

## Menstrual disorders and postmenopausal bleeding after administration of COVID-19 vaccines

### Introduction

To date, the European Medicines Agency (EMA) authorised four COVID-19 vaccines for active immunisation against SARS-CoV-2: BioNTech/Pfizer (Comirnaty®), Moderna (SpikeVax®), AstraZeneca (Vaxzevria®) and Janssen [1]. BioNTech/Pfizer and Moderna are both mRNA vaccines, encoding the viral spike (S) protein while AstraZeneca and Janssen are using an Adenovirus vector. All COVID-19 vaccines are subject to additional monitoring [2-5].

The most widely given vaccine in the Netherlands is the Pfizer/BioNTech vaccine (Comirnaty®) [6]. It is indicated for *active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 16 years of age and older* [2]. Comirnaty® has been registered in Europe since December 21<sup>st</sup>, 2020 [2].

Menstrual disorders are diverse and quite common among women. Symptoms are diverse, like dysmenorrhoea, heavy menstrual bleeding (menorrhagia), amenorrhoea, oligomenorrhoea or irregular and intermenstrual blood loss. Reported prevalence and incidence are varying per symptom from 6-90%. Differences were also seen because of difference in study population (age, clinical setting or population based, selection at recruitment) or outcome definitions. [7-15].

This signal provides an overview of all reports of menstrual disorders following COVID-19 vaccinations reported to the Netherlands Pharmacovigilance Centre Lareb. In addition we described the reports of postmenopausal bleeding.

### Reports

Until December 1<sup>st</sup>, 2021 the Netherlands Pharmacovigilance Centre Lareb received 17.735 unique individual case reports of a broad spectrum of menstrual disorders and postmenopausal blood loss following vaccination with all available COVID-19 vaccines in total. For the menstrual disorders all Preferred Terms (PT) from the High Level Group Term (HLGT) Menstrual cycle and uterine bleeding disorders were included, in combination with the PT Vaginal haemorrhage and PT Postmenopausal haemorrhage. These PT's were divided into predetermined categories based on the definitions of the Dutch General Practitioners Guidelines (NHG-Standaard [15, 16]). The following categories were used (definition is given when described in the NHG-Standaard):

- Heavy menstrual blood loss: cyclic heavy and bothersome blood loss.
- Less menstrual blood loss.
- Irregular blood loss: non-cyclical blood loss, menstrual periods no longer recognizable.
- Intermenstrual blood loss: blood loss between recognizable periods.
- Postmenopausal blood loss: blood loss > 1 year after the last menstrual period (menopause).
- Amenorrhoea / Oligomenorrhoea: for definitions see below.
- Dysmenorrhoea: painful menstruation that can obstruct the patient in her normal activities.
- Withdrawal blood loss abnormal
- Other

Amenorrhea is defined in the NHG-Standaard [16] as 'lack of menstrual blood loss in the reproductive life phase'.

- Primary amenorrhoea: absence of menarche until after the 16th birthday
- Secondary amenorrhoea: ≥ 6 months of absence of (previously present) menstruation
- Oligomenorrhoea: interval between periods > 35 days and < 6 months
- Functional amenorrhoea: amenorrhea as a result of a disturbance in the hormonal regulation of the cycle, without (indications of) an organic cause

Appendix 1 shows the division of the menstrual PT's into these categories. Table 1 gives an overview of the total received reports per vaccine and per age group. This table also shows a breakdown per category: reporting rates, seriousness, vaccination moment, whether or not the patient had COVID prior to vaccination, BMI and the number of received reports per menstrual category. Excluded from this table where the reports where the vaccine or the age of the patient where unknown.

**Table 1: Overview total number of reports and numbers per menstrual category.**

vaccine	COVID-19 VACCINE ASTRAZENECA				COVID-19 VACCINE JANSSEN				COVID-19 VACCINE MODERNA				COVID-19 VACCINE PFIZER					Total
Age group	15-19	20-45	>45	Total	15-19	20-45	>45	Total	15-19	20-45	>45	Total	10-14	15-19	20-45	>45	Total	Total
No. reports	17	364	152	<b>534</b>	71	893	243	<b>1.211</b>	86	1.489	449	<b>2.025</b>	282	675	10.744	2.250	<b>13.965</b>	<b>17.735</b>
No. Menstrual PT's	24	465	175	<b>664</b>	90	1.191	293	<b>1.574</b>	113	1.962	562	<b>2.637</b>	339	842	14.112	2.858	<b>18.151</b>	<b>23.026</b>
No. serious	0	6	1	<b>7</b>	0	2	0	<b>2</b>	0	6	3	<b>9</b>	1	1	43	16	<b>61</b>	<b>79</b>
Percentage serious of No. reports	0,0%	1,6%	0,7%	<b>1,3%</b>	0,0%	0,2%	0,0%	<b>0,2%</b>	0,0%	0,4%	0,7%	<b>0,4%</b>	0,4%	0,1%	0,4%	0,7%	<b>0,4%</b>	<b>0,4%</b>
<b>Vaccination moment</b>																		
1	8	171	69	<b>249</b>	71	893	243	<b>1.211</b>	51	682	164	<b>897</b>	174	398	5.655	920	<b>7.155</b>	<b>9.512</b>
2	9	193	83	<b>285</b>	0	0	0	<b>0</b>	35	806	285	<b>1.127</b>	108	277	5.088	1.329	<b>6.808</b>	<b>8.220</b>
3	0	0	0	<b>0</b>	0	0	0	<b>0</b>	0	1	0	<b>1</b>	0	0	1	1	<b>2</b>	<b>3</b>
<b>Reporting rates per 100.000 vaccinations (per vaccination moment)</b>																		
1	237,9	175,5	11,6	<b>35,8</b>	423,8	522,1	173,7	<b>369,6</b>	398,3	283,4	63,5	<b>175,3</b>	104,3	118,8	345,4	32,4	<b>143,8</b>	<b>146,1</b>
2	287,1	214,8	15,1	<b>44,3</b>	0	0	0	<b>0</b>	318,4	365,8	118,4	<b>238,7</b>	76,5	98,6	351,6	48,8	<b>148,2</b>	<b>144,0</b>
<b>COVID prior</b>																		
No.	1	79	20	<b>100</b>	11	165	43	<b>219</b>	20	263	67	<b>350</b>	25	154	1.894	344	<b>2.421</b>	<b>3.090</b>
Percentage	5,9%	21,7%	13,2%	<b>18,7%</b>	15,5%	18,5%	17,7%	<b>18,1%</b>	23,3%	17,7%	14,9%	<b>17,3%</b>	8,9%	22,8%	17,6%	15,3%	<b>17,3%</b>	<b>17,4%</b>
<b>Reporter</b>																		
No. consumer	17	359	147	<b>524</b>	71	890	243	<b>1.208</b>	86	1.483	448	<b>2.018</b>	265	665	10.697	2.236	<b>13.877</b>	<b>17.627</b>
Percentage consumer	100%	98,6%	96,7%	<b>98,1%</b>	100%	99,7%	100%	<b>99,8%</b>	100%	99,6%	99,8%	<b>99,7%</b>	94,0%	98,5%	99,6%	99,4%	<b>99,4%</b>	<b>99,4%</b>
No. hcp	0	5	5	<b>10</b>	0	3	0	<b>3</b>	0	6	1	<b>7</b>	17	10	47	14	<b>88</b>	<b>108</b>
Percentage hcp	0,0%	1,4%	3,3%	<b>1,9%</b>	0,0%	0,3%	0,0%	<b>0,2%</b>	0,0%	0,4%	0,2%	<b>0,3%</b>	6,0%	1,5%	0,4%	0,6%	<b>0,6%</b>	<b>0,6%</b>
<b>BMI</b>																		
<18	0,0%	0,5%	0,7%	<b>0,6%</b>	2,8%	1,8%	0,4%	<b>1,6%</b>	10,5%	0,9%	0,2%	<b>1,2%</b>	24,5%	5,8%	1,1%	0,4%	<b>1,7%</b>	<b>1,6%</b>
18-24.9	76,5%	46,2%	36,8%	<b>44,6%</b>	77,5%	64,5%	46,9%	<b>61,5%</b>	68,6%	62,7%	55,0%	<b>61,2%</b>	66,7%	73,0%	60,3%	49,9%	<b>59,4%</b>	<b>59,3%</b>
25-29.9	11,8%	27,2%	31,6%	<b>27,9%</b>	14,1%	22,7%	35,8%	<b>24,8%</b>	15,1%	22,4%	27,8%	<b>23,4%</b>	5,0%	14,4%	24,7%	30,6%	<b>24,7%</b>	<b>24,7%</b>
30-39.9	5,9%	16,8%	21,7%	<b>17,8%</b>	4,2%	8,6%	15,6%	<b>9,7%</b>	3,5%	10,6%	13,1%	<b>10,9%</b>	1,1%	3,9%	10,5%	15,7%	<b>10,8%</b>	<b>10,9%</b>
>40	0,0%	5,8%	5,3%	<b>5,4%</b>	0,0%	0,1%	0,0%	<b>0,1%</b>	1,2%	1,3%	1,3%	<b>1,3%</b>	0,4%	0,3%	1,1%	1,3%	<b>1,1%</b>	<b>1,2%</b>
Unknown	5,9%	3,6%	3,9%	<b>3,7%</b>	1,4%	2,2%	1,2%	<b>2,3%</b>	1,2%	2,1%	2,4%	<b>2,1%</b>	2,5%	2,7%	2,4%	2,1%	<b>2,3%</b>	<b>2,4%</b>

