bijwerkingen centrumlareb

Postmenopausal bleeding after administration of COVID-19 vaccines

Introduction

As of date, the European Medicines Agency has authorised five vaccines for the prevention of COVID-19 in the European Union: Comirnaty®, Spikevax®, Vaxzevria®, COVID-19 Vaccine Janssen and Nuvaxovid® (1). Comirnaty® and Spikevax® are both so called mRNA vaccines, while Vaxzevria® and the Janssen vaccine are vector vaccines (2-5). Comirnaty® was the most widely used COVID-19 vaccine in the Dutch vaccination program (6). The newly approved subunit vaccine Nuvaxovid® has not been rolled out in The Netherlands as of March 1st 2022 (6). All the authorised COVID-19 vaccines are under additional monitoring (7).

Postmenopausal bleeding is defined as vaginal blood loss that occurs more than 12 months after the last menstrual bleeding. The highest incidence of postmenopausal bleeding is seen in the age group of 50-59 years: 7 per 1000 women per year. In 10% of postmenopausal bleeding cases, the bleeding is caused by an endometrial carcinoma with an increased chance with higher age (8). A Swedish prospective study from 1995 found in a group of 457 women with postmenopausal bleeding no endometrial carcinoma in women younger than 50 years. However, 23.8% of women older than 80 years did have endometrial carcinoma (8, 9). One third of women with postmenopausal bleeding are found to have an endometrial or endocervical polyp. Lastly, with additional testing more than 50% of women with postmenopausal bleeding were found to have an atrophic endometrium (8).

Reports

Spontaneous case reports with a COVID-19 vaccine as suspect drug and Postmenopausal haemorrhage (MedDRA ® Preferred Term (PT)) coded as reaction were selected. Internal coding agreements ensured vaginal bleeding was coded as Postmenopausal haemorrhage (PT) if the last menstrual bleeding occurred more than 12 months prior. Until February 8th 2022, The Netherlands Pharmacovigilance Centre Lareb received 669 spontaneous case reports of postmenopausal bleeding associated with a COVID-19 vaccine. After sending follow-up questions to the reporters for a subset of these reports, Lareb received additional information such as test results and menopause duration.

Table 1 provides an overview of the received case reports on vaccination moment, age, the reporter, BMI, time to onset, outcome, duration of bleeding and elapsed time after last menstrual period.

Table 1 – Overview of postmenopausal bleeding case reports

Vaccine	Comirnaty ®	Spikevax®	Vaxzevria®	Janssen	Unknown	Total
Number of reports	451	81	69	67	1	**669**
Number of postmenopausal bleedings	457	85	72	70	1	**685**
Number of serious PT's	3	-	-	-	-	**3**
Vaccination moment*						
1	145 (32%)	22 (26%)	31 (43%)	70 (100%)	-	**268 (39%)**
2	295 (65%)	52 (61%)	41 (57%)	-	-	**388 (57%)**
3	17 (4%)	11 (13%)	-	-	1 (100%)	**29 (4%)**
Reporter						
Consumer	444 (98%)	80 (99%)	66 (96%)	67 (100%)	1 (100%)	**658 (98%)**
Other health professional	5 (1%)	-	-	-	-	**5 (1%)**
Physician	2 (0%)	1 (1%)	3 (4%)	-	-	**6 (1%)**
Age groups (year)						
<45	9 (2%)	3 (4%)	1 (1%)	-	-	**13 (2%)**
45-49	53 (12%)	12 (15%)	2 (3%)	1 (1%)	-	**68 (10%)**
50-54	187 (41%)	30 (37%)	16 (23%)	59 (88%)	-	**292 (44%)**
55-59	119 (26%)	23 (28%)	13 (19%)	3 (4%)	-	**158 (24%)**
60-64	12 (3%)	1 (1%)	29 (42%)	1 (1%)	-	**43 (6%)**
65-69	25 (6%)	3 (4%)	2 (3%)	-	-	**30 (4%)**

