



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 October 2022
EMA/PRAC/897385/2022
Pharmacovigilance Risk Assessment Committee (PRAC)

Signal assessment on heavy menstrual bleeding with COVID-19 mRNA vaccine (Spikevax)

EPITT no: 19780

Procedure no: SDA 059 report

Confirmation assessment report	04 February 2022
Adoption of first PRAC recommendation	10 February 2022
Preliminary assessment report on additional data	16 May 2022
Deadline for comments	30 May 2022
Updated rapporteur assessment report	03 June 2022
Adoption of second PRAC recommendation	10 June 2022
Preliminary assessment report on second additional data	03 October 2022
Deadline for comments	17 October 2022
Updated rapporteur assessment report	20 October 2022
Adoption of second PRAC recommendation	27 October 2022

Official address Domenico Scarlattilaan 6 • 1083 HS Amsterdam • The Netherlands

Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us

Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

An agency of the European Union



Administrative information

Active substance(s) (invented name)	COVID-19 mRNA vaccine (nucleoside modified) (Spikevax)
Strength(s)	<Text> <i>[Only if relevant to the signal]</i>
Pharmaceutical form(s)	<Text> <i>[Only if relevant to the signal]</i>
Route(s) of administration	<Text> <i>[Only if relevant to the signal]</i>
Indication(s)	<Text> <i>[Only if relevant to the signal]</i>
Marketing authorisation holder(s)	Moderna Switzerland GmbH
Authorisation procedure <i>[Tick the appropriate box(es) below.]</i>	
<input checked="" type="checkbox"/>	Centralised
<input type="checkbox"/>	Mutual recognition or decentralised
<input type="checkbox"/>	National

Adverse event/reaction:	Heavy menstrual bleeding
-------------------------	--------------------------

Signal validated by:	NO
Date of circulation of signal validation report:	14. January 2022
Signal confirmed by:	DK
Date of confirmation:	04 February 2022
PRAC Rapporteur appointed for the assessment of the signal:	Brigitte Keller-Stanislowski

Table of contents

Administrative information	2
1. Background	4
2. Initial evidence	5
2.1. Signal validation	5
2.2. Signal confirmation	8
2.3. Proposed recommendation	8
2.4. Adopted PRAC recommendation	9
3. Additional evidence	11
3.1. Assessment of additional data	11
3.1.1. Review of data on heavy menstrual bleeding	11
3.2. Rapporteur's proposed recommendation	27
3.3. References	28
3.4. Comments from other PRAC members and MAH(s).....	30
3.5. Updated rapporteur's proposed recommendation	37
3.6. Adopted PRAC recommendation	38
4. Additional evidence II	40
4.1. Assessment of further information.....	40
4.1.1. Item 1	40
4.1.2. Item 2	41
4.1.3. Item 3	45
4.1.1. Item 4	50
4.2. Co-Rapporteur's proposed recommendation	52
4.3. References	53
4.4. Comments from other member states	53
4.5. Updated Rapporteurs recommendation	64
4.6. Adopted PRAC recommendation	64

1. Background

The broad clinical issue of “menstrual disorders” was reviewed in the 8th MSSR for Spikevax.

The conclusion by the PRAC Rapporteur in the 8th MSSR report with a DLP of 31 August 2021 was the following: “The PRAC Rapporteur indeed acknowledges that the currently available evidence is insufficient to justify a causal association between menstrual disorders/postmenopausal haemorrhage and Spikevax. Routine pharmacovigilance is considered sufficient for monitoring menstrual disorders/postmenopausal haemorrhage.”

However, the issue of menstrual disturbances is somewhat difficult to analyse, due to the range of clinical entities included, the difficulty in estimating their background incidences in relevant populations and the fact that reports are mainly from patients and lacking thorough clinical evaluation. We therefore find it necessary to extract those reactions/patterns that we consider the most severe and evaluate these in separate signal procedures. This would make the assessment more tailored to the reactions in question.

We believe that a new evaluation beyond routine pharmacovigilance is warranted, mainly for the following reasons:

1. The data have changed. Since the time of the 8th MSSR updated AR Norway has received an increased numbers of reports of heavy menstrual bleeding. Most women of reproductive age (18-54 years) in Norway were vaccinated from the beginning of summer 2021 and onwards. (Per 31.05.21 59 873 doses of Spikevax had been given to women aged 18 – 54. Per 15.11.21 the exposure was 565 190, i.e., it had increased by a tenfold. The total population is 5.4 million) Because of the time that has passed since the MSSR updated AR more reports of heavy menstrual bleedings have been received also providing a better clinical description of the issue.
2. The time that has elapsed since the DLP of the 8th MSSR (31 Aug 2021) and the volume of reports. The number of post- marketing reports included in the review were 3,619. A more recent search in Vigibase per 14.01.22 yields a result of 16,375 reports of amenorrhea globally for “Spikevax”/ “Covid-19 vaccine Moderna” and “Moderna covid –19 vaccine” when the same HLTs and PTs were used as were used in the MAH’s search, ie the increase in number is substantial. We have gained more knowledge through an increased number of reports, which also means more qualitative information/details.

Based on our own ICSRs, we are under the impression that menstrual disorders are by far the most commonly reported ADR from women. However, we do not have absolute numbers, due to a large volume of non-serious cases in backlog. Most of the reports of menstrual disorders are non-serious. In Norway, 4,2 million doses of Comirnaty and approx. 1 mill doses of Spikevax have been distributed to women per 14.01.22. NoMA has currently received approximately 50 000 ICSRs in total after vaccination with the covid-19 vaccines, 81% from women. We estimate through manual sampling and screening of incoming reports since June when the signal/issue was first raised nationally, that approximately 30% of reports received by women could be related to the issue of menstrual disturbances. The large amount of these reports relative to the total amount of reports, is a new aspect that warrants our attention.

Normally, a menstrual bleeding lasts around 2 – 7 days, and women lose about 3 to 5 tablespoons of blood in a period.

Some reports are categorised as serious due to the long duration or due to hospitalisation. The blood loss has in some cases led to syncope, treatment with iron and blood transfusion(s).

mRNA vaccines have been shown to be highly reactogenic and this could be a biologically plausible explanation through secondary stress on the hormonal system.

COVID-19 vaccination is a powerful immune stimulant. It is therefore plausible that the sensitive immune system of the endometrium is briefly modified by vaccination, thus potentially leading to menstrual disorders. However, no systematic investigations of the effect of COVID-19 vaccination on endometrial function have been carried out to date. A study designed specifically to investigate this relationship is currently ongoing at the Johns Hopkins Department of Gynecology and Obstetrics in the USA [1]

2. Initial evidence

2.1. Signal validation

Spontaneous reports:

As the majority of the ICSRs on the issue of menstrual disturbances are reported and/or classified as non-serious, there is a huge backlog of uncoded/unhandled cases in Norway and most likely in other European countries.

However, per 12 JAN 2022, for both mRNA-vaccines NoMA has fully processed over 3400 ICSRs belonging to the SOC "Reproductive system and breast disorders" where of 2800 cases belong to the HLGT "Menstrual cycle and uterine bleeding disorders" which have been submitted to EudraVigilance.

NoMA has registered 230 cases belonging to the PT 'heavy menstrual bleeding' as of 3 JAN 22, but our back log is significant.

It is interesting to note that LAREB (the Netherlands pharmacovigilance centre) who currently has no back log, has registered 558 ICSRs coded with the PT 'heavy menstrual bleeding' related to Spikevax in their report dated 22.12.21 [3].

Positive rechallenge cases:

NoMA has registered approximately 100 cases of women experiencing changes in menstrual cycle or bleeding pattern after both the first and second dose of an mRNA-vaccine (including mix and match vaccine schedule). These are indicative of a link between reactions related to menstrual cycle and mRNA vaccines. A list of cases could be provided to the PRAC-Rapporteur on request.

Below are two examples:

This case from a health care professional concerns an adult female patient who describes intense menstrual pain that she had never experienced before, and large amounts of blood when menstruating after the first dose of Spikevax. After the second dose, she experienced fever, extreme menstrual pain, extreme amounts of blood, nausea, headache, cough, congested nose and fatigue.

This is a report from an adult consumer who reports of heavy menstrual bleeding during menstruation after being vaccinated with Spikevax. She states that she experienced the same after her first vaccine dose.

Population cohort studies:

There is an increase in the incidence of menstrual changes among young women after vaccination against coronavirus, according to initial findings from population studies by the Norwegian Institute of Public Health (N = 6000), age 18 – 30 years).

This evidence was not available at time of review in the MSSR [4].

Examples of cases with heavy menstrual bleedings:

This case concerns a well described health care professional report on a young woman who was hospitalised due to severe bleeding. An adult female, previously healthy with a regular menstrual cycle, who uses a contraceptive implant, was vaccinated with a second dose of Spikevax on Q3 2021. (First dose was Comirnaty) Around 47 days after receiving the second dose, she presented with a persisting vaginal bleeding. She has at times had to change sanitary products frequently, and the blood contained clots. She saw the ER around 76 days after receiving the second dose and was prescribed tranexamid acid. Two days later she saw the ER again and was admitted due to increased lethargy the last few weeks and a reduced general condition, dizziness and nausea. No fever. Syncope twice on the day after the visit to the ER, and once two days after the visit to the ER, the day of admission. No syncopes in her medical history. No heavy breathing, chest pain, stomach pain or other bleeding foci. Hb measured at ER was measured 4 times and was between 2.0 and 2.9. When admitted to hospital she was exhausted. Blood pressure 109/71mmHg, heart rate 130 – 145 bpm, respiratory frequency 24, saturation 91%, normal clinical examination apart from pale and peripheral coldness. Feeling of cold, but body temperature normal. Cardiac murmur that can be explained by significant thinning of the blood. Blood test at admission shows Hb 3.0 g/dL, HCT 0,11, leucocytes 20.2 (15.7 neutrophils), thrombocytes 541, reticulocytes 120, serum iron 1, transferrin saturation 2%, serum ferritin 4 microgram/L, normal coagulation status, electrolytes, liver/bile and kidney assays. Gynecologic examination confirmed fresh bleeding and the ultrasound didn't show any gynecological morphological abnormalities. At time of reporting, the patient is receiving blood transfusions and is monitored in the intensive care unit.

Case concerning a severe perimenopausal menstrual bleeding lasting 5 weeks. An adult woman got dizzy and felt unwell minutes after vaccination with Spikevax, first dose, in Q2 2021. The following days she experienced several abnormal symptoms and contacted her GP. She also experienced a swollen arm from the elbow to the wrist with pruritus which disappeared after a few hours. The patient has not been menstruating for almost one year. But 2-3 months after the first dose, she got her period back. She had such a heavy menstrual bleeding that she was unable to work some of the days. She became very unwell and fainted. The bleeding stopped by itself after 5 weeks. The fatigue is still present. She was examined by her gynaecologist and treated with medroxyprogesterone to stop the bleeding, without any effect. She was then treated with tranexamic acid without any effect.

This is a health care professional report, reporting on herself, concerning an adult female vaccinated with Spikevax on Q3 2021. The reporter states that she started to experience heavy bleeding on the day when she received the last dose of Spikevax (the first dose was Pfizer). Bleeding continued until the day when the report was submitted (90 days after the last vaccine dose), with 1-2 days not bleeding. She had changed a contraceptive implant in the month after the last vaccine dose, but bleeding continued. The subject reports not having had her period while having a contraceptive implant before.

This report concerns an adult 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 required additional sanitary products 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. 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.

This is a serious report from a consumer, concerning an adult female who experienced heavy menstrual bleeding causing hospitalisation. She reports of having heavy menstrual bleeding 4 hours after administration of the vaccine. Especially the first two days increased number of sanitary products were necessary and had to be changed frequently. She was hospitalized for three days because of very low haemoglobin, iron decreased, platelets too low in combination with cardiac disorders in her medical history. CT and ultrasound were performed: no results reported. Blood tests showed decreased Hb, Fe and thrombocytes (exact values not reported). Treatment consisted of iron infusion and blood transfusion. The patient is recovering from fatigue, is recovering from heavy menstrual bleeding 2 weeks after onset and recovered from chills. Concomitant medication: Losartan tablet 100mg, hydrochlorothiazide, pantoprazole tablet msr 40 mg, sotalol tablet 40 mg, acenocoumarol tablet 1 mg, digoxine tablet 0,125 mg.

Publications:

In a retrospective cross-sectional study by Li et al. [5] laboratory and clinical data from hospitalised women of child-bearing age diagnosed with COVID-19 were analysed. Menstrual data from 177 women were analysed. The authors conclude that the average sex hormone concentrations and ovarian reserve did not change significantly. Nearly one-fifth of patients exhibited a menstrual volume decrease or cycle prolongation. The authors propose that the menstruation changes of these patients might be the consequence of transient sex hormone changes caused by suppression of ovarian function that quickly resume after recovery. It should be noted that the patients were followed up, and 84% returned to a normal menstrual volume and 99% returned to their normal cycle within 1-2 months of discharge, suggesting that changes in menstruation caused by covid-19 were most likely temporary changes and resolved in a short period. One 44-year-old patient indicated in the follow-up that she had stopped menstruating for 4 months after COVID-19 onset and had excluded pregnancy as a cause, but considering that she was within her perimenopausal period, they believed that the observation time of menstruation should be extended in her case.

Recommendation:

The MAH should review data from clinical trials and post marketing data, including:

Provide an overview of the age of the female study participants in the reactogenicity subgroup of the clinical study, including median age, and provide the number of women of childbearing potential the study included.

Perform a follow up with all female participants of childbearing age in the clinical trial to investigate for any reaction related to their menstruation and ovulation/fertility, including pregnancy and pregnancy outcome.

Signal assessment on heavy menstrual bleeding with COVID-19 mRNA vaccine (Spikevax)
EMA/PRAC/897385/2022

Analyse a number of post marketing reports to investigate when the time of vaccination took place relating to the time of ovulation, the luteal phase and so on, in those ICSRs where the information of the menstrual cycle is known, to see if there might be a pattern.

2.2. Signal confirmation

NO have raised a signal of Heavy Menstrual Bleeding based on evidence retrieved from national signal detection activities. In NO there were, per 4 JAN 2022, 230 cases belonging to the PT 'Heavy menstrual bleeding'. It should be noted that NO have processed a large amount of cases related to the SOC "Reproductive system and breast disorders".

A selection of cases was presented, which included 2 cases of heavy menstrual bleeding after both 1st and 2nd dose of Spikevax and 5 cases in temporal association after the 1st or 2nd dose of Spikevax. In the cases, 'heavy menstrual bleeding' was reported both in relation to very heavy bleeding and prolonged bleeding periods exceeding the normal 7 days. Two of the presented cases caused hospitalization due to extensive bleeding. Unfortunately, most of the presented cases are missing thorough clinical evaluation.

Since the last evaluation of menstrual disorders in the 8th MSSR (covering 01-31 august 2021), there have been an increase in the exposure in women of childbearing age. On 24th of January there were reported 2840 cases of 'heavy menstrual bleeding' with Spikevax in EudraVigilance. In comparison there were reported 1143 cases in the 8th MSSR.

In addition to the presented cases, a recent Norwegian cohort study finds an increase in incidence of menstrual changes among young women (18-39) after vaccination. In this study both "more heavy bleeding" and "prolonged bleeding" has been addressed and a higher relative risk have been observed for both outcomes in this study.

Furthermore, it should be noted that in the pivotal P301 clinical trial there was observed a minor imbalance regarding "Menorrhagia". There were observed 0 cases in placebo and 2 cases in the mRNA-1273 group.

Considering the above, heavy menstrual bleeding should be further evaluated as new information about the risk has arisen. The signal is confirmed.

2.3. Proposed recommendation

Based on the newly identified information, a further investigation of Spikevax and heavy menstrual bleeding is warranted.

The MAH (Moderna) is requested to provide an analysis of heavy menstrual bleeding as described in the list of questions below:

List of Questions for Spikevax MAH on heavy menstrual bleeding:

1. The MAH should provide an updated cumulative review of heavy menstrual bleeding cases from all sources, including, but not limited to, post marketing and clinical trials. The case review should include a WHO-UMC Causality assessment, and a justification of causality category should be given for each case.

- a. It should be noted when the time of vaccination took place relating to the time of ovulation, the luteal phase and so on, in those ICSRs where the information of the menstrual cycle is known, to see if there might be a pattern.
 - b. Focus should be on well described cases, where risk factors and medical history is included.
2. The MAH should provide an overview and clinical evaluation of cases of heavy menstrual bleeding, reported during pivotal clinical trials. The clinical evaluation should include age, childbearing potential, reported risk factors for heavy menstrual bleeding, and patient medical history including previous menstruation pattern.
3. Investigate the feasibility to perform a follow up with all female participants of childbearing age in the pivotal clinical trials to investigate for any reaction related to their menstruation and ovulation/fertility, including pregnancy and pregnancy outcome.
4. The MAH should carry out a literature review of the association between heavy menstrual bleeding and COVID-19 mRNA vaccines with focus on Spikevax. Furthermore, the MAH should discuss the study "Increased occurrence of menstrual disturbances in 18- to 30-year-old women after COVID-19 vaccination" by Lill Trogstad et al. 2022.
5. The MAH should discuss the pathophysiology of heavy menstrual bleeding, and consider if there is a biological plausibility that Spikevax could be associated with development of heavy menstrual bleeding.
6. The MAH should provide an estimation of the number of women of childbearing age that have been vaccinated with Spikevax

The MAH should also discuss the need for any potential amendment to the product information and/or the risk management plan and make accordingly a proposal for the changes to the relevant sections within this discussion.

A 60/60 timetable is considered sufficient

2.4. Adopted PRAC recommendation

Having considered the available evidence from national reviews (post marketing cases and published studies), the PRAC has agreed that the MAH for COVID-19 mRNA Vaccine Spikevax (Moderna Biotech Spain, S.L.) should perform a cumulative review of all cases of heavy menstrual bleeding from all sources, including, but not limited to, available data from clinical trials, literature and post marketing exposure. The MAH should provide by 7 April 2022 answers to the below List of Questions concerning clinical trials, literature, case overview and review, possible mechanism of action and exposure in females of childbearing potential.

1. Clinical trials

The MAH should provide an overview and clinical evaluation of cases of heavy menstrual bleeding, reported during pivotal clinical trials. The clinical evaluation should include age, childbearing potential, reported risk factors for heavy menstrual bleeding, concomitant medication, patient medical history including previous menstruation pattern, duration of the event and outcome. This information should be considered in the context of the total number of females, including of childbearing potential participating in the study.

The MAH should clarify how adverse events related to heavy menstrual bleeding were reported, i.e. if these were solicited adverse events or spontaneously reported by the participants.

2. Published literature

The MAH should perform a literature review on the possible association between heavy menstrual bleeding and COVID-19 mRNA vaccine Spikevax. The literature review should include, but not be limited to a discussion on the studies by: Lill Trogstad et al.¹, Nguyen et al.² and Edelman et al.³.

3. Case overview

The MAH should list the number of reported cases of the preferred term heavy menstrual bleeding stratified by:

- worldwide and region
- country in the EU/EEA
- dose number in series
- seriousness
- reporter (medically/non-medically confirmed)
- positive rechallenge.

4. Case review

The case review should prioritise serious and/or medically confirmed cases, where information on risk factors and medical history is included. Special focus should be given to cases in which the previous menstruation pattern is known, and to cases of heavy menstrual bleeding with positive rechallenge.