Categories																		
Heavy menstrual blood loss	4	92	28	<b>124</b>	19	230	72	<b>25</b>	23	396	138	<b>558</b>	49	137	2.742	600	<b>3.533</b>	<b>4.537</b>
Less menstrual blood loss	1	17	0	<b>18</b>	1	23	1	<b>241</b>	0	57	1	<b>58</b>	9	22	367	44	<b>442</b>	<b>543</b>
Irregular blood loss	3	70	11	<b>85</b>	17	200	23	<b>243</b>	20	318	78	<b>416</b>	51	122	2.213	382	<b>2.770</b>	<b>3.512</b>
Intermenstrual blood loss	5	57	16	<b>78</b>	17	200	26	<b>57</b>	16	265	50	<b>331</b>	24	152	1.967	282	<b>2.427</b>	<b>3.079</b>
Postmenopausal blood loss	0	1	59	<b>60</b>	0	1	56	<b>343</b>	0	2	53	<b>56</b>	0	0	11	351	<b>364</b>	<b>537</b>
Amenorrhoea / Oligomenorrhoea	5	134	23	<b>162</b>	11	287	43	<b>145</b>	25	545	135	<b>705</b>	158	234	3.881	562	<b>4.841</b>	<b>6.051</b>
Dysmenorrhoea	3	29	7	<b>39</b>	8	121	16	<b>21</b>	16	163	25	<b>205</b>	19	83	1.307	184	<b>1.595</b>	<b>1.984</b>
Withdrawal blood loss abnormal	1	7	0	<b>8</b>	2	17	2	<b>181</b>	1	18	0	<b>19</b>	0	9	178	9	<b>196</b>	<b>244</b>
Other	2	58	31	<b>91</b>	15	112	54	<b>25</b>	12	198	82	<b>292</b>	29	83	1.446	444	<b>2.003</b>	<b>2.567</b>

Distribution of the number of reported menstrual PT's in the categories per age group and vaccine																		
Heavy menstrual blood loss	16,7%	19,8%	16,0%	<b>18,7%</b>	21,1%	19,3%	24,6%	<b>20,5%</b>	20,4%	20,2%	24,6%	<b>21,2%</b>	14,5%	16,3%	19,4%	21,0%	<b>19,5%</b>	<b>19,7%</b>
Less menstrual blood loss	4,2%	3,7%	0,0%	<b>2,7%</b>	1,1%	1,9%	0,3%	<b>1,6%</b>	0,0%	2,9%	0,2%	<b>2,2%</b>	2,7%	2,6%	2,6%	1,5%	<b>2,4%</b>	<b>2,4%</b>
Irregular blood loss	12,5%	15,1%	6,3%	<b>12,8%</b>	18,9%	16,8%	7,8%	<b>15,3%</b>	17,7%	16,2%	13,9%	<b>15,8%</b>	15,0%	14,5%	15,7%	13,4%	<b>15,3%</b>	<b>15,3%</b>
Intermenstrual blood loss	20,8%	12,3%	9,1%	<b>11,7%</b>	18,9%	16,8%	8,9%	<b>15,4%</b>	14,2%	13,5%	8,9%	<b>12,6%</b>	7,1%	18,1%	13,9%	9,9%	<b>13,4%</b>	<b>13,4%</b>
Postmenopausal blood loss	0,0%	0,2%	33,7%	<b>9,0%</b>	0,0%	0,1%	19,1%	<b>3,6%</b>	0,0%	0,1%	9,4%	<b>2,1%</b>	0,0%	0,0%	0,1%	12,3%	<b>2,0%</b>	<b>2,3%</b>
Amenorrhoea / Oligomenorrhoea	20,8%	28,8%	13,1%	<b>24,4%</b>	12,2%	24,1%	14,7%	<b>21,8%</b>	22,1%	27,8%	24,0%	<b>26,7%</b>	46,6%	27,8%	27,5%	19,7%	<b>26,7%</b>	<b>26,3%</b>
Dysmenorrhoea	12,5%	6,2%	4,0%	<b>5,9%</b>	8,9%	10,2%	5,5%	<b>9,2%</b>	14,2%	8,3%	4,4%	<b>7,8%</b>	5,6%	9,9%	9,3%	6,4%	<b>8,8%</b>	<b>8,6%</b>
Withdrawal blood loss abnormal	4,2%	1,5%	0,0%	<b>1,2%</b>	2,2%	1,4%	0,7%	<b>1,3%</b>	0,9%	0,9%	0,0%	<b>0,7%</b>	0,0%	1,1%	1,3%	0,3%	<b>1,1%</b>	<b>1,1%</b>
Other	8,3%	12,5%	17,7%	<b>13,7%</b>	16,7%	9,4%	18,4%	<b>11,5%</b>	10,6%	10,1%	14,6%	<b>11,1%</b>	8,6%	9,9%	10,2%	15,5%	<b>11,0%</b>	<b>11,1%</b>

In the 17.735 spontaneous reports, a total of 23.026 menstrual PT's were coded. 79 reports were serious according to one of the CIOMS criteria (0,4%). The percentage of serious reports varies per vaccine and per age group from 0% to 1,6%. The category with the most serious reports were the patients in the age group of 20-45 year-olds who received the AstraZeneca vaccine (1,6%). The majority of the reports concern a menstrual disorder after the first vaccination (n = 9.512), followed by the second vaccination (n = 8.220). In the Netherlands, the third vaccinations were not given in a large amount yet on the 1<sup>st</sup> of December, so Lareb received only 3 reports that concern a menstrual disorder after the third vaccination. The vast majority of the menstrual disorders were reported by the consumer herself (n = 17.627; 99,4%). This number varies per vaccine and age group from 94,0% to 100,0%. The category with the most reports reported by a health care professional were the patients in the age group 10-14 year-olds who received the Pfizer vaccine (6,0%).

The number of patients who had COVID-19 prior to receiving the vaccination varies from 5,9% to 23,3%. In total, 17,4% of the patients had COVID-19 prior to vaccination, varying from 18,7% with patients who received the AstraZeneca vaccine, 18,1% with patients who received the Janssen vaccine, 17,3% with patients who received the Moderna vaccine to 17,3% with patients who received the Pfizer/BioNTech vaccine.

The body mass index of the different age groups varies. In total, most of the patients had a BMI between 18-25 kg/m<sup>2</sup> (59,3%), followed by a BMI between 25-30 kg/m<sup>2</sup> (24,7%) and a BMI between 30-40 kg/m<sup>2</sup> (10,9%). 1,6% of the patients had a BMI of less than 18-25 kg/m<sup>2</sup> and 1,2% had a BMI above 40 kg/m<sup>2</sup>.

*Media attention and receive dates of reports*

In the Netherlands, but also internationally, menstrual disorders in relation with the COVID-19 vaccinations were widely discussed in the media and on Internet forums. At Lareb, an increase in the amount of reports could be observed the days after (social) media attention. But Lareb received reports almost directly from the start of the vaccination campaign in January, before the first news items or about this possible relation. This can be observed in figure 1. This figure shows the number of reports Lareb received over the course of 2021. By example, there was media attention in the Netherlands for menstrual disorders in the period of July to begin August and end of September to the start of October. These are visible in the figure as obvious periods with more reports. This figure also shows that Lareb received reports about menstrual disorders from the start of the vaccination program in January, albeit less than after the media attention.

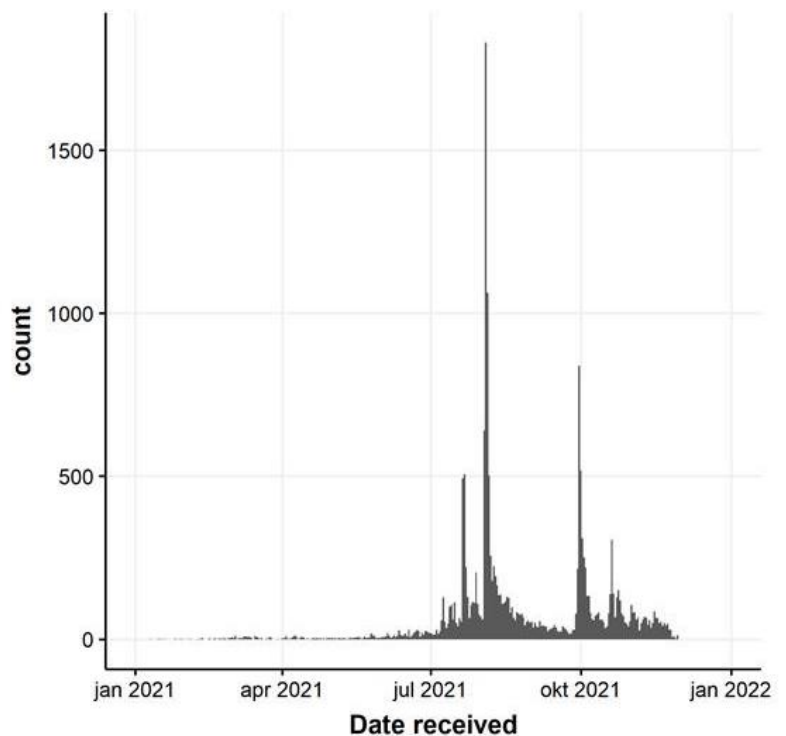


Figure 1. Histogram of the number of reports with at least one menstrual PT per day over the course of 2021.