70-74	9 (2%)	4 (5%)	1 (1%)	-	-	**14 (2%)**
≥75	8 (2%)	1 (1%)	-	-	1 (100%)	**10 (1%)**
Unknown	29 (6%)	4 (5%)	5 (7%)	3 (4%)	-	**41 (6%)**
BMI (kg/m^2)						
<20	16 (4%)	6 (7%)	1 (1%)	2 (3%)	-	**25 (4%)**
20-24	183 (41%)	30 (37%)	17 (25%)	24 (36%)	1 (100%)	**255 (38%)**
25-29	139 (31%)	30 (37%)	29 (42%)	27 (40%)	-	**225 (34%)**
30-34	58 (13%)	8 (10%)	8 (12%)	7 (10%)	-	**81 (12%)**
≥35	39 (9%)	3 (4%)	11 (16%)	4 (6%)	-	**57 (9%)**
Unknown	16 (4%)	4 (5%)	3 (4%)	3 (4%)	-	**26 (4%)**
Time to onset (days)						
Mean	23.8	27.8	38.6	27.7	3.0	**26.3**
Range	0 – 230	0 – 179	1 – 219	0 – 132	N/A	**0 -230**
Median	12	12	21	7	N/A	**13**
Time to onset groups (days)*						
<3	98 (21%)	19 (22%)	9 (13%)	21 (30%)	-	**147 (21%)**
3-7	87 (19%)	15 (18%)	11 (15%)	11 (16%)	1 (100%)	**125 (18%)**
8-14	71 (16%)	9 (11%)	9 (13%)	5 (7%)	-	**95 (14%)**
15-28	80 (18%)	11 (13%)	12 (17%)	6 (9%)	-	**109 (16%)**
29-42	38 (8%)	12 (14%)	7 (10%)	9 (13%)	-	**66 (10%)**
43-56	15 (3%)	2 (2%)	7 (10%)	4 (6%)	-	**28 (4%)**
>56	58 (13%)	14 (16%)	17 (24%)	13 (19%)	-	**103 (15%)**
Unknown	10 (2%)	3 (4%)	-	1 (1%)	-	**12 (2%)**
Outcome*						
Recovered/resolved	234 (51%)	43 (51%)	39 (54%)	44 (63%)	1 (100%)	**361 (53%)**
Recovering/resolving	31 (7%)	10 (12%)	7 (10%)	6 (9%)	-	**54 (8%)**
Not recovered/not resolved/ongoing	146 (32%)	26 (31%)	24 (33%)	13 (19%)	-	**209 (31%)**
Unknown	46 (10%)	6 (7%)	2 (3%)	7 (10%)	-	**61 (9%)**
Duration bleeding (days)*						
0-1	29 (6%)	6 (7%)	10 (14%)	3 (4%)	-	**48 (7%)**
2-3	39 (9%)	4 (5%)	4 (6%)	3 (4%)	1 (100%)	**51 (7%)**
4-5	39 (9%)	4 (5%)	5 (7%)	14 (20%)	-	**62 (9%)**
6-7	56 (12%)	12 (14%)	8 (11%)	11 (16%)	-	**87 (13%)**
8-14	33 (7%)	4 (5%)	1 (1%)	4 (6%)	-	**42 (6%)**
15-28	2 (0%)	-	2 (3%)	1 (1%)	-	**5 (1%)**
29-56	5 (1%)	2 (2%)	-	2 (3%)	-	**9 (1%)**
>56	8 (2%)	4 (5%)	2 (3%)	-	-	**14 (2%)**
Unknown or not recovered	246 (54%)	49 (58%)	40 (56%)	32 (46%)	-	**367 (54%)**
Elapsed time after last menstrual period (years)						
1-2	56 (12%)	7 (9%)	5 (7%)	14 (21%)	-	**82 (12%)**
3	11 (2%)	3 (4%)	3 (4%)	1 (1%)	-	**18 (3%)**
4	4 (1%)	1 (1%)	-	-	-	**5 (1%)**
5	4 (1%)	-	1 (1%)	-	-	**5 (1%)**
6-9	10 (2%)	-	7 (10%)	-	-	**17 (3%)**
≥10	10 (2%)	1 (1%)	5 (7%)	1 (1%)	-	**17 (3%)**
Unknown**	356 (79%)	69 (85%)	48 (70%)	51 (76%)	1 (100%)	**525 (78%)**

*Note that the total number adds up to 685, since the data provides information on individual postmenopausal bleedings.

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

In total, Pharmacovigilance Centre Lareb received 669 case reports of postmenopausal bleeding associated with a COVID-19 vaccine with the majority after Comirnaty® (451 cases). In 15 case reports postmenopausal bleeding was reported twice or three times after 1 vaccine and was thus coded multiple times: 685 times in total over all case reports. Majority of the case reports were reported after the second dose of a COVID-19 vaccine excluding the Janssen vaccine. Nearly all case reports were submitted by consumers (98%). 6 cases were reported by physicians and 5 cases by other health professionals (2 nurses, 1 physician assistant and 2 unknown). Most case reports concerned women aged between 50 and 54 years. Figure 1 shows the age distribution over all received case reports.