The case review should include a WHO-UMC Causality assessment, and a justification of causality category should be given for each case. The MAH should provide for all cases a clear breakdown of the number of cases that were either supportive of causality/ unsupportive due to presence of other causes, risk factors, underlying conditions, confounding medication/ unassessable.

The following information should be stratified:

- Details of medically relevant co-reported adverse events (if any)
- Cases in which women used hormonal contraception (including hormonal intrauterine devices)
- Cases with other types of intrauterine devices
- Cases that received heterologous primary or booster schemes.

If available, the MAH should provide information on when vaccination took place relating to the time of ovulation, the luteal phase and so on, in those ICSRs where the information on the menstrual cycle is known and discuss whether a pattern might exist.

When excluding cases from the review, a justification for doing so should be provided by the MAH.

Based on a review of case reports with inconclusive causality due to confounding factors and/or lacking information, the MAH should provide a nuanced discussion of whether Spikevax may have aggravated the condition in cases where causality cannot be firmly established.

¹ Trogstad, Lill, Increased Occurrence of Menstrual Disturbances in 18- to 30-Year-Old Women after COVID-19 Vaccination (January 1, 2022). Available at SSRN: <https://ssrn.com/abstract=3998180> or <http://dx.doi.org/10.2139/ssrn.3998180>

² Nguyen BT, Pang RD, Nelson AL, Pearson JT, Benhar Noccioli E, Reissner HR, et al. (2021) Detecting variations in ovulation and menstruation during the COVID-19 pandemic, using real-world mobile app data. PLoS ONE 16(10): e0258314. <https://doi.org/10.1371/journal.pone.0258314>

³ Edelman A, Boniface ER, Benhar E, Han L, Matteson KA, Favaro C, Pearson JT, Darney BG. Association Between Menstrual Cycle Length and Coronavirus Disease 2019 (COVID-19) Vaccination: A U.S. Cohort. Obstet Gynecol. 2022 Jan 5. doi: 10.1097/AOG.0000000000004695. Epub ahead of print. PMID: 34991109

Signal assessment on heavy menstrual bleeding with COVID-19 mRNA vaccine (Spikevax)
EMA/PRAC/897385/2022

5. Mechanism of action

The MAH should discuss the pathophysiology of heavy menstrual bleeding and whether any biological plausibility/mechanism of action exists.

6. Exposure in females of childbearing potential

The MAH should provide an estimation of the number of women of childbearing age that have been vaccinated with Spikevax.

The MAH should discuss the need for any potential amendment to the product information and/or the risk management plan and make accordingly a proposal for changes to the relevant sections within this discussion. The PRAC will assess the cumulative review within a 60 days' timetable.

3. Additional evidence

On 07 April 2022 the MAH submitted a signal evaluation report and a response to the questions on heavy menstrual bleeding, which are summarized below.

3.1. Assessment of additional data

According to the MAH, all information available at the time of the document preparation was included in the analysis. The subject of heavy menstrual bleeding associated with the administration of mRNA-1273 in patients aged 18 years or older was assessed.

3.1.1. Review of data on heavy menstrual bleeding

3.1.1.1. Question 1: Clinical trials

The MAH should provide an overview and clinical evaluation of cases of heavy menstrual bleeding, reported during pivotal clinical trials. The clinical evaluation should include age, childbearing potential, reported risk factors for heavy menstrual bleeding, concomitant medication, patient medical history including previous menstruation pattern, duration of the event and outcome. This information should be considered in the context of the total number of females, including of childbearing potential participating in the study.

The MAH should clarify how adverse events related to heavy menstrual bleeding were reported, i.e. if these were solicited adverse events or spontaneously reported by the participants.

MAH Response:

The MAH's database of the phase 3 study NCT04470427 [7] with a data-lock point of 04 May 2021 was searched using the MedDRA version 24.0 preferred terms (PTs) "heavy menstrual bleeding", "menometrorrhagia", and "polymenorrhagia".

From the clinical trial data, data lock point of May 4th, 2022, six spontaneously reported treatment-emergent adverse event of heavy menstrual bleeding were identified; five in the mRNA-1273 arm and one in placebo arm, and all had a medical history or use of concomitant medication that provided an

alternate etiology for heavy menstrual bleeding. The median age of the six cases was 41 years, range 20s-50s years; the adult woman (subject 4) was in active arm and reported post-menopausal bleeding. All six cases were considered non-serious. The outcome is described as recovered/resolved in four cases (three in the verum group, one in the placebo group) and as ongoing in two cases.

Table 1: Details of clinical Trial Reports as of 04 May 2021

ID	Age range	Tx Code	Relevant Medical History	Relevant Concomitant Medications	TTO first dose, days	TTO second dose, days	PI Causality	Duration (days)	Outcome
1.	adult	mRNA-1273	Attention Deficit Disorder Menorrhagia	Not Available	114	85	Not related	N/A	Ongoing
2.	Adult	mRNA-1273	Not Available	Combined oral contraceptive	31	5	Not related	8	Recovered /Resolved
3.	Adult	mRNA-1273	Hypothyroidism	Levothyroxine	32	5	Related	6	Recovered /Resolved
4.	adult	mRNA-1273	Uterine fibroids Breast cancer	Letrozole	57	29	Not related	121	Recovered /Resolved
5.	adult	mRNA-1273	Irregular menstruation	Nexplanon	2	N/A	Related	N/A	Ongoing
6.	adult	Placebo	Obesity Tubal ligation	Not Available	79	49	Not related	75	Recovered /Resolved

***Postmenopausal*

Comment PRAC Co-Rapporteur:

Concerning search strategy and reporting of AEs from CTs: The MedDRA PT "polymenorrhea" (10036086) was not integrated into the search, nor was the more general PT "vaginal hemorrhage" (10046910).

The MAH did not explain how adverse events related to heavy menstrual bleeding were reported (solicited/non-solicited reporting). In this signal evaluation report, the MAH does not specify the number of female study participants of childbearing age and the length of follow-up of this cohort. Considering the disproportionate number of adverse events in the verum versus placebo group, it would be important to take into account the numbers of events related to person years (females of childbearing age) of exposure.

Little medical details have been presented by the MAH concerning the clinical trial cases of heavy menstrual bleeding. From Table 1 the following information can be derived: Four of five vaccine case reports occurred after the second dose, age range of the vaccine reports between 20s and 50s years of age (3 reports \geq 45 years of age)). TTO varied between 2 days (after 1st dose) and 85 days (2nd dose). In the case with TTO 85 days following second dose most likely two regular cycles followed the vaccination before onset of symptoms. Confounding factors in the trial cases are listed in the table above. Thus, according to the very limited information presented, no consistent clinical pattern can be identified in CT case reports.

3.1.1.2. Question 2:

Published literature

The MAH should perform a literature review on the possible association between heavy menstrual bleeding and COVID-19 mRNA vaccine Spikevax. The literature review should include, but not be limited to a discussion on the studies by: Lill Trogstad et al., Nguyen et al. and Edelman et al.

MAH Response:

A literature search and review was performed using PubMed and Google Scholar databases. Multiple search strategies were used to identify articles related to heavy menstrual bleeding and the COVID-19 pandemic, SARS-CoV-2 infection, and COVID-19 mRNA vaccine, Spikevax.

Of the 230 unique articles captured, five discussed heavy menstrual bleeding after vaccination with Spikevax. Three articles were cross-sectional studies and two presented spontaneous, post-authorization data (Netherlands and United States of America). Although the cross-sectional studies reported that 20-41% women vaccinated with Spikevax reported heavy menstrual bleeding after vaccination, compared to prior menstrual pattern, the studies were limited because they lacked an unvaccinated comparator group which is crucial given heavy menstrual bleeding is common; additionally, some published studies have indicated that the pandemic itself was associated with changes in menstruation. Additionally, the studies were limited due to recall bias, use of unvalidated questionnaires and selection bias. The published data currently does not support an association between heavy menstrual bleeding and Spikevax.

Edelman et al.: The authors analyzed prospectively tracked menstrual cycle data using an existing menstrual cycle tracking app (Natural Cycles) and included 3,959 individuals (vaccinated 2,403 [35% received Spikevax] and unvaccinated 1,556) aged 18-45 years with normal cycle lengths who logged at least six consecutive cycles. In the adjusted models, the first dose of vaccine had no effect on timing of the subsequent period, while the second dose was associated with a delay of 0.45 days (98.75% confidence interval 0.06 to 0.84). Most affected were the 358 individuals who received both doses of the vaccine in the same cycle, reporting a 2.32 day (98.75% CI 1.59 to 3.04) delay to their next period. In all groups, cycle lengths returned to normal by two cycles after vaccination. The study limitations include study population that might not be generalizable to the U.S. population (Natural Cycle users are more likely to be White, college educated, not using hormonal contraception and have lower BMIs) or individuals whose menstruation is not consistent with normal cycle lengths (e.g., obese persons), self-reported data and lack of data on SARS-CoV-2 status of the study population. However, the findings are reassuring and did not find any population-level clinically meaningful change in menstrual cycle length associated with COVID-19 vaccination.

Trogstad et al.: The authors analyzed data collected from mobile-phone questionnaire obtained from a pre-existing population-based Norwegian Young Adult Cohort of 5688 women aged 18-30 year. They were asked whether they had experienced specific menstrual changes (such as unexpected breakthrough bleeding or worse than normal period pain) in the cycles before and after each vaccine dose. The prevalence of any menstrual disturbance was 37.8% prior to vaccination, highlighting the high level of variation in normal cycles. The study identified heavier than normal bleeding as the change most associated with vaccination (first dose: relative risk 1.9, 95% confidence interval 1.69 to

2.13; second dose: 1.84, 1.66 to 2.03). The study limitations include lack of an unvaccinated comparator group, recall bias, and use of unvalidated questionnaire. Although, this study found an increase in heavier bleeding after vaccination, it also showed that menstrual disturbances are generally common regardless of vaccination.

Nguyen et al.: The authors analyzed menstrual cycle data using an existing menstrual cycle tracking app (Natural Cycles) and included 18,076 individuals accounting for 214,426 cycles. Data from March-September 2019 (pre-pandemic) to March-September 2020 (during pandemic) were compared to determine difference in proportion of users experiencing menstrual changes. 45.4% of the app users reported more pandemic-related stress. Changes in average cycle and menstruation lengths were not clinically significant, remaining at 29 and 4 days, respectively. The authors concluded that the COVID-19 pandemic did not induce population-level changes to ovulation and menstruation among women using a mobile app to track menstrual cycles and predict ovulation. The study limitations include self-reported data, recall bias, and potential limited generalizability of results given their study population (well-educated women over age of 30, from high income countries).

The MAH briefly described 5 articles on Spikevax and heavy menstrual bleeding (Table 2) and 4 articles on SARS-CoV-2 infection and heavy menstrual bleeding

Table 2: Summary of Relevant Articles on Spikevax and Heavy Menstrual Bleeding

Study	Design and Methodology	Sample Size	Select Results: Bleeding Volume
Trogstad L	Self-controlled case series using mobile- phone questionnaires to collect reports of menstrual disturbances from 5,688 women aged 18-30 years, participating in the population-based Norwegian Young Adult Cohort. Estimated relative risk of menstrual disturbances using the first six weeks after vaccination as the exposed period compared to unexposed period both after the first dose and second dose of vaccine.	N= 5,688 Dose 1: N=634 Dose 2: N=557	The prevalence of more heavy bleeding during menstruation was 7.6% in the last menstrual cycle prior to the first vaccine dose compared to 13.6% in the first cycle after vaccination. Similarly, the prevalence of heavy bleeding was 8.2% before and 15.3% after the second vaccine dose. The relative risk of more heavy bleeding than usual during the exposed compared to unexposed period for first dose vaccination was 1.90 (95% CI: 1.69-2.13), while it was 1.84 (1.66-2.03) for the second dose. The risk of heavy bleeding after the second dose, given that it had occurred after the first, was 65.7%
Lee K et al	Cross-sectional study using an emergent, exploratory, mixed methods survey instrument intended to capture a wide range of responses from current and formerly menstruating adults between the ages of 18 to 80 years old who were fully vaccinated and had not contracted COVID-19. Determined percentage of regularly menstruating people with no diagnosed reproductive conditions who experienced change in bleeding heaviness following vaccination.	N= 39,129 (N=13,001 received Spikevax)	Among spontaneously cycling people, 40.83% (3,911/9,579) experienced heavier bleeding after vaccination and 45.81% (4,388/9,579) experienced no change. Among people using hormonal contraceptives, 41.2% (1,334/3,237) experienced heavier bleeding after vaccination and 42.8% (1,384/3,237) experienced no change.

Male V et al	<p>Retrospective cohort study of 1,273 people over 18 years of age who had received at least one dose of a COVID-19 vaccination, have periods or withdrawal bleeds, keep a record of their menstrual cycles and vaccination dates. The data was collected using a web-based form.</p> <p>Examined the proportion of respondents reporting a change in flow of the period following vaccination.</p>	<p>N= 1,273 (N=136; 10.7% received Spikevax)</p>	<p>Among spontaneously cycling respondents reporting a change in flow of the period following vaccination, 32% experienced flow that was heavier than usual, 14% reported lighter than usual while 54% reported same as usual.</p> <p>Among respondents on hormonal contraception, 42% experienced flow that was heavier than usual, 19% reported lighter than usual while 39% reported same as usual.</p> <p>Among respondents who received Spikevax (data not stratified by contraceptive use), 31% experienced flow that was heavier than usual, 17% reported lighter than usual while 52% reported same as usual.</p>
--------------	---	--	---



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Study	Design and Methodology	Sample Size	Select Results: Bleeding Volume
Netherland PV Lareb	Analysis of spontaneous post-authorization data received by Netherlands Pharmacovigilance Centre Lareb	N= 17,735 (2,025 received Spikevax)	Heavy menstrual blood loss was reported for 19.7% of the total reported menstrual PTs and for 21.2% of the reported menstrual PTs for Spikevax. Less menstrual blood loss was reported for 2.4% of the total reported menstrual PTs and for 2.2% of the reported menstrual PTs for Spikevax
Zhang B et al	Analysis of spontaneous reports received by the Vaccine Adverse Events Reporting System database. Determined the percentage of cases with menstrual disorder that reported Menorrhagia following vaccination.	N= 13,118 cases for COVID-19 vaccines (N= 2,748 (20.95%) received Spikevax) N= 1,313 cases for Non-COVID-19 vaccines	Menorrhagia was reported in 28 cases (0.21%) for all COVID-19 vaccines, 232 cases (17.67%) for non-COVID-19 vaccines and in 2 cases (0.7%) for Spikevax.

PRAC Co-Rapporteur Assessment Comment

The MAH identified five literature articles describing heavy menstrual bleeding after vaccination with Spikevax, three cross-sectional studies and two reviews of spontaneous reports post-marketing (Netherlands and United States of America). The articles themselves are not discussed in detail; the studies of Edelman et al. Trogstad et al, and Nguyen et al. are briefly summarized. (Of these three studies only the study by Trogstad et al has investigated heavy menstrual bleeding). The MAH emphasizes the frequency of heavy menstrual bleeding in general and limitations of the studies, such as the lack of an unvaccinated comparison group, changes in the menstrual cycle due to the pandemic itself, recall and selection bias. Thus, the critical assessment of the studies is limited to a few general comments. There is no in-depth analysis of individual studies, their methodology, conclusions and limitations.

Edelman et al.: According to authors "no population-level clinically meaningful change in menstrual cycle length" following a vaccination against Covid-19 was identified in this study. The menses length was not affected by the vaccination. The authors prospectively tracked menstrual cycle data using the application "Natural Cycles". U.S. residents aged 18–45 years with normal cycle lengths were evaluated for three consecutive cycles before the first vaccine dose followed by vaccine-dose cycles (cycles 4–6). An unvaccinated group was also evaluated. The study results are reassuring based on the observed less than 1 day change in cycle length after first and second dose of a COVID-19 vaccine (35 % of participant vaccinated with Spikevax). The study however did not investigate menstrual symptoms, unscheduled bleeding, and the quality and quantity of menstrual bleeding. 835 (34.7%) of the 2,403 vaccinated individuals had received Spikevax.

Official address Domenico Scarlattilaan 6 • 1083 HS Amsterdam • The Netherlands

Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us

Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union



Nguyen et al.: Prospective data from a cycle-tracking app before and during the Covid-19 pandemic were analyzed. Vaccines against Covid-19 were not yet approved during the periods studied. The authors found that COVID-19 vaccination is associated with a small not meaningful change in cycle length but not menses length. The authors did not study other menstrual disorders such as such as menstrual symptoms, unscheduled bleeding, and changes in the quality and quantity of menstrual bleeding. Whether the study population and App user are representative for the female US population at childbearing age is questionable.

Trogstad et al. [preprint]: The authors investigated in a retrospective survey a large cohort of young females and found an increase in heavier bleeding than usual (relative risk, first vaccine dose, 1.90, 95% confidence interval (CI) 1.69-2.13; second vaccine dose, 1.84, 95% CI 1.66-2.03) and other menstrual disturbances. Menstrual disturbances were generally common regardless of vaccination (37.8% prior to vaccination). Spikevax had been given to 2,020 (35.5%) of the 5,688 study participants as the first vaccine dose, and to 2,736 (48.1%) as the second vaccine dose. The limitations of the study are briefly described by the MAH and endorsed by the assessor. The retrospective nature, the use of a non-validated questionnaire and the response rate of 68.4% of contacted females may have introduced biases.

Lee et al [preprint]: In this study 42% of people with regular menstrual cycles bleed more heavily than usual (note: nearly a third of this subgroup also experienced a longer duration of menstrual bleeding), while 44% reported no change, after being vaccinated. The authors found increased bleeding was significantly associated with age, other vaccine side effects (fever, fatigue), history of pregnancy or birth, and ethnicity. The authors classified self-reported bleeding after vaccination in three categories ("heavier", "no change in flow", "not heavier" which is a combination of no change and lighter bleeding flow). The study is based on an online survey, which was announced via Twitter and other social media ("extensive snowball sampling via many channels"). The analysed data represents the download of reported data in a time interval of 12 weeks. The study is prone to multiple biases (e.g. recall bias) as outlined by the MAH. Benevolently, the study could be hypothesis generating.

Male [preprint]: The survey did not provide a signal that vaccination against Covid-19 is associated with menstrual changes. (10.7%) of the 1273 retrospectively recruited participants reported having been vaccinated with Spikevax.

The Netherlands Pharmacovigilance Centre Lareb: Overall reporting rates for heavy menstrual blood loss following vaccination with Spikevax were 51.4 per 100,000 first vaccinations and 62.5 per 100,000 second vaccinations.

Zhang et al. [preprint]: The authors analysed spontaneous reports of menstrual disorders in the Vaccine Adverse Event Reporting System (VAERS). Most reports after vaccination against Covid-19 (4,626 of 13,118 reports, corresponding to 35.3%) involved the MedDRA term "menstruation irregular"; less frequently reported were "metrorrhagia" (1,671 reports, corresponding to 12.7%), "menorrhagia" (28 reports, corresponding to 0.2%), and "intermenstrual bleeding" (2,088 reports, corresponding to 15.9%). 2,748 reports concerned Spikevax.

Alvergne et al. [preprint]: The authors describe menstrual irregularities in 20% of 4,989 vaccinated individuals. As far as known, the participants had not been vaccinated with Spikevax.