*Reporting rates*

The reporting rates are calculated based on numbers Lareb received from the RIVM (CIMS database), which provides information on the number of vaccinations per vaccine, sex and age group until the 1<sup>st</sup> of December, 2021. Appendix 2 shows the number of vaccinations that were given to females in the Netherlands until the 1<sup>st</sup> of December, 2021, per vaccine, vaccination moment and age group. Based on these numbers, the reporting rates could be calculated (also shown in appendix 2). The reporting rates are therefore stratified to the number of females that received a vaccine, in the specified age groups who received the specified vaccine. Table 2 shows a heatmap of these calculated reporting rates. It should be

noted that the calculated reporting rates are just an estimation. Not everyone that gets a vaccine gives permission to share vaccination data, so the numbers Lareb received from the RIVM are not complete. The number of vaccinations are therefore an underestimate of the true number of vaccinations. While on the other hand, even though Lareb received a lot of reports, not every woman with a menstrual disorder will have reported this. The reporting rates are therefore just to give an indication.

Age groups	10-14	15-19	20-45	45+	Total
<b>AstraZeneca</b>					
1		237,9	175,5	11,6	35,8
2		287,1	214,8	15,1	44,3
<b>Janssen</b>					
1		423,8	522,1	173,7	369,6
<b>Moderna</b>					
1		398,3	283,4	63,5	175,3
2		318,4	365,8	118,4	238,7
<b>Pfizer</b>					
1	104,3	118,8	345,4	32,4	143,8
2	76,5	98,6	351,6	48,8	148,2

The reporting rates vary from 522,1 reports per 100.000 vaccinations with patients from 20-45 years who received the Janssen vaccine to 11,6 reports per 100.000 vaccinations with patients from above 45 years who received the first AstraZeneca vaccine. Overall, the reporting rates were the highest with patients who received the Janssen vaccine (369,6 reports per 100.000 vaccinations), followed by Moderna (238,7 reports per 100.000 second vaccinations and 175,3 reports per 100.000 first vaccinations), Pfizer (148,2 reports per 100.000 second vaccinations and 143,8 reports per 100.000 first vaccinations) and AstraZeneca (44,3 reports per 100.000 second vaccinations and 35,8 reports per 100.000 first vaccinations).

#### *Menstrual categories*

As mentioned before, the menstrual PT's were divided into predetermined categories based on the definitions described in the Dutch General Practitioners Guidelines. In total, 23.026 menstrual PT's were coded by Lareb. Most of these PT's were reported after vaccination with the Pfizer/BioNTech vaccine (n = 18.151), followed by the Moderna vaccine (n = 2.637), the Janssen vaccine (n = 1.574) and the AstraZeneca vaccine (n = 664). Table 3 shows a heatmap of the distribution of all these reported menstrual PT's in the predetermined categories.

Vaccine	Heavy menstrual blood loss	Less menstrual blood loss	Irregular blood loss	Intermenstrual blood loss	Postmenopausal blood loss	Amenorrhoea / Oligomenorrhoea	Dysmenorrhoea	Withdrawal blood loss abnormal	Other
<b>AstraZeneca</b>	18,7%	2,7%	12,8%	11,7%	9,0%	24,4%	5,9%	1,2%	13,7%
<b>Janssen</b>	20,5%	1,6%	15,3%	15,4%	3,6%	21,8%	9,2%	1,3%	11,5%
<b>Moderna</b>	21,2%	2,2%	15,8%	12,6%	2,1%	26,7%	7,8%	0,7%	11,1%
<b>Pfizer</b>	19,5%	2,4%	15,3%	13,4%	2,0%	26,7%	8,8%	1,1%	11,0%
<b>Total</b>	19,7%	2,4%	15,3%	13,4%	2,3%	26,3%	8,6%	1,1%	11,1%

Table 3 shows that the most reported categories are Amenorrhoea / Oligomenorrhoea (26,3% of total reported menstrual PT's) and Heavy menstrual blood loss (19,7% of total reported menstrual PT's). These categories are followed by Irregular blood loss (15,3% of total reported menstrual PT's) and Intermenstrual blood loss (13,4% of total reported menstrual PT's). Dysmenorrhoea was reported in 8,6% of the cases, less menstrual blood loss in 2,4%, postmenopausal blood loss in 2,3% and abnormal withdrawal blood loss in 1,1%. The PT's from the category Other were reported in 11,1%. This category contains reports where the reporter did not specify the menstrual disorder enough to fit into one of the other categories.

Based on these outcomes, it was decided to focus on Amenorrhoea and Heavy menstrual blood loss first. In this signal, the focus will also be on Postmenopausal haemorrhage, because this is a very specific category which is different from the other categories.

### Reports PT Amenorrhoea

To ensure an unambiguous way of coding of the menstrual disorders, Lareb made coding agreements. The coding agreements about the amenorrhoea cases are shown in table 4.

Reporting text	LLT	PT
Menstruation stays away (duration unknown)	Absence of menstruation	Amenorrhoea
≥ 6 months of absence of (previously present) menstruation	Secondary amenorrhoea	Amenorrhoea
Menstruation later than normal, but did not stay away for ≥ 6 months.	Late period	Menstruation delayed

All reports with the PT Amenorrhoea after administration of one of the authorized COVID-19 vaccines are selected and shown in table 5. For this signal, it was decided not to look into the oligomenorrhoea cases yet to get a good insight in the cases where the menstruation was absent and to keep this demarcated. Lareb is planning to look into the reports of oligomenorrhoea as well at a later stage. Table 5 shows a breakdown per age group of the number of serious reports, vaccination moment, administered vaccine, reporting rates, COVID-19 prior to vaccination, reporter, BMI and information about the course of the amenorrhoea.

Age groups	10-14	15-19	20-45	45+	Unknown	Total
Number of reports	114	162	2.474	441	7	<b>3.198</b>
Number serious	0	1	6	3	0	<b>10</b>
Percentage serious	0,0%	0,6%	0,2%	0,7%	0	<b>0,3%</b>
<b>Vaccine and vaccination moment</b>						
<b>Pfizer</b>	114	141	1.975	317	5	<b>2.552</b>
1	66	77	999	141	2	<b>1.285</b>
2	48	64	975	176	3	<b>1.266</b>
3	0	0	1	0	0	<b>1</b>
<b>Moderna</b>	0	16	267	80	0	<b>363</b>
1	0	9	132	31	0	<b>172</b>
2	0	7	135	49	0	<b>191</b>
<b>AstraZeneca</b>	0	3	79	14	0	<b>96</b>
1	0	1	33	6	0	<b>40</b>
2	0	2	46	8	0	<b>56</b>
<b>Janssen</b>	0	2	153	30	2	<b>187</b>
1	0	2	153	30	2	<b>187</b>
<b>Reporting rates per 100.000 vaccinations</b>						
<b>Pfizer</b>						
1	39,5	23,0	61,0	5,0	-	25,8
2	34,0	22,8	67,4	6,5	-	27,6
<b>Moderna</b>						
1	0	70,3	54,9	12,0	-	33,6

<b>2</b>	0	63,7	61,3	20,4	-	40,5
AstraZeneca						
<b>1</b>	0	29,7	33,9	1,0	-	5,8
<b>2</b>	0	63,8	51,2	1,5	-	8,7
Janssen						
<b>1</b>	0	11,9	89,5	21,4	-	57,1
<b>COVID prior</b>						
No. (% of reports)	10 (8,8%)	34 (21,0%)	457 (18,5%)	61 (13,8%)	2 (28,6%)	<b>564 (17,6%)</b>
<b>Reporter</b>						
Consumer	106 (93,0%)	160 (98,8%)	2.464 (99,6%)	440 (99,8%)	7 (100%)	<b>3.177 (99,3%)</b>
Health care professional	8 (7,0%)	2 (1,2%)	10 (0,4%)	1 (0,2%)	0 (0,0%)	<b>21 (0,7%)</b>
<b>BMI</b>						
% bmi <18	27,2%	7,4%	1,1%	0,5%	0,0%	<b>2,2%</b>
% bmi 18-24.9	61,4%	74,1%	57,6%	55,6%	28,6%	<b>58,3%</b>
% bmi 25-29.9	6,1%	13,6%	25,4%	27,0%	0,0%	<b>24,3%</b>
% bmi 30-39.9	0,0%	1,2%	11,7%	12,5%	0,0%	<b>10,8%</b>
% bmi >40	0,9%	0,6%	1,7%	1,1%	28,6%	<b>1,6%</b>
% bmi unknown	4,4%	3,1%	2,5%	3,4%	42,9%	<b>2,7%</b>
<b>Time to onset</b>						
Range (days)	0 – 91,5	0 – 70	0 – 244	0 – 152,5	0 – 27	<b>0 – 244</b>
Mean (days)	11,5	15,3	18,6	15,3	10,4	<b>17,7</b>
Median (days)	7	11	13	9	9	<b>12</b>
No. Unknown (%)	38 (33,3%)	51 (31,5%)	639 (25,8%)	119 (27,0%)	2 (28,6%)	<b>849 (26,5%)</b>
<b>Outcome at time of reporting</b>						
Recovered/resolved	5 (4,4%)	7 (4,3%)	153 (6,2%)	56 (12,7%)	4 (57,1%)	<b>225 (7,0%)</b>
Recovering / resolving	1 (0,9%)	4 (2,5%)	95 (3,8%)	15 (3,4%)	0 (0,0%)	<b>115 (3,6%)</b>
Not recovered / not resolved / ongoing	96 (84,2%)	139 (85,8%)	1.956 (79,1%)	316 (71,7%)	2 (28,6%)	<b>2.509 (78,5%)</b>
Unknown	12 (10,5%)	12 (7,4%)	270 (10,9%)	54 (12,2%)	1 (14,3%)	<b>349 (10,9%)</b>
<b>Duration of recovered/resolved cases (n = 225)</b>						
Mean (days)	42,6	32,0	38,2	64,0	30,8	<b>44,5</b>
<b>Time between start date of reaction and receive date of report of <u>not recovered</u> cases (“duration” at time of reporting) (n = 2.509)</b>						
Range (days)	0 – 147	1 – 279	0 – 243	1 – 183	21 – 61	<b>0 – 279</b>
Mean (days)	39,8	40,5	37,0	53,3	41,0	-
Median (days)	29	30	22	46	41	-
No. cases lasting >100 days at time of reporting	5	5	157	37	0	<b>204</b>

