Introduction

As of date, the European Medicines Agency authorised five COVID-19 vaccines: Comirnaty®, Spikevax®, Vaxzevria®, COVID-19 Vaccine Janssen and Nuvaxovid®. Comirnaty® and Spikevax® are both mRNA vaccines encoding SARS-CoV-2 virus spike protein, while Vaxzevria® and the Janssen vaccine are vector-based vaccines encoding SARS-CoV-2 virus spike protein as well. The newly approved subunit vaccine (SARS-CoV-2 virus spike protein) Nuvaxovid® has only been used on-demand in a limited amount of vaccinated persons. All the authorised COVID-19 vaccines are subject to additional monitoring (1-7).

Anecdotal reports of the COVID-19 vaccines altering women's menstrual cycle have been circulating on the internet since the beginning of 2021. In July 2021, at the time the Dutch vaccination program reached younger age groups, the Dutch media started to cover this topic frequently. In the meantime several studies were set up in order to investigate the possible effect and as of date some of them are published or awaiting peer review (8-13). In addition, The Netherlands Pharmacovigilance Centre Lareb has published a signal covering menstrual disorder reports in December 2021 (14).

Menstrual disorders are abnormalities related to women's menstrual cycle. This includes absence of menstruation (amenorrhea), abnormal heavy menstrual bleeding (menorrhagia), painful menstrual periods (dysmenorrhea), irregular periods and blood loss between two periods (intermenstrual blood loss). Menstrual disorders are quite common amongst women, but exact incidence numbers are hard to determine. Studies assessing the frequencies of the different menstrual disorders reported prevalence and incidence numbers of 6 to 90%. Differences can partially be explained by differences in study population and different outcome definitions. (15-22)

This signal provides an update on the spontaneous reports of menstrual disorders received by The Netherlands Pharmacovigilance Centre Lareb with the focus on amenorrhea and heavy menstrual bleeding. For a subset of the reports follow-up questions were sent. The results from this questionnaire are discussed in this report as well. This signal also provides results from the Lareb Intensive Monitoring (LIM) COVID-19 study, a prospective cohort study.

Reports

Spontaneous case reports

8 different menstrual disorder categories were defined and corresponding MedDRA® Preferred Terms (PTs) were determined (see Table 1).

Table 1 – Menstrual disorder categories

Category	MedDRA® Preferred Terms
Heavy menstrual blood loss	Heavy menstrual bleeding
Less menstrual blood loss	Hypomenorrhoea
Irregular blood loss	Polymenorrhoea, Menstruation irregular
Intermenstrual blood loss	Intermenstrual bleeding
Amenorrhoea/oligomenorrhoea	Menstruation delayed, Amenorrhoea, Oligomenorrhoea
Dysmenorrhoea	Dysmenorrhoea, Premenstrual pain, Premenstrual syndrome, Premenstrual headache, Premenstrual dysphoric disorder, Menstrual discomfort
Withdrawal blood loss abnormal	Abnormal withdrawal bleeding, Withdrawal bleed
Other	Anovulatory cycle, Menometrorrhagia, Menstrual disorder, Vaginal haemorrhage

Spontaneous case reports with a COVID-19 vaccine as suspect drug and a menstrual disorder MedDRA® Preferred Terms coded as reaction were selected. Table 2 provides information on the received menstrual disorder reports per vaccine.

Table 2 – Overview of spontaneous menstrual disorder case reports						
Vaccine	**Comirnaty®**	**Spikevax®**	**Janssen**	**Vaxzevria®**	**Unknown**	**Total**
Number of reports	19079	2727	1647	614	23	24090
Number of PTs	53978	10977	5342	2079	57	72433
Number of serious reports*	92	16	6	9	0	123
Number of serious menstrual PTs	25	5	1	7	0	38
COVID-19 infection prior						
	3686 (19.3%)	518 (19%)	318 (19.3%)	123 (20%)	5 (21.7%)	4650 (19.3%)
Vaccination moment						
1	8638 (45.3%)	1061 (38.9%)	1642 (99.7%)	281 (45.8%)	13 (56.5%)	11635 (48.3%)
2	9506 (49.8%)	1476 (54.1%)	5 (0.3%)	333 (54.2%)	6 (26.1%)	11326 (47%)
3	935 (4.9%)	190 (7%)	0 (0%)	0 (0%)	4 (17.4%)	1129 (4.7%)
Reporter						
Consumer	18973 (99.4%)	2720 (99.7%)	1638 (99.5%)	606 (98.7%)	21 (91.3%)	23958 (99.5%)
Health professional	106 (0.6%)	7 (0.3%)	9 (0.5%)	8 (1.3%)	2 (8.7%)	132 (0.5%)
Age (year)						
<25	3303 (17.3%)	357 (13.1%)	387 (23.5%)	82 (13.4%)	5 (21.7%)	4133 (17.2%)
25-34	7466 (39.1%)	808 (29.6%)	560 (34%)	224 (36.5%)	10 (43.5%)	9067 (37.6%)
35-44	5382 (28.2%)	808 (29.6%)	351 (21.3%)	174 (28.3%)	4 (17.4%)	6718 (27.9%)
45-54	2782 (14.6%)	712 (26.1%)	345 (20.9%)	107 (17.4%)	4 (17.4%)	3949 (16.4%)
55-64	121 (0.6%)	37 (1.4%)	8 (0.5%)	25 (4.1%)	0 (0%)	190 (0.8%)
≥65	22 (0.1%)	5 (0.2%)	1 (0.1%)	2 (0.3%)	0 (0%)	29 (0.1%)
Unknown	9 (0%)	0 (0%)	1 (0.1%)	0 (0%)	0 (0%)	10 (0%)
BMI (kg/m^2)						
<18	329 (1.7%)	31 (1.1%)	25 (1.5%)	4 (0.7%)	0 (0%)	389 (1.6%)
18-24.9	11509 (60.3%)	1636 (60%)	1046 (63.5%)	296 (48.2%)	14 (60.9%)	14501 (60.2%)
25-29.9	4586 (24%)	665 (24.4%)	395 (24%)	150 (24.4%)	7 (30.4%)	5803 (24.1%)
30-39.9	1985 (10.4%)	303 (11.1%)	148 (9%)	111 (18.1%)	1 (4.3%)	2548 (10.6%)
≥40	200 (1%)	34 (1.2%)	4 (0.2%)	33 (5.4%)	0 (0%)	271 (1.1%)
Unknown	470 (2.5%)	58 (2.1%)	29 (1.8%)	20 (3.3%)	1 (4.3%)	578 (2.4%)
Menstrual disorder category**						
Heavy menstrual blood loss	5559 (29.1%)	818 (30%)	518 (31.5%)	178 (29%)	9 (39.1%)	7082 (29.4%)
Less menstrual blood loss	680 (3.6%)	91 (3.3%)	55 (3.3%)	23 (3.7%)	0 (0%)	849 (3.5%)
Irregular blood loss	4303 (22.6%)	642 (23.5%)	396 (24%)	130 (21.2%)	4 (17.4%)	5475 (22.7%)
Intermenstrual blood loss	3585 (18.8%)	480 (17.6%)	336 (20.4%)	106 (17.3%)	6 (26.1%)	4513 (18.7%)
Dysmenorrhoea	2462 (12.9%)	316 (11.6%)	223 (13.5%)	66 (10.7%)	1 (4.3%)	3068 (12.7%)
Amenorrhoea/ oligomenorrhoea	6478 (34%)	859 (31.5%)	473 (28.7%)	198 (32.2%)	6 (26.1%)	8014 (33.3%)
Withdrawal blood loss abnormal	242 (1.3%)	25 (0.9%)	30 (1.8%)	8 (1.3%)	0 (0%)	305 (1.3%)
Other menstrual disorder	112 (18.2%)	248 (15.1%)	438 (16.1%)	3 (13%)	2641 (13.8%)	3442 (14.3%)

*A serious report does not necessarily means that the reported menstrual disorder was serious as well.
**Women can report menstrual disorders from multiple categories in one report.