Other papers published after 15 February 2022 describe menstrual changes following a vaccination against Covid-19. In the article by Muhaidat et al., 66.3% of 2,269 women reported mostly within two months self-limiting changes in their menstruation, predominantly after the first dose (menorrhagia, 8.9%; prolonged duration of menstruation, 8.5%; intermenstrual bleeding, 1.1%).

35.3% of the participants already experienced menstrual abnormalities during the Covid-19 pandemic before vaccination. Only 16 females (0.7%) had been vaccinated with Spikevax. In contrast, the survey of 164 women (19 with a first dose of Spikevax, 14 with a second dose of Spikevax) by Laganà et al showed a slightly higher proportion of menstrual abnormalities after the second vaccine dose. This study describes the occurrence of menstrual irregularities in 50-60% of the participants (regardless of the type of administered vaccine), mainly anticipated, longer, and heavier menstrual cycles than expected and usual. The study has several limitations in addition to the limited sample size such as self-administration of a customised questionnaire, without previous validation and high potential for recall bias (study announced via social media).

In summary, studies investigating potential heavy menstrual bleeding following Spikevax vaccination have serious limitations and do not provide robust evidence that Spikevax is associated with heavy menstrual bleeding.

3.1.1.3. Question 3:

The MAH should list the number of reported cases of the preferred term heavy menstrual bleeding stratified by: worldwide and region, country in the EU/EEA, dose number in series, seriousness, reporter (medically/non-medically confirmed), positive rechallenge.

MAH Response:

Cases by Worldwide and Region: 60.0% of cases reported are from the European Economic Area, with only 9.9% of cases reported from the United States.

Table 3: Cases by Worldwide and Region

Region	Total # of Cases	Total % of Cases
Asia	10	0.3
Australia	1	0.0
Canada	19	0.5
European Economic Area	2,399	60.0
Switzerland	123	3.1
United Kingdom	1,049	26.2
United States	397	9.9
(Empty)	2	0.1
Grand total	4,000	100.0

Table 4: Cases by Country (*EU/EEA countries in bold*)

Country	Total # of Cases	Total % of Cases
Australia	1	0.0
Austria	23	0.6
Belgium	62	1.6
Brunei Darussalam	2	0.1

Bulgaria	3	0.1
Canada	19	0.5
Croatia	4	0.1
Czech Republic	6	0.2
Denmark	94	2.4
Estonia	1	0.0
Finland	13	0.3
France	202	5.1
Germany	684	17.1
Greece	3	0.1
Hungary	1	0.0
Iceland	49	1.2
Ireland	28	0.7
Italy	68	1.7
Japan	2	0.1
Latvia	1	0.0
Lithuania	1	0.0
Luxembourg	2	0.1
Netherlands	669	16.7
Northern Ireland	11	0.3
Norway	310	7.8
Philippines	6	0.2
Portugal	8	0.2
Romania	7	0.2
Spain	117	2.9
Sweden	32	0.8
Switzerland	123	3.1
Taiwan, Province of China	2	0.1
United Kingdom	1049	26.2
United States	397	9.9
Grand Total	4000	100.0

Events by Dose and Time to Onset: 39% of events with missing dose, 31% of events occurred after first dose and 24% after second dose and 7% after the third dose. There was no unusual pattern and clustering seen regarding dose (keeping in mind that more dose 1 vaccines have been administered compared to dose 2 and dose 3) and time to onset. However, it is very difficult to interpret the TTO without putting it into context of the menstrual cycle

Table 5: Event Time to Onset by Dose

Dose Number	TTO All Doses (Days)	# Events	% Events
Dose 1	<i>Subtotal</i>	<i>1,318</i>	<i>30.6</i>
	0 days	198	4.6
	01-02	268	6.2
	03-04	119	2.8
	05-06	88	2.0
	07-13	266	6.2
	14-29	255	5.9
	30+	124	2.9

Dose 2	<i>Subtotal</i>	<i>1,021</i>	<i>23.7</i>
	0 days	141	3.3
	01-02	210	4.9
	03-04	107	2.5
	05-06	57	1.3
	07-13	125	2.9
	14-29	205	4.8
	30+	176	4.1
Dose 3	<i>Subtotal</i>	<i>282</i>	<i>6.5</i>
	0 days	31	0.7
	01-02	92	2.1
	03-04	33	0.8
	05-06	20	0.5
	07-13	55	1.3
	14-29	41	1.0
	30+	10	0.2
Unknown	<i>Subtotal</i>	<i>1,688</i>	<i>39.2</i>
	Missing	1,688	39.2
Grand total		4,309	100.0

Events by Preferred Term and Seriousness: A vast majority (80.4%) of the events were non-serious.

Table 6: Events by Preferred Term and Seriousness

PT	Non-Serious		Serious		# Total of Events	% Total of Events
	# Events	% Of Events	# Events	% Of Events		
Heavy menstrual bleeding	3,371	78.2	829	19.2	4,200	97.5
Menometrorrhagia	89	2.1	16	0.4	105	2.4
Polymenorrhagia	3	0.1	1	0.0	4	0.1
Grand total	3,463	80.4	846	19.6	4,309	100.0

Cases by reporter: 13.7% of cases were reported by health care professional and majority of the cases (86.4) were reported as Not Medically Confirmed.

Re-challenge: The 1,247 cases (serious cases and medically confirmed cases) were medically reviewed and no cases of positive rechallenge were identified.

PRAC Co-Rapporteur Assessment Comment: The MAH provided the requested information. The MAH's safety database with a data-lock point of 15 February 2022 was queried using the MedDRA version 24.1 preferred terms (PTs) "heavy menstrual bleeding", "menometrorrhagia", and "polymenorrhagia" as of 15 February 2022. This search returned 4,000 cases with 4,309 events. 998 cases or 846 events were serious, and 546 cases (13.7%) were medically confirmed.

Notably, there is a disproportional share in some EEA countries and UK compared USA, Ca, Australia. Even in case reports with dose number unknown, information on the TTO may be available. Table 6 does not provide any data in this regard.

3.1.1.4. Question 4:

Case review

The case review should prioritise serious and/or medically confirmed cases, where information on risk factors and medical history is included. Special focus should be given to cases in which the previous menstruation pattern is known, and to cases of heavy menstrual bleeding with positive re-challenge.

The case review should include a WHO-UMC Causality assessment, and a justification of causality category should be given for each case. The MAH should provide for all cases a clear breakdown of the number of cases that were either supportive of causality/ unsupportive due to presence of other causes, risk factors, underlying conditions, confounding medication/ unassessable.

The following information should be stratified:

- **Details of medically relevant co-reported adverse events (if any)**
- **Cases in which women used hormonal contraception (including hormonal intrauterine devices)**
- **Cases with other types of intrauterine devices**
- **Cases that received heterologous primary or booster schemes.**
- **If available, the MAH should provide information on when vaccination took place relating to the time of ovulation, the luteal phase and so on, in those ICSRs where the information on the menstrual cycle is known and discuss whether a pattern might exist.**
- **When excluding cases from the review, a justification for doing so should be provided by the MAH.**
- **Based on a review of case reports with inconclusive causality due to confounding factors and/or lacking information, the MAH should provide a nuanced discussion of whether Spikevax may have aggravated the condition in cases where causality cannot be firmly established.**

MAH Response:

Post marketing data for heavy menstrual bleeding events were retrieved from the Company safety database using the following three MedDRA preferred term: Heavy menstrual bleeding', 'Menometrorrhagia', and 'Polymenorrhagia' with a data-lock point (DLP) of 15 February 2022, using Medical Dictionary for Regulatory Activities (MedDRA) version 24.1. 4000 cases were identified, and all the serious cases not medically confirmed (701) and medically confirmed cases (546) were reviewed.

The International Federation of Gynecology and Obstetrics-Abnormal Uterine Bleeding case definition for heavy menstrual bleeding was used. (Heavy menstrual bleeding is defined as a volume that interferes with the patient's physical, social, emotional, and/or material quality of life). The World Health Organization- Uppsala Monitoring Centre (WHO-UMC) system was used for causality assessment.

The MAH identified 14 cases with date of vaccination and onset, known previous menstruation pattern. The median age of the 14 cases was 38.5 years (range: 21-50), 21% (3/14) received heterologous boosters (Pfizer BioNTech vaccine for their primary series), 43% (6/14) reported use of hormonal contraception including Mirena IUD and Nexplanon. There was no unusual pattern or clustering by dose and time to onset as well as time of vaccination during menstrual cycle. Seven of the 14 cases were spontaneously cycling and timing of vaccination during the menstrual cycle occurred at various points throughout the menstrual cycle (Day 2, Day 5, Day 6, Day 14, Day 21, Day 23, and Day 25); In these 14 cases no timing according to the menstrual cycle (Menstrual phase, Proliferative phase Ovulatory phase; Luteal phase) *was observed*. Based on the WHO-UMC system all 14 cases were possibly related due to temporal association, however 71% of them had medical conditions or concomitant medications (including age \geq 45 years, obesity, postpartum status, h/o breast cancer, hypothyroidism, and inflammatory bowel syndrome) that provided an alternate aetiology.

According to the MAH this review highlighted the challenges with using spontaneous data to explore this topic which includes the high level of missing data (e.g., menstrual history, medical history, concomitant medications, clinical course including testing and duration) with spontaneous reports.

PRAC Co-Rapporteur Assessment Comment: The MAH identified 14 cases with date of vaccination and onset, known previous menstruation pattern. Interestingly, half of the case reports experienced heavy menstrual bleeding flowing the third dose (dose 1 n=4 case reports, dose 2 n=3, dose 3 n=7).

Although, it is acknowledged that spontaneous reports frequently lack important clinical information, it appears somewhat astonishing that only in 14 out of 4000 reports relevant information concerning vaccination and onset date and previous menstruation pattern were available. The MAH apparently did not analyse cases of positive re-challenge (app. 100 cases in No). Examples of a positive re-challenge had been given by the Norwegian Medicines Agency One of them is a medically-confirmed case report. Thus, a review of case reports with positive re-challenge (positive re-challenge may not only be detected by searching the E2B field but may be mentioned in the narrative) would have been useful.

Observed to Expected Analyses

The MAH presented an observed versus expected analysis. The MAH estimated the Spikevax doses administered based on the following information: US CDC, ECDC, Health Canada, the Swiss Federal Office of Public Health and Our World in Data ((data retrieved on 16th February 2022).

Using the overall age and gender distribution of all vaccinees in the US (Comirnaty, Spikevax, Janssen, and AstraZeneca) as reported by CDC (<https://covid.cdc.gov/covid-data-tracker/#vaccination-demographic>), the age and gender distribution for Spikevax was mirrored. Further, the number of Spikevax recipients were capped at 3% for <18 years of age as majority of vaccinees <18 years received Comirnaty. The total number of <18 years SPIKEVAX vaccinees were further divided in <12 and 12-17 years using ratio of 0.05:0.95. These ratios were based on the

proportion of reports in the safety database. To estimate, the number of female Spikevax vaccines from 15-17 years of, number of female vaccines 12-17 years were divided in 12-14 and 15 – 17 years using ratio of 0.25:0.75. These ratios were based on the proportion of reports in the safety database.

To calculate the person-years for 21-day risk window, the total number of doses administered were multiplied by 21 and dividing by 365.25. To obtain the age and genders stratified 21-day risk window person-years the US age and gender distribution of SPIKEVAX was mirrored.

The observed to expected analysis for menstrual disorders included observed cases of heavy menstrual bleeding (heavy menstrual bleeding, menometrorrhagia, and polymenorrhagia) and amenorrhea (amenorrhea, delayed menarche, and premature menopause). For this analysis only cases with known female gender were included.

Stahlman et al. has characterized the incidence in menorrhagia in active service women, US Armed Forces from 2012-2016. The incidence rate was similar to the incidence of heavy menstrual bleeding in general practice in Netherlands (2004 -2013).

The cumulative number of cases with heavy menstrual bleeding were 3940 (reporting rate of 0.12 per 100 person-years). These were less compared to the expected number of cases (N = 36,1230 with reporting rate of 10.09 per 100 person-years). The overall and the age-specific rate ratio was lower than 0.05 (Table below). The sensitivity analysis (assuming 25% and 50% capture of the observed cases) does not change the interpretation. In conclusion, the observed rates of heavy menstrual bleeding were lower than expected background rates.

Table 7: Observed to Expected (OvE) Analysis for Heavy Menstrual Bleeding

Outcome	Person Years	Observed		Expected		As observed RR (95 % CI)	Assuming 50% of cases were reported: RR (95% CI)	Assuming 25% of cases were reported: RR (95% CI)
		cases	rates	cases	rates			
All	3,314,041	3940	0.12	361230	10.9	0.01 (0,01-0.01)	0.02 (0,02-0.02)	0.04 (0,04-0.04)
female								
<12 years	4971	0	0.00	220	4.42	NA	NA	NA
12-17 years	94450	18	0.02	4175	4.42	0 (0, 0.01)	0.01 (0.01, 0.01)	0.02 (0.01, 0.02)
18-24 years	298264	370	0.12	12945	4.34	0.03 (0.03, 0.03)	0.06 (0.05, 0.06)	0.11 (0.11, 0.12)
25-39 years	729089	1900	0.26	73857	10.13	0.03 (0.02, 0.03)	0.05 (0.05, 0.05)	0.1 (0.1, 0.11)
40-49 years	497106	1084	0.22	179952	36.2	0.01 (0.01, 0.01)	0.01 (0.01, 0.01)	0.02 (0.02, 0.02)
50-64 years	861651	260	0.03	311918	36.2	0 (0, 0)	0 (0, 0)	0 (0, 0)
65-74 years	497106	2	0.00	179952	36.2	0 (0, 0)	0 (0, 0)	0 (0, 0)
75+ years	331404	1	0.00	119968	36.2	0 (0, 0)	0 (0, 0)	0 (0, 0)

PRAC Co- Rapporteur Assessment Comment:

The OvE calculations presented by the MAH are not correct. The incidence rates in the cited paper by Stahlman et al. for menorrhagia (2012 to 2016 service women armed US forces) are one tenth of the incidence rates used for the analyses of the present signal evaluation report, 100.9 per 10,000 person-years correspond to 1.009 per 100 person-years, not 10.9, etc. However, even with the correct background incidence rates, OvE would not exceed 1 according to the calculation of the MAH. Notably is also a decline of the incidence from 2012 to 2016.

Otherwise, the incidence rate in the manuscript of Stahlman et al. is similar to that reported in a retrospective Dutch study, which found a mean incidence rate of 9.3 per 1,000 person-years (95% confidence interval 8.5-10.2) for heavy menstrual bleeding, with the highest incidence rates for women aged 35-54 years.

Limitations of the OvE analysis need to be acknowledged. Menstrual disorders are generally common, however they do not always result in a presentation to healthcare professionals (electronic health care data were used to calculate the incidence in the Stahlman publication). This would result in an underestimation of menorrhagia background incidence. There are a number of assumptions concerning age and sex stratified exposure for which the impact on the results of the OvE analysis are unclear.

Not all spontaneous reports are likely to meet the criteria of the (much stricter) case definition of background incidence (used by the Armed Forces Health Surveillance Center (AFHSC)). In addition, as menstrual disturbances are usually common and a high proportion of female may experience menstrual disturbances at some time, underreporting after vaccination is expected. Whether the unknown underreporting rate and back-log of reporting (90 day reporting requirements for non-serious case reports of NCAs) is adequately addressed in the sensitivity analysis of potential underreporting conducted by the MAH is unclear.

In conclusion, the number of reports of heavy menstrual bleeding following Spikevax vaccination is lower than the expected number, although important limitations of the OvE analysis need to be considered. The result of the OvE analysis presented by the MAH do not suggest a link between changes to menstrual periods and Spikevax.

The MAH has also presented in the separate signal report disproportionality analyses. VAERS and EVDAS were queried with regard to the PTs mentioned above, yielding an EB05 of 0.777 (VAERS) and a ROR of 3.68 (EVDAS) for "heavy menstrual bleeding", an EB05 of 0.687 and a ROR of 1.94 for "menometrorrhagia", and an EB05 of 0.383 and a ROR of 1.22 for "polymenorrhagia". These analyses may reflect the uneven reporting rate in the USA and EEA.

Other copy and paste errors are also note in the response document (mentioning amenorrhea instead of heavy menstrual bleeding).

3.1.1.5. Question 5

Mechanism of action

The MAH should discuss the pathophysiology of heavy menstrual bleeding and whether any biological plausibility/ mechanism of action exists.

Response of MAH:

The basic biology of the menstrual cycle is a complex, coordinated sequence of events involving the hypothalamus, anterior pituitary, ovary, and endometrium. Heavy menstrual bleeding in a female of reproductive age is related to the disturbance of normal hormonal, physiological mechanism, or female anatomic abnormalities. The normal physiological mechanism works by balancing hormones and providing feedback between the hypothalamus, pituitary, ovaries, and uterus. Physiologically, menstruation is controlled by the release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, and it works on the pituitary to release follicle-stimulating hormone (FSH) and luteinizing hormone (LH) and these two hormones from the pituitary act on ovaries and ovaries finally make estrogen and progesterone to work on the uterus to carry out the follicular and secretory phase of the menstrual cycle.

The causes of heavy menstrual bleeding are numerous and often unknown; any process that interferes with the normal endocrine, paracrine or hemostatic functions of the endometrium as well as possibly any interference with myometrial contractility may cause heavy menstrual bleeding.

According to the Federation of Gynecology and Obstetrics classification of abnormal uterine bleeding AUB, nine categories are listed according to the acronym PALM-COEIN. The PALM (polyp, adenomyosis, leiomyoma, and malignancy) group consists of structural abnormalities that can be visualized using imaging techniques or diagnosed by histopathology; whereas nonstructural disorders that cannot be imaged or diagnosed with histopathology are included in the COEIN (coagulopathy, ovulatory dysfunction, endometrial, iatrogenic including medication and not yet classified) group.

To date, the evidence is insufficient to demonstrate association between menstrual disorder and vaccination. The relationship between heavy menstrual bleeding and Spikevax is unclear. Some proposed hypothetical biological mechanisms include the ACE2 receptors have been found on ovarian and endometrial tissue and hence vaccination may hypothetically affect ovarian hormone production and/or the endometrial response at menses, alterations in coagulation system, which is a critical component of endometrial function at menstruation, and possible endometrial inflammatory response mediated by immune cells in the lining of uterus.

PRAC Co-Rapporteur Assessment Comment: Abnormal uterine bleeding in women of reproductive age is a manifestation of a number of disorders or pathologic entities. The MAH gives an overview of the topic of heavy menstrual bleeding and refers to the FIGO classification of causes underlying an abnormal uterine bleeding (PALM-COEIN). The complexity of various causes of heavy menstrual bleeding highlights the importance collecting information concerning the menstrual cycle in a subject, previous menstrual disorders, medical history and concomitant medication as well as other confounding factors when assessing individual case reports. The various causes of heavy menstrual bleeding should also be considered when designing a study. In this respect, cross-sectional studies based on self-reported changes are not suitable to adequately investigate the issue.

The discussion of possible pathomechanisms of heavy menstrual bleeding and mRNA vaccination is very brief and does not address potential biological mechanisms other than ACE2 receptor presence in the endometrium and ovarian tissue, e.g. more general inflammatory vaccine response.

3.1.1.6. Question 6:

Exposure in females of childbearing potential

The MAH should provide an estimation of the number of women of childbearing age that have been vaccinated with Spikevax.