In total, amenorrhoea was reported in 3.198 cases after vaccination with one of the authorized COVID-19 vaccines, with the vast majority of cases in the age group of 20-45 year-olds (n = 2.474). 10 of these cases were serious based on the CIOMS criteria (0,3%). Most reports were reported after the first vaccination (n = 1.684), followed closely by the second vaccination (n = 1.513). Only 1 report was reported after the third vaccination. The majority of the cases were reported by the consumer herself (99,3%).

The number of patients who had COVID-19 prior to receiving the vaccination varies from 8,8% (10-14 year-olds) to 21,0% (15-19 year-olds). In total, 17,6% of the patients had COVID-19 prior to vaccination. The body mass index of the different age groups varies. In total, most of the patients had a BMI between 18-25 kg/m<sup>2</sup> (58,3%), followed by a BMI between 25-30

kg/m<sup>2</sup> (24,3%) and a BMI between 30-40 kg/m<sup>2</sup> (10,8%). Only 2,2% of the patients had a BMI of less than 18-25 kg/m<sup>2</sup> and only 1,6% had a BMI above 40 kg/m<sup>2</sup>.

#### *Reporting rates*

Most reports were reported after vaccination with the Pfizer/BioNTech vaccine (n = 2.552). Appendix 3 shows the calculation of the reporting rates of the PT Amenorrhoea. The reporting rates vary from 89,5 reports per 100.000 vaccinations with patients from 20-45 years who received the Janssen vaccine to 1,0 report per 100.000 vaccinations with patients from above 45 years who received the first AstraZeneca vaccine. Overall, the reporting rates were the highest with patients who received the Janssen vaccine (57,1 reports per 100.000 vaccinations), followed by Moderna (33,6 reports per 100.000 first vaccinations and 40,5 reports per 100.000 second vaccinations), Pfizer (25,8 reports per 100.000 first vaccinations and 27,6 reports per 100.000 second vaccinations) and AstraZeneca (5,8 reports per 100.00 first vaccinations and 8,7 reports per 100.000 second vaccinations).

#### *Course of the amenorrhoea*

The mean time to onset varies in the different age groups, from 11,5 days with 10-14 year-olds (range: 0 – 91,5 days), 15,3 days with 15-19 year-olds (range: 0 – 70 days), 18,6 days with 20-45 year-olds (range: 0 – 244 days) and 15,3 days with patients older than 45 (range: 0 – 152,5 days). The median time to onset also varies in the different age groups, from 7 days with 10-14 year-olds, 11 days with 15-19 year-olds, 13 days with 20-45 year-olds and 9 days with patients older than 45.

In the majority of the cases, the patient was not recovered at time of reporting (78,5%). This means that the menstruation did not return/did not start yet at the time the patient reported her menstrual disorder at Lareb. In most of these cases, it is unknown whether or not the menstruation did return again and how long the menstruation stayed away for. It could be that the menstruation was not absent as reported (“menstruation stays away”), but that the menstruation started later than planned (“late period”) and the patient reported before the eventual start of the menstruation. Therefore, also the number of days between the start date of the amenorrhoea and the date Lareb received the report are shown in table 5. This can be considered as the ‘duration’ of the reaction at time of reporting, but is not always reliable. Therefore it is just to give an indication about the length of the amenorrhoea. The mean time between the start date and the receive date was 39,8 days with 10-14 year-olds (range: 0 – 147 days), 40,5 days with 15-19 year-olds (range: 1 – 279 days), 37,0 days with 20-45 year-olds (range: 0 – 243 days) and 53,3 days with patients older than 45 (range: 1 – 183 days). The median time between the start date and the receive date also varies in the different age groups, from 29 days with 10-14 year-olds, 30 days with 15-19 year-olds, 22 days with 20-45 year-olds and 46 days with patients older than 45. In 204 cases, the amenorrhoea was not recovered after more than 100 days, so it was lasting longer than 3 menstrual cycles at time of reporting. This means that not all cases of amenorrhoea were actually periods that “only” started too late, but that there are a lot of patients that experience a lack of menstruation for a longer period of time since the vaccination.

In 7,0% of the cases (n = 225) the patient reported that the amenorrhoea was recovered/resolved at time of reporting. The mean duration of these cases of amenorrhoea varies in the different age groups, from 42,6 days with 10-14 year-olds, 32,0 days with 15-19 year-olds, 38,2 days with 20-45 year-olds and 64,0 days with patients older than 45. This means that the menstruation stayed away for approximately 1 to 2 months and returned after that as normal.

#### ***Detailed description of selected cases***

To illustrate, a description of four well documented cases is given below. These cases show women with (secondary) amenorrhoea shortly after vaccination with one of the COVID-19 vaccinations. These women visited a GP and tests are performed that did not show any clear cause of the sudden amenorrhoea.

1. This report concerns a 20-30 year-old woman with secondary amenorrhoea after the second vaccination with the Moderna vaccine. This vaccination was during the last menstruation on day 2 of the menstruation cycle. This was the last menstruation and after that, the menstruation did not return again for at least 6 months (at the moment of the most recent follow-up information). Blood tests showed no abnormalities in FSH, LH, estradiol and free T4. TSH was slightly increased (4.4). Patient also went to an energetic therapist, who found slightly low magnesium and vitamin D levels. Patient is waitlisted for the gynecologist. Patient stated that her cycle was never very regularly (always between 30-44 days). Patient did not use any hormonal contraception. Patient had a covid-19 infection four months before first vaccination. BMI is normal. Co-med: ascorbic acid.



- This report, reported by a GP, concerns a 20-30 year-old woman with absence of menstruation after the second vaccination with the Pfizer/BioNTech vaccine. Patient had a light menstruation approximately 2 weeks after this vaccine and after that the menstruation stayed away for 4 months. Then, during an episode of fever, the patient had a menstruation of 5 days. It is unknown whether the menstruation cycle is fully normal again. Patient presented 3.5 months after onset and it was decided to wait to perform tests until the menstruation stayed away for 6 months. A pregnancy test was performed, but this was negative. Menstruation cycle was always very regularly before vaccination. Patient did not use any hormonal contraception. Patient did not have a covid-19 infection prior to vaccination.
- This report, reported by a GP, concerns a 10-20 year-old girl with absence of menstruation after the first vaccination with the Pfizer/BioNTech vaccine. Menstruation was expected one week after the vaccination, but it never came. At the moment of the most recent follow-up information, the menstruation did not return for 3 months already. Blood tests at the GP showed no abnormalities: LH: 3 U/L, FSH 3,2 U/L, Estradiol 104 pmol/L. Patient opted out for the echography. Before vaccination, the menstruation was always very regularly for at least one year. The menstruation cycle was always 28 days. Patient did not use any hormonal contraception. Patient is not yet sexually active. Patient had a covid-19 infection two months before vaccination, without any symptoms.
- This report concerns a 30-40 year-old woman with absence of menstruation after the first vaccination with the Pfizer/BioNTech vaccine. One week after the vaccination, the patient had a little blood loss and since then the menstruation did not return. At the moment of the most recent follow-up information, the menstruation did not return for 5 months already. Patient went to the GP and blood tests were performed to rule out the menopause, high stress levels and an abnormal thrombocyte count. All these test showed no abnormalities. The GP advised to withdraw her contraception pill to induce the natural menstruation, 3 months after onset. 2 months later, this did not have an effect. Patient did not have a covid-19 infection prior to vaccination. BMI is high (30). Concomitant medication: salbutamol inhalation, budesonide/formoterol inhalation, non-specified OAC.

#### Reports from category Heavy menstrual blood loss

All reports from the category Heavy menstrual blood loss are taken into account and a summary is shown in table 6. This category includes only the reports with the PT Heavy menstrual bleeding. Table 6 shows a breakdown per age group of the number of serious reports, vaccination moment, administered vaccine, reporting rates, COVID-19 prior to vaccination, reporter, BMI and information about the course of the heavy menstrual blood loss.