Until March 29 2022, The Netherlands Pharmacovigilance Centre Lareb received a total of 24,090 reports containing at least one menstrual disorder PT associated with a COVID-19 vaccine. Most reports were reported following Comirnaty® vaccination (19,076), followed by Spikevax® (2,731) and Janssen COVID-19 vaccine (1,646). Overall, 19.3% of the women have had COVID-19 in the past. For all vaccines, with the exception of the Janssen and unknown vaccines, more reports were received on the second vaccine dose compared to the first vaccine dose, although there was no major difference between the doses. The vast majority of reports were sent in by consumers (23,958) and a total of 132 reports were sent in by a health professional. A few health professional cases were looked into more closely and showed a variation of menstrual disorders, from mild to more severe where intervention or testing was needed. The largest age group was 25-34 years (37.6%), followed by the age group of 35 to 44 years (27.9%). Most women had a BMI between 18 and 24.9 kg/m^2 (60.2%) followed by a BMI between 25 and 29.9 kg/m^2 (24.1%). No large differences between vaccines were observed. Lastly, amenorrhoea/oligomenorrhoea was the most reported menstrual disorder (33.3%) followed by heavy menstrual blood loss (29.4%) and irregular blood loss (22.7%) with no major differences between vaccines.

Serious reports

A total of 123 reports were serious according to the CIOMS criteria. This does not necessarily means that all the reported menstrual disorder were serious as well. A serious report can contain a combination of serious and non-serious reactions. In total, 38 menstrual disorder reactions were considered serious by the reporter. Index cases of serious menstrual disorder reports are listed below.

- NL-LRB-00661596 – A 40-50-year old woman experienced heavy and prolonged menstrual bleeding which caused severe anaemia following the first administration of Vaxzevria®. The patient had to be treated with a blood transfusion and a uterine surgery was planned.
- NL-LRB-00686951 – A 10-20-year old girl experienced amenorrhea for 7 months after her the first Comirnaty® dose. The girl was examined by a gynecologist but no abnormalities were found. After recovery she had an irregular menstrual cycle.
- NL-LRB-00745231– A 20-30-year old woman, using an oral anticonceptive, reported monthly breakthroughs. She usually would get a breakthrough bleeding once every 3/4 months. This led to a pregnancy according the reporter.

Outcome

Table 3 shows the reported outcomes for the 8 menstrual disorder categories and the co-reported adverse drug reactions. The number of women with menstrual disorders who had recovered at the time of reporting varied per menstrual disorder from 15.3% to 28.4%. Overall, most women had not recovered at time of reporting (52.4% to 64.4%).

Table 3 – Outcome of the menstrual disorders and co-reported adverse drug reactions

Outcome	Not recovered/not resolved/ongoing	Recovered/ resolved	Recovered/ resolved with sequelae	Recovering/ resolving	Unknown	Total
Heavy menstrual blood loss	4165 (54.6%)	1780 (23.3%)	0 (0%)	1034 (13.5%)	656 (8.6%)	7635
Less menstrual blood loss	465 (52.7%)	176 (20%)	0 (0%)	66 (7.5%)	175 (19.8%)	882
Irregular blood loss	3579 (64.4%)	852 (15.3%)	0 (0%)	560 (10.1%)	569 (10.2%)	5560
Intermenstrual blood loss	2658 (58.7%)	1123 (24.8%)	0 (0%)	495 (10.9%)	255 (5.6%)	4531
Dysmenorrhoea	1916 (59.5%)	567 (17.6%)	0 (0%)	478 (14.8%)	261 (8.1%)	3222
Amenorrhoea/ oligomenorrhoea	4835 (59.7%)	1607 (19.8%)	0 (0%)	540 (6.7%)	1118 (13.8%)	8100
Withdrawal blood loss abnormal	176 (52.4%)	86 (25.6%)	0 (0%)	26 (7.7%)	48 (14.3%)	336
Other menstrual disorder	1859 (53.3%)	988 (28.4%)	1 (0%)	340 (9.8%)	297 (8.5%)	3485

Reporting rates

The reporting rates per age group were calculated for the four vaccines, see Table 4. (Calculations and number of administrated vaccine doses can be found in Appendix A). The reporting rates varied from 0.2 reports per 100,000 vaccinations in the age group ≥65 (third Comirnaty® dose) and 1149.5 reports per 100,000 vaccinations in the age group 35-44 (Janssen). Overall, the reporting rates were high (more than 150 reports per 100,000 vaccinations) for all first and second doses in the age groups younger than 45 years. The reporting rate was the highest for the age group 25 to 34 years with exception of the Janssen COVID-19 vaccine. Lastly, Janssen had the highest overall reporting rate (523.0 reports per 100,000 vaccinations).

Table 4 – Reporting rates per 100.000 vaccinations per vaccine per vaccination moment

Age group	<25	25-34	35-44	45-54	55-64	≥65	Total
Comirnaty®							
1	206.3	636.9	331.4	143.7	4.8	0.4	177.8
2	223.0	689.5	471.3	224.0	8.9	0.8	210.0
3	35.5	81.8	62.9	46.0	2.9	0.2	40.4
Spikevax®							
1	309.4	553.9	273.2	134.1	1.1	2.6	213.3
2	407.1	664.7	490.2	261.8	10.7	0.0	319.6
3	*	*	*	31.9	2.6	0.3	8.7
Vaxzevria®							
1	174.7	352.9	195.1	72.5	1.8	0.7	40.8
2	241.8	441.9	245.2	91.1	3.9	0.7	52.1
Janssen							
1	575.7	1091.6	1149.5	185.5	17.2	0.0	523.0

***The reporting rate is left out due to very low numbers of administrated vaccines in this age group (less than 5000 nationwide).

Lareb Intensive Monitoring

The Netherlands Pharmacovigilance Centre Lareb collected data for the patient-reported cohort event monitoring study between February 2021 and March 2022. The cohort included men and women who have had at least one of the four widely used COVID-19 vaccines in The Netherlands administered (Comirnaty®, Spikevax®, Janssen and Vaxzevria®) (23, 24). Table 5 shows the number of women per age group who experienced menstrual disorders in this cohort. A total of 540 out of 16,987 women (3.18%) experienced a menstrual disorder. Amenorrhoea/oligomenorrhoea (0.82%) and heavy menstrual blood loss (0.75%) were the most reported menstrual disorders, followed by irregular blood loss (0.67%). The highest frequency of menstrual disorders was seen in the age group 26-35 years (7.31%).