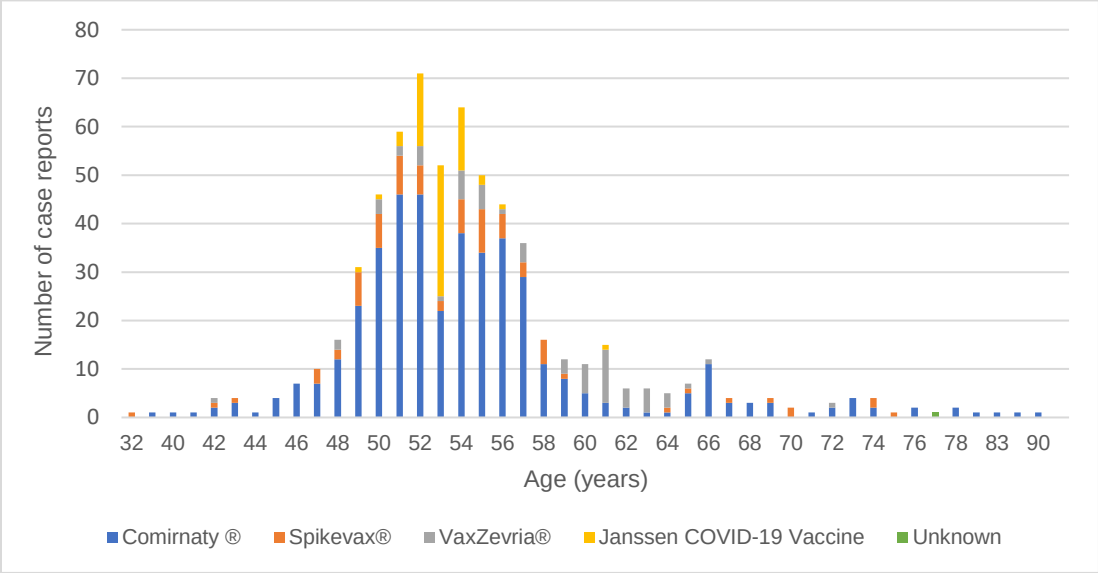

Figure 1 – Age distribution of case reports of women with postmenopausal bleeding after receiving a COVID-19 vaccine

72% of all women had a BMI between 20 and 24 kg/m^2 or between 25 and 29 kg/m^2 (38 and 34% respectively).

Serious case reports

3 of the cases (all after vaccination with Comirnaty®) were considered serious according to the CIOMS criteria. In 2 of these cases were the women, aged 50-60 and 70 years and older, hospitalised after postmenopausal bleeding. In the third case did the woman, aged 40-50 years, report the reaction as serious due to her medical history. The woman had a hormone-sensitive breast tumour in the past and was treated with chemotherapy, immunotherapy and tamoxifen which caused menopause. An ultrasound was done after experiencing postmenopausal bleeding after vaccination and showed an active ovary. The woman reported that elevated hormone levels were risky in her case.

Postmenopausal bleeding

Time to onset showed a wide range from 0 to 230 days with a mean of 26.3 days and a median of 13 days. Women recovered from postmenopausal bleeding in approximately half of the case reports (53%). A large number of women did not recover at the time of reporting (31%). In most cases the duration of the postmenopausal bleeding was unknown or the woman was not recovered yet (54%). For the cases with known duration of bleeding the vast majority of the women recovered within 14 days (248 out of 318 cases [78%]). Lastly, 144 women provided additional information on the elapsed time after their last menstrual bleeding. More than half of the women in this subset had their last menstrual bleeding less than 2 years prior (82 cases [57%]).

Reporting rates

The reporting rates per age group were calculated for the four vaccines, see Table 2. (Calculations and number of administrated vaccine doses can be found in Appendix A). The reporting rates varied from 0.1 reports per 100,000 vaccinations in the age group <45 and ≥75 (Comirnaty®) and 58.2 reports per 100,000 vaccinations in the age group 50-54 (Janssen). The reporting rate was the highest for the age group 50 to 54 years with the exception of the third dose of Comirnaty®. Overall, Janssen had the highest reporting rate of 21.4 reports per 100,000 vaccinations.