Table 6: Overview reports of category Heavy menstrual blood loss and covid-19 vaccines						
Age groups	10-14	15-19	20-45	45+	Unknown	Total
Number of reports	49	183	3.460	838	7	4.537
Number serious	1	0	20	5	0	26
Percentage serious	2,0%	0,0%	0,6%	0,6%	0,0%	0,6%
Vaccine and vaccination moment						
<b>Pfizer</b>	49	137	2.742	600	5	3.533
1	35	80	1.475	240	3	1.833
2	14	57	1.267	360	2	1.700
<b>Moderna</b>	0	23	396	138	1	558
1	0	13	192	58	0	263
2	0	10	204	80	1	295
<b>AstraZeneca</b>	0	4	92	28	0	124
1	0	2	48	13	0	63
2	0	2	44	15	0	61
<b>Janssen</b>	0	19	230	72	1	322
1	0	19	230	72	1	322
Reporting rates per 100.000 vaccinations (per vaccine and vaccination moment)						
<b>Pfizer</b>						
1	21,0	23,9	90,1	8,5	-	36,8
2	9,9	20,3	87,5	13,2	-	37,0

<b>Moderna</b>						
1	0,0	101,5	79,8	22,4	-	51,4
2	0,0	91	92,6	33,2	-	62,5
<b>AstraZeneca</b>						
1	0,0	59,5	49,3	2,2	-	9,1
2	0,0	63,8	49,0	2,7	-	9,5
<b>Janssen</b>						
1	0,0	113,4	134,5	51,5	-	98,3
<b>COVID prior</b>						
No. (% of reports)	4 (8,2%)	45 (24,6%)	609 (17,6%)	124 (14,8%)	1 (14,3%)	<b>783 (17,3%)</b>
<b>Reporter</b>						
Consumer	45 (91,8%)	181 (98,9%)	3.442 (99,5%)	835 (99,6%)	7 (100%)	<b>4.510 (99,4%)</b>
Health care professional	4 (8,2%)	2 (1,1%)	18 (0,5%)	3 (0,4%)	0 (0%)	<b>27 (0,6%)</b>
<b>BMI</b>						
% bmi <18	20,4%	5,5%	1,4%	0,2%	0,0%	<b>1,5%</b>
% bmi 18-24.9	75,5%	74,9%	59,2%	52,3%	42,9%	<b>58,7%</b>
% bmi 25-29.9	2,0%	14,2%	24,1%	29,1%	28,6%	<b>24,4%</b>
% bmi 30-39.9	2,0%	4,4%	11,8%	15,4%	14,3%	<b>12,1%</b>
% bmi >40	0,0%	0,0%	1,4%	1,4%	0,0%	<b>1,3%</b>
% bmi unknown	0,0%	1,1%	2,1%	1,6%	14,3%	<b>1,9%</b>
<b>Time to onset</b>						
Range (days)	0 - 122	0 - 159	0 - 224	0 - 221	0 - 42	<b>0 - 224</b>
Mean (days)	11,6	17,2	15,5	16,5	16,0	<b>15,7</b>
Median (days)	6	9	10	9	15	<b>10</b>
No. Unknown (%)	7 (14,3%)	29 (15,8%)	480 (13,9%)	93 (11,1%)	1 (14,3%)	<b>610 (13,4%)</b>
<b>Outcome at time of reporting</b>						
Recovered/resolved	15 (30,6%)	32 (17,5%)	852 (24,6%)	279 (33,3%)	0 (%)	<b>1.178 (26,0%)</b>
Recovering / resolving	4 (8,2%)	16 (8,7%)	473 (13,7%)	119 (14,2%)	2 (28,6%)	<b>614 (13,5%)</b>
Not recovered / not resolved / ongoing	25 (51,0%)	121 (66,1%)	1.749 (50,5%)	357 (42,6%)	4 (57,1%)	<b>2.256 (49,7%)</b>
Unknown	5 (10,2%)	14 (7,7%)	385 (11,1%)	83 (9,9%)	1 (14,3%)	<b>488 (10,8%)</b>
<b>Duration of recovered/resolved (n = 1.178)</b>						
Mean (days)	8,3	10,7	12,5	14,8	-	<b>13,0</b>

In total, heavy menstrual blood loss was reported in 4.537 cases after vaccination with one of the authorized COVID-19 vaccines, with the vast majority of cases in the age group of 20-45 year-olds (n = 3.460). 26 of these cases were serious based on the CIOMS criteria (0,6%). Most reports were reported after the first vaccination (n = 2.481), followed closely by the second vaccination (n = 2.056). Nothing was reported after the third vaccination. The majority of the cases were reported by the consumer herself (99,4%).

The number of patients who had COVID-19 prior to receiving the vaccination varies from 8,2% (10-14 year-olds) to 24,6% (15-19 year-olds). In total, 17,3% of the patients had COVID-19 prior to vaccination. The body mass index of the different age groups varies. In total, most of the patients had a BMI between 18-25 kg/m<sup>2</sup> (58,7%), followed by a BMI between 25-30 kg/m<sup>2</sup> (24,4%) and a BMI between 30-40 kg/m<sup>2</sup> (12,1%). Only 1,5% of the patients had a BMI of less than 18-25 kg/m<sup>2</sup> and only 1,3% had a BMI above 40 kg/m<sup>2</sup>.

#### Reporting rates

Appendix 4 shows the calculation of the reporting rates of the PT Heavy menstrual bleeding. The reporting rates vary from 134,5 reports per 100.000 vaccinations with patients from 20-45 years who received the Janssen vaccine to 2,2 reports per

100.000 vaccinations with patients from older than 45 years who received the first AstraZeneca vaccine. Other high reporting rates are found in the 20-45 year-olds who received Pfizer (first dose: 90,1 reports per 100.000 vaccinations, second dose: 87,5 reports per 100.000 vaccinations) or the Moderna vaccine (first dose: 79,8 reports per 100.000 vaccinations, second dose: 92,6 reports per 100.000 vaccinations), and in the 15-19 year-olds who received the Moderna vaccine (first dose: 101,5 reports per 100.000 vaccinations, second dose: 91 reports per 100.000 vaccinations) or the Janssen vaccine (113,4 reports per 100.000 vaccinations).

Overall, the reporting rates were the highest with patients who received the Janssen vaccine (98,3 reports per 100.000 vaccinations), followed by Moderna (51,4 reports per 100.000 first vaccinations and 62,5 reports per 100.000 second vaccinations), Pfizer (36,8 reports per 100.000 first vaccinations and 37,0 reports per 100.000 second vaccinations) and AstraZeneca (9,1 reports per 100.000 first vaccinations and 9.5 reports per 100.000 second vaccinations).

#### *Course of the heavy menstrual blood loss*

The mean time to onset varies in the different age groups, from 11,6 days with 10-14 year-olds (range: 0 – 122 days), 17,2 days with 15-19 year-olds (range: 0 – 159 days), 15,5 days with 20-45 year-olds (range: 0 – 224 days) and 16,5 days with patients older than 45 (range: 0 – 221 days). The median time to onset also varies in the different age groups, from 6 days with 10-14 year-olds, 9 days with 15-19 year-olds, 10 days with 20-45 year-olds and 9 days with patients older than 45.

In the majority of the cases, the patient was not recovered at time of reporting (49,7%). Whereas 26,0% of the patients were recovered at time of reporting and 13,5% of the patients were recovering at time of reporting. The mean duration of the recovered cases of heavy menstrual bleeding (n = 1.178) varies in the different age groups, from 8,3 days with 10-14 year-olds, 10,7 days with 15-19 year-olds, 12,5 days with 20-45 year-olds and 14,8 days with patients older than 75. Overall, the mean duration was 13 days after which the heavy blood loss stopped again.

#### **Detailed description of selected cases**

To illustrate, a description of five well documented cases is given below. These cases show women with heavy menstrual blood loss (either longer periods or a lot of blood loss or both) shortly after vaccination with one of the COVID-19 vaccinations. In some cases this even led to anaemia and therefore hospitalization and/or treatment with surgery, blood transfusion, iron infusion or oral contraceptive to control the bleeding. The heavy menstrual bleeding came back in the following menstrual cycles in some of the cases. Also, a case of positive rechallenge was included where the patient did not have a menstruation for 9 years because of an IUD and after both vaccinations the menstruation came back very severe.

1. This serious report concerns a 20-30 year-old female with menorrhagia which caused anaemia and hospitalization after first vaccination with the Pfizer/BioNTech vaccine. The first menstruation after vaccination was on time, but did not stop. The patient experienced continuing menstruation. After 3 months, the menstruation was increased significantly and caused anaemia for which the patient was hospitalized. Blood tests were performed: Hb 4 days prior to hospitalization: 7.6, at the day of hospitalization: 5.2, the day after hospitalization: 3.7 and after blood transfusion: 5.0. An ultrasound of the uterus showed a large blood clot in the uterus which had to be removed surgically. The patient was treated with blood transfusion and iron infusion, ferrous fumarate and tranexamic acid. The patient recovered from menorrhagia 3.5 months after onset. The patient never had any menstrual related or gynaecological problems before. Co-med: estradiol/nomegestrol tablet 1,5/2,5mg.
2. This report concerns a 30-40 year-old female with painful periods and menorrhagia after first vaccination with Pfizer/BioNTech vaccine. The patient experienced very painful menstruation with a lot of blood loss and large clots and bleeding during 9 to 10 days. She was treated with oral contraceptive in order to regulate the menstruation again. Patient is not recovered from these painful and heavy menstruations 5 months after onset. The patient never had any menstrual related or gynaecological problems before. Other medical history: suspected covid-19 infection, brain injury after meningitis (2018).
3. This report concerns a 10-20 year-old female with heavy menstrual bleeding one day after the first vaccination with Pfizer/BioNTech vaccine. On the day of the vaccination, the patient was on her period. This was a normal period, not severe. The day after the vaccination, it suddenly became very severe and lasted for 19 days. This caused anaemia and caused the patient to feel very weak. The GP prescribed a non-specified OAC to regulate the menstruation and an iron elixir for the anaemia. One and a half month after onset, the patient is recovered from the heavy menstrual bleeding but still has an irregular menstrual cycle. Patient has a history of arrhythmia. One time,

after a cardiac catheterization and the use of carbasalate calcium in the past, she had a not specified problem with her menstruation. Other than that, she never had any menstrual problems before. Concomitant medication: sotalol.