MAH Response:

Estimation of exposure of Spikevax in women of childbearing potential. Spikevax supply chain estimates are used to define the number of doses SPIKEVAX distributed by country; however, administration data are tracked by health officials within countries receiving the vaccine. Therefore, Moderna estimates administration of SPIKEVAX based on information retrieved through the US Centers for Disease Control and Prevention (<https://covid.cdc.gov/covid-data-tracker/#vaccinations>), the European Centres for Disease Control (<https://qap.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#distribution-tab>), Health Canada (<https://health-infobase.canada.ca/covid-19/vaccination-coverage/>), the Swiss Federal Office of Public Health (<https://www.covid19.admin.ch/en/epidemiologic/vacc-doses>), and Our World in Data (<https://ourworldindata.org/covid-vaccinations>) (data retrieved on 16th February 2022).

Using the overall age and gender distribution of all vaccinees in the US (Comirnaty, Spikevax, Janssen, and AstraZeneca) as reported by CDC (<https://covid.cdc.gov/covid-data-tracker/#vaccination-demographic>), the age and gender distribution for Spikevax was mirrored. Further, the number of Spikevax recipients were capped at 3% for <18 years of age as majority of vaccinees <18 years received Comirnaty. The total number of <18 years Spikevax vaccines were further divided in <12 and 12-17 years using ratio of 0.05:0.95. These ratios were based on the proportion of reports in the safety database. To estimate, the number of female Spikevax vaccinees from 15 -17 years of, number of female vaccines 12-17 years were divided in 12-14 and 15 – 17 years using ratio of 0.25:0.75. These ratios were based on the proportion of reports in the safety database.

World health organization (WHO) defines the women of reproductive age as women between 15 and 49 years of age. Based on the estimated age and gender specific estimations of Spikevax administration, globally total number of women of childbearing potential with exposure of Spikevax was 63,645,605 (as of 16th Feb 2022). The age distribution is shown in Table 8.

Table 8: Age Distribution of women of Childbearing Potential with SPIKEVAX Exposure

Age group	Number of vaccinees
15 -17 years	2,826,123
18 -24 years	11,899,464
25- 39 years	29,087,578
40 -49 years	19,832,440
Total	63,645,605

PRAC Co-Rapporteurs Assessment Comment: The exposure calculation in general is endorsed. The impact of the extrapolation from age and gender distribution from the USA to EEA and UK

(Vaxzevria exposure in the EEA and UK is apparently higher, COVID-19 vaccine Janssen apparently lower) is unclear.

3.1.1.7. Conclusion of the MAH

Although there have been reports of heavy menstrual bleeding after vaccination, it is important to note that normal variations exist within women over the lifespan and menstrual disturbances are common. Additionally, menstrual cycle features (such as bleeding volume) are subjective, not standardized, and collected by self-report which can introduce multiple biases including misclassification. The studies identified are not able to determine the frequency with which people experience heavy menstrual bleeding following Spikevax or determine whether there is a link between Spikevax and heavy menstrual bleeding; studies were limited due to lack of unvaccinated control group, recruitment of participants retrospectively, use of unvalidated questionnaires, selection and recall bias.

Despite the limitations, findings from these studies were reassuring, the reported changes were small compared to natural variation and quickly reverse. Last there is no clear biological plausibility linking Spikevax and heavy menstrual bleeding; all cases reviewed (clinical trial and post-marketing data) were only temporally associated with Spikevax and a vast majority of them had medical conditions or were on concomitant medications that provided alternate etiologies.

Thus, based on the analysis of all available safety data as of 15 February 2022, the MAH considers that there is insufficient information to establish a causal relationship between the administration of Spikevax and the development of heavy menstrual bleeding. No new or emerging safety issue of concern was identified. This health authority validated signal is refuted (refer to Appendix C for the SER) and no change to the reference safety information, labeling or risk management plan is required. The MAH will continue to monitor events for heavy menstrual bleeding through routine pharmacovigilance activities.

3.2. Rapporteur's proposed recommendation

Heavy menstrual bleeding is common according to the literature. The number of spontaneous reports of heavy menstrual bleeding is lower than what would be expected. Notably, the number of cases reported after vaccination with Spikevax in different countries varies widely. Assessment of individual case safety reports post-marketing is challenging considering the lack of important clinical information. Unfortunately, the MAH has not analyzed cases of positive re-challenge.

Five cases of heavy menstrual bleeding have been reported in clinical trials in the vaccine group. Although only very brief clinical information have been presented, confounding factors and alternative etiologies have been identified in these reports.

The quality of the published non-interventional studies, which obtained mixed results, have a number of methodological limitations.

No potential pathomechanism has been identified.

The available data is not sufficient to conclude on a reasonable causal relationship between vaccination and heavy menstrual bleeding nor on the potential pathomechanism.

Many women across the world after receiving mRNA COVID vaccines are complaining of irregularities in their menstrual bleeding; some experiencing heavy menstrual bleeding. Thus,

robust research is needed to further investigate this issue. Clinical trials provide the ideal setting in which to differentiate between menstrual changes caused by interventions from those that occur by chance. Therefore, the MAH is asked to further explore whether this issue may be investigated in subsequent or ongoing clinical trials. For the time being there is no need to change the product information.

List of Questions:

The MAH is asked to present an assessment of reports of positive re-challenge considering information on potential confounding factors.

The MAH is kindly asked to explore the possibility in further investigate the issue of heavy menstrual bleeding in studies (e.g. clinical trials).

3.3. References

1. <https://www.hopkinsmedicine.org/news/newsroom/news-releases/covid-19-news-study-to-investigate-impacts-of-covid-vaccines-on-menstruation>
2. https://admin.meddra.org/sites/default/files/guidance/file/000636_whatsnew_24_1.pdf
3. [https://www.lareb.nl/media/uoneih5z/signals_2021_menstrual_disorders-and-postmenopausal_bleeding-and-covid-19-vaccines.pdf]
4. <https://www.fhi.no/en/news/2021/menstrual-changes-following-covid-19-vaccination/>
5. Li K, Chen G, Hou H, Liao Q, Chen J, Bai H, et al. Analysis of sex hormones and menstruation in COVID-19 women of child-bearing age. *Reprod Biomed Online*. 2021 Jan;42(1):260-267. doi: 10.1016/j.rbmo.2020.09.020. PMID: 33288478.
6. Trogstad L, Laake I, Robertson AH, Mjaaland S, Caspersen IH, Juvet LK, et al. Increased occurrence of menstrual disturbances in 18- to 30-year-old women after COVID-19 vaccination. *SSRN* 2022, doi:10.2139/ssrn.3998180.
7. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med*. 2021 Feb 4;384(5):403-416. doi: 10.1056/NEJMoa2035389. PMID: 33378609.
8. Liu T, Shi F, Ying Y, Chen Q, Tang Z, Lin H. Mouse model of menstruation: An indispensable tool to investigate the mechanisms of menstruation and gynaecological diseases. *Mol Med Rep*. 2020 Dec; 22(6):4463–4474. doi: 10.3892/mmr.2020.11567. PMID: 33174022.
9. Stahlman S, Williams VF, Taubman SB. Incidence and burden of gynecologic disorders, active component service women, U.S. Armed Forces, 2012-2016. *MSMR*. 2017 Nov;24(11):30-38. PMID: 29211492.
10. Van den Brink MJ, Saaltink AL, Groenhof F, Kollen BJ, Berger MY, Lisman-van Leeuwen Y, Dekker JH. Incidence and treatment of heavy menstrual bleeding in general practice. *Fam Pract*. 2017 Nov 16;34(6):673-678. doi: 10.1093/fampra/cmz050. PMID: 28586411.

11. Fraser IS, Mansour D, Breyman C, Hoffman C, Mezzacasa A, Petraglia F. Prevalence of heavy menstrual bleeding and experiences of affected women in a European patient survey. *Int J Gynaecol Obstet*. 2015 Mar;128(3):196-200. doi: 10.1016/j.ijgo.2014.09.027. PMID: 25627706.
12. Munro MG, Critchley HOD, Fraser IS, for the FIGO Menstrual Disorders Committee. The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions. *Int J Gynaecol Obstet*. 2018 Dec;143(3):393-408. doi: 10.1002/ijgo.12666. PMID: 30198563.
13. Hallberg L, Hôgdahl AM, Nilsson L, Rybo G. Menstrual blood loss--a population study. Variation at different ages and attempts to define normality. *Acta Obstet Gynecol Scand*. 1966;45(3):320-51.
doi: 10.3109/00016346609158455. PMID: 5922481.
14. Edelman A, Boniface ER, Benhar E, Han L, Matteson KA, Favaro C, et al. Association between menstrual cycle length and coronavirus disease 2019 (COVID-19) vaccination: A U.S. cohort. *Obstet Gynecol*. 2022;139(4):481-489, doi: 10.1097/AOG.0000000000004695. PMID: 34991109.
15. Nguyen BT, Pang RD, Nelson AL, Pearson JT, Benhar Noccioli E, Reissner HR, et al. Detecting variations in ovulation and menstruation during the COVID-19 pandemic, using real-world mobile app data. *PLoS One*. 2021;16(10):e0258314, doi: 10.1371/journal.pone.0258314. PMID: 34669726.
16. Lee KMN, Junkins EL, Fatima UA, Cox ML, Clancy KBH. Characterizing menstrual bleeding changes occurring after SARS-CoV-2 vaccination. *medRxiv* 2021.10.11.21264863; doi: <https://doi.org/10.1101/2021.10.11.21264863>.
17. Male V. Effect of COVID-19 vaccination on menstrual periods in a retrospectively recruited cohort. *medRxiv* 2021.11.15.21266317; doi: <https://doi.org/10.1101/2021.11.15.21266317>.
18. Zhang B, Yu X, Liu J, Liu P. COVID-19 vaccine and menstrual conditions in female: data analysis of the Vaccine Adverse Event Reporting System. *Research Square*, posted on 07 April 2022. doi: <https://doi.org/10.21203/rs.3.rs-1388159/v2>.
19. Alvergne A, Kountourides G, Argentieri MA, Agyen L, Rogers N, Knight D, et al. COVID-19 vaccination and menstrual cycle changes: A United Kingdom (UK) retrospective case-control study. *medRxiv* 2021.11.23.21266709; doi: <https://doi.org/10.1101/2021.11.23.21266709>.
20. Muhaidat N, Alshrouf MA, Azzam MI, Karam AM, Al-Nazer MW, Al-Ani A. Menstrual symptoms after COVID-19 vaccine: A cross-sectional investigation in the MENA region. *Int J Womens Health*. 2022 Mar 28;14:395-404. doi: 10.2147/IJWH.S352167. PMID: 35378876.
21. Laganà AS, Veronesi G, Ghezzi F, Ferrario MM, Cromi A, Bizzarri M, et al. Evaluation of menstrual irregularities after COVID-19 vaccination: Results of the MECOVAC survey. *Open Med (Wars)*. 2022 Mar 9;17(1):475-484. doi: 10.1515/med-2022-0452. PMID: 35350834.
22. Ding T, Wang T, Zhang J, Cui P, Chen Z, Zhou S, et al. Analysis of ovarian injury associated with COVID-19 disease in reproductive-aged women in Wuhan, China: An observational study. *Front Med (Lausanne)*. 2021 Mar 19;8:635255. doi: 10.3389/fmed.2021.635255. PMID: 33816526.
23. Madendag IC, Madendag Y, Ozdemir AT. COVID-19 disease does not cause ovarian injury in women of reproductive age: an observational before-and-after COVID-19 study. *Reprod Biomed Online*. 2022, in press. <https://doi.org/10.1016/j.rbmo.2022.03.002>.

24. Khan SM, Shilen A, Heslin kM, Ishimwe P, Allen AM, Jacobs ET, et al. SARS-CoV-2 infection and subsequent changes in the menstrual cycle among participants in the Arizona CoVHORT study. Am J Obstet Gynecol. 2022 Feb;226(2):270-273. doi: 10.1016/j.ajog.2021.09.016. PMID: 34555320.

3.4. Comments from other PRAC members and MAH(s)

Comment MS1:

The PRAC co-rapporteur's conclusions are endorsed. However, the PRAC rapporteur has some additional comments regarding the proposed recommendation. Please see below:

From the proposed recommendation it is not entirely clear how (procedure wise) or when the MAH's response to the LoQ should be assessed. Additionally, experience from various previous procedures has shown that the more specific the request, the higher the likelihood of an acceptable response. With regard to the request on positive rechallenge proposed by the co-rapporteur, the MAH states that "The 1,247 cases (serious cases and medically confirmed cases) were medically reviewed and no cases of positive rechallenge were identified." It is unclear how the MAH has reached this conclusion as rechallenge cases have indeed been identified in section 2.1. It is suggested to specify the requests as follows:

1. The MAH is kindly asked to explore the possibility of further investigating the issue of heavy menstrual bleeding in ongoing or subsequent studies (e.g. clinical trials). The MAH should outline which possibilities have been explored.
2. The MAH should provide the following information not included in the response:
 - i. An explanation how adverse events related to heavy menstrual bleeding were reported (solicited/non-solicited reporting).
 - ii. A specification of the number of female study participants of childbearing age and the length of follow-up of this cohort.
3. The MAH is asked to clarify how the conclusion regarding number of re-challenge cases in response to ITEM 3 was reached.
4. The MAH is asked to perform a new evaluation of cases with the aim to identify possible re-challenge cases. If re-challenge cases are identified, an assessment of these should be provided. During assessment, information on potential confounding factors should be considered.

The PRAC Rapporteur proposes that the responses to the LoQ should be assessed in the next PSUR.

PRAC Co-Rapporteur Comment: The questions of MS1 are endorsed.

As pointed out in the preliminary assessment report we assessor was wondering why positive re-challenge ICSRs were not detected by the MAH. By further reviewing this issue, we realized that in several ICSRs this information may only be available in the narrative, but not in the structured field for re-challenge. The MAH is therefore kindly asked to consider all available ICSR information for identifying re-challenge cases.

Comment MS2:

The conclusion of assessment of the MAH, that is endorsed by Rapporteur, is that the available evidence is insufficient to establish a causal relationship between heavy menstrual bleeding and Spikevax. We do not agree with this assessment and believe that there are some issues that need to be discussed properly before a final conclusion can be made.

The character of menstrual disorders should be taken into consideration. There are mainly non-serious cases with short-term duration and mainly self-evaluation and patient self-reporting. We are aware, that patient's reporting is not ideal for demonstrating causal relationship, however because of the character of menstrual disorders we believe that higher portion of medically confirmed cases cannot be expected (even less after awareness of this issues in future). Majority of women do not visit their gynaecologist due to transient menstrual disorder only. This will probably never change and therefore, waiting for better HCPs reported cases could mean that we never could conclude on this signal. In this case, predominant patients' reports should not be a reason for rejection of this problem. Moreover, in accordance with pharmacovigilance legislation, the patient cases should be taken into account during the assessment. The role of patient cases is significantly more important in situations, where causal relationship cannot be established based on the confirmed cases because of the nature of condition. Moreover, medical confirmation of heavy menstrual bleeding in fact will not increase credibility of patients' reports – in this situation the physician can only confirm what the woman told him.

Ad Q1: The review of clinical trial data identified 5 cases of heavy menstrual bleeding in active arm vs. 1 case from placebo arm. Despite stated medical history and concomitant medications in the provided table of these cases it is not clear how the causality with the vaccination of Spikevax was assessed. However, 2 of 5 cases of heavy menstrual bleeding in active arm were described as "related" vs. 0 "related" cases in placebo arm. Moreover, as the Rapporteur highlighted, the MAH did not mention the number of female participants of childbearing age and length of FU of these reports. The MAH did not discuss even the numerical imbalance of the clinical trials and its statistical significance. There is too little information presented by the MAH that no conclusion can be made from the clinical data but it aroused reasonable suspicion of possible causal relationship of heavy menstrual bleeding and Spikevax vaccine. The MAH should provide the missing information regarding the clinical data, elucidate all the questions and make the proper assessment with critical discussion.

Ad Q2: We do not agree with the conclusion of the MAH that the presented studies are not able to determine the frequency with which the women experienced heavy menstrual bleeding after the Spikevax vaccination or to determine whether there is a link between vaccination and heavy menstrual bleeding. The MAH constantly rejects the findings of all studies because of study limitations such as unvalidated questionnaire, recall bias or selection bias but did not provide detailed review and discussion of methodology of the mentioned studies. We are of the opinion that the findings from the literature could not be trivialised, and the results should be critically discussed and taken into consideration.

The study of Trogstad et al. (preprint) is focusing on number of menstrual disorders. For reduction of bias of awareness at the menstrual disorders, the questionnaire included several topics not related to menstruation to be answered prior to the questions of menstrual disorders. This study assessed 5,688 Norwegian women aged 18-30 year and the data of individuals before and after vaccination was compared. The self-control case series design is described as a suitable design for investigation of vaccines. The bias between a case and a control caused by inter-individual differences is minimized

using this type of study. Currently, when the exposure to vaccines is high in a general population, it could be expected that the populations of vaccinated and unvaccinated women are considerably different, and comparison of these groups could be less suitable. The selection bias is minimized by random assorting of women from another ongoing population study. Therefore, inclusion of women was not driven by the existing menstrual disorders following vaccination. The recall bias was significantly solved by the app which was used by almost 60% of women. Specifically for the Spikevax, the study identified heavier menstrual bleeding after first dose of Spikevax with relative risk 1.86 (95% CI 1.54 to 2.26) and after second dose of Spikevax with relative risk 1.92 (1.67 to 2.21).

The MAH stated that menstrual disturbance was common resulting in 37.8 % prior to the vaccination (Trogstad et al.). However, it should be highlighted that this number includes any menstrual disturbance and not only heavy menstrual bleeding. This number (37.8 %) should not be compared with the other findings such as significant risks of heavier menstrual bleeding after first and second dose of vaccines that are very specific. Overall, the prevalence of the heavy menstrual bleeding (as a single observed issue) was only 7.6 % (and not the 37.8 %) prior to first dose of COVID-19 vaccination in comparison with 13.6 % in the first cycle after COVID-19 vaccination and similarly 8.2 % prior to second dose of COVID-19 vaccination in comparison with 15.3 % after second dose of COVID-19 vaccination.

Similarly in study by Lee et al. (2022) and specifically for Spikevax vaccine, among women with the spontaneous regular menstrual cycles and no diagnosed reproductive conditions, 42.5 % (from 3499 participants) experienced heavier bleeding after vaccination and 44.5 % experienced no change in their bleeding heaviness. Women using hormonal contraceptives who report regular menstrual cycles and no diagnosed reproductive conditions reported similar trends, 42.5 % (from 1251 participants) experienced heavier bleeding after vaccination and 42.5 % experienced no change in their bleeding heaviness. The percentages of participants with heavier menstrual bleeding after Spikevax vaccine administration was even slightly higher than those for Pfizer. There was no significant difference in post-vaccination menstrual flow between Pfizer and Moderna in any of the subgroups.