Table 5 – Number of women with menstrual disorders in Lareb Intensive Monitoring (LIM) COVID-19 cohort

Age group	≤25	26-35	36-45	46-55	56-65	>65	Total
Number of women	**1277**	**2625**	**2994**	**3882**	**3141**	**3068**	**16987**
Amenorrhoea/oligomenorrhoea	14 (1.1%)	48 (1.83%)	40 (1.34%)	37 (0.95%)	0 (0%)	0 (0%)	139 (0.82%)
Heavy menstrual blood loss	9 (0.71%)	42 (1.6%)	42 (1.4%)	33 (0.85%)	1 (0.03%)	0 (0%)	127 (0.75%)
Irregular blood loss	7 (0.55%)	45 (1.71%)	30 (1%)	30 (0.77%)	1 (0.03%)	0 (0%)	113 (0.67%)
Intermenstrual blood loss	4 (0.31%)	28 (1.07%)	32 (1.07%)	13 (0.34%)	0 (0%)	0 (0%)	77 (0.45%)
Dysmenorrhoea	3 (0.24%)	14 (0.53%)	10 (0.33%)	4 (0.1%)	1 (0.03%)	0 (0%)	32 (0.19%)
Less menstrual blood loss	1 (0.08%)	7 (0.27%)	10 (0.33%)	5 (0.13%)	0 (0%)	0 (0%)	23 (0.14%)
Withdrawal blood loss abnormal	1 (0.08%)	3 (0.11%)	1 (0.03%)	0 (0%)	0 (0%)	0 (0%)	5 (0.03%)
Other menstrual disorder	1 (0.08%)	5 (0.19%)	8 (0.27%)	8 (0.21%)	2 (0.06%)	0 (0%)	24 (0.14%)

Total menstrual disorders	40 (3.13%)	192 (7.31%)	173 (5.78%)	130 (3.35%)	5 (0.16%)	0 (0%)	540 (3.18%)

Co-reported adverse drug reactions

In total there were 39,685 co-reported adverse drug reactions (ADRs). See Table 6 for all co-reported ADRs that were reported more than 100 times. The most co-reported ADRs were systemic ADRs such as fatigue, headache, malaise and myalgia. Injection site reactions were also co-reported frequently. These reactions are known ADRs of vaccines and COVID-19 vaccines specifically (2-5). Some notable frequently co-reported ADRs are menstruation symptoms such as breast complaints (pain, swelling, tenderness), mood swings, depressed mood and hot flushes. The latter can be related to menopause as well.

Table 6 – Number of co-reported PTs that were reported more than 100 times

Co-reported adverse drug reaction	Comirnaty®	Spikevax®	Janssen	Vaxzevria®	Unknown	Total
Fatigue	5867	1221	595	252	8	**7943**
Headache	4666	1084	561	232	5	**6548**
Malaise	4239	1166	536	231	4	**6176**
Myalgia	4345	1019	430	213	6	**6013**
Injection site pain	3168	847	226	125	1	**4367**
Chills	1934	807	424	167	5	**3337**
Nausea	2070	520	275	95	3	**2963**
Arthralgia	1735	570	221	131	4	**2661**
Pyrexia	1404	599	360	138	2	**2503**
Injection site inflammation	1568	612	111	79	1	**2371**
Injection site swelling	1378	537	109	87	0	**2111**
Injection site warmth	1106	502	82	51	1	**1742**
Injection site erythema	822	422	50	53	1	**1348**
Abdominal pain	591	114	37	37	0	**779**
Injection site haematoma	509	120	35	22	0	**686**
Body temperature increased	390	103	52	6	0	**551**
Injection site pruritus	305	167	13	29	0	**514**
Breast pain	392	56	20	9	1	**478**
Dizziness	279	30	33	20	0	**362**
Lymphadenopathy	266	64	8	1	0	**339**
Extensive swelling of vaccinated limb	160	93	11	12	0	**276**
Condition aggravated	220	29	3	17	0	**269**
Back pain	195	20	24	18	0	**257**
Migraine	178	27	13	7	0	**225**
Hot flush	176	22	8	5	0	**211**
Diarrhoea	165	22	10	5	0	**202**
Palpitations	136	26	16	5	0	**183**
Breast swelling	141	12	9	2	0	**164**
Mood swings	107	24	11	2	0	**144**
Abdominal distension	114	16	8	5	0	**143**
Injection site induration	77	53	3	10	0	**143**
Hyperpyrexia	57	32	28	25	0	**142**
Dyspnoea	99	20	8	11	0	**138**
Breast tenderness	112	11	11	1	0	**135**

Hyperhidrosis	93	22	5	15	0	**135**
Depressed mood	85	18	11	9	0	**123**
Pain in extremity	83	12	14	5	0	**114**
Acne	94	8	6	1	0	**109**
Alopecia	74	20	5	5	0	**104**
Tinnitus	78	7	13	3	0	**101**

Heavy menstrual blood loss

Table 7 shows an overview the received case reports of heavy menstrual blood loss following COVID-19 vaccination. A total of 7,068 heavy menstrual blood loss cases were reported, with the majority following Comirnaty® (78%). 47 case reports were considered serious according to the CIOMS criteria and within this set there were 21 serious menstrual events. 463 out of 7,068 women reported using a hormonal contraceptive and 37 women reported an antithrombotic drug as concomitant medication. Similar to all menstrual disorders combined (Table 2), the age group of 25-34 was the largest group (33.9%) followed by 35-44 (31.4%). For most women the duration of the bleeding was either unknown or the woman was not recovered yet (95.6%). Out of 312 women with a known duration, 212 (67.9%) had a bleeding duration of less than 14 days. Around half of the women (54.8%) had not recovered at the time of reporting. 23% had recovered and 13.5% was recovering at the time of reporting.

The following results are collected from the previous mentioned follow-up sent to a small number of women. Out of 422 women who have answered the question of how much their menstrual blood loss changed 298 (70.6%) answered “more than twice as much”, 100 (23.7%) “twice as much” and 24 (5.7%) “a little more”. Women were asked when they expected their next menstrual cycle to start at time of vaccination in order to find out at what time in their menstrual cycle the vaccination was administered. 211 women provided this information: 65.4% were expecting their next menstrual cycle to start in 14 days or less and the other 34.6% expected their next cycle to start in more than 14 days at the time of vaccination. 246 women answered the question whether their first cycle was affected. 222 out of 246 women (90.2%) answered that the first cycle after vaccination was abnormal and 24 women (9.8%) answered that the first cycle after vaccination was normal. Some women experienced heavy menstrual bleeding after the first vaccination and would later receive the second dose. The second dose is then regarded as a ‘rechallenge’. In our dataset, 112 women experienced heavy menstrual bleeding after the first vaccination and were known to have received their second dose. Half of these women (50.8%) experienced the same complaints after the second dose. Lastly, 58 women consulted their general practitioner, 25 women consulted their gynaecologist and 3 women were hospitalised due to the complaints. Some index cases where women consulted a doctor were a 30-40-year old woman with persistent menstrual blood loss of 14 days that needed a hormonal treatment to stop (case NL-LRB-00648531) and a 50-60-year old woman who was vaccinated at the end of her period and who started bleeding again for another week. A blood test and an uterine ultrasound were done and showed no abnormalities (case NL-LRB-00651025). Some women consulted a doctor due to their medical history, for example a 20-30-year old woman with factor VII deficiency who usually does not bleed because of her intrauterine device. Six hours after the first vaccination she started bleeding and needed treatment to stop the vaginal blood loss. This recurred after the second vaccination (case NL-LRB-00654376).