4. This serious report concerns a 20-30 year-old female with heavy menstrual bleeding starting 6 hours after second vaccination with the Pfizer/BioNTech vaccine. The menstrual bleeding had to be stopped with medication (blood thickeners). Patient has an IUD for 9 years now and never had a menstruation in all those years. Patient has factor VII deficiency and bleeding is very dangerous for her because of her condition. Now after both the first and the second vaccination she had a very severe menstrual bleeding, despite the IUD. No further diagnostics are performed. No other concomitant medication. Patient did not have a covid-19 infection prior to vaccination. BMI is high.
5. This report concerns a 50-60 year-old female with heavy menstrual bleeding 4 weeks after second vaccination with the Moderna vaccine. The patient experienced heavy menstruation with a lot of large blood clots. She had to wear diapers and could not leave the house. The heavy menstrual bleeding occurred for 4 days, during 2 cycles. Between the 2 months, she had slight menstrual blood loss every day. Her Hb decreased to 5,6. She was treated with oral ferro pills and had a gynecological examination which revealed a thick endometrium (2cm). No further examinations were performed and no other treatment was given. The patient never had any gynecological or menstruation related problems before. No concomitant medication. No covid-19 infection prior to vaccination.

### Reports from category Postmenopausal haemorrhage

To ensure an unambiguous way of coding of the menstrual disorders, Lareb made coding agreements based on the Dutch General Practitioners Guidelines. The coding agreements about the postmenopausal haemorrhage cases are shown in table 7.

Reporting text	LLT	PT
Menstruation after menopause (last menstruation > 12 months ago)	Postmenopausal bleeding	Postmenopausal haemorrhage
Menstruation after menopause (last menstruation < 12 months ago)	Vaginal bleeding	Vaginal haemorrhage

All reports from the category Postmenopausal haemorrhage after administration of one of the authorized COVID-19 vaccines are selected and shown in table 8. This category includes only the reports with the PT Postmenopausal haemorrhage. It was decided not to include the cases of the PT Vaginal haemorrhage in this signal because of the definition of the Dutch General Practitioners Guidelines. Table 8 shows a breakdown per age group of the number of serious reports, vaccination moment, administered vaccine, reporting rates, COVID-19 prior to vaccination, reporter, BMI and information about the course of the postmenopausal haemorrhage.

Age groups	<45	45-54	55-64	65-74	>75	Unknown	Total
Number of reports	15	355	136	22	6	3	537
Number serious	0	3	1	2	1	0	7
Percentage serious	0,0%	0,8%	0,7%	9,1%	16,7%	0,0%	1,3%
Vaccine and vaccination moment							
<b>Pfizer</b>	11	238	88	19	6	2	364
1	2	78	33	6	1	1	121
2	9	160	55	13	5	1	243
<b>Moderna</b>	2	42	10	1	0	1	56
1	0	12	4	0	0	0	16
2	2	30	6	1	0	1	40
<b>AstraZeneca</b>	1	21	36	2	0	0	60
1	1	11	15	1	0	0	28
2	0	10	21	1	0	0	32
<b>Janssen</b>	1	54	2	0	0	0	57
1	1	54	2	0	0	0	57

Reporting rates per 100.000 vaccinations (per vaccine and vaccination moment)							
<b>Pfizer</b>							
1	0,1	11,4	5,6	0,8	0,1	-	2,4
2	0,5	25,3	9,7	1,7	0,6	-	5,3
<b>Moderna</b>							
1	0,0	8,8	4,4	0,0	0,0	-	3,1
2	0,9	23,8	7,0	4,9	0,0	-	8,5
<b>AstraZeneca</b>							
1	1,0	17,2	3,8	0,8	0,0	-	4,0
2	0,0	17,0	5,8	0,8	0,0	-	5,0
<b>Janssen</b>							
1	0,6	38,0	10,8	0,0	0,0	-	17,4
<b>COVID prior</b>							
No. (% of reports)	3 (20,0%)	53 (14,9%)	16 (11,8%)	1 (4,6%)	1 (16,7%)	0 (0,0%)	74 (13,8%)
<b>Reporter</b>							
Consumer	15 (100%)	353 (99,4%)	131 (96,3%)	22 (100%)	3 (50%)	3 (100%)	527 (98,1%)
Health care professional	0 (0%)	2 (0,6%)	5 (3,7%)	0 (0,0%)	3 (50%)	0 (0,0%)	10 (1,9%)
<b>BMI</b>							
% bmi <18	0,0%	0,0%	1,5%	0,0%	0,0%	0,0%	0,4%
% bmi 18-24.9	33,3%	41,7%	32,4%	27,3%	33,3%	0,0%	38,2%
% bmi 25-29.9	66,7%	35,5%	34,6%	54,5%	16,7%	100,0%	37,1%
% bmi 30-39.9	0,0%	18,0%	26,5%	18,2%	33,3%	0,0%	19,7%
% bmi >40	0,0%	2,3%	2,9%	0,0%	0,0%	0,0%	2,2%
% bmi unknown	0,0%	2,5%	2,2%	0,0%	16,7%	0,0%	2,4%
<b>Time to onset</b>							
Range (days)	1 – 66	0 – 166	0 – 122	0 – 101	1 – 98	4 – 42	0 – 166
Mean (days)	17,8	24,3	23,1	23,8	37,7	23,0	24,0
Median (days)	10,5	14	14	14,5	23	23	14
No. Unknown (%)	0 (0,0%)	13 (3,7%)	10 (7,4%)	0 (0,0%)	0 (0,0%)	1 (33,3%)	24 (4,5%)
<b>Outcome at time of reporting</b>							
Recovered/resolved	2 (13,3%)	186 (52,4%)	73 (53,7%)	14 (63,6%)	4 (66,7%)	1 (33,3%)	280 (52,1%)
Recovering / resolving	1 (6,7%)	28 (7,9%)	8 (5,9%)	3 (13,6%)	0 (0,0%)	1 (33,3%)	41 (7,6%)
Not recovered / not resolved / ongoing	10 (66,7%)	102 (28,7%)	44 (32,4%)	5 (22,7%)	2 (33,3%)	1 (33,3%)	164 (30,5%)
Unknown	2 (13,3%)	39 (11,0%)	11 (8,1%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	52 (9,7%)
<b>Duration of recovered/resolved (n = 280)</b>							
Mean (days)	0,5	7,9	11,9	18,7	11,5	4	9,5

In total, postmenopausal haemorrhage was reported in 537 cases after vaccination with one of the authorized COVID-19 vaccines, with the vast majority of cases in the age group of 45-54 year-olds (n = 355). 7 of these cases were serious based on the CIOMS criteria (1,3%). Most reports were reported after the second vaccination (n = 315), followed closely by the first vaccination (n = 222). Nothing was reported after the third vaccination. The majority of the cases were reported by the consumer herself (98,1%).

The number of patients who had COVID-19 prior to receiving the vaccination varies from 4,6% (65-74 year-olds) to 20,0% (<45 year-olds). In total, 13,8% of the patients had COVID-19 prior to vaccination. The body mass index of the different age groups varies. In total, most of the patients had a BMI between 18-25 kg/m<sup>2</sup> (38,2%), followed by a BMI between 25-30 kg/m<sup>2</sup> (37,1%) and a BMI between 30-40 kg/m<sup>2</sup> (19,7%). Only 0,4% of the patients had a BMI of less than 18-25 kg/m<sup>2</sup> and only 2,2% had a BMI above 40 kg/m<sup>2</sup>.

### *Reporting rates*

Appendix 5 shows the calculation of the reporting rates of the PT Postmenopausal haemorrhage. The reporting rates vary from 38,0 reports per 100.000 vaccinations with patients from 45-54 years who received the Janssen vaccine to 0,1 reports per 100.000 vaccinations with patients from under 45 years and above 75 years who received the Pfizer/BioNTech vaccine. Overall, the reporting rates were the highest with patients who received the Janssen vaccine (17,4 reports per 100.000 vaccinations), followed by Moderna (3,1 reports per 100.000 first vaccinations and 8,5 reports per 100.000 second vaccinations), AstraZeneca (4,0 reports per 100.000 first vaccinations and 5,0 reports per second 100.000 vaccinations) and Pfizer (2,4 reports per 100.000 first vaccinations and 5,3 reports per 100.000 second vaccinations).

### *Course of the postmenopausal haemorrhage*

The mean time to onset varies in the different age groups, from 17,8 days with <45 year-olds (range: 1 – 66 days), 24,3 days with 45-54 year-olds (range: 0 – 166 days), 23,1 days with 55-64 year-olds (range: 0 – 122 days), 23,8 days with 65-74 year-olds (range: 0 – 101 days) and 37,7 days with patients older than 75 (range: 1 – 98,0 days). The median time to onset also varies in the different age groups, from 10,5 days with <45 year-olds, 14 days with 45-54 year-olds, 14 days with 55-64 year-olds, 14,5 days with 65-74 year-olds and 23 days with patients older than 75.