Table 2 – Reporting rates per 100.000 vaccinations per vaccine per vaccination moment

Age group (year)	<45	45-49	50-54	55-59	60-64	65-69	70-74	≥75	Total
Comirnaty®									
1	0.1	5.9	16.7	11.1	0.7	3.5	0.2	0.1	**3.0**
2	0.4	11.1	40.3	17.1	6.4	3.6	1.7	0.7	**6.4**
3	-	0.8	3.2	3.7	0.7	1.1	1.2	0.4	**0.8**
Spikevax®									
1	0.4	9.3	10.4	8.0	-	-	-	-	**4.0**
2	0.9	10.0	35.0	22.7	-	9.5	-	-	**11.1**
3	-	-	0.4	0.4	0.3	0.6	1.3	0.2	**0.5**
Vaxzevria®									
1	1.1	3.8	25.0	14.1	3.2	0.8	-	-	**4.4**
2		4.2	21.1	17.7	5.6	0.9	14.2	-	**6.1**
Janssen									
1	-	2.8	58.2	22.4	24.6	-	-	-	**21.4**

Ultrasounds

In 132 out of 669 cases it was confirmed that the women had an ultrasound after experiencing postmenopausal bleeding. Table 3 shows the results of the ultrasounds.

Table 3 – Results ultrasound

	Comirnaty ®	Spikevax®	Vaxzevria®	Janssen	Total
No abnormalities	37 (45%)	6 (35%)	7 (47%)	7 (37%)	**57 (43%)**
Thickened endometrium	7 (9%)	5 (29%)	2 (13%)	5 (26%)	**19 (14%)**
Active ovary/ovaries	2 (2%)	-	-	-	**2 (2%)**
Cyst(s)	2 (2%)	-	-	-	**2 (2%)**
Thin endometrium	1 (1%)	-	-	1 (5%)	**2 (2%)**
Endometrium carcinoma	1 (1%)	-	-	-	**1 (1%)**
Follicle	1 (1%)	-	-	-	**1 (1%)**
Inflammation	-	-	1 (7%)	-	**1 (1%)**
Myoma	1 (1%)	1 (6%)	1 (7%)	1 (5%)	**4 (3%)**
Results unknown	30 (37%)	5 (29%)	4 (27%)	5 (26%)	**44 (33%)**
Total	**82 (100%)**	**17 (100%)**	**15 (100%)**	**19 (100%)**	**132 (100%)**

No abnormalities found was most reported (43%). 44 out of 132 reporters (33%) did not report any results of the ultrasound. The results showed a thickened endometrium in 19 cases (14%).

Co-suspects and concomitant medication

In 15 case reports another drug or vaccine was reported as co-suspect. Table 4 shows an overview of the co-suspects. In 6 cases the hormonal drugs dydrogesterone / estrogen or estradiol were reported as co-suspects. In 3 of the 6 cases there was a relative short time to onset (2 months or less). A corticosteroid was co-suspect in 3 cases and other vaccines were co-suspect in 3 other cases.

Table 4 – Reported co-suspect drugs

Co-suspect	Number of reports
Dydrogesterone and estrogen	4
Estradiol	2
Hydrocortisone	2
Influenza vaccine	2
Amoxicillin and beta-lactamase inhibitor*	1
Formoterol and beclometasone	1
Human Papilloma Virus vaccine	1
Prednisolone	1
Sertraline	1

*Used for a tick bite

In 182 out of 669 cases there was at least 1 concomitant medication reported. In total there were 395 drugs reported as concomitant. Table 5 shows an overview of the 20 most reported concomitant medication. The most common reported concomitant medications were levothyroxine and metoprolol which were both reported 20 times.