Table 7 – Overview of heavy menstrual blood loss reports after COVID-19 vaccination

	Comirnaty®	Spikevax®	Janssen	Vaxzevria®	Unknown	Total
Number of reports	5548	816	517	178	9	7068
Number of serious reports	31 (0,6%)	10 (1,2%)	3 (0,6%)	3 (1,7%)	0 (0%)	47 (0.7%)
Number of serious menstrual PTs	13 (0,2%)	4 (0,5%)	1 (0,2%)	3 (1,7%)	0 (0%)	21 (0.3%)
Vaccination moment						
1	2453 (44,2%)	331 (40,6%)	514 (99,4%)	86 (48,3%)	4 (44.4%)	3388 (47.9%)
2	2796 (50,4%)	436 (53,4%)	3 (0,6%)	92 (51,7%)	2 (22.2%)	3329 (47.1%)

3	299 (5,4%)	49 (6%)	0 (0%)	0 (0%)	3 (33.3%)	351 (5%)
Reporter						
Consumer	5517 (99,4%)	814 (99,8%)	514 (99,4%)	176 (98,9%)	8 (88.9%)	7029 (99.4%)
Health professional	31 (0,6%)	2 (0,2%)	3 (0,6%)	2 (1,1%)	1 (11.1%)	39 (0.6%)
Concomitant medication						
Hormonal contraception	353 (6,4%)	56 (6,9%)	46 (8,9%)	8 (4,5%)	0 (0%)	463 (6.6%)
Antithrombotic drug	29 (0,5%)	3 (0,4%)	0 (0%)	5 (2,8%)	0 (0%)	37 (0.5%)
Age (years)						
<25	813 (14,7%)	100 (12,3%)	96 (18,6%)	17 (9,6%)	3 (33.3%)	1029 (14.6%)
25-34	1953 (35,2%)	221 (27,1%)	162 (31,3%)	59 (33,1%)	4 (44.4%)	2399 (33.9%)
35-44	1783 (32,1%)	255 (31,3%)	125 (24,2%)	54 (30,3%)	1 (11.1%)	2218 (31.4%)
45-54	962 (17,3%)	234 (28,7%)	131 (25,3%)	40 (22,5%)	1 (11.1%)	1368 (19.4%)
55-64	34 (0,6%)	6 (0,7%)	2 (0,4%)	8 (4,5%)	0 (0%)	50 (0.7%)
>65-69	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Unknown	3 (0,1%)	0 (0%)	1 (0,2%)	0 (0%)	0 (0%)	4 (0.1%)
Intensity menstrual blood loss*						
“A little more"	22 (0,4%)	2 (0,2%)	0 (0%)	0 (0%)	0 (0%)	24 (0.3%)
"Twice as much"	87 (1,6%)	11 (1,3%)	2 (0,4%)	0 (0%)	0 (0%)	100 (1.4%)
"More than twice as much"	219 (3,9%)	46 (5,6%)	25 (4,8%)	8 (4,5%)	0 (0%)	298 (4.2%)
Unknown	5220 (94,1%)	757 (92,8%)	490 (94,8%)	170 (95,5%)	9 (100%)	6646 (94%)
Outcome						
Not recovered/not resolved/ongoing	3021 (54,5%)	425 (52,1%)	313 (60,5%)	107 (60,1%)	6 (66,7%)	3872 (54.8%)
Recovering/resolving	760 (13,7%)	103 (12,6%)	67 (13%)	26 (14,6%)	1 (11,1%)	957 (13.5%)
Recovered/resolved	1279 (23,1%)	208 (25,5%)	100 (19,3%)	34 (19,1%)	2 (22,2%)	1623 (23%)
Recovered/resolved with sequelae	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Unknown	488 (8,8%)	80 (9,8%)	37 (7,2%)	11 (6,2%)	0 (0%)	616 (8.7%)
Duration (days)						
0-2	28 (0,5%)	3 (0,4%)	4 (0,8%)	0 (0%)	0 (0%)	35 (0.5%)
3-6	93 (1,7%)	16 (2%)	4 (0,8%)	0 (0%)	0 (0%)	113 (1.6%)
7-13	53 (1%)	8 (1%)	2 (0,4%)	1 (0,6%)	0 (0%)	64 (0.9%)
≥14	80 (1,4%)	15 (1,8%)	3 (0,6%)	2 (1,1%)	0 (0%)	100 (1.4%)
Unknown	5294 (95,4%)	774 (94,9%)	504 (97,5%)	175 (98,3%)	9 (100%)	6756 (95.6%)
Time to expected new menstrual cycle (days)*						
≤14	117 (2,1%)	13 (1,6%)	5 (1%)	3 (1,7%)	0 (0%)	138 (2%)
>14	59 (1,1%)	12 (1,5%)	1 (0,2%)	1 (0,6%)	0 (0%)	73 (1%)
Unknown	5372 (96,8%)	791 (96,9%)	511 (98,8%)	174 (97,8%)	9 (100%)	6857 (97%)
Affected first menstrual cycle after vaccination*						
First cycle normal	18 (0,3%)	3 (0,4%)	3 (0,6%)	0 (0%)	0 (0%)	24 (0.3%)
First cycle abnormal	182 (3,3%)	29 (3,6%)	7 (1,4%)	4 (2,2%)	0 (0%)	222 (3.1%)
Unknown	5348 (96,4%)	784 (96,1%)	507 (98,1%)	174 (97,8%)	9 (100%)	6822 (96.5%)
Rechallenge at the time of reporting or follow-up*						
No rechallenge was done	371 (6,7%)	54 (6,6%)	31 (6%)	9 (5,1%)	0 (0%)	465 (6.6%)

Rechallenge was done, outcome unknown	30 (0,5%)	5 (0,6%)	0 (0%)	1 (0,6%)	0 (0%)	36 (0.5%)
Rechallenge was done, reaction did not recur	16 (0,3%)	3 (0,4%)	0 (0%)	0 (0%)	0 (0%)	19 (0.3%)
Rechallenge was done, reaction recurred	52 (0,9%)	5 (0,6%)	0 (0%)	0 (0%)	0 (0%)	57 (0.8%)
Unknown	5079 (91,5%)	749 (91,8%)	486 (94%)	168 (94,4%)	9 (100%)	6491 (91.8%)
Doctor consultation*						
General practitioner	44 (0,8%)	7 (0,9%)	4 (0,8%)	3 (1,7%)	0 (0%)	58 (0.8%)
Gynaecologist	16 (0,3%)	4 (0,5%)	4 (0,8%)	1 (0,6%)	0 (0%)	25 (0.4%)
Hospitalisation	2 (0%)	0 (0%)	0 (0%)	1 (0,6%)	0 (0%)	3 (0%)
No consultation	119 (2,1%)	25 (3,1%)	1 (0,2%)	0 (0%)	0 (0%)	145 (2.1%)
Unknown	5367 (96,7%)	780 (95,6%)	508 (98,3%)	173 (97,2%)	9 (100%)	6837 (96.7%)

* The number of unknown is high due to information being mostly only available in subset with follow-up.