The study of Laganà et al. (2022) showed significant increase of menstrual abnormalities after COVID-19 vaccination regardless of the type of vaccine; these reactions had 50 – 60 % of participants after first dose and even higher proportion after second dose of vaccination. It is agreed that the sample size is small, but still accepted in clinical studies. We would like to kindly disagree to some mentioned study limitations by Rapporteur; the questionnaire was designed to be self-administered which could be accepted in this kind of issue including mostly non-serious cases of menstrual disorders when the patients do not need to visit a physician. The questionnaire was self-administrated only one time per respondent and the survey was available only for 30 days from 10/9/2021 to 10/10/2021. The questionnaire was distributed by social media (LinkedIn, Facebook, Twitter) which are currently used instruments to spread the questionnaire to the whole country and to the appropriate age groups. It should be also noted that the questionnaire consisting of 26 multiple-choice questions where the first 13 items aimed to age, BMI, concurrent gynaecological and non-gynaecological disorders, use of hormonal and non-hormonal treatments, number of previous pregnancies and abortions, reproductive or (peri)menopausal status and type of covid-19 vaccine; items 14-16 assessed the frequency, length and quantity of the menstrual cycles before first dose of vaccine, items 17-21 assessed the phase of the menstrual cycle in which the first dose of the covid-19 vaccine was administered, the frequency, length and quantity of the menstrual cycle after the administration and how long this effect lasted in case of menstrual cycle irregularities and/or abnormal menstrual bleeding; the last items 22-26 assessed the phase of the menstrual cycle in which the second dose of the covid-19 vaccine was administered. Of note, to avoid the potential

biases, the authors excluded women with gynaecological and non-gynaecological disease, undergoing hormonal and non-hormonal treatments, in perimenopause or menopause, as well as those who had irregular menstrual cycles in the last 12 months before vaccine administration. After that there remained 164 women who were in reproductive age and declared regular menstrual cycle before the vaccination with mean age 35.8 ± 7.2 years. According to their analysis, approximately 50-60 % of reproductive age women reported menstrual cycle irregularities after the first dose and 60-70 % of them after the second dose of COVID-19 vaccine regardless of the type of vaccine. After both first and second vaccine, the most common alternations seem to be anticipated, longer, and heavier menstrual cycle than expected and usual. Hypothetically, one can compare the general number of 37.8 % of menstrual disturbances prior to the vaccination (Trogstad et al.) with these results of 50-60 % of reported menstrual irregularities after the first dose and 60-70 % after the second dose of COVID-19 vaccine. The increase of the percentage of menstrual disturbances after COVID-19 vaccine is evident.

Despite the study limitations, the critical discussion and analysis of studies' methodology and their conclusions should be performed. Thus, the MAH is requested to perform the critical in-depth analyses of the mentioned studies, their methodology, conclusions and limitations along with the character of studied disorder. The MAH is asked mainly for the analyses of studies of Trogstad et al., Lee et al., Male et al., Zhang et al., Netherland PV Lareb and Laganà et al.

Ad Q4: The MAH assessed in detail only 14 cases from a total of 4000 cases from post-marketing data. These 14 cases were serious or medically confirmed and at the same time with the date of vaccination and onset, known previous menstruation pattern. MAH stated that based on the WHO-UMC system all these 14 cases were possibly related due to temporal association.

Unfortunately, there is no discussion and information on the other serious or medically confirmed cases. Similarly, no cases with positive rechallenge from MAH's database or EudraVigilance have been presented by MAH. The review, analyses and discussion presented by MAH is very poor and insufficient to make any conclusion. The MAH is therefore asked to perform the proper analyses and discussion of serious cases, medically confirmed cases and cases with positive rechallenge. The discussion of cases should be done according to instructions of question 4 included the case review of all the cases with WHO-UMC Causality assessment; a justification of causality category should be given for each case.

Beside the incorrect calculation of the O/E analyses provided by MAH, corrected by the Rapportuer, the MAH also included only the cases where known female gender was reported. We are missing the meaning for exclusion of other cases of heavy menstrual bleeding without any discussion. Moreover, the consideration of back log data in O/E analysis provided by MAH is unclear. However, the O/E analyses is difficult to be calculated given the high rate of underreported cases as well as underestimated background incidence; the significance of this analysis is thus lower.

The proper mechanism of action for menstrual disorders after the vaccination is still unclear. Of note, the study of Nguyen et al. did not demonstrate higher risk of menstrual disorders in relation to pandemic situation. The question of Rapp to the MAH is supported. Is there a better way how to study non-serious menstrual disorders such as heavy menstrual bleeding after vaccination by MAH?

Overall, the MAH's assessment is of poor quality. We agree that causal relationship should be determined especially on the medically confirmed cases, but concurrently the nature of this particular condition should be taken into account. In some cases, the nature of condition cannot allow medical confirmation. The majority of reported cases are non-serious but still unexpected according to SmPC

of Spikevax. Thus, the proper analyses and discussion needs to be done and another round of this signal (EPITT no: 19780) is required.

Of note, MS1 proposed that the responses to the LoQ should be assessed in the next PSUR. We are of the opinion that this signal should be better run as a single signal procedure, as the MAH should performed the proper analyses and discussions, and comprehensive review of this issue is expected. However, further assessment could alternatively be done also in the next PSUR based on preference of the PRAC.

Overall, we are of the opinion that the imbalance of clinical data and data from literature indicate at least reasonable possibility of causal relationship between heavy menstrual bleeding and Spikevax vaccination; and after further proper assessment we expect that PI could be updated with the risk of heavy menstrual bleeding.

PRAC Co-Rapporteur Assessment Comment: As stated by MS2 colleagues the majority of ICSRs are non-serious reports with short-term duration and mainly self-evaluation and patient self-reporting. As pointed out, this is not an ideal situation for establishing causal relations for demonstrating causal relationship (lack of case definition, subjective assessment). A disproportional reporting of heavy menstrual bleeding in different regions and different EU is noted, which may indicate reporting bias. It may be of interest to analyse case reports prior and after media attention of this issue.

Observational studies with mixed results have addressed this issue. The evidence of cross-sectional studies and the published spontaneous reports are considered to be low and thus should be interpreted with caution.

Concerning the imbalance of cases of heavy menstrual bleeding observed in clinical trials the MAH provided only brief information. Based on this brief information, no consistent pattern could be detected. All case reports were apparently confounded and/or alternative causes have more likely caused the event. Based on this data, a reasonable causal relationship with vaccination cannot be established.

Comment MS3:

We overall agree with both PRAC Rapporteurs that more data are needed to include heavy menstrual bleeding in section 4.8 of the product information. Specially, the cases with positive rechallenge should be investigated in detail. In addition, more studies would be necessary to reach firm conclusions, although we believe that a proper study design may be difficult in practice.

However, it is a fact that a large number of reports on heavy menstrual bleeding for both Comirnaty and Spikevax, some of them with positive rechallenge, have been reported and that available major studies (Torgstad and Carpensen), albeit limitations, points towards heavy menstrual bleeding.

Therefore, although it is unclear a causal relationship with the vaccine, this issue may create unnecessary worries in women, being normally mild and transitory disorders, we propose that a general warning in section 4.4 could be implemented to offer information about the temporal association with the vaccine as well as to state that the reported cases are mostly transitory and mild:

"Cases of heavy menstrual bleeding temporarily associated with <Comirnaty> <Spikevax> vaccination have been reported. Most of them are transient and mild in nature"

Co-Rapporteur Assessment Comment: The proposal of MS3, MS4 and MS5 in favour of a warning statement need to be discussed by PRAC. The Co-Rapporteur supports the view of MS3 and MS4 that heavy menstrual bleeding should not be labelled in section 4.8 of the SmPC.

Comment MS6:

The information provided by the MAH for Spikevax had similar limitations than that of Comirnaty's, with significant number of the spontaneous reports excluded from the analysis (initially 4000 ICSRs, of which finally 14 cases were considered by the MAH). Despite the lower number of reports for Spikevax, we consider, that the overall picture of the data is similar, and therefore the end result of this signal should be similar for these two products.

For Comirnaty we endorse the Rapporteur's view that the Trogstad et al study and the spontaneous reporting data indicate a potential causal relationship or at least a reasonable possibility of that, and endorse the Rapporteur's proposed recommendation.

Therefore, we suggest that the that "heavy menstrual bleeding" should be listed in section 4.8 of the SmPC for Spikevax as well. Further, we suggest the use of the MedDRA PT 'heavy menstrual bleeding' instead of the LLT 'heavy period' in the SmPC section 4.8.

Heavy menstrual bleeding is an ADR that seldomly leads to contacts with health care and thus is likely to be reported mostly by consumers. Since the diagnosis of heavy menstrual bleeding relies on the anamnesis given by the patient, no medical confirmation is necessary for a reliable case, and the non-serious cases are as relevant for the causality consideration as the serious. We acknowledge that case-level analysis is not possible for all the cases given the number of reports. However, we do not agree with the approach that this leads to dismissing majority of the ICSRs when assessing the causal relationship.

Consumer reporting has also been promoted for a decade in the EU, and these reports cannot be excluded from safety analyses, at least when received in unforeseen quantities, although they are of limited quality. If they are considered of no value, the whole concept of consumer reporting should be re-evaluated.

PRAC Co-Rapporteur Assessment Comment. The arguments are acknowledged. Heavy menstrual bleeding in particular if self-limited and transient will not result in a HCP contact in the majority of cases, in particular under the conditions of a pandemic.

For individual ICSRs is usually difficult (if not mostly impossible) to establish a causal association or absence of association independent whether they are consumer or HCP reports. (Consumer and HCP reports may differ concerning diagnostic certainty). Therefore, even positive re-challenge cases may not provide much more evidence

The Co-Rapporteur is of the opinion that the totality of data does not justify a labelling in 4.8 for the reasons provided in the preliminary ASR.

Comment MS7:

We agree that the data provided in support of the signal has limitations. The nature of the condition provides challenges in an evaluation (such as it being transient and therefore not necessarily reported to a physician, underreporting due to the benign condition and its high prevalence in the population at baseline). We agree with the PRAC Co-Rapporteurs comment on the limitations in the O/E-analyses provided in the MAHs response. O/E-analysis are of less use for a common medical condition such as menstrual disturbances, compared to rarer diagnoses and diseases with more stringent definitions. The focus of the assessment should include review of case narratives with focus on cases with positive rechallenge, but unfortunately this was not adequately analysed by the MAH, and therefore the data in this evaluation has severe shortcomings.

Given the guidance statements in the SmPC Guideline 2009 of «..at least a reasonable possibility...» we are of the opinion that the conclusion by the PRAC Co-rapporteur sets the bar for including this in the product information too high. We consider it unrealistic to address this issue in future controlled trials. Post-marketing data do not support dismissing the signal. Overall, we consider that there is at least a reasonable possibility of a causal association. This supports the inclusion of the term in the PI.

PRAC Co-Rapporteur Assessment Comment: The points are acknowledged, however the assessor is of the opinion that lowering the standards for the evaluation of potential causal association may create unforeseeable problems for future assessments of potential signals.

Comment MS5:

MS5 partially endorses the Rapporteur assessment report.

It appears that some information is still missing from MAH such as narratives of clinical cases and assessment of positive re-challenge cases.

MS5 considers that the available data cannot be ruled out a causal relationship between vaccination and heavy menstrual bleeding. For a more robust evaluation of this potential signal, the MAH should further review all positive re-challenge cases and should propose, as needed, an update of the product information or additional minimisation risk measure.

MS5 proposes that the MAH provide the cumulative review and the PRAC assess this review within a next turn of this signal and not close the signal for now.

In addition, awaiting for more comprehensive analyses on this important topic from the MAH, MS5 proposes a warning information to the public and healthcare professionals to be added in the section 4.4 of the SmPC. If accepted for Spikevax, considering the uncertainties in the mechanism of action, the number of cases with both Spikevax and Comirnaty and heterologous vaccination patterns, this warning information should be also added in the SmPC of Comirnaty.

PRAC Co-Rapporteur Assessment Comment: The points raised by MS5 are acknowledged. The proposal for a 4.4 warning needs to be discussed by PRAC.

Comment MS8:

We generally endorse the PRAC (Co)-Rapporteurs conclusions and have some additional comments.

It is agreed that clinical trials provide the ideal setting for assessing the association between vaccines and menstrual changes. Nevertheless, we consider that further information could be also retrieved from observational, self-controlled studies. Thus, we propose to request to the MAH whether this issue may be investigated in the ongoing PASS studies planned in the RMP.

PRAC Co-Rapporteur Assessment Comment: The points are endorsed.

Comment MS4:

We endorse the PRAC Rapporteur's recommendation that current data is not sufficient to conclude on a reasonable causal relationship between vaccination and heavy menstrual bleeding.

We also support MS8 comment that the MAH should be requested to investigate whether additional data could also be collected through PASS studies planned in the RMP.

Finally, we support the comment from MS3 that changes in menstruations being an important concern among women of childbearing age, a general warning in section 4.4 could be implemented for reassurance, stating that the reporting cases are mostly transitory and mild. The text we propose is amended as:

"Menstrual changes, such as heavier menstrual bleeding, temporarily associated with <Comirnaty> <Spikevax> vaccination have been reported. Most of them are transient and mild in nature"

PRAC Co-Rapporteur Assessment Comment: See comments above

Comment MS9:

MS9 agrees with the assessment conclusions of the PRAC rapporteur for the above-mentioned procedure. We have no further comments.

Comment MS10:

MS10 agrees with the conclusions of the PRAC Rapp AR for the above-mentioned procedure.

Comment MS11:

The assessment by the PRAC-Rapporteur is fully endorsed. We have no additional comments.

3.5. Updated rapporteur's proposed recommendation

The signal of heavy menstrual bleedings should be closed and further assessed in the next PSUR.

1. The MAH is kindly asked to explore the possibility of further investigating the issue of heavy menstrual bleeding in a structured and prospective way in ongoing or subsequent studies, e.g. PASS studies planned in the RMP and clinical trials. The MAH should outline

which possibilities have been explored and should provide this evaluation in the next PSUR.

2. The MAH should provide the following information not included in the response in the next PSUR:
 - i. An explanation how adverse events related to heavy menstrual bleeding were reported (solicited/non-solicited reporting).
 - ii. A specification of the number of female study participants of childbearing age and the length of follow-up of this cohort.
 - iii. A critical discussion of the numerical imbalance of heavy menstrual bleeding events in the clinical trial considering detailed clinical information of these case reports.
3. The MAH is kindly asked
 - i. to clarify in the next PSUR how the conclusion regarding number of re-challenge cases in response to ITEM 3 was reached.
 - ii. to perform a new evaluation of cases with the aim to identify possible re-challenge cases. If re-challenge cases are identified, an assessment of these should be provided. During assessment, information on potential confounding factors should be considered. Narrative information should be included in the identification of cases with positive re-challenge. The analyses of re-challenge reports should be presented in the next PSUR.
 - iii. to carefully and comprehensively analyze and discuss, besides all cases with a positive rechallenge, all serious cases and all medically confirmed cases. The discussion of cases should be done according to the instructions of question 4 and include the case review of all the cases with WHO-UMC causality assessment; a justification of causality category should be given for each case. Information should be presented in the next PSUR.
4. The MAH is requested to perform an in-depth analyses of the available studies, their methodology, conclusions and limitations along with the character of studied disorder in addition to the brief discussion presented in the response of this signal procedures. The studies to be reviewed should include, but are not limited to, those conducted by Trogstad et al., Lee et al., Male et al., Zhang et al., Netherland PV Lareb, and Laganà et al. The detailed analysis of the evidence from studies are expected to be presented in the next PSUR.

3.6. Adopted PRAC recommendation

Having considered the data submitted by the Marketing Authorisation Holder (MAH), the PRAC concluded that the current evidence is insufficient to warrant an update to the product information at present.

The PRAC has agreed that the MAH of COVID-19 mRNA vaccine (nucleoside-modified) Spikevax, (Moderna Biotech Spain, S.L.) should provide an updated cumulative review of heavy menstrual

bleeding post-vaccination by 24/08/2022. The MAH should provide responses to the following list of questions:

List of Questions:

1. The MAH should discuss the possibility of further investigating the issue of heavy menstrual bleeding in a structured and prospective way in ongoing or subsequent clinical studies. The MAH should outline which possibilities have been explored.
2. The MAH should include in the updated review the following information on clinical trials:
 - a. The exposure (patients' years) of female study participants of childbearing age in clinical trials.
 - b. A detailed presentation (complete narrative and relevant case report form information) of cases of heavy menstrual bleeding in clinical trials.
3. The MAH should provide an updated case review, as per the below:
 - a. All serious cases of heavy menstrual bleeding.
 - b. All case reports of re-challenge of heavy menstrual bleedings with subsequent vaccination.
 - c. The MAH should include in the case review also the cases in which there was concomitant use of other medicinal products (including concomitant use of contraceptives), or lack of information on medical history. Should confounders make a case a clear explanation should be provided.
 - d. An assessment of the case reports according to UMC causality assessment criteria
 - e. The MAH should justify the causality assessment, if "unlikely" or "non assessable /unclassifiable" is used.
4. In addition to the above-mentioned review which should include all case narratives, the MAH should provide a table as specified below. The table should include all serious and/or positive rechallenge cases and information including the categories shown in the separate columns. The MAH can suggest additional columns, if deemed useful. Data from this table should be easily extractable for assessment.

EudraVigilance case ID	Case narrative	Age	Time to onset	Duration	WHO-UMC causality category	Justification if causality is 'unlikely' or 'unassessable'	Confounded yes/no	Medically confirmed yes/no	Concomitant medication	Medical history	Positive rechallenge

The MAH should prioritize all ICSRs relating to this signal when handling the backlog of cases and report on the backlog at time of DLP.

The MAH should discuss the need for any potential amendment to the product information and/or the risk management plan and make accordingly a proposal for changes to the relevant sections with this discussion.

The PRAC will assess this updated review within a 60 days' timetable.

4. Additional evidence II

On 26 August 2022, the PRAC Co-Rapporteur received responses from the MAH to the PRAC's questions listed in section 3.6.

4.1. Assessment of further information

4.1.1. Item 1

"The MAH should discuss the possibility of further investigating the issue of heavy menstrual bleeding in a structured and prospective way in ongoing or subsequent clinical studies. The MAH should outline which possibilities have been explored."

MAH response:

The MAH points out that menstrual cycle disorders are challenging to study even in clinical trials. The physiology of the menstrual cycle is complex, and variations in cycle length and bleeding intensity are expected even under normal circumstances. The MAH refers to the International Federation of Gynecology and Obstetrics (FIGO) definition of heavy menstrual bleeding, i.e. a volume that interferes with the patient's physical, social, emotional, and/or material quality of life. This measure is subjective and implies a comparison to the individual baseline. If information was collected only after a vaccination event, it would be difficult to interpret. Since menstrual disorders historically were not a topic of potential concern in vaccine trials, baseline menstrual data were not collected in the clinical program. Now that the benefit of the approved vaccines against coronavirus disease 2019 (COVID-19) has been clearly demonstrated, placebo-controlled trials are no longer standard and no longer feasible. The existing trials lack a control group. On the one hand, only very large trials with a substantial number of women of childbearing age would be conclusive. However, given the expected natural variation in menstruation and the high prevalence of heavy menstrual bleeding, a control arm is critical because data from an uncontrolled cohort would be difficult to interpret. The MAH acknowledges that the sensitivity of the capture of heavy menstrual bleeding could be enhanced by soliciting this adverse event during follow-up. At the same time, it expresses concern that the "impact of solicited reporting might disproportionately increase this subjective measure". The MAH assures to continue monitoring heavy menstrual bleeding through routine surveillance as well as the ongoing prospective cohort studies which are conducted by independent third party investigators (e.g., NIH funded studies conducted by Boston University, Harvard Medical School, John's Hopkins University, Michigan State University, and Oregon Health and Science University).