Table 5 – 20 most reported concomitant medication

Concomitant medication	Number of reports
Levothyroxine	20
Metoprolol	20
Hydrochlorothiazide	14
Colecalciferol	12
Omeprazole	12
Dydrogesterone and estrogen	11
Simvastatin	10
Atorvastatin	9
Clopidogrel	7
Lisinopril	7
Pantoprazole	7
Paracetamol	7
Paroxetine	6
Rivaroxaban	6
Salbutamol	6
Levocetirizine	5
Losartan	5
Metformin	5
Pregabalin	5
Venlafaxine	5

Other reported adverse drug reactions

Spontaneous case reports can contain multiple reported adverse drug reactions (ADR). In 338 case reports one or more ADRs were reported in addition to postmenopausal bleeding which added up to 1132 ADRs in total. In Table 6 the 25 most reported adverse drug reaction are showed. Most of the listed ADRs including the most co-reported ADR, fatigue, are known ADRs of the COVID-19 vaccines(2-5). 11 of the top 25 ADRs are not listed in the SmPCs of the COVID-19 vaccines: dysmenorrhoea, breast pain, hot flushes, back pain, heavy menstrual bleeding, breast discomfort, abdominal pain lower, breast swelling, breast tenderness and mood swings.

Table 6 – 25 most reported adverse drug reactions other than postmenopausal bleeding

Reported adverse drug reaction	Number of reports
Fatigue	117
Headache	92
Malaise	82
Myalgia	82
Arthralgia	54
Injection site pain	53
Chills	44
Nausea	39
Pyrexia	36
Abdominal pain	36
Injection site inflammation	33
Dysmenorrhoea	32
Injection site warmth	29
Injection site erythema	28
Breast pain	27
Injection site swelling	24
Hot flush	20
Back pain	14
Heavy menstrual bleeding	14
Breast discomfort	13
Abdominal pain lower	11
Breast swelling	10
Breast tenderness	9
Body temperature increased	9
Mood swings	8

It was observed that a large number of the co-reported ADRs were similar to normal symptoms of menstruation or premenstrual syndrome (PMS), see Table 7. None of these reported ADRs are known ADRs of the COVID-19 vaccines with exception of abdominal pain which is listed as ADR in the SmPC of Spikevax® and Vaxzevria®. Of these ADRs, ADRs related to the breasts (breast pain, breast discomfort, breast swelling, breast tenderness, breast enlargement, breast disorder) were the most reported ADRs (63 times).

Table 7 – Reported adverse drug reactions similar to menstruation or premenstrual syndrome symptoms	
Reported adverse drug reaction	**Number of reports**
Abdominal pain	36
Dysmenorrhoea	32
Breast pain	27
Back pain	14
Heavy menstrual bleeding	14
Breast discomfort	13
Abdominal pain lower	11
Breast swelling	10
Breast tenderness	9
Mood swings	8
Hyperhidrosis	6
Abdominal distension	4
Nipple pain	4
Breast enlargement	3
Depressed mood	3
Menstrual discomfort	3
Menstrual disorder	3
Premenstrual syndrome	3
Hormone level abnormal	2
Mood altered	2
Premenstrual pain	2
Abdominal discomfort	1
Breast disorder	1
Emotional distress	1
Libido increased	1
Nipple disorder	1
Total	**214**

Some reported ADRs seem to be related to menopause symptoms, such as hot flushes (20 cases), night sweats (2 cases) and flushing (1 case). Furthermore, there were ADRs that could be related to normal menstruation or PMS, but that were too atypical to categorise, such as fatigue (117 cases), headache (92 cases), migraine (6 cases) and palpitations (1 case).

Other sources of information

SmPC

Postmenopausal haemorrhage is not listed as an adverse effect in the Summary of Product Characteristics of the five authorised COVID-19 vaccines (2-5, 10).

Other databases

The WHO global database of individual case safety reports, VigiBase, has a total of 5,333 postmenopausal haemorrhage reports after all COVID-19 vaccines. Postmenopausal bleeding was most reported after vaccination with Comirnaty® (3765 cases), followed by Spikevax® (747 cases), Vaxzevria® (544 cases), Janssen COVID-19 vaccine (264 cases) and an unknown vaccination (13 cases) (11).

Literature

Menstruation disorders have been associated with certain vaccines in the past and recently with COVID-19 vaccines. Earlier this year Edelman et al. published a study using data from a phone application. This study found that the vaccination was associated with a small change in cycle length (12). However, for postmenopausal haemorrhage a literature search on PubMed resulted in no results describing an association with COVID-19 vaccines or other vaccines. Lee et al. did publish a preprint article based on a survey study in the United States on changes in menstrual bleeding after COVID-19 vaccines. The article stated 66% of post-menopausal women reported breakthrough bleeding(13). However, the pre-peer reviewed 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