In the majority of the cases, the patient was recovered at time of reporting (52,1%). Whereas 30,5% of the patients were not recovered at time of reporting and 7,6% of the patients were recovering at time of reporting. In most of these cases, it is unknown whether or not the patient recovered from the postmenopausal haemorrhage and how long the patient was experiencing this haemorrhage.

The mean duration of the recovered cases of postmenopausal haemorrhage (n = 280) varies in the different age groups, from 0,5 days with <45 year-olds, 7,9 days with 45-54 year-olds, 11,9 days with 55-64 year-olds, 18,7 days with 65-74 year-olds and 11,5 days with patients older than 75. Overall, the mean duration was 9,5 days after which the haemorrhage stopped again.

### **Detailed description of selected cases**

To illustrate, a description of three well documented cases is given below. These cases show women with postmenopausal blood loss shortly after vaccination with one of the COVID-19 vaccinations. In most of the cases the woman went to a GP and a gynecologist and were no other causes were found. Also, a case of positive rechallenge was included where the patient did not have a menstruation for 13 years prior to vaccination and after both the first and the second vaccination she had a bleeding. After these two bleedings, it did not reoccur.

1. This report concerns a 70 years and older-woman with a postmenopausal bleeding ten days after the second vaccination with the Pfizer/BioNTech vaccine. She recovered of this one time bleeding after one day and did not experience any other menstrual symptoms. An ultrasound was performed, as well as a biopsy of the uterus, a hysteroscopy and a gel infusion sonohysterography. No abnormalities were found. Patient has a history of migraine, but did not experience this in the weeks around vaccination. No other (relevant) medical history was reported. Patient did not have a covid-19 infection prior to vaccination. BMI is high (30.4).
2. This report concerns a 60-70 year-old woman who had a postmenopausal bleeding after both the first and the second vaccination with the AstraZeneca vaccine. The first bleeding occurred 20 days after the first vaccination. The last menstruation prior to the vaccination was 13 years ago. The patient did not visit a GP, because it only happened after the vaccination and because of the media attention in the Netherlands she made a connection between her bleedings and the vaccination. It did not reoccur afterwards. Patient did not have a covid-19 infection prior to vaccination. BMI is a little high (28.4).
3. This report concerns a 60-70 year-old woman with a postmenopausal bleeding, 12 days after the first AstraZeneca vaccination. She recovered from this bleeding after two weeks and did not experience blood loss for six weeks. Then, after the second vaccination with the AstraZeneca vaccine, she had another bleeding for three days. The last menstruation prior to the vaccinations was around 8 years ago. She went to the gynecologist and no abnormalities were found in the PAP smear test and the ultrasound of the uterus. The patient is familiar with scoliosis and irritable bowel syndrome. Concomitant medication is chlorhexidine mouthwash, betamethasone gel, plantago ovata granulate and mebeverine. She used vaginal estradiol tablets for one month and she stopped using this three weeks

before the first bleeding. Both the GP and the gynecologist said both the use and the withdrawal of this medication is no cause of postmenopausal bleedings. The SmPC mentions vaginal bleeding as a side effect. Patient did not have a covid-19 infection prior to vaccination. BMI is normal.

## Other sources of information

### SmPC

Menstrual disorders are not listed in the SmPC of the Covid-19 vaccines [2-5].

### Other databases

In VigiBase, the WHO global database of individual case safety reports (ICSRs), 29.079 reports with PT Heavy Menstrual bleeding, 16.422 reports with PT Menstrual disorders, 15.932 with PT Menstruation Delayed, 15.007 with Menstruation irregular, 13.370 with Dysmenorrhea, 10.556 with Intermenstrual bleeding, 8.323 with Amenorrhea, and 3.034 with Postmenopausal haemorrhage were found for the Covid-19 vaccines (version date dataset: 26-09-2021). This number includes the reports from the Netherlands. The highest number of reports was related to the Pfizer/BioNTech vaccine (Comirnaty®) [17], but it is not possible to compare this with the number of given vaccinations per vaccine.

### Data on usage

Table 9 provides an overview of number of dose administered per vaccine in the Netherlands.

	Startdate vaccination	Number of vaccinations until November 28 <sup>th</sup> , 2021
<b>Comirnaty®</b>	January 6 <sup>th</sup> , 2021	24.597.355
<b>Vaxzevria®</b>	January 25 <sup>th</sup> , 2021	2.778.729
<b>SpikeVax®</b>	February 12 <sup>th</sup> , 2021	2.007.230
<b>Janssen vaccine</b>	April, 21 <sup>st</sup> , 2021	863.600

### Literature

Menstruation disorders have been described for several vaccines in the past; A study from 1913 identified that the typhoid vaccine was associated with menstrual irregularities, which included missed, late, and early menstruation, discomfort, and heavy bleeding in more than half of their female sample [18]. Hepatitis B studies have also indicated that menstruation could be altered [19]. There is some evidence that HPV vaccination may be associated with heavier or irregular periods [20]. Gong et al. [21] detected disproportionate reports of premature ovarian insufficiency (POI) and related events, including amenorrhea, menstruation irregular, FSH increased, and premature menopause, following human papillomavirus (HPV) vaccine from FDA Vaccine Adverse Event Reporting System (VAERS). Although the association was statistically disproportionate, the authors state that the study has a number of limitations and causality should be further investigated. In a Nationwide Cohort from Denmark, no association Between Human Papillomavirus Vaccination and Primary Ovarian Insufficiency was found [22].

For the COVID-19 vaccines some information has been published, although not all articles discussed below have been peer-reviewed yet. In a cohort, recruited retrospectively, of 1273 people who keep a record of their menstrual cycles and vaccination dates, no strong signals were detected to support the idea that COVID-19 vaccination is linked to menstrual changes. Because the participants were recruited retrospectively, the data is likely to be enriched with people who noticed a change to their cycle, no estimate could be made how common postvaccination menstrual changes are [23].

In a large survey in the US, 42% of people with regular menstrual cycles bled more heavily than usual, while 44% reported no change, after being vaccinated with a COVID-19 vaccine. Among people who typically do not menstruate, 71% of people on long-acting reversible contraceptives, 39% of people on gender-affirming hormones, and 66% of post-menopausal people reported breakthrough bleeding [24].

Following vaccination for COVID-19, menstrual disturbance occurred in 20% of individuals in a UK sample. Diverse experiences were reported, from menstrual bleeding cessation to heavy menstrual bleeding [25].

### Mechanism

There is also evidence that viral infection, including with SARS-CoV2 itself, can alter the menstrual cycle [26, 27]. This may suggest that immune stimulation can affect the menstrual cycle. Biologically plausible mechanisms by which this could occur

include effects mediated by immunological influences on the hormones driving the menstrual cycle [28] or by immune cells in the lining of the uterus, which are involved in the cyclical build-up and breakdown of this tissue [29]. There are in fact multiple plausible biological mechanisms to explain a relationship between an acute immune challenge like a vaccine [30] its corresponding and well-known systemic effects on hemostasis and inflammation [31], and menstrual repair mechanisms of the uterus [32-35]

### Discussion and conclusion

In the period from January 6<sup>th</sup>, 2021 until December 1<sup>st</sup>, 2021 the Netherlands Pharmacovigilance Centre Lareb received an unprecedented amount of reports of menstrual disorders with administration of COVID-19 vaccines. The reporting rates, stratified for vaccinations given to females and specific age groups, for the menstrual disorders in general are very high. The reporting rates are the highest for the 20-45 year-olds who received the Janssen vaccine (522,1 reports per 100.000 vaccinations). This means that 1 in 200 women in the age group 20-45 years who received the Janssen vaccine, reported a menstrual disorder at Pharmacovigilance Centre Lareb.

The reporting rates for Janssen are consistently the highest in all the categories where the reporting rates are calculated. Overall, the reporting rates are the highest for Janssen as well (369,6 reports per 100.000 vaccinations), but also the other vaccines have high reporting rates (238,7 reports per 100.000 second Moderna vaccinations and 175,3 reports per 100.000 first Moderna vaccinations; 148,7 reports per 100.000 second Pfizer vaccinations and 143,8 reports per 100.000 first Pfizer vaccinations; 44,3 reports per 100.000 second AstraZeneca vaccinations and 35,8 reports per 100.000 first AstraZeneca vaccinations). Even though the reporting rates are very high, not all menstrual disorder that occurred will have been reported.

#### *Menstrual disorders*

Heavy menstrual bleeding and amenorrhoea were the categories that were most reported and the reporting rates are also high for both these categories. That both these categories are often reported, shows that the menstrual disorders can be very diverse. On top of the high reporting rates, many patient reported that what they experienced after vaccination was different than their usual menstruation. Also in some cases, the menstrual disorder occurred both after the first and after the second vaccination. In most of the reports information about the duration is lacking. In a part of the reports the duration of disorders was longer than one cycle period up to several months.

The high amount of reports of menstrual disorders after vaccination causes concern among patients and can lead to doubt among other (young) females to get vaccinated. Although very common, the nature of the reports indicates that the disorders differ from what females experienced normally. In addition, there is a possible biological mechanism. Despite possible other causes, like covid-19 infection, other infections or stress, it is plausible that the vaccine caused the menstrual disorders. Further research is necessary to investigate these possibly vaccine-induced menstrual disorders. Therefore, Pharmacovigilance Centre Lareb started intensive follow-up research on a sample of 1.500 – 2.000 reports.