Comment PRAC Co-Rapporteur:

The PRAC Co-Rapporteur agrees with the MAH that for a meaningful evaluation, data would need to be collected over both pre- and post-vaccination intervals. The PRAC Co-Rapporteur also acknowledges the challenges of such investigations. The PRAC Co-Rapporteur does not support the MAH's statement "[...] it is expected that the impact of solicited reporting might disproportionately increase this subjective measure". Medicine and health encompass numerous subjective aspects that must be taken into account just as much as objectively measurable parameters. Subjective measures are the endpoints of clinical trials for many drugs and therapeutic interventions, although this can be challenging. Examples include pain, quality of life and patient satisfaction. However, in lieu of further elaboration, reference is made to the literature on vaccines and patient-related outcomes [1,2].

The discussion of this signal should prompt consideration of the menstrual cycle in future studies.

However, concrete concepts on how this could be realized are not to be found in the MAH's response. Question not resolved.

4.1.2. Item 2

"The MAH should include in the updated review the following information on clinical trials:

- a. The exposure (patients' years) of female study participants of childbearing age in clinical trials.
- b. A detailed presentation (complete narrative and relevant case report from information) of cases of heavy menstrual bleeding in clinical trials"

MAH response:

4.1.2.1. Exposure in clinical trials

The MAH reviewed the two studies mRNA-1273-P301 (NCT04470427) and mRNA-1273-P203 (NCT04649151).

- a. mRNA-1273-P301 is an ongoing 3-part (A, B, C), phase 3, randomized, observer-blind, placebo-controlled, stratified, efficacy, immunogenicity, and safety study conducted at multiple sites across the United States with participants 18 years of age and older. In part A, individuals are randomly assigned 1:1 to receive either 2 injections of 100 µg of mRNA-1273 or 2 injections of placebo control each given 28 days apart. Part B is an open-label observational phase designed to offer participants who received placebo in part A and who meet the emergency use authorization (EUA) eligibility criteria an option to request and receive mRNA-1273. Part C is an open-label observational phase to evaluate the safety and immunogenicity of a 50 µg booster dose of mRNA-1273.
- b. Similarly, study mRNA-1273-P203 is a 3-part (A1, B1, C) study of the safety, reactogenicity, and efficacy of mRNA-1273 in healthy adolescents aged 12 to under 18 years. In part A, adolescents are randomly assigned 2:1 to receive either 2 injections of 100 µg of mRNA-1273 or 2 injections of placebo control each given 28 days apart. Part B is an open-label observational phase designed to offer participants who received placebo in part A of the study and who meet the EUA eligibility criteria an option to request and receive mRNA-1273. Upon availability of another COVID-19 vaccine authorized for emergency use in adolescents, the study transitioned to part B, the open-label observational phase. In part B, participants who were age-eligible for a COVID-19 vaccine authorized for emergency use could request unblinding. Placebo recipients were subsequently offered mRNA-1273. Part C is an open-label observational phase designed to offer a 50 µg mRNA-1273 booster dose to ongoing study participants in part A1 and part B1. The booster dose was administered at least 5 months after completion of the mRNA-1273 primary series.

Two clinical studies (mRNA-1273-P301 and mRNA-1273-P203) sponsored by Moderna were reviewed as part of the updated response to the agency's request for information. mRNA-1273-P301 is an ongoing 3-part (Part A, Part B, and Part C), Phase 3 randomized, observer-blind, placebo-controlled, stratified, efficacy, immunogenicity, and safety study conducted at multiple sites across United States with participants 18 years of age and older.

Prespecified cohorts of participants who were either ≥ 65 years of age or 18 to < 65 years of age, including those with comorbid medical conditions, were included. Part A, is a randomized, placebo-controlled, observer-blind phase study of individuals >18 years of age, randomly assigned 1:1 to receive either 2 injections of 100 μg of mRNA-1273 or 2 injections of placebo control each given 28 days apart. Part B is an open-label observational phase designed to offer participants who received placebo in Part A of the study and who meet the EUA eligibility criteria an option to request and receive mRNA-1273. Part C is an open-label observational phase of the study to evaluate the safety and immunogenicity of a 50- μg booster dose of mRNA-1273.

Study mRNA-1273-P301: The MAH defines the duration of follow-up as days between the first mRNA dose and either booster vaccination, death, discontinuation of the study, or the data cutoff of 05 April 2022. According to the MAH, female participants aged 18-55 years ($n = 7,421$) were followed up for a median of 359 days (range 4-618 days, 1st quartile 281 days, 3rd quartile 427 days), resulting in an exposure of 7,220.96 person-years.

Study mRNA-1273-P203 is a 3-part (Part A1, Part B1, and Part C) study of the safety, reactogenicity, and efficacy of mRNA-1273 in healthy adolescents ages 12 to < 18 years. Part A is a randomized, observer-blind, placebo-controlled study of adolescents randomly assigned 2:1 to receive either 2 injections of 100 μg of mRNA-1273 or 2 injections of placebo control each given 28 days apart. Part B is an open-label observational phase designed to offer participants who received placebo in Part A of the study and who meet the EUA eligibility criteria an option to request and receive mRNA-1273. Upon availability of another COVID-19 vaccine authorized for emergency use in adolescents, the study transitioned to Part B, the Open-label Observational Phase. In Part B, participants who were age-eligible for a COVID-19 vaccine authorized for emergency use could request unblinding. Placebo recipients were subsequently offered mRNA-1273. Part C is an open-label observational phase designed to offer a 50- μg mRNA-1273 booster dose to ongoing study participants in Part 1A and Part 1B. A booster dose was administered at least 5 months after completion of the mRNA-1273 primary series.

Comment PRAC Co-Rapporteur:

The exposure of female participants aged between 18 and 55 years in study mRNA-1273-P301 is given, but not the exposure in study mRNA-1273-P203.

4.1.2.2. Detailed presentation of cases in clinical trials

The MAH searched its clinical database of the studies mRNA-1273-P301 (data cutoff 05 April 2022) and mRNA-1273-P203 (data cutoff 31 January 2022) using the MedDRA version 23.0 preferred terms (PTs) "menorrhagia", "polymenorrhagia", "menometrorrhagia", "polymenorrhea", and "vaginal hemorrhage".

The MAH identified three participants (between 13 and 15 years old) of the study mRNA-1273-P203 who reported heavy menstrual bleeding via unsolicited reporting. All three cases were in the mRNA-1273 arm, considered non-serious and assessed as not related to mRNA-1273 by the principal investigator. According to the MAH, two of the three participants had a medical history or use of concomitant medication that provided a plausible alternate explanation for the heavy menstrual bleeding.

Subject	Age band	Tx Code	Dictionary-Derived	Event Seriousness	Relevant Medical History	Relevant concomitant meds	TTO First dose (days)	TTO second dose (days)	Duration	PI Causality	Outcome
1	adolescent	mRNA-1273	Menorrhagia	Nonserious	History of heavy menstrual bleeding and premenstrual syndrome		175	147	82	Not related	Recovered Resolved
2	adolescent	mRNA-1273	Polymenorrhea	Nonserious	History of irregular periods	Oral combined hormonal contraception	51	23	Ongoing	Not related	Not recovered
3	adolescent	mRNA-1273	Menorrhagia	Nonserious			205	171	26	Not related	Recovered Resolved

Table 1: Unsolicited reports of heavy menstrual bleeding, study mRNA-1273-P203.

In the study mRNA-1273-P301 (A, B, C), the MAH identified 67 of 13,252 female participants who reported heavy menstrual bleeding via unsolicited reporting. When the search was restricted to women of childbearing age (18-55 years), 58 of 7,421 women reported heavy menstrual bleeding (Table 2).

Category	
Number of female participants received mRNA-1273 in Part A or Part B*	7421
Median duration of follow-up, days	359 (4-618)
Number of female participants reporting HMB**	58 (0.8% [58/7421])
Age, years (median)	44 (range 20-54)
Postmenopausal	4 (6.9%)
Confounders***, N %	44 (75.9%)
Non-Serious event, N (%)	53 (91.4%)
Recovered/Recovering	49 (84.5%)
Principal investigator Causality, related N (%)	5 (8.6%)

Exposure, patient's years = 7220.96

** Cases identified using the 5 PTs "Menorrhagia," "Polymenorrhagia," "Menometrorrhagia," "Polymenorrhea," and "Vaginal hemorrhage"

*** Presence of uterine structural lesion, coagulopathy, endocrine disorder, menstrual disorder, hormonal therapy, COVID-19 and heterologous vaccination

Table 2: Unsolicited reports of heavy menstrual bleeding by females between 18 and 55 years old who received at least one 100 µg dose of mRNA-1273, study mRNA-1273-P301.

Comment PRAC Co-Rapporteur:

In the MAH's first report on this signal, the database of the phase 3 study NCT04470427 with a data lock point of 04 May 2021 was searched using the MedDRA version 24.0 PTs "heavy menstrual bleeding", "menometrorrhagia", and "polymenorrhagia". The PRAC Co-Rapporteur had suggested to include the PTs "polymenorrhea" and "vaginal bleeding" in the search in order to identify more potential cases. Now, the MAH states to have searched using the MedDRA version 23.0 PTs "menorrhagia", "polymenorrhagia", "menometrorrhagia", "polymenorrhea" and "vaginal hemorrhage". However, "menorrhagia" (10027313) is a lowest level term (LLT) under the PT

“heavy menstrual bleeding” (10085423). Therefore, it might be the case that not all terms subordinate to the PT “heavy menstrual bleeding” have been considered in the MAH’s current search. Besides, the FIGO recommends not to use the term “menorrhagia” anymore.

In one sentence, the MAH mentions six instead of three cases of heavy menstrual bleeding in the study mRNA-1273-P203, probably a typographical error. The time to onset of menorrhagia is rather long in two of the three cases with apparently several regular cycles between vaccination and AEs. Thus, the causal relationship between HMB and vaccination is considered to be unlikely. Comment on the third case: Under hormonal contraception, withdrawal bleeding is usually weaker and lasts less long than natural menstruation. This side effect is perceived as beneficial by women with irregular or particularly heavy bleeding. Hormone preparations are also frequently used to treat polymenorrhea, i.e. a cycle lasting less than 25 days.

In its first report, with a data cutoff 04 May 2021, the MAH had identified six cases of heavy menstrual bleeding in study mRNA-1273-P301, five from the mRNA-1273 arm and one from the placebo arm. Now, according to the MAH, all 7,421 study participants aged between 18 and 55 years had been treated with mRNA-1273 and its Table 2 refers only to people vaccinated with mRNA-1273. Appendix 1 lists 7 females who reported their bleeding event after treatment with placebo. However, if these 7 patients were not included in the MAH’s Table 2, there were not 58 cases under 56 years of age. Presumably the MAH refers to all cases with bleeding events, including the 7 cases in which the event occurred before a vaccination with mRNA-1273.

Comment on Appendix 1, study mRNA-1273-P301: Appendix 1 lists five serious events in women in between 20s and 40s years of age. All these patients eventually underwent hysterectomy. TTO is very long and the causal association of the AEs and vaccination is considered to be unlikely.

Age [years]	Therapy	Dose number	Time to onset from last dose	Risk factor for heavy menstrual bleeding
adult	mRNA-1273	2	105	obesity
adult	mRNA-1273	2	214	uterine fibroids
adult	mRNA-1273	2	235	
adult	mRNA-1273	3*	146	sertraline
adult	unclear	2**	251	history of menorrhagia

Table 3: Serious events of menorrhagia or menometrorrhagia in study mRNA-1273-P301.

**The patient received both placebo and 100 µg mRNA-1273; since the event occurred after the booster vaccination and no placebo was administered in this study phase, the time to onset obviously refers to the booster vaccination. **The patient received both placebo and 100 µg mRNA-1273; it is unclear what the time to onset refers to.*

The age data in Appendix 1 show a median age of 42 years for all patients (n = 67, range 20-66) with a bleeding event, and 40.5 years (contradictory to the MAH’s Table 2) for patients aged 18-55 years (n = 58, range 20-54). 18 of 60 women with heavy menstrual bleeding after application of (presumably) Spikevax reported a time to onset of less than 36 days (dose 1: n = 4; dose 2: n = 7; dose 3: n = 7). The other females had at least one normal cycle between the vaccination and the onset of heavy menstrual bleeding. Of the patients aged 18 to 55 years, 7 had been last treated with placebo (dose 1: n = 1; dose 2: n = 6) and 41 with mRNA-1273 (dose 1: n = 3; dose 2: n = 23; dose 3: n = 15) before the bleeding event occurred. An additional 10 patients had received both placebo and mRNA-1273; it is not clear from the MAH’s table to which intervention the time to onset refers, but all events occurred after the second dose. For the 41 bleeding events clearly following the administration of mRNA-1273, the median time to onset was 90 days (range

1-431 days, 1st quartile 27 days, 3rd quartile 174 days). In summary, the data from clinical trials do not constitute a signal for heavy menstrual bleeding associated with Spikevax.

4.1.3. Item 3

"The MAH should provide an updated case review as per below:

- a. All serious cases of heavy menstrual bleeding
- b. All case reports of re-challenge of heavy menstrual bleeding with subsequent vaccination.
- c. The MAH should include in the case review also the cases in which there was concomitant use of other medicinal products (including concomitant use of contraceptives), or lack of information on medical history. Should confounders make a case "not assessable", a clear explanation should be provided.
- d. An assessment of the case reports according to UMC Causality assessment criteria.
- e. The MAH should justify the causality assessment, if "unlikely" or "non assessable, unclassifiable" is used."

MAH response:

4.1.3.1. Serious cases of heavy menstrual bleeding

The MAH states having reviewed cases of heavy menstrual bleeding derived from all sources. For the interval between 18 December 2020 and 18 June 2022, it searched for valid spontaneous reports from healthcare professionals, authorities, consumers, and literature. Search terms were "Spikevax" and the MedDRA version 24.1 PTs "heavy menstrual bleeding", "polymenorrhagia", and "menometrorrhagia". The MAH applied the FIGO-definition for heavy menstrual bleeding, which it describes as "excessive menstrual blood loss, which interferes with a woman's physical, social, emotional and/or material quality of life" and refers only to cyclic (ovulatory) menses. For causality assessment, the MAH employed the WHO-UMC system and, in the absence of an established risk window and biological plausibility, 60 days as an arbitrary upper limit for time to onset.

Observed to expected analyses. For observed to expected analyses, the same procedure as described in chapter 3.1.1.4 was applied: "To estimate a reporting rate, the number of doses of Spikevax administered globally [...] first was multiplied by 21 days to estimate exposed person-time. The count of cases was then divided by this person-time. In order to err on the side of a more conservative reporting rate estimate, all cases were included regardless of whether or not they fell during the 21 days following a dose of Spikevax. The age and gender stratified expected number of cases were calculated by multiplying the background incidence rate by the total person-years of estimated exposure accrued. The observed rate was then divided by the expected and presented with a 95% confidence interval." In addition, the MAH carried out sensitivity analyses on the assumption that only 50% or 25% of the actual cases of heavy menstrual bleeding were recorded in the Moderna global safety database.

Outcome	Person-years	Observed		Expected		As observed: RR (95% CI)	Assuming 50% of cases were reported: RR (95% CI)	Assuming 25% of cases were reported: RR (95% CI)
		Cases	Rate	Cases	Rate			
All	20,266,072	5,727	28.3	204,485	1009	0.03 (0.03, 0.03)	0.06 (0.05, 0.06)	0.11 (0.11, 0.11)
By age								
<12	29,304	2	6.8	130	442	0.02 (0, 0.06)	0.03 (0.01, 0.08)	0.06 (0.03, 0.13)
12-17	556,781	30	5.4	2,461	442	0.01 (0.01, 0.02)	0.02 (0.02, 0.03)	0.05 (0.04, 0.06)
18-24	2,369,832	527	22.2	10,285	434	0.05 (0.05, 0.06)	0.1 (0.1, 0.11)	0.2 (0.2, 0.21)
25-39	3,883,926	2,681	69.0	20,391	525	0.13 (0.13, 0.14)	0.26 (0.26, 0.27)	0.53 (0.51, 0.54)
40-49	3,822,515	1,670	43.7	138,375	3620	0.01 (0.01, 0.01)	0.02 (0.02, 0.02)	0.05 (0.05, 0.05)
50-64	4,901,232	427	8.7	177,425	3620	0 (0, 0)	0 (0, 0.01)	0.01 (0.01, 0.01)
65-74	3,171,105	2	0.1	114,794	3620	0 (0, 0)	0 (0, 0)	0 (0, 0)
75+	1,531,377	1	0.1	55,436	3620	0 (0, 0)	0 (0, 0)	0 (0, 0)

Table 4: Age-stratified observed to expected analysis of heavy menstrual bleeding as of 18 June 2022. The background incidences were taken from the study by Stahlman et al. [3].

Comment PRAC Co-Rapporteur:

Background incidence (ICD coded events) may underestimate the true incidence as not all concerned females may consult a healthcare professional.

Overview of cases. Cumulatively, through 18 June 2022, 5,791 cases (thereof 1,118 serious, 91 associated with hospitalization, 647 medically confirmed, and 5,594 from regulatory authorities) with 6,291 events (thereof 999 serious, and 6,090 under the PT heavy menstrual bleeding) were reported.

Age Group	# Cases	% Cases
<2	2	0.0
12-15	4	0.1
16-17	26	0.4
18-29	1,255	21.7
30-39	1,970	34.0
40-49	1,683	29.1
50-64	431	7.4
65-74	2	0.0
75+	1	0.0
Unknown	417	7.2
Grand total	5,791	100.0

Table 5: Age distribution of cases. Median age 37 years (range 0-81), mean age 36.7 years. (Note the two reports in children < 2 years are a reporting error of a NCA.)

The MAH received most cases from the European Economic area and the United Kingdom. The disproportionate reporting (EEA and for example USA) is notable.

Region	# Total Cases	% Total Cases
European Economic Area	4,122	71.2
United Kingdom	1,088	18.8
United States	400	6.9
Switzerland	143	2.5
Canada	21	0.4
Asia	14	0.2
Australia	1	0
Unknown	2	0
Grand total	5,791	100

Table 6: Distribution of cases by region.

In 46.6% of events, the dose number was unknown; global vaccination numbers by dose are also limited. Thus, as far as assessable, the MAH did not detect significant reporting differences by 1st and 2nd dose. The MAH gives the time to onset – under the condition that time to onset and dose number are known – as a mean of 15.3 days (standard deviation 83.5) and a median of 6.0 days.

Serious events. 915 serious cases reported 999 serious events; 91 of these cases involved hospitalization. According to the MAH, distribution by age, gender, source, and region of origin is similar to the cumulative distribution presented above. As far as can be specified under the above-mentioned limitations, more serious events were reported after the 1st than after subsequent vaccine doses. When time to onset and dose number were known, 60-68% of the serious events occurred within less than 14 days of vaccination for doses 1-3. The mean time to onset was 13.5 days (standard deviation 23.1), the median time to onset 7 days (range 0-372).

After medical review, 30 of the 915 serious cases were excluded: 13 after a different COVID-19 vaccine, 16 with non-menstrual bleeding (including one vaginal bleeding during pregnancy and 15 reports of postmenopausal bleeding), and one case was identified as a duplicate. 350 of the 885 cases had confounders, 419 cases lacked information on potential confounders, and two cases provided too little information for a causality assessment. The list of confounders included age (≥ 45 or < 18 years), coagulopathy, infections, endocrine disorders, hormonal therapy, a history of menstrual disorders, and structural causes.