Although postmenopausal bleeding can be a sign of endometrial carcinoma and should always be investigated further, it is not the most common cause of bleeding. A study from the United Kingdom attempted to identify the cause of postmenopausal bleeding in a group of 3047 referred women with postmenopausal bleeding. The most common cause of postmenopausal bleeding was atrophy (44.5%). Benign histology was found in 37.5% of the women. In 10.1% of the cases benign endometrial polyps were the cause of the bleeding. Endometrial carcinoma was found in 5% of the women (14). The risk of postmenopausal bleeding increases more than 5 times for women who use hormone therapy (15). Exogenous oestrogens stimulate the proliferation of the endometrium which can result in bleeding when the endometrium is shed(16). Postmenopausal bleeding might also be caused by endogenous oestrogens (16). The main source of endogenous oestrogen in postmenopausal women comes from conversion of androgens to oestrogens in adipose tissue. This also explains the higher levels of oestrogens found in obese postmenopausal women(16, 17). It could be theorised that the COVID-19 vaccines somehow have an effect on reproductive hormone levels with postmenopausal bleeding as result.

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received 669 case reports of postmenopausal haemorrhage in the period from the start of the vaccination program in The Netherlands on January 6th 2021 until February 8th 2022. Most case reports were reported after the use of Comirnaty®, the most widely used COVID-19 vaccine in The Netherlands. However, the reporting rate was the highest for the Janssen vaccine. Majority of the case reports were reported after the second dose of the vaccination. This could be explained by the media attention for menstrual disorders that started in July 2021. People aged 45 years and older were already invited for their first dose at that time(18). However, as Figure 2 shows, although the receive date peaks correspond to moments of media attention, women were experiencing postmenopausal bleeding following COVID-19 prior to widespread media attention in July 2021.

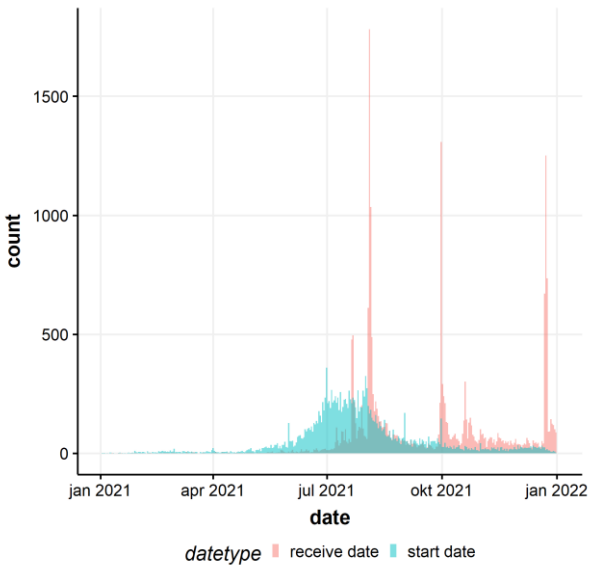

Figure 2 – Receive date and start date of the postmenopausal bleeding associated with a COVID-19 vaccine over time

Most reports (44%) were received on women aged 50 to 54 years. The second biggest age group was 55 to 59 years with 158 (24%) case reports. The average age a woman has when she reaches menopause in The Netherlands is 50 to 51 years(19). This could suggest that the women who experienced postmenopausal bleeding after receiving a COVID-19 vaccine have not been

postmenopausal for a long time. Most women for whom this information was available had their last menstrual bleeding less than 3 years prior (69%) and more than half less than 2 years prior (57%). This in line with a Danish prospective study from 2004 in which more women experienced postmenopausal bleeding in the first year after menopause compared with women who had their last menstrual bleeding more than 3 years prior (20). Assuming that hormone imbalance is the underlying mechanism of postmenopausal bleeding after vaccination, most women not being postmenopausal for a long time could argue for a possible causal relationship. Since postmenopausal bleeding has a high background incidence, there could be other underlying causes for the cases of older women.

As described above, fat tissue and thus BMI could have an effect on the risk of postmenopausal bleeding. The case reports show that approximately half of the women were overweight with a body mass index (BMI) of more than 25 kg/m2 (54%) and 21% of women were considered obese with a BMI of more than 30 kg/m2. This does not differ much from the population. Numbers from 2021 show that 48.7 to 53.3% of women ≥35 years were overweight and 17.5 to 19.1% of women ≥35 years were obese (21) in The Netherlands.