#### *Postmenopausal haemorrhage*

Postmenopausal haemorrhage is a very specific kind of vaginal bleeding and therefore was also separately focused on in this signal. The reporting rates were the highest in the 45-64 year-olds. But it also occurred with patients above 75 years and with patients who were postmenopausal for more than 10 years. The cases that were described in this signal show that gynaecological examination showed no other explanation and that it sometimes occurred after both vaccines. At least one gynaecologist mentioned in a report that there were several other cases like this after vaccination. This possible association should be further investigated as well.

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*This signal has been raised on December 22, 2021. 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.cbq-meb.nl](http://www.cbq-meb.nl)*

Appendix 1: Distribution of menstrual PT's in predetermined categories based on the Dutch General Practitioners Guidelines (NHG-Standaard [15, 16]).

Categories	PT 1	PT 2	PT 3	PT 4	PT 5	PT 6
<b>Heavy menstrual blood loss</b>	Heavy menstrual bleeding					
<b>Less menstrual blood loss</b>	Hypomenorrhoea					
<b>Irregular blood loss</b>	Polymenorrhoea	Menstruation irregular				
<b>Intermenstrual blood loss</b>	Intermenstrual bleeding					
<b>Postmenopausal blood loss</b>	Postmenopausal haemorrhage					
<b>Amenorrhoea / Oligomenorrhoea</b>	Menstruation delayed	Amenorrhoea	Oligomenorrhoea			
<b>Dysmenorrhoea</b>	Dysmenorrhoea	Premenstrual pain	Premenstrual syndrome	Premenstrual headache	Premenstrual dysphoric disorder	Menstrual discomfort
<b>Withdrawal blood loss abnormal</b>	Abnormal withdrawal bleeding	Withdrawal bleed				
<b>Other</b>	Menstrual disorder	Vaginal haemorrhage				

Appendix 2: Calculation of reporting rates per 100.000 vaccinations of the menstrual disorders. Based on the number of reports and the number of given vaccinations in the Netherlands until 1 <sup>st</sup> of December, 2021 (only females).							
Vaccine	Age groups	N reports (1 <sup>st</sup> dose)	N reports (2 <sup>nd</sup> dose)	First dose (vaccinations)	Second dose (vaccinations)	Reporting rates per 100.000 vaccinations (1 <sup>st</sup> dose)	Reporting rates per 100.000 vaccinations (2 <sup>nd</sup> dose)
AstraZeneca	10 – 14	0	0	15	12	0,0	0,0
	15 – 19	8	9	3.363	3.135	237,9	287,1
	20 – 45	171	193	97.421	89.831	175,5	214,8
	45+	69	83	594.243	550.691	11,6	15,1
	Total	249	285	695.042	643.669	35,8	44,3
Janssen	10 – 14	0	0	22	0	0,0	0,0
	15 – 19	71	0	16.754	1	423,8	0,0
	20 – 45	893	0	171.031	112	522,1	0,0
	45+	243	0	139.871	117	173,7	0,0
	Total	1.211	0	327.678	230	369,6	0,0
Moderna	10 – 14	0	0	9	11	0,0	0,0
	15 – 19	51	35	12.806	10.992	398,3	318,4
	20 – 45	682	806	240.652	220.331	283,4	365,8
	45+	164	285	258.363	240.747	63,5	118,4
	Total	897	1.127	511.830	472.081	175,3	238,7
Pfizer	10 – 14	174	108	166.888	141.189	104,3	76,5
	15 – 19	398	277	334.935	280.996	118,8	98,6
	20 – 45	5.655	5.088	1.637.461	1.447.183	345,4	351,6
	45+	920	1.329	2.837.091	2.723.518	32,4	48,8
	Total	7.155	6.808	4.976.375	4.592.886	143,8	148,2

**Appendix 3: Calculation of reporting rates per 100.000 vaccinations of PT Amenorrhoea. Based on the number of reports and the number of given vaccinations in the Netherlands until 1<sup>st</sup> of December, 2021 (only females).**

Vaccine	Age groups	N reports (1 <sup>st</sup> dose)	N reports (2 <sup>nd</sup> dose)	First dose (vaccinations)	Second dose (vaccinations)	Reporting rates per 100.000 vaccinations (1 <sup>st</sup> dose)	Reporting rates per 100.000 vaccinations (2 <sup>nd</sup> dose)
AstraZeneca	10 – 14	0	0	15	12	0,0	0,0
	15 – 19	1	2	3.363	3.135	29,7	63,8
	20 – 45	33	46	97.421	89.831	33,9	51,2
	45+	6	8	594.243	550.691	1,0	1,5
	Total	40	56	695.042	643.669	5,8	8,7
Janssen	10 – 14	0	0	22	0	0,0	0,0
	15 – 19	2	0	16.754	1	11,9	0,0
	20 – 45	153	0	171.031	112	89,5	0,0
	45+	30	0	139.871	117	21,4	0,0
	Total	187	0	327.678	230	57,1	0,0
Moderna	10 – 14	0	0	9	11	0,0	0,0
	15 – 19	9	7	12.806	10.992	70,3	63,7
	20 – 45	132	135	240.652	220.331	54,9	61,3
	45+	31	49	258.363	240.747	12,0	20,4
	Total	172	191	511.830	472.081	33,6	40,5
Pfizer	10 – 14	66	48	166.888	141.189	39,5	34,0
	15 – 19	77	64	334.935	280.996	23,0	22,8
	20 – 45	999	975	1.637.461	1.447.183	61,0	67,4
	45+	141	176	2.837.091	2.723.518	5,0	6,5
	Total	1.285	1.266	4.976.375	4.592.886	25,8	27,6

**Appendix 4: Calculation of reporting rates per 100.000 vaccinations of the category Heavy menstrual blood loss. Based on the number of reports and the number of given vaccinations in the Netherlands until 1<sup>st</sup> of December, 2021 (only females).**

Vaccine	Age groups	N reports (1 <sup>st</sup> dose)	N reports (2 <sup>nd</sup> dose)	First dose (vaccinations)	Second dose (vaccinations)	Reporting rates per 100.000 vaccinations (1 <sup>st</sup> dose)	Reporting rates per 100.000 vaccinations (2 <sup>nd</sup> dose)
AstraZeneca	10 – 14	0	0	15	12	0,0	0,0
	15 – 19	2	2	3.363	3.135	59,5	63,8
	20 – 45	48	44	97.421	89.831	49,3	49,0
	45+	13	15	594.243	550.691	2,2	2,7
	Total	63	61	695.042	643.669	9,1	9,5
Janssen	10 – 14	0	0	22	0	0,0	0,0
	15 – 19	19	0	16.754	1	113,4	0,0
	20 – 45	230	0	171.031	112	134,5	0,0
	45+	72	0	139.871	117	51,5	0,0
	Total	322	0	327.678	230	98,3	0,0
Moderna	10 – 14	0	0	9	11	0,0	0,0
	15 – 19	13	10	12.806	10.992	101,5	91
	20 – 45	192	204	240.652	220.331	79,8	92,6
	45+	58	80	258.363	240.747	22,4	33,2
	Total	263	295	511.830	472.081	51,4	62,5
Pfizer	10 – 14	35	14	166.888	141.189	21,0	9,9
	15 – 19	80	57	334.935	280.996	23,9	20,3
	20 – 45	1.475	1.267	1.637.461	1.447.183	90,1	87,5
	45+	240	360	2.837.091	2.723.518	8,5	13,2
	Total	1.833	1.700	4.976.375	4.592.886	36,8	37,0

**Appendix 5: Calculation of reporting rates per 100.000 vaccinations of the category Postmenopausal blood loss. Based on the number of reports and the number of given vaccinations in the Netherlands until 1<sup>st</sup> of December, 2021 (only females).**

Vaccine	Age groups	N reports (1 <sup>st</sup> dose)	N reports (2 <sup>nd</sup> dose)	First dose (vaccinations)	Second dose (vaccinations)	Reporting rates per 100.000 vaccinations (1 <sup>st</sup> dose)	Reporting rates per 100.000 vaccinations (2 <sup>nd</sup> dose)
AstraZeneca	<45	1	0	96.017	88.594	1,0	0,6
	45 – 54	11	10	63.799	58.890	17,2	17,0
	55 – 64	15	21	391.710	362.280	3,8	5,8
	65 – 74	1	1	125.831	118.683	0,8	0,8
	>75	0	2	17.688	15.287	0	0,0
	Total	28	32	695.045	643.734	4,0	5,0
Janssen	<45	1	0	163.936	110	0,6	0,0
	45 – 54	54	0	142.210	53	38,0	0,0
	55 – 64	2	0	18.451	58	10,8	0,0
	65 – 74	0	0	2.137	7	0,0	0,0
	>75	0	0	945	2	0,0	0,0
	Total	57	0	327.679	230	17,4	0,0
Moderna	<45	0	2	245.208	223.747	0,0	0,9
	45 – 54	12	30	135.814	126.301	8,8	23,8
	55 – 64	4	6	91.884	86.271	4,4	7,0
	65 – 74	0	1	21.402	20.255	0,0	4,9
	>75	0	0	17.523	15.721	0,0	0,0
	Total	16	40	511.831	472.295	3,1	8,5
Pfizer	<45	2	9	2.089.549	1.824.382	0,1	0,5
	45 – 54	78	160	686.189	632.334	11,4	25,3
	55 – 64	33	55	587.136	564.488	5,6	9,7
	65 – 74	6	13	781.600	758.417	0,8	1,7
	>75	1	5	831.913	814.964	0,1	0,6
	Total	121	243	4.976.387	4.594.585	2,4	5,3