The MAH points out the subjectivity of the FIGO definition of heavy menstrual bleeding. The patients' own perception does not reliably reflect the amount of blood loss. However, measuring blood loss required collecting and sending in all menstrual products, which the MAH considers cumbersome, expensive, and impractical in the post-marketing setting. Since there are many possible causes of heavy menstrual bleeding, sufficient information must be available, including age, medical and gynecological history, baseline characteristics of the menstrual cycle, concomitant medications, results of the diagnostic evaluation, treatment and response, and clinical course. The MAH notes that most of the reports had insufficient or missing information and case reports with none of the aforementioned information including time to onset of heavy menstrual bleeding and/or date of vaccination were assessed as "unassessable". Causality for reports where temporal association was present, with at least information on medical history and concomitant medication or results of at least one gynecologic diagnostic evaluation for heavy menstrual bleeding and one or more confounders was assessed as "possible", as well as causality for reports of recurrence of heavy menstrual bleeding after subsequent vaccination.

According to the WHO-UMC causality assessment, the MAH did not rate any of the 885 serious cases as "certain" or "probable". Because of the lack of clear biological plausibility, natural

background variation in menstrual cycle, lack of evidence of a full resolution of heavy menstrual bleeding prior to subsequent vaccination in most of the case reports, and incomplete and insufficient information needed to perform a comprehensive case and causality assessment to determine the presence or absence of other plausible alternate explanations for heavy menstrual bleeding, the MAH deemed causality “possible” even in the presence of elements of a positive rechallenge. It classified 75 cases as “possible” and 39 cases as “unlikely”, the latter based on other more likely causes of heavy menstrual bleeding and/or a time to onset greater than 60 days. The remaining 771 cases were categorized as “unassessable” due to insufficient evidence or missing data.

Comment PRAC Co-Rapporteur:

Heavy menstrual bleeding is defined as “excessive menstrual blood loss which interferes with the woman’s physical, emotional, social and material quality of life” [4,5]. A cyclic occurrence is not required by definition, but may provide clues to the underlying etiology. Nor is the term limited to ovulatory cycles. On the contrary, anovulatory cycles can be a reason for heavy menstrual bleeding, especially in adolescence or perimenopause. The “O” in PALM-COEIN stands for ovulatory dysfunction such as anovulation [4].

The PRAC Co-Rapporteur agrees with the MAH that actually measuring menstrual blood in the post-marketing setting is not really feasible. However, the exact amount of menstrual blood loss is not the key problem, but its consequences, such as fatigue, limitations in work and social life, and anemia. In the clinical trial as well as in the post-marketing setting, surveys might be conceivable, for example, with the help of pictorial methods, since these offer a good balance between ease of use and accuracy [6].

The MAH’s tabular case presentation (Appendix 2, pp. 23-106) is appreciated. It is striking that, in none of the 885 cases presented, the question about confounders is answered with “no”. Either the case lacks information or confounders are present. The categorization of the MAH that contraceptives are in general confounders is highly questionable and cannot be supported.

The data in Appendix 2 give a median age of 36 years (range 16-81 years, 1st quartile 30 years, 3rd quartile 43 years), and a median time to onset of 7 days (range 0-372 days, 1st quartile 1 day, 3rd quartile 17 days).

According to the MAH's analysis, 350 of the 885 serious cases have potential confounders, including age in 147 cases (≥ 45 years, $n = 146$ cases; 16 years, $n = 2$ cases; in the cases of one 40-49 and one >75 year old, reference is made to missing information and no confounder is mentioned, while in the case of a 30-39 year old, age is listed as a confounder), a heterologous vaccination schedule in 86 cases, and contraception in 80 cases. Unfortunately, the MAH does not always distinguish between different contraceptive products, such as hormonal contraception and the copper intrauterine device (IUD, $n = 2$).

4.1.3.2. Case reports of re-challenge of heavy menstrual bleeding with subsequent vaccination

The MAH emphasizes that the assessment of a positive rechallenge is complicated because of incomplete data regarding (i) the preceding menstrual characteristics, (ii) the duration of heavy menstrual bleeding, and (iii) the normalization of menstruation before revaccination. Furthermore, the short interval between the first and second vaccination is probably not sufficient to observe a recovery of menstrual bleeding before the subsequent vaccination. Therefore, when evaluating the rechallenge cases, the MAH focused on participants who reported having received at least three

doses of a COVID-19 vaccine as the timing of the 3rd dose is flexible. Of 784 case reports identified reporting three or more doses of a COVID-19 vaccine, 370 (47.2%) were unassessable and excluded because they were missing information on the dose that immediately preceded the initial report of heavy menstrual bleeding or on the outcome of the rechallenge or lack of clarity regarding whether a rechallenge was performed. Five (0.6%) cases did not report a rechallenge, 371 (47.3%) cases only reported one event of heavy menstrual bleeding with three doses of a COVID-19 vaccine and 38 (4.8%) cases reported recurrence of heavy menstrual bleeding on rechallenge. Most of these 38 cases reported heavy menstrual bleeding after all three COVID-19 vaccine doses. The MAH deemed causality "possible" for the majority (94.7%) of the cases, but assessed none as "certain" or "probable".

Category	Cases with recurrence of HMB, N (%)
Confounders	23 (60.5)
Heterologous Vaccination	16 (42.1)
Resolution of HMB prior to subsequent vaccination	6 (15.8)
Rechallenge	
Dose 3	13 (34.2)
Dose 2 and 3	25 (65.8)
Causality	
Possible	36 (94.7)
Unlikely	1 (2.6)
Unassessable	1 (2.6)

Table 7: Cases with three doses of a COVID-19 vaccine, reporting the recurrence of heavy menstrual bleeding after subsequent vaccination. Most of the individuals with heterologous vaccination had a non-company vaccine to complete the primary series and then got Spikevax as a booster.

In addition, the MAH also reviewed 54 cases that were coded in the global safety database as positive rechallenge cases, and the 915 serious cases. Of the total of 1501 cases reviewed, the MAH concludes that there was evidence of recurrent heavy menstrual bleeding in 69 cases. However, it judges the classification as true rechallenge cases to be very difficult in view of the natural variations in the menstrual cycle, the high background incidence of heavy menstrual bleeding and incomplete data in spontaneous reports.

Comment PRAC Co-Rapporteur:

The PRAC Co-Rapporteur is of the opinion that the mere lack of information on the outcome of the rechallenge does not allow a report to be classified as unassessable. The relevant factor is that the event occurred again and not necessarily whether it has (not) recovered/resolved. Events with unknown outcome must be considered in evaluations.

In their response, the MAH tabulates 69 cases of a positive rechallenge (38 cases of rechallenge of heavy menstrual bleeding after dose 1 and/or dose 2 with subsequent vaccination [dose 3 or dose 4], 21 serious cases of heavy menstrual bleeding with recurrence of heavy menstrual bleeding after subsequent vaccination, and 10 case reports coded as "rechallenge = yes" in the global safety database), with a median patient age of 36 years (range 20s-50s years, 1st quartile 29,5 years, 3rd quartile 43 years). Time to onset is given in 46 cases and ranges from 0 to 43 days (median 4 days, 1st quartile 1 day, 3rd quartile 18,5 days). In 67 cases, WHO-UMC causality was classified as "possible" and in one case each as "unlikely" and "unassessable". In 37 cases, the MAH recorded confounders, and in 32 cases, it considered the information provided to be insufficient. A heterologous vaccination regimen was specified as a confounder in 19 of the 32 cases, the patient's

age (≥ 45 years) in 11 cases, and hormonal contraception in 9 cases. However, whether and, if so, what role a heterologous COVID-19 vaccination regimen might play in the occurrence of menstrual disorders has not yet been determined. Besides, progesterone can help reduce heavy menstrual bleeding, as can a levonorgestrel-releasing intrauterine system [7,8]. A patient reported having an IUD with normally none to sparse menstruation. The MAH cannot consider this circumstance as a factor predisposing to heavy menstrual bleeding. Similarly, a report described having an "irregular menstruation cycle", an intrauterine device and "normally [...] no or hardly any bleeding". Some narratives are incomplete; apparently only the first paragraphs of the text are included in the table.

4.1.3.3. Case review including WHO-UMC causality assessment

The MAH refers to Appendix 2.

Comment PRAC Co-Rapporteur:

Causality is rated as possible in 75 cases, unlikely in 39 cases, and unassessable in all remaining 771 cases. The MAH attributes this to the fact that in most cases insufficient information was provided.

In general, it appears that information is very limited in the overall majority of the ICSRs and it is acknowledged that assessment is difficult without sufficient clinical information on previous menstrual cycles, last menstrual period, medical history and concomitant medication as well as potential individual stress factors.

The re-analysis of ICSRs did not provide additional evidence on the signal.

4.1.1. Item 4

"In addition to the above-mentioned review which should include all case narratives, the MAH should provide a table as specified below. The table should include all serious and/or positive rechallenge cases and information including the categories shown in the separate columns. The MAH can suggest additional columns, if deemed useful. Data from this table should be easily extractable for assessment.

The MAH should prioritize all ICSRs relating to this signal when handling the backlog of cases and report at the time of DLP.

The MAH should discuss the need for any potential management plan [sic] and make accordingly a proposal for changes to the relative sections within this discussion."

MAH response:

The MAH refers to Appendix 2 and Appendix 3.

Discussion. The MAH emphasizes that, with a reporting rate of 28.3 per 100,000 person-years, post-marketing cases of heavy menstrual bleeding were below those expected. The observed number of cases was lower than the expected number of cases with a rate ratio of 0.03 (95% CI 0.03, 0.03). There was also a geographical imbalance with cases reported predominantly from the European Economic Area (71.2%) and the United Kingdom (18.8%), whereas the highest exposure of Spikevax was in the USA. No ICSR was assessed as certain or probable according to UMC criteria. The majority of reports had missing critical information on baseline menstrual cycle characteristics and medical history.

The MAH points out that the events in clinical trials were mostly non-serious, transient and could be explained by other factors.

Consistent with the Netherlands Pharmacovigilance Centre Lareb report, the evaluation of a recurrence of heavy menstrual bleeding after subsequent vaccination was challenging, and only a small number of reports had sufficient information to make an assessment. Of the 784 cases reporting at least three doses of COVID-19 vaccine, a small percentage (4.8%) reported recurrence of heavy menstrual bleeding, however in the setting of natural variation in the menstrual cycle, high background incidence of heavy menstrual bleeding as well as lack of evidence of a full resolution of heavy menstrual bleeding prior to subsequent vaccination, the data do not support the suggestion that heavy menstrual bleeding with the subsequent vaccination is truly a positive rechallenge particularly given the incomplete data from spontaneous passive reports.

The MAH's literature review identified studies, but these were mostly cross-sectional and collected information using unvalidated questionnaires. As heavy menstrual bleeding is a common phenomenon, the menstrual cycle naturally varies and numerous causes can result in heavy menstrual bleeding, the lack of a comparator group or a self-controlled design make the results from these studies difficult to interpret. The MAH points to the recent systematic review by Nazir et al. [9] which included 78,138 women from 14 studies. 52.0% of these females reported some form of a menstrual problem after vaccination, most commonly menorrhagia, metrorrhagia, and polymenorrhea. The incidence rate of menstrual abnormalities varied widely from 0.83% to 90.9% across different studies evaluating all types of COVID-19 vaccine. As the authors point out, all of the studies are limited by lack of comparator groups and the heterogeneity in cohorts limits the generalizability of the results. The authors close that individuals subjected to COVID-19 vaccines may experience menstrual abnormalities, but that conclusions regarding the impact of COVID-19 vaccination on the menstrual cycle can only be drawn once more high-powered studies, such as randomized controlled trials or longitudinal prospective population-based studies, enrolling genetically and socioeconomically diverse populations, are conducted.

The MAH points out that although there have been reports of heavy menstrual bleeding after COVID-19 vaccination, it is important to note that normal variations exist within women over the lifespan and menstrual disturbances are common. Additionally, menstrual cycle features (such as bleeding volume) are subjective, not standardized, and collected by self-report which can introduce multiple biases including misclassification.

The MAH emphasizes that there are theoretical hypotheses, such as the immune response leading to changes in hormones or an endometrial inflammation mediated by immune cells in the lining of the uterus, but no clear biological plausibility and no evidence to demonstrate a causal association between menstrual disorders and vaccination.

A frequency with which women experience heavy menstrual bleeding after vaccination with Spikevax cannot be inferred from the published data. According to the MAH, as of 18 June 2022, 184,939,184 (27.9%) of all 662,871,167 Spikevax doses were administered in women of childbearing potential (12-49 years) worldwide. Compared to this figure and given the frequency of menstrual disorders, the number of reports of vaginal bleeding after vaccination is low. Therefore, the MAH did not identify a new safety concern. It does not consider a change to the reference safety information, labelling or risk management plan to be necessary. Events of heavy menstrual bleeding will continue to be monitored through routine pharmacovigilance activities.

Comment PRAC Co-Rapporteur:

Even though menstruation can be influenced by a wide variety of factors, the reporting women obviously noticed a marked difference after vaccination compared to before.

However, even in the case of serious events and/or positive rechallenge, causality apparently cannot be assessed in most cases mainly because of a lack of information. Furthermore, the reporting rate of heavy menstrual bleeding from clinical trials and post-marketing sources is not unexpected. In this context disproportionate reporting between EEA, UK and North America does not support the signal.

As already discussed, currently available studies are mostly subject to multiple biases and are not capable to provide evidence of an association between heavy menstrual bleeding and Spikevax. The PRAC Co-Rapporteur agrees with the MAH that the topic of heavy menstrual bleeding can only be meaningfully addressed in prospective studies and that the current evidence is insufficient to establish a (at least reasonable) causal association.

4.2. Co-Rapporteur's proposed recommendation

In summary, the MAH adequately responded to most of the PRAC's questions. A more detailed review and presentation of ways to integrate the topic of menstrual disorders into future study designs would have been desirable.

Exposure numbers in the mRNA-1273-P203 study are not provided. In this study with 12 to 17 year old individuals, an imbalance is probably not present given the 2:1 design and three reports of heavy menstrual bleeding in the mRNA-1273 arm (thereof two with implausible time to onset) versus none in the placebo arm.

The data from the study mRNA-1273-P301 do not constitute a signal of an increased risk of heavy menstrual bleeding, although there was no expedited reporting for this adverse event.

The MAH's observed versus expected analyses of the post-marketing data do not indicate an increased reporting of heavy menstrual bleeding. The review of individual cases contributes little to the knowledge on bleeding disorders after vaccination. Prospective studies on this subject are therefore indispensable. From the additional data presented, the PRAC Co-Rapporteur cannot conclude a risk of heavy menstrual bleeding after Spikevax that would warrant a change in the summary of product characteristics.

Recently, an analysis of prospectively collected data was published [10]. This study included 19,622 individuals, mostly younger than 35 years ($n = 15,713$) and from the UK, USA/Canada or Europe. 17.46% of the vaccinated cohort ($n = 2,608$) received Spikevax. In summary, vaccination against COVID-19 was associated with a small and likely to be temporary change in menstrual cycle length but no change in menses length. The intensity of the menstrual flow was not investigated, but at least the duration of bleeding was not prolonged. Another analysis of data collected by a menstrual cycle tracking smartphone application did not indicate "significant variations in the percentages of cycles with abnormal blood loss or pain intensity" [11]. However, the evaluations published to date are inconsistent in terms of their data quality, methodology and statements. So far, no clear conclusion can be drawn from them.

4.3. References

- [1] Curran D, Cabrera ES, Nelsen L. Patient-reported outcomes in vaccines research: relevance for decision-making. *Hum Vaccin Immunother* 2022;18(1):1–8. <https://doi.org/10.1080/21645515.2021.1875762>.
- [2] Subbiah IM, Williams LA, Peek A, Shete S, Granwehr BP, D'Achiardi D et al. Real-world patient-reported and clinical outcomes of BNT162b2 mRNA COVID-19 vaccine in patients with cancer. *JCO* 2021;39(15_suppl):6510. https://doi.org/10.1200/JCO.2021.39.15_SUPPL.6510.
- [3] Stahlman S, Williams VF, Taubman SB. Incidence and burden of gynecologic disorders, active component service women, U.S. Armed Forces, 2012–2016. *MSMR* 2017;24(11):30–8.
- [4] Munro MG, Critchley HOD, Fraser IS. The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions. *Int J Gynaecol Obstet* 2018;143(3):393–408. <https://doi.org/10.1002/ijgo.12666>.
- [5] Fraser IS, Critchley HOD, Broder M, Munro MG. The FIGO recommendations on terminologies and definitions for normal and abnormal uterine bleeding. *Semin Reprod Med* 2011;29(5):383–90. <https://doi.org/10.1055/s-0031-1287662>.
- [6] Magnay JL, O'Brien S, Gerlinger C, Seitz C. A systematic review of methods to measure menstrual blood loss. *BMC Womens Health* 2018;18(1):142. <https://doi.org/10.1186/s12905-018-0627-8>.
- [7] Kiseli M, Kayikcioglu F, Evliyaoglu O, Haberal A. Comparison of Therapeutic Efficacies of Norethisterone, Tranexamic Acid and Levonorgestrel-Releasing Intrauterine System for the Treatment of Heavy Menstrual Bleeding: A Randomized Controlled Study. *Gynecol Obstet Invest* 2016;81(5):447–53. <https://doi.org/10.1159/000443393>.
- [8] Creinin MD, Barnhart K, Gawron LM, Eisenberg D, Mabey RG, Jensen JT. Heavy Menstrual Bleeding Treatment With a Levonorgestrel 52-mg IUS [A116]. *Obstetrics & Gynecology* 2022;139(1):34S–34S. <https://doi.org/10.1097/01.AOG.0000825744.11181.29>.
- [9] Nazir M, Asghar S, Rathore MA, Shahzad A, Shahid A, Khan AA et al. Menstrual abnormalities after COVID-19 vaccines: A systematic review. *Vacunas* 2022. <https://doi.org/10.1016/j.vacun.2022.07.001>.
- [10] Edelman A, Boniface ER, Male V, Cameron ST, Benhar E, Han L et al. Association between menstrual cycle length and covid-19 vaccination: global, retrospective cohort study of prospectively collected data. *bmjmed* 2022;1(1):e000297. <https://doi.org/10.1136/bmjmed-2022-000297>.
- [11] Velasco-Regulez B, Fernandez-Marquez JL, Luqui N, Cerquides J, Lluís Arcos J, Fukelman A et al. Is the phase of the menstrual cycle relevant when getting the covid-19 vaccine? *Am J Obstet Gynecol* 2022. <https://doi.org/10.1016/j.ajog.2022.07.052>.

4.4. Comments from other member states

Comments from MS1, MS8, MS10, and the MS11

The four member states agreed with the PRAC Co-Rapporteur's assessment report.

Comment MS5

We thank the Rapporteur about this preliminary assessment report for the second round. However, MS5 does not agree with the conclusion from the Rapporteur assessment report and has additional comments.