Another point of interest was the use of hormonal contraception. From the small subset of women (659 total), 197 women did not provide any information on the use of hormonal contraception. The other 462 cases are shown in Table 8. One of the differences between women who were using hormonal contraception and women who were not is age: women who were using hormonal contraception were younger (mean 32) compared to non-users (mean 38). Other differences were that women who were using hormonal contraception experienced heavier and longer menstrual blood loss compared to non-users.

Table 8 – Heavy menstrual blood loss after COVID-19 vaccination stratified by hormonal contraception

Hormonal contraception	**Yes**	**No**
Number of reports	135	327
Vaccination moment		
1	75 (55.6%)	182 (55.7%)
2	60 (44.4%)	145 (44.3%)
3	0 (0%)	0 (0%)
Reporter		
Consumer	134 (99.3%)	325 (99.4%)
Health professional	1 (0.7%)	2 (0.6%)
Age (years)		
<25	30 (22.2%)	29 (8.9%)
25-34	49 (36.3%)	99 (30.3%)
35-44	40 (29.6%)	116 (35.5%)
45-54	16 (11.9%)	81 (24.8%)
55-64	0 (0%)	2 (0.6%)
≥65	0 (0%)	0 (0%)
Unknown	0 (0%)	0 (0%)
Intensity menstrual blood loss		
“A little more"	5 (3.7%)	16 (4.9%)
"Twice as much"	6 (4.4%)	65 (19.9%)
"More than twice as much"	77 (57%)	156 (47.7%)
Unknown	47 (34.8%)	90 (27.5%)
Outcome		
Not recovered/not resolved/ongoing	36 (26.7%)	98 (30%)
Recovering/resolving	12 (8.9%)	20 (6.1%)
Recovered/resolved	78 (57.8%)	170 (52%)

Recovered/resolved with sequelae	0 (0%)	0 (0%)
Unknown	9 (6.7%)	39 (11.9%)
Duration (days)		
0-2	2 (1.5%)	26 (8%)
3-6	18 (13.3%)	56 (17.1%)
7-13	15 (11.1%)	29 (8.9%)
≥14	35 (25.9%)	47 (14.4%)
Unknown	65 (48.1%)	169 (51.7%)
Rechallenge at the time of follow-up		
No rechallenge was done	95 (70.4%)	248 (75.8%)
Rechallenge was done, outcome unknown	8 (5.9%)	19 (5.8%)
Rechallenge was done, reaction did not recur	6 (4.4%)	9 (2.8%)
Rechallenge was done, reaction recurred	14 (10.4%)	29 (8.9%)
Unknown	12 (8.9%)	22 (6.7%)
Doctor consultation		
General practitioner	18 (13.3%)	23 (7%)
Gynaecologist	3 (2.2%)	15 (4.6%)
Hospitalisation	0 (0%)	3 (0.9%)
No consultation	29 (21.5%)	97 (29.7%)
Unknown	85 (63%)	189 (57.8%)

Amenorrhoea

Table 9 shows all received amenorrhoea case reports. In total, there were 4,065 women who experienced amenorrhoea following COVID-19 vaccination. The majority of these women received Comirnaty® (80.5%). In total there were 14 amenorrhoea case reports that were considered to be serious according to the CIOMS criteria. The vaccination moment, reporter and women's age did not differ much from all menstrual disorders combined (Table 2). The majority of women (79%) had not recovered at the time of reporting. 7.3% did recover and 3.7% was recovering at the time of reporting. Out of 298 women who recovered, 149 women (50%) reported that their menstruation was delayed for longer than 14 days.

The subsequent results were collected through follow-up. For women with amenorrhoea, the timing of vaccination in relation to the menstrual cycle was also a point of interest. 45 out of 64 women (70.3%) reported that at the time of their vaccination they were expecting their menstruation in 14 days or less. Some women reported that the first menstrual cycle after vaccination was normal (8.3%) and that they noticed the absence of menstruation in the next cycle. But most women (91.7%) reported that the first expected cycle after vaccination was absent. For amenorrhoea cases there were 32 rechallenge cases; women who experienced an absence of menstruation after the first vaccination and later received the second vaccination. 13 women had absent menstruation after the second dose as well, 5 did not and for 14 women it was unknown. Lastly, from the women who provided additional information, 12 consulted their general practitioner and 5 consulted their gynaecologist. The most reported reason for consultation of a doctor was an exceptionally long absence of menstruation. For example in case NL-LRB-00697160, a 20-30-year old woman with a child wish had an absent menstrual cycle for 2.5 months and had not recovered at the time of reporting. Additional testing did not show any abnormalities. Another example is case NL-LRB-00701682 about a 30-40-year old woman who had an absent menstruation for 8 months after vaccination and had not recovered at the time of reporting. Additional testing did not result in finding a cause.

Table 9 - Overview of PT amenorrhoea reports after COVID-19 vaccination						
	Comirnaty®	**Spikevax®**	**Janssen**	**Vaxzevria®**	**Unknown**	**Total**
Number of reports	3274	425	251	111	4	4065
Number of serious reports	13 (0.4%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	14 (0.3%)
Number of serious menstrual PTs	2 (0.1%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	3 (0.1%)
Vaccination moment						
1	1502 (45.9%)	189 (44.5%)	249 (99.2%)	47 (42.3%)	2 (50%)	1989 (48.9%)
2	1659 (50.7%)	227 (53.4%)	2 (0.8%)	64 (57.7%)	2 (50%)	1954 (48.1%)
3	113 (3.5%)	9 (2.1%)	0 (0%)	0 (0%)	0 (0%)	122 (3%)
Reporter						
Consumer	3251 (99.3%)	423 (99.5%)	251 (100%)	109 (98.2%)	4 (100%)	4038 (99.3%)
Health professional	23 (0.7%)	2 (0.5%)	0 (0%)	2 (1.8%)	0 (0%)	27 (0.7%)
Concomitant medication						
Hormonal contraception	106 (3.2%)	14 (3.3%)	10 (4%)	5 (4,5%)	0 (0%)	135 (3.3%)
Antithrombotic drug	10 (0.3%)	5 (1.2%)	1 (0.4%)	1 (0,9%)	0 (0%)	17 (0.4%)
Age (years)						
<25	655 (20%)	57 (13.4%)	55 (21.9%)	18 (16.2%)	0 (0%)	785 (19.3%)
25-34	1400 (42.8%)	164 (38.6%)	91 (36.3%)	44 (39.6%)	2 (50%)	1701 (41.8%)
35-44	749 (22.9%)	92 (21.6%)	48 (19.1%)	25 (22.5%)	1 (25%)	915 (22.5%)
45-54	460 (14.1%)	111 (26.1%)	55 (21.9%)	24 (21.6%)	1 (25%)	651 (16%)
55-64	6 (0.2%)	1 (0.2%)	2 (0.8%)	0 (0%)	0 (0%)	9 (0.2%)
>65-69	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Unknown	655 (20%)	57 (13.4%)	55 (21.9%)	18 (16.2%)	0 (0%)	785 (19.3%)
Outcome						
Not recovered/not resolved/ongoing	2615 (79.9%)	317 (74.6%)	195 (77.7%)	83 (74.8%)	3 (75%)	3213 (79%)
Recovering/resolving	112 (3.4%)	19 (4.5%)	16 (6.4%)	3 (2.7%)	1 (25%)	151 (3.7%)
Recovered/resolved	229 (7%)	39 (9.2%)	18 (7.2%)	12 (10.8%)	0 (0%)	298 (7.3%)
Recovered/resolved with sequelae	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Unknown	318 (9.7%)	50 (11.8%)	22 (8.8%)	13 (11.7%)	0 (0%)	403 (9.9%)
Duration of recovered women (days)*						
0-2	8 (3.5%)	1 (2.6%)	0 (0%)	2 (16.7%)	0 (0%)	11 (3.7%)
3-6	13 (5.7%)	2 (5.1%)	0 (0%)	0 (0%)	0 (0%)	15 (5%)
7-13	17 (7.4%)	4 (10.3%)	0 (0%)	0 (0%)	0 (0%)	21 (7%)
≥14	114 (49.8%)	17 (43.6%)	12 (66.7%)	6 (50%)	0 (0%)	149 (50%)
Unknown	77 (33.6%)	15 (38.5%)	6 (33.3%)	4 (33.3%)	0 (0%)	102 (34.2%)
Time to expected new menstrual cycle (days)**						
≤14	37 (1.1%)	3 (0.7%)	2 (0.8%)	3 (2.7%)	0 (0%)	45 (1.1%)
>14	14 (0.4%)	3 (0.7%)	1 (0.4%)	1 (0.9%)	0 (0%)	19 (0.5%)
Unknown	3223 (98.4%)	419 (98.6%)	248 (98.8%)	107 (96.4%)	4 (100%)	4001 (98.4%)