Time to onset varied quite much. The largest group had the postmenopausal bleeding within 2 weeks (54%), but there were also numerous cases with a time to onset of more than 8 weeks after vaccination (15%). A large number of women had not recovered at the time of reporting. Most women that did recover reported that they recovered within 2 weeks (290 cases out of 318 [91%]), which is consistent with the theoretical mechanism of hormone imbalance.

Some reporters provided information on additional testing. In this report there is a focus on uterine ultrasound testing, since it may provide more information on the nature of the postmenopausal bleeding. 57 out of 135 women (42%) who had an ultrasound reported no abnormalities. It is most likely that the endometrium was thin in these cases, considering the normal state of a postmenopausal woman's endometrium (8). Thin endometrium was explicitly mentioned in 2 other cases. No abnormalities could indicate a possible relationship with the vaccine, since no other cause could be found. Ultrasound testing showed thickened endometrium in 19 out of 135 cases (14%). For a large group ultrasound testing was reported without results (44 cases [33%]).

Dydrogesterone and estrogen, hormone replacement therapy, was reported as co-suspect in 4 cases and as concomitant in 11 cases. As described above, a common adverse drug reaction of this drug is postmenopausal bleeding (22). Corticosteroids, that were reported as co-suspect in 3 cases, are associated with menstrual disorders and postmenopausal bleeding as well(8). For these cases it is possible that the co-suspect drug may have contributed significantly to the postmenopausal bleeding. Although not uncommon in the studied age group, some women were also using an anticoagulant concomitantly.

Lastly, there were many reported ADRs other than postmenopausal bleeding that were similar to symptoms of normal menstruation, PMS or menopause. Theoretically, hormone imbalance could explain this observation as well since most women that consult their general practitioner or gynaecologist with postmenopausal bleeding, do so without these symptoms.

In conclusion, a causal relationship between the COVID-19 vaccines and postmenopausal bleeding seems possible, and should be further investigated.

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This signal has been raised on April 28, 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

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Appendix A

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)**
<45	2	7	-	2044252	1802213	1207884	0.098	0.388	-
45-49	19	33	1	321827	298361	126763	5.904	11.060	0.789
50-54	56	126	5	334819	312592	155106	16.725	40.308	3.224
55-59	46	67	6	413335	392670	161303	11.129	17.063	3.720
60-64	1	10	1	152111	156395	134511	0.657	6.394	0.743
65-69	12	12	1	338626	329884	92466	3.544	3.638	1.081
70-74	1	7	1	428802	418105	85626	0.233	1.674	1.168
≥75	1	6	1	817161	800112	255660	0.122	0.750	0.391
Total	**145**	**289**	**17**	**4850933**	**4510332**	**2219319**	**2.989**	**6.408**	**0.766**

*Administrated vaccine doses to women per age group in The Netherlands until February 18th 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)**
<45	1	2	-	237080	216437	5120	0.422	0.924	-
45-49	6	6	-	64574	60072	185532	9.292	9.988	-
50-54	7	22	1	67399	62875	248838	10.386	34.990	0.402
55-59	6	16	1	74606	70440	269503	8.042	22.714	0.371
60-64	-	-	1	14876	13879	292717	-	-	0.342
65-69	-	1	2	11065	10531	311318	-	9.496	0.642
70-74	-	-	4	10141	9652	307394	-	-	1.301
≥75	-	-	1	17685	15943	470697	-	-	0.212
Total	**20**	**51**	**10**	**497426**	**459829**	**2091119**	**4.021**	**11.091**	**0.478**

*Administrated vaccine doses to women per age group in The Netherlands until February 18th 2022

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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)**
<45	1	-	92841	85107	1.077	-
45-49	1	1	26017	23868	3.844	4.190
50-54	9	7	36060	33188	24.958	21.092
55-59	6	7	42438	39525	14.138	17.710
60-64	11	18	347501	322160	3.165	5.587
65-69	1	1	118482	112321	0.844	0.890
70-74	-	1	7550	7018	-	14.249
≥75	-	-	17808	15445	-	-
Total	**30**	**39**	**688697**	**638632**	**4.356**	**6.107**

*Administrated vaccine doses to women per age group in The Netherlands until February 18th 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)**
<45	-	156258	-
45-49	1	36001	2.778
50-54	59	101382	58.196
55-59	3	13378	22.425
60-64	1	4058	24.643
65-69	-	1177	-
70-74	-	700	-
≥75	-	861	-
Total	**67**	**313815**	21.350

*Administrated vaccine doses to women per age group in The Netherlands until February 18th 2022