each died one day after vaccination with Comirnaty Original/Omicron BA.1 or Spikevax bivalent/Omicron BA.1. A heart attack was given as the cause of death in one case, and suspected pulmonary embolism in the other case.

The Paul-Ehrlich-Institut does not see a causal connection with the respective vaccination in either case based on the available information and the underlying diseases. A study from France found no increased risk of myocardial infarction or pulmonary embolism in subjects aged 75 years and older after the first and second vaccinations with Comirnaty.1 Barda et al.2 also found after administration of the first two vaccination doses in Israel no increased risk of myocardial infarction or pulmonary embolism according to Comirnaty.2 Post-approval epidemiological data on the risk of arterial and venous thrombosis of the bivalent vaccines are not yet available.

Although deaths around the world have been reported around the time of the COVID-19 vaccination,3 several studies have shown that COVID-19 vaccinations do not lead to excess mortality overall, and especially among older people.4-7

Six suspected cases were reported as permanent damage, including three cases of stroke (apoplexy) four to 14 days after vaccination with Comirnaty Original/Omicron BA.1 (n=2) or Comirnaty

Original/Omicron BA.4-5 (n=1) in patients aged 55, 73 and 89 years. The transmitted medical information is currently very limited. In epidemiological studies in France and Israel, no increased risk of stroke (apoplexy) was found after the first two vaccinations with Comirnaty.1, 2 A causal relationship with the bivalent vaccination appears questionable in the three cases mentioned above. The other reports included fatigue, muscle pain, body aches one day after vaccination with Comirnaty Original/Omicron BA.1, ageusia and anosmia three days after vaccination with Comirnaty Original/Omicron BA.4-5 and nightmares, neck pain, increased blood pressure, body aches, Blood glucose, disorientation according to Comirnaty Original/ Omicron BA.4-5. Three of the six suspicious activity reports have been medically confirmed. No new risk signal can be identified from the six reports.

ADVERSE REACTIONS OF SPECIAL INTEREST

Due to official convention, adverse events of special interest (AESI) are generally classified as serious, even if they do not correspond to the legal definition in Section 4 of the Medicines Act (AMG).

After administration of the bivalent vaccine Comirnaty, 63 AESI were reported. The most common AESI were dyspnea (n=23), syncope (n=7), cardiac arrhythmia (n=4), pulmonary embolism (n=3), respiratory disorder (n=3), myocardial infarction (n=3), sudden hearing loss (n=3) and Apoplex (n=3, already mentioned above). Other AESIs were thrombosis (n=2) and, with one report each, were facial nerve palsy, deep vein thrombosis, seizure, loss of consciousness, myelitis, and subarachnoid hemorrhage. Four AESIs (dyspnoea, arrhythmia, pulmonary embolism and syncope) have been reported after bivalent Spikevax.

Two cases of myocarditis ten and twelve days after the fifth and first COVID-19 vaccination (n=1 Comirnaty Original/Omicron BA.4-5, n=1 Comirnaty Original/Omicron BA.1) affected one younger and one older Man. In one case, further clinical information was requested from the Paul-Ehrlich-Institut to assess the diagnostic reliability. The other case corresponded to the case definition according to the Brighton Collaboration (BC Level 1 as the highest diagnostic certainty).8 In both cases, the myocarditis was assessed according to WHO criteria by the Paul Ehrlich Institute as consistent with a causal connection with the vaccination.

Myocarditis and pericarditis are very rare side effects of mRNA vaccines that can occur not only after the primary immunization, and especially after the second vaccination, but also after booster vaccinations.

Three reports describe an anaphylactic reaction (n=2 anaphylactic shock, n=1 anaphylactic reaction) in three women. In two cases the diagnostic certainty was according Brighton Collaboration case definition with level 1 (highest diagnostic certainty).9 The undesirable reactions occurred a few minutes after the vaccination (fourth vaccination dose in one case, no information given in the second case) and lasted briefly due to immediate suitable therapy. In the third case, the diagnosis is currently still unclear (BC Level 4), also because of multiple confounders (influencing factors).

Anaphylaxis is a very rare, well-known side effect of mRNA vaccines. A comparison of anaphylactic reactions after COVID-19 vaccinations based on spontaneous reports in the US database VAERS (Vaccine Adverse Event Reporting System) and the European EudraVigilance database at the EMA office showed that the reporting rate of anaphylactic reactions after COVID-19 19 vaccines is in the range of the reporting rate of other non-COVID-19 vaccines.10 This result is also consistent with the literature data on the frequency of anaphylactic reactions after vaccination with other vaccines (for overview see11).

CONCLUSION

The reporting of suspected cases of side effects and vaccination complications is a central pillar for assessing the safety of vaccines, as new risk signals can be quickly detected on the basis of this information. It should be noted, however, that adverse reactions may occur after a vaccination, but not always in a causal connection.

About 90 percent of the 444 reports of suspected side effects were not serious.

The reporting rate of suspected cases of side effects after the above bivalent mRNA booster vaccines was lower for reports to the Paul Ehrlich Institute by October 31, 2022 than after administration of the monovalent mRNA vaccines from Comirnaty and Spikevax, although there was a systematic bias, e.g cannot be ruled out due to the shorter follow-up period.

No new risk signal was received by October 31, 2022 based on reports of suspected side effects or vaccination complications to the Paul Ehrlich Institute in Germany for the bivalent mRNA vaccines Comirnaty Original/Omicron BA.1, Comirnaty Original/Omicron BA.4- 5 or Spikevax bivalent/Omicron BA.1 detected.

The spontaneous reports about suspected side effects or vaccination complications after bivalent mRNA vaccines are consistent with international data.12 Known, very rare risks of mRNA vaccines including bivalent vaccines are myocarditis and/or pericarditis and anaphylaxis.

The Paul Ehrlich Institute will continue to consistently research and evaluate further reports of suspected side effects or vaccination complications.

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