Affected first menstrual cycle after vaccination**						
First cycle normal	3 (0.1%)	3 (0.7%)	0 (0%)	1 (0.9%)	0 (0%)	7 (0.2%)
First cycle abnormal	62 (1.9%)	7 (1.6%)	6 (2.4%)	2 (1.8%)	0 (0%)	77 (1.9%)
Unknown	3209 (98%)	415 (97.6%)	245 (97.6%)	108 (97.3%)	4 (100%)	3981 (97.9%)
Rechallenge at the time of follow-up**						
No rechallenge was done	129 (3.9%)	27 (6.4%)	15 (6%)	4 (3.6%)	0 (0%)	175 (4.3%)
Rechallenge was done, outcome unknown	11 (0.3%)	1 (0.2%)	0 (0%)	2 (1.8%)	0 (0%)	14 (0.3%)
Rechallenge was done, reaction did not recur	4 (0.1%)	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)	5 (0.1%)
Rechallenge was done, reaction recurred	12 (0.4%)	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)	13 (0.3%)
Unknown	3118 (95.2%)	395 (92.9%)	236 (94%)	105 (94.6%)	4 (100%)	3858 (94.9%)
Doctor consultation**						
General practitioner	7 (0.2%)	4 (0.9%)	1 (0.4%)	0 (0%)	0 (0%)	12 (0.3%)
Gynaecologist	2 (0.1%)	1 (0.2%)	1 (0.4%)	1 (0.9%)	0 (0%)	5 (0.1%)
Hospitalisation	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
No consultation	29 (0.9%)	5 (1.2%)	0 (0%)	1 (0.9%)	0 (0%)	35 (0.9%)
Unknown	3236 (98.8%)	415 (97.6%)	249 (99.2%)	109 (98.2%)	4 (100%)	4013 (98.7%)

*Percentages are calculated for recovered women (n=298)
** The number of unknown is high due to information being mostly only available in subset with follow-up.

The follow-up questions sent to women with amenorrhoea included a question about the use of hormonal contraception. For 112 women the use of hormonal contraception remained unknown and for 140 women the use of hormonal contraception was known (see Table 10). There were no large differences between hormonal contraceptive users and non-users other than age; hormonal contraception users were younger than non-users.

Table 10 – Amenorrhoea after COVID-19 vaccination stratified by hormonal contraception

Hormonal contraception	**Yes**	**No**
Number of reports	27	113
Vaccination moment		
1	18 (66.7%)	54 (47.8%)
2	9 (33.3%)	59 (52.2%)
3	0 (0%)	0 (0%)
Reporter		
Consumer	26 (96.3%)	113 (100%)
Health professional	1 (3.7%)	0 (0%)
Age (year)		
<25	5 (18.5%)	15 (13.3%)
25-34	11 (40.7%)	39 (34.5%)
35-44	9 (33.3%)	27 (23.9%)
45-54	2 (7.4%)	32 (28.3%)
55-64	0 (0%)	0 (0%)
≥65	0 (0%)	0 (0%)
Unknown	0 (0%)	0 (0%)
Outcome		
Not recovered/not resolved/ongoing	0 (0%)	4 (3.5%)

Recovering/resolving	0 (0%)	0 (0%)
Recovered/resolved	2 (7.4%)	7 (6.2%)
Recovered/resolved with sequelae	0 (0%)	0 (0%)
Unknown	25 (92.6%)	102 (90.3%)
Duration (days)		
0-2	0 (0%)	0 (0%)
3-6	0 (0%)	5 (4.4%)
7-13	1 (3.7%)	1 (0.9%)
≥14	1 (3.7%)	3 (2.7%)
Unknown	25 (92.6%)	104 (92%)
Rechallenge at the time of follow-up		
No rechallenge was done	19 (70.4%)	77 (68.1%)
Rechallenge was done, outcome unknown	2 (7.4%)	9 (8%)
Rechallenge was done, reaction did not recur	2 (7.4%)	2 (1.8%)
Rechallenge was done, reaction recurred	1 (3.7%)	9 (8%)
Unknown	3 (11.1%)	16 (14.2%)
Doctor consultation		
General practitioner	2 (7.4%)	7 (6.2%)
Gynaecologist	0 (0%)	4 (3.5%)
Hospitalisation	0 (0%)	0 (0%)
No consultation	7 (25.9%)	18 (15.9%)
Unknown	18 (66.7%)	(0%)

Other sources of information

SmPC

Menstrual disorders are not listed as an adverse effect in the Summary of Product Characteristics of the five authorised COVID-19 vaccines(2-6).

Other databases

The WHO global database of individual case safety reports, VigiBase, has 47.486 reports of Heavy menstrual bleeding (PT), 34.118 reports of Menstrual disorder (PT), 22.764 reports of Menstruation delayed (PT), 25.708 reports of Menstruation irregular (PT), 22.134 reports of Dysmenorrhea (PT), 18.455 reports of Intermenstrual bleeding and 16.297 reports of Amenorrhea (PT) after all COVID-19 vaccines(25). Comirnaty® had the largest number of case reports associated with the above mentioned menstrual disorders.

Literature

There is not much evidence of vaccinations causing menstrual disorders. Two small studies from 1913 and 1987 described short-term changes in menstruation associated with the typhoid and hepatitis B vaccine respectively. In a larger and more recent questionnaire-based study from 2018 Suzuki et al. found significantly increased age-adjusted odds of attending hospital for heavier menstrual bleeding (1.43 [95% CI: 1.13–1.82]) and irregular menstruation (1.29 [95% CI: 1.12–1.49]) associated with the human papillomavirus (HPV) vaccine. Using data from the FDA Adverse Event Reporting System Gong et al. detected disproportionate reports of premature ovarian insufficiency (POI) and related events such as amenorrhea and irregular menstruation (26) associated with the HPV vaccine as well. However, a large Danish retrospective cohort study using data from 996.300 girls and women did not find an association between HPV vaccination and POI (27).

For the COVID-19 vaccines, some studies assessing the effect on women's menstrual cycle have been published or awaiting peer-review. Earlier this year Edelman et al. published a retrospective cohort study using data from 2,403 vaccinated and 1,556 unvaccinated women that used a digital menstrual cycle tracking application for 6 consecutive cycles. This study found that the vaccination was associated with a less than 1-day increase in cycle length although not significant in adjusted models. The largest difference was seen in the group that received the first and second dose within the same cycle (358 women); a 2-day increase in cycle length (2.38 days, 98.75% CI 1.52–3.24). 10.6% had a clinically significant increase in cycle length of 8 days compared with 4.3% in the unvaccinated group ($p<0.001$) (8). Another study, published in 2022, found that 66.3% of a group of 2269 women reported menstrual cycle abnormalities including irregular menstruation, menstrual cramps and increased period frequency after receiving a COVID-19 vaccine. However, since data was collected through an online survey that was distributed via social media, the study might have been subject to selection and recall bias (9).

The following studies are published as preprints and are not peer-reviewed yet. The results of these studies should be considered with caution. A study from the United Kingdom recruited 1,273 individuals that kept a record of their menstrual cycle and the date of their COVID-19 vaccinations retrospectively. This study found that women on hormonal contraceptives reported more changes to menstrual flow compared to women without hormonal contraceptives. Other than that, the study was not able to detect strong signals that the COVID-19 vaccination is associated with menstrual changes (10). Alvergne et al. performed a secondary analysis of a retrospective online survey titled "The Covid-19 Pandemic and Women's Reproductive Health" conducted in the United Kingdom in March 2021 before widespread media attention. This survey included a question regarding menstrual cycle changes after COVID-19 vaccination. 80% out of 4,989 pre-menopausal and non-pregnant women with a cycle in the last 12 months reported no changes following COVID-19 vaccination. 6.1% reported more disruption, 1.5% reported less disruption and 11.5% reported "other changes". Smoking and history of COVID-19 infection were found to be risk factors and using oestradiol-containing contraceptives was found to be a protective factor (11). Another study, from Norwegian, used an existing cohort, the Young Adult Cohort. This cohort consists of 8,576 randomly selected Norwegian women and 4,281 men aged 18 to 30 years and was formed to study the consequences of COVID-19 pandemic. The sample used in this study consists 5,756 women who responded to an electronic questionnaire sent in October 2021 asking whether they experienced specific disturbances in their menstruation before COVID-19 vaccination and after the first and second dose. 37.8% of women reported at least one menstrual disturbance prior to vaccination. The vaccination was found to be associated with heavier bleeding after vaccination (first dose: relative risk 1.90 [95% CI: 1.69-2.13], second dose: relative risk 1.84 [95% CI: 1.66-2.03]) (12). Lastly, Lee et al. found in a observational retrospective study that 42.1% of a sample of 39,129 individuals from the United States of America with a regular menstrual cycles reported heavier bleeding after COVID-19 vaccination. 43.6% reported no change after vaccination. Among non-menstruating respondents, individuals using hormonal contraceptives and/or gender-affirming treatment, 65.7 % reported breakthrough bleeding after vaccination. There was a significant difference between individuals using hormonal contraceptives (70.5%) and individuals on gender-affirming treatment (38.5%) (13). However, the study used convenience sampling for the web-based survey, circulating on social media. Many women learned of the survey after searching online to investigate their own experiences. Therefore the study may have been subjected to significant selection bias.

Mechanism

Women's menstrual cycle can be affected by immune responses including immune activation caused by a COVID-19 infection (28, 29). This could suggest that menstrual disorders associated with COVID-19 vaccines are caused by the immune response following vaccination. Possible biological mechanisms may include changes in hormones driving the menstrual cycle caused by an immune response and changes caused by immune cells in the lining of the uterus that are involved in the build-up and breakdown of the endometrium (30, 31).

Discussions and conclusion

This updated report provides additional information on the menstrual disorder reports following COVID-19 vaccination that The Netherlands Pharmacovigilance Centre received. Until March 29 2022 Lareb received a total of 24,090 menstrual disorder case reports associated with Comirnaty®, Spikevax®, Janssen and Vaxzevria®. As mentioned before, there was widespread media attention for the possible relationship between the COVID-19 vaccines and menstrual disorders. This shows when looking at the received reports over time (Figure 1). It shows clear peaks at times when menstrual disorders were discussed in the media. However, the start dates of the menstrual disorder reactions shows no obvious peaks and seems to correlate with the Dutch vaccination program.

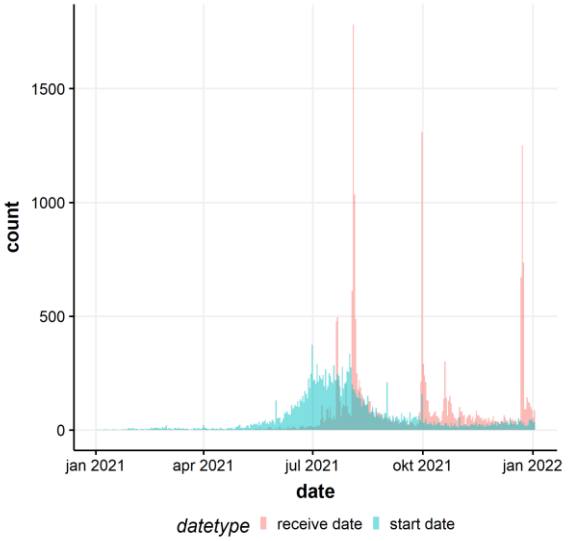

Figure 1 - Receive date and start date of the menstrual disorder reports associated with a COVID-19 vaccine over time

The majority of the received reports were associated with Comirnaty® (79%) which is in line with expectations since Comirnaty® was the most widely used vaccine in The Netherlands. The reporting rates, however, showed that the Janssen COVID-19 vaccine had the highest reporting rates compared to the other vaccines, overall 523.0 reports per 100,000 vaccinations. This means that around 1 in 200 women who received the Janssen vaccine reported a menstrual disorder at The Netherlands Pharmacovigilance Centre Lareb. This was even higher in the age group 35-44 years; around 1 in 90 women reported a menstrual disorder. However, it is important to note that the Janssen COVID-19 vaccine is the only single-dose vaccine. Menstrual disorders are very common and have high incidence rates regardless of vaccination which means that women who received the Janssen vaccine would contribute a coincidental menstrual disorder to one single dose. Whereas women who received one of the other vaccines would contribute their coincidental menstrual disorder to either the first, second or third dose. Thus the reporting rates for the Janssen vaccine would be higher.

In the LIM cohort, 3.18% of all women reported a menstrual disorder. The highest frequency was found in the age group 26-35 year: 7.31% of women reported a menstrual disorder. Even though the high background incidence rates should be taken into account for both the spontaneous reports and the LIM study, the vast number of reports remains significant.

Overall there were no large differences between vaccine brands when looking at the studied characteristics of the case reports such as the reporter, age groups, BMI and menstrual disorder categories. This strengthens the theory that menstrual disorders could be caused by the immune response that follows vaccination rather than a specific vaccination brand or type.

The most co-reported ADRs showed mainly known systemic and local reactions. These are very common reactions and were to be expected. Other reactions that were frequently co-reported were reactions related to the menstrual cycle, such as breast complaints and mood swings. However, without context of the reports these findings do not provide more insight on the possible relationship between COVID-19 vaccines and menstrual disorders.

It is notable that 52.4 to 64.4% of women had not recovered of their menstrual disorder at the time of reporting. Women reported their complaints before they fully recovered which is understandable since menstrual disorders such as amenorrhoea and irregular menstrual cycle can take a longer time to recover.

The most reported menstrual disorders were amenorrhoea/oligomenorrhoea, followed by heavy menstrual blood loss and irregular blood loss. These menstrual disorders were the most reported reaction in the LIM cohort as well. Amenorrhoea/oligomenorrhoea was reported by 0.82% of the women in the cohort, heavy menstrual blood loss 0.75% and irregular blood loss 0.67%. The

frequencies were the highest in the age group 26-35 years (1.83%, 1.6% and 1.71% respectively) The frequencies are in line with the high reporting rates seen for the spontaneous case reports.

Since heavy menstrual bleeding and amenorrhoea were the most reported menstrual disorders, these menstrual disorders were analysed more closely. The follow-up questions sent had the aim to gain more insight in these two menstrual disorder. For heavy menstrual bleeding most women reported a heavier menstrual flow of “more than twice as much”. For both heavy menstrual bleeding and amenorrhoea most women seem to have been vaccinated in the second half of their menstrual cycle. Whether vaccination during a certain time in the menstrual cycle has effect on developing a menstrual disorder after vaccination is not known and should be further investigated. Some women with heavy menstrual bleeding or amenorrhoea reported that the first cycle after vaccination was normal, but the following cycle was not. This could theoretically be caused in case women are vaccinated in a later stage of their menstrual cycle. Nonetheless, a causal relationship with the vaccination seems less likely in these cases. For both amenorrhoea and heavy menstrual bleeding, the use of hormonal contraception did not show large differences.

Providing more information on duration of amenorrhoea remains difficult. Firstly, many women with a delayed menstruation had not recovered at the time of reporting and/or follow-up. Secondly, due to internal coding agreements the term “amenorrhoea” is used for absence of menstruation regardless of the duration even though it is clinically defined as an absence of menstruation for longer than 6 months. Nonetheless, an absent menstruation can be impactful for women even if it was shorter than 6 months absent. It can cause concerns and difficulties, for example for women with a child wish.

Another aspect to consider is the wide variety of case reports received. Menstrual disorders can be very diverse and different per individual. Although the reported menstrual ADRs were categorised in 8 categories, many of the reports contained multiple menstrual ADRs and fell into multiple categories. Ideally, such cases would be assessed individually, but with such a vast amount of case reports, this is not possible. Reports that were assessed individually were serious case reports, case reports in which women consulted a doctor and some health professional cases. These were usually the more severe cases such as a long absent menstrual cycle or prolonged and heavy menstrual bleeding that needed treatment or led to anaemia.

In conclusion, although menstrual disorders are very common and can have different causes, 24,090 women noticed a change in their cycle after COVID-19 vaccination. Menstrual disorders can be cause concern in women, e.g. an absent menstrual cycle or be restrictive in daily life, e.g. heavier menstrual bleeding. The vast amount of spontaneous reports and the relatively high frequency from the cohort study indicate that there is a possible causal relationship between COVID-19 vaccination and menstrual disorders.

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This signal has been raised on May 17, 2022. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl

Appendix A Reporting Rates

Table 1 – Calculations of the reporting rates per 100.000 Comirnaty® vaccinations of postmenopausal bleeding.									
Age group	**N reports (1st dose)**	**N reports (2nd dose)**	**N reports (3rd dose)**	**1st dose vaccinations***	**2nd dose vaccinations***	**3rd dose vaccinations***	**Reporting rate per 100.000 vaccinations (1st dose)**	**Reporting rate per 100.000 vaccinations (2nd dose)**	**Reporting rate per 100.000 vaccinations (3rd dose)**
<25	1669	1528	105	809029	685299	295386	206.3	223.0	35.5
25-34	3915	3840	364	614731	556934	445031	636.9	689.5	81.8
35-44	2072	2702	321	625308	573317	510623	331.4	471.3	62.9
45-54	944	1370	135	656973	611541	293324	143.7	224.0	46.0
55-64	27	49	9	565717	549448	309365	4.8	8.9	2.9
≥65	7	12	1	1586871	1550716	462879	0.4	0.8	0.2
Total	**8634**	**9501**	**935**	**4858629**	**4527255**	**2316608**	**177.8**	**210.0**	**40.4**

*Administrated vaccine doses to women per age group in The Netherlands until March 28th 2022

Table 2 – Calculations of the reporting rates per 100.000 Spikevax® vaccinations of postmenopausal bleeding.									
Age group	**N reports (1st dose)**	**N reports (2nd dose)**	**N reports (3rd dose)**	**1st dose vaccinations***	**2nd dose vaccinations***	**3rd dose vaccinations***	**Reporting rate per 100.000 vaccinations (1st dose)**	**Reporting rate per 100.000 vaccinations (2nd dose)**	**Reporting rate per 100.000 vaccinations (3rd dose)**
<25	165	191	1	53332	46914	572	309.4	407.1	174.8
25-34	424	467	12	76548	70253	769	553.9	664.7	1560.5
35-44	293	487	19	107247	99344	4126	273.2	490.2	460.5
45-54	177	322	140	132000	122988	439553	134.1	261.8	31.9
55-64	1	9	15	89501	84337	568865	1.1	10.7	2.6
≥65	1	0	3	38896	38063	1165940	2.6	0.0	0.3
Total	**1061**	**1476**	**190**	**497524**	**461899**	**2179825**	**213.3**	**319.6**	**8.7**

*Administrated vaccine doses to women per age group in The Netherlands until March 28th 2022

Table 3 – Calculations of the reporting rates per 100.000 Vaxzevria® vaccinations of postmenopausal bleeding.						
Age group	**N reports (1st dose)**	**N reports (2nd dose)**	**1st dose vaccinations***	**2nd dose vaccinations***	**Reporting rate per 100.000 vaccinations (1st dose)**	**Reporting rate per 100.000 vaccinations (2nd dose)**
<25	36	46	20606	19023	174.7	241.8
25-34	114	130	32301	29417	352.9	441.9
35-44	78	90	39973	36700	195.1	245.2
45-54	45	52	62101	57076	72.5	91.1
55-64	7	14	389955	361640	1.8	3.9
≥65	1	1	143852	134760	0.7	0.7
Total	**281**	**333**	**688788**	**638616**	**40.8**	**52.1**

*Administrated vaccine doses to women per age group in The Netherlands until March 28th 2022

Table 4 – Calculations of the reporting rates per 100.000 Janssen COVID-19 vaccinations of postmenopausal bleeding.			
Age group	**N reports (1st dose)**	**1st dose vaccinations***	**Reporting rate per 100.000 vaccinations (1st dose)**
<25	384	313997	575.7
25-34	597	66685	1091.6
35-44	402	54692	1149.5
45-54	255	34972	185.5
55-64	3	137433	17.2
≥65	0	20187	0.0
Total	**1641**	**627966**	**523.0**

*Administrated vaccine doses to women per age group in The Netherlands until March 28th 2022