In MS5, menstrual disorders following vaccination against Covid-19 are closely monitored and analysed since December 27, 2020 in the context of a national safety monitoring for all Covid-19 vaccines. **As of April 2022**, as described in table 1, an initial analysis regarding menstrual disorders had revealed 734 cases of haemorrhages with Spikevax (including 50 serious cases), of which **192** cases of "heavy menstrual bleeding" (12 serious cases) after vaccination with Spikevax. Of these 192 cases, **36 cases (18,8%) showed a positive rechallenge**. To note, 53% of

menstrual disorders cases were not resolved at the time of this first analysis.. This report regards available data from January 2021 to April 2022:

Table 8: Descriptions of menstrual haemorrhages cases reported cumulatively after vaccination with Spikevax (up to April 28, 2022)

	Non Serious cases	Serious cases	Total cases
Haemorrhages	684	50	734
Intermenstrual haemorrhage	245	19	264
Heavy menstrual bleeding	180	12	192
Menometrorrhagia	174	19	193
Polymenorrhoea	71	0	71
Vaginal haemorrhage	5	0	5
Postmenopausal haemorrhage	7	0	7
Abnormal uterine bleeding	1	0	1
Uterine haemorrhage	1	0	1

During the previous round in June 2022, in this context and after a qualitative and quantitative analysis of these cases, we supported the update of the SmPC and PL to add a warning regarding this risk (Comirnaty and Spikevax).

In parallel, we have collaborated for several months with various patients' associations and HCP representatives, including obstetrician-gynecologists specialists, to better quantify and characterise the events related to menstrual disorders following COVID-19 vaccination.

From these reports, as summarised in table 2, a new analysis regarding cases of menstrual disorders (reported **between 19 July 2022 and 1 September 2022**) has revealed 336 cases of haemorrhages (153 serious cases), including 182 cases of "heavy menstrual bleeding" (82 serious cases). Regarding these cases of heavy menstrual bleeding reported in MS5 during this period with Spikevax, 14 cases (7.6%) showed a positive rechallenge⁴.

Table 9: Descriptions of menstrual haemorrhages cases reported after vaccination with Spikevax (reported between July 19, 2022 to August 31, 2022)

	Non Serious cases	Serious cases	Total cases
Haemorrhages	183	153	336
Intermenstrual haemorrhage	29	23	52
Heavy menstrual bleeding	100	82	182
Menometrorrhagia	16	35	51
Polymenorrhoea	29	13	42
Vaginal haemorrhage	5	0	5
Abnormal uterine bleeding	1	0	1
Uterine haemorrhage	3	0	3

These data are still being analysed qualitatively and this is a preliminary analysis.

Moreover, we disagree with some points about the Rapporteur's assessment:

- The Rapporteur defines "heavy menstrual bleeding" as "excessive menstrual blood loss which interferes with the woman's physical, emotional, social and material quality of life" then writes that "menstrual cycle features (such as bleeding volume) are subjective, not standardized, and collected by self-report which can introduce multiple biases including misclassification".

It is acknowledged that "heavy menstrual bleeding" could be considered as subjective in nature and cannot be measured in practice by standard medical criteria. They can also strongly vary from one vaccinee to another and throughout the life course. However, it cannot preclude a scientific conclusion whether this effect can be considered as an ADR. In a general way, numerous ADRs can be considered as subjective in nature and can nevertheless be listed as ADR based on spontaneous reports (e.g. fatigue, nausea, dizziness, tinnitus, reactogenicity in small children).

- The Rapporteur states that there is no clear biological plausibility and no evidence to demonstrate a causal association between menstrual disorders and vaccination.

In our view, and in line with the Rapporteur for the signal with Comirnaty, the limited knowledge regarding the pathophysiological pathway is considered to neither strengthen nor weaken the signal.

Consequently, considering:

- the high number of reports (>4 000) on heavy menstrual bleeding,
- some of them requiring blood transfusion,
- dozens of reported cases with with positive rechallenge, even assessed by the MAH as "possible" (67 cases),
- two major studies (Trogstad and Caspensen) pointing towards an association with heavy menstrual bleeding.

MS5 considers that the available data supports at least a reasonable possibility of a causal association between heavy menstrual bleeding and the vaccination with Spikevax, the SmPC and PIL should be updated to reflect current knowledge, adding "heavy menstrual bleeding" to section 4.8.

Considering the uncertainties in the mechanism of action, the number of cases with both Spikevax and Comirnaty and heterologous vaccination patterns, such information should also be added in the SmPC of Comirnaty.

Comment PRAC Co-Rapporteur:

The PRAC Co-Rapporteur thanks MS5 for the detailed feedback and agrees with parts of its arguments. For example, in section 4.1.1, the PRAC Co-Rapporteur had addressed the need to include subjective variables, which is now a standard part of many clinical studies.

However, the definition of heavy menstrual bleeding as “a volume that interferes with the patient's physical, social, emotional, and/or material quality of life” does not originate from the PRAC Co-Rapporteur's considerations, but corresponds to a generally accepted one (FIGO definition). The quote “menstrual cycle features (such as bleeding volume) are subjective, not standardized, and collected by self-report which can introduce multiple biases including misclassification” is from chapters 3.1.1.7 and 4.1.1, which both summarise the conclusions of the MAH and do **not** reflect those of the PRAC Co-Rapporteur. The statement about biological plausibility also comes from the MAH and **not** from the PRAC Co-Rapporteur. The PRAC Co-Rapporteur's comments are either in the boxes at the end of the chapters or in the chapters provided for this purpose. Other formatting measures may need to be considered so that a clearer distinction can be made between the MAH's argumentation and the PRAC Co-Rapporteur's assessment, thus avoiding such misunderstandings.

Despite the identification of cases of a positive rechallenge, it is obviously difficult to specifically attribute the occurrence of heavy menstrual bleeding to the application of mRNA vaccines. Heavy menstrual bleeding is a common phenomenon, and apparently the data quality in spontaneous reports often does not allow a sufficient assessment of the situation. Considering the extensive exposure to Spikevax, spontaneous reports of heavy menstrual bleeding (including rechallenge case reports) are per se not unexpected.

The PRAC Co-Rapporteur believes that menstrual characteristics can and should be included in future clinical studies. Then, the actual incidence could be better estimated. Also, one would gain knowledge whether and how often menstrual disorders also occur after other, non-mRNA vaccinations (cf. publications on vaccinations against human papillomavirus, poliovirus, and typhoid fever, <https://doi.org/10.1016/j.pvr.2018.02.002>, <https://doi.org/10.5694/j.1326-5377.1958.tb58387.x>, and doi:10.1001/archinte.1913.00070050082008, respectively).

Comment MS6

The conclusion of assessment of the MAH and endorsed by Co-rapporteur is that the available evidence is insufficient to establish a causal relationship between heavy menstrual bleeding and Spikevax. We do not agree with this assessment.

Regarding the evaluation of the postmarketing reports, we find the MAH's causality assessment to be too strict and evaluation of the possible alternative explanations to be too exclusive. For example, it seems that use of an oral hormonal contraception, a hormonal IUD or an SSRI has categorically been evaluated to be a plausible alternative explanation/confounder for heavy menstrual bleeding, without an evaluation on how long the treatment has been used. If the patient has been using the same hormonal contraception or an SSRI for a longer period, we consider it to be quite unlikely cause for a sudden change in the menstrual pattern. Also, concomitant medical condition of hypothyroidism has been assessed as an alternative explanation, although if the diagnosis is not recent, these patients are likely euthyreotic due to substitution therapy. Further, also a heterologous vaccination has been assessed to be a confounder although, as the Co-rapporteur pointed out, it has not yet been determined what role, if any, a heterologous COVID-19 vaccination regimen might play in the occurrence of menstrual disorders. Therefore we consider that the analysis by the MAH cannot be considered to support the absence of causality.

The MAH has identified 69 cases of a positive rechallenge. According to the table 7, it seems that in 25 reports with rechallenge, heavy menstrual bleeding has occurred after all three COVID-19 vaccine doses, further supporting a causal relationship. We disagree with the MAH that medical and gynecological history including baseline menstrual cycle characteristics, diagnostic evaluation and treatment are critical for evaluation in all these cases, since a pattern can be seen even without full

details. Below are a few examples of reports we consider to support positive causality even though they lack details:

- : an adult female reported that after each dose of the vaccine, the following monthly menstrual cycle has been very severe. Much more severe cramping, much more bleeding and clotting, the cramps and heaviness of flow almost debilitating. Cycle usually returns to normal the following month.
- : an adult female patient experienced heavier menstruation after 1st, 2nd and 3rd vaccination in the period after. Has an IUD with normally none to sparse menstruation. The patient had no other reported health issues.
- : an adult female had heavy periods for two months following each one of the 3 vaccinations
- : an adult female experienced heavy menstrual bleeding approximately 21 days after the third dose. The period came at the same time as normal, but it was a far heavier period than usual. The same happened with the periods following both the first and the second dose of the vaccine.
- : an adult female patient reported having heavy periods after two vaccinations (Astra Zeneca). Finished her period and received third dose of Moderna vaccine on the same day and then started bleeding heavily two days later.

We think that the conclusion by the MAH and the PRAC Co-rapporteur sets the bar for establishment of causality and inclusion in the product information too high. There are >5700 reports of heavy menstrual bleeding for Spikevax, with an average TTO of 15.3 days and a median TTO of 6.0 days. We think that the relatively short TTO supports more the likelihood of causality with Spikevax than a co-incidental event. Also, the review of rechallenge cases supports causality, as even with lack of all details it shows that in many cases the women have experienced the same kind of menstrual symptom after two or three vaccinations. Overall, we consider that there is at least a reasonable possibility of a causal association and that "heavy menstrual bleeding" should be listed in section 4.8 of the SmPC for Spikevax.

Comment PRAC Co-Rapporteur:

The PRAC Co-Rapporteur appreciates the detailed feedback including excerpts of exemplary narratives. It also criticised the overall classification of possible confounders and the categorisation of several cases by the MAH.

It is acknowledged that ICSR causality assessment has a subjective element and that assessment of the same ICSRs may vary among different assessors. In order to strengthen individual causality assessment of adverse events following immunization (AEFI), WHO has developed an algorithm which is different from the UMC criteria. The different approaches of ICSR causality assessment show the difficulty of consistent assessment of spontaneous reports which frequently lack important medical information.

A re-discussion of the issue in the PRAC seems to be necessary in order to decide whether the available evidence is sufficient to require an update of the SmPC and PIL.

Comment MS2

The conclusion of the MAH, which is endorsed by PRAC Co-Rapporteur, is that the current evidence is insufficient to establish a causal relationship between heavy menstrual bleeding and Spikevax. We are of the opinion that at least reasonable causal association has been already provided.

We support the Co-Rapp's view that medicine and health encompass numerous subjective aspects that should be taken into account together with objectively measurable parameters. We would like to remind that subjective measures were taken into account when new ADRs relating to pain or paraesthesia were assessed after the vaccination. **In these cases, the information was also collected only after a vaccination event** with the difficulty to interpret it. Moreover, medical confirmation of these subjective symptoms does not increase credibility of patients' reports, because in this situation the physician can only confirm what the patient told him. Similarly in the case of heavy menstrual bleeding, the predominant patients' reports should not be a reason for rejection of this problem. The role of patient cases is significantly more important in situations, where causal relationship cannot be established based on the confirmed cases because of the nature of condition.

The review of clinical trial mRNA-1273-P201 data identified 58 cases (from 7421 women, i.e. 0,8 %) of heavy menstrual bleeding in active arm vs. 7 cases (from remaining 5831 women, i.e. 0,1 %) from placebo arm. However, the MAH did not discuss this numerical imbalance and its statistical significance, even when the increase of the percentage of heavy menstrual bleeding in active arm versus placebo is evident. Additionally, the choice of the LLT MedDRA term ("menorrhagia") and omitting the superior PT MedDRA term ("heavy menstrual bleeding") predispose the results of heavy menstrual bleeding to be underestimated. In the 18 cases of heavy menstrual bleeding reported by women in active arm, the TTO was lower than 36 days. There is no information about TTO in placebo arm. **We are of the opinion that the available data from clinical trial support the reasonable causal association between the heavy menstrual bleeding and vaccination with Spikevax.**

We would like to remind the supportive data and significant statistical results from the study of Trogstad et al. (commented in the first round of the signal). This study was focusing on number of menstrual disorders. For reduction of bias of awareness at the menstrual disorders, the questionnaire included several topics not related to menstruation to be answered prior to the questions of menstrual disorders. This study assessed 5688 Norwegian women aged 18-30 year and **the data of individuals before and after vaccination was compared.** The self-control case series design is described as a suitable design for investigation of vaccines. The bias between a case and a control caused by inter-individual differences is minimized using this type of study. When the exposure to vaccines is high in a general population, it could be expected that the populations of vaccinated and unvaccinated women are considerably different, and comparison of these groups could be less suitable. The selection bias was minimized by random assorting of women from another ongoing population study. Therefore, inclusion of women was not driven by the existing menstrual disorders following vaccination. The recall bias was significantly solved by the app which was used by almost 60% of women. **Specifically for the Spikevax, the study identified heavier menstrual bleeding after first dose of Spikevax with relative risk 1.86 (95% CI 1.54 to 2.26) and after second dose of Spikevax with relative risk 1.92 (1.67 to 2.21). The prevalence of heavy menstrual bleeding was only 7.6 % prior to first dose of COVID-19 vaccination in comparison with 13.6 % in the first cycle after COVID-19 vaccination and similarly 8.2 % prior to second dose of COVID-19 vaccination in comparison with 15.3 % after second dose of COVID-19 vaccination.** We are of the opinion that these findings from the literature should be taken into consideration.

Regarding to spontaneous reports, there are 5791 reported cases, from which 647 were medically confirmed (11,2 %), 1118 serious (19,3 %) and 91 cases with hospitalized patients (1,6%). Unfortunately, the MAH assesses the spontaneous reports in a questionable way; i.e. no information was provided to the TTO without knowing the specific number of dose used or no case

of positive rechallenge was assessed if the outcome of the positive rechallenge was unknown. We agree with the Co-Rapp that it is not necessary to know the outcome of the rechallenge to conclude that the rechallenge has already occurred. Unfortunately, no assessment of medically confirmed and non-serious cases which could give more information was provided. **The majority of reported cases are non-serious but still unexpected according to SmPC of Spikevax.** The MAH's assessment is still lacking the detailed discussion and information.

We agree with Co-Rapp that even though menstruation can be influenced by a wide variety of factors, the reporting women obviously noticed a marked difference after vaccination compared to before. Overall, we are of the opinion that the imbalance of clinical data and data from literature **indicate at least a reasonable possibility of causal relationship between heavy menstrual bleeding and Spikevax** vaccination.

Therefore, member state 4 proposes update of PI with the ADR heavy menstrual bleeding with the frequency unknown:

Text for SmPC

Section 4.8, frequency unknown: Heavy menstrual bleeding.

Text for PIL

Section 4 (possible side effects), frequency unknown: Heavy menstrual bleeding

Comment PRAC Co-Rapporteur:

The PRAC Co-Rapporteur values this thorough feedback. Ultimately, the majority of studies on heavy menstrual bleeding are retrospective surveys, which are subject to several biases. In the study "Increased Occurrence of Menstrual Disturbances in 18- to 30-Year-Old Women after COVID-19 Vaccination" by Trogstad et al., the participants were part of an already ongoing cohort study. 52.2% (first dose) and 52.8% (second dose) of the women documented their cycle using an app. This rules out a major selection bias, but not a recall bias.

Menstrual disorders have been described not only for mRNA vaccines but also for vector vaccines against COVID-19 (and in the past also for non-COVID vaccines). Thus, a general reaction to the immune stimulus may be assumed rather than a specific side effect of mRNA-containing products. In view of scientific uncertainties, the PRAC Co-Rapporteur is of the opinion that the evidence is not sufficient to distinguish between causal and coincident effects.

Whether it is proportionate to include one specific disorder – heavy menstrual bleeding – for mRNA vaccines only must be decided by PRAC.

In case PRAC would decide to label heavy menstrual bleeding, the Co-Rapporteur is of the opinion that it is important to point out that usually heavy menstrual bleeding events are non-serious and transient. In our view this would be important to avoid that women with long-lasting symptoms may believe in a vaccine effect and may therefore not consult a gynaecologist in due time with the consequence of potential delayed diagnosis of other underlying diseases.

Comment MS7

The PRAC Co-Rapporteur's conclusion is not endorsed. The Co-Rapporteur emphasizes the O/E-analysis, the challenges caused by limited information in the majority of the ICSRs and the study by Edelman et al.

Regarding ICSRs: Taking into account the nature of the reaction (reported from patients, being subjective) a high level of detailed information is not always realistic. Therefore, the bar for what the ICSRs must contain in order to be assessed is set unrealistically high from a medical point of view. According to the MAH, "most of the 38 cases" in which women received 3 doses of vaccination reported a heavy menstrual bleeding after each of 3 doses of vaccination. As such cases are normally considered to strongly indicate a causal association, a further discussion on these cases would have been useful.

O/E-analysis: The MAH has provided an O/E-analysis, which was not requested by the PRAC, but was nevertheless assessed by the PRAC Co-Rapporteur. We consider that the value of an O/E-analysis at this stage of the assessment for this particular signal is limited. An O/E-analysis is primarily used as a tool for signal detection and preliminary signal evaluation, and at present less emphasis should be made on this method.

The publication by Edelman: The PRAC Co-Rapporteur discusses the study by Edelman et al in their recommendation section however this study did not evaluate heavy menstrual bleeding and is therefore of less relevance.

Overall, we maintain our position that there is "at least a reasonable possibility" of a causal association, and thus the SmPC should be updated in accordance with the SmPC Guideline.

Comment PRAC Co-Rapporteur:

The O/E analysis indeed needs to be interpreted with caution, as it tends to underestimate the SMR (background rate based on medical visits which is known to reflect only a subset of heavy menstrual bleeding cases). Thus, the O/E analysis provides a flavour that reported number of cases are within the expected range.

The publication of Edelman et al. was cited because (in addition to mentioning the first study from the United States by Edelman et al. in the first round of questions) it includes a large number (n = 19,622) of participants of childbearing age and a comparison is made between vaccinated (n = 14,936) and unvaccinated (n = 4,686) individuals. In fact, the extent of blood flow was not investigated. However, heavy menstrual bleeding is often associated with prolonged menses, so the study is not entirely irrelevant in the context of the present signal. The larger study confirmed the result of the first study by Edelman et al based on United States data. The result showed a slightly longer menstrual cycle in particular in females with two vaccinations in one cycle. Observed changes were similar across different vaccine types and not only related to mRNA vaccines. Changes were resolved as soon as the next cycle after vaccine receipt. Thus, results of the study are reassuring with regard to the impact of COVID-19 vaccination on menstrual cycle length. Besides, we rate the data quality of the study higher than that of numerous retrospective surveys and cross-sectional studies.

Comment MS4

Although evidence to demonstrate an association between Spikevax and heavy menstrual bleeding is not very strong, such association cannot be completely excluded. After considering epidemiological data, some well-described cases and the cases with positive rechallenge, member

state 9 considers that a causal association is reasonably possible and that “heavy menstrual bleeding” should be included in 4.8.

Comment PRAC Co-Rapporteur:

We agree that the signal of heavy menstrual bleeding is not very strong. The argument that an association cannot be excluded cannot (in our view) justify labelling. However, the weight of the evidence needs to be discussed by PRAC.

Comment MS3

After a careful review of the updated data presented regarding this procedure, MS3 does not endorse the conclusions reached by the co-Rapporteur.

In one hand, clinical trials data is inconclusive. In the study conducted in adults participants (NCT04470427), it seems that 58 cases of HMB were reported in participants that received mRNA-1273 in phase A (randomly assignment to receive either mRNA-1273 or placebo control) or B (offer patients receiving placebo in phase A to request and receive mRNA-1273) of the study without further distinction between arms or study phases. However, in Annex I presented by the MAH there are HMB cases reported in placebo arm (7), mRNA-1273 arm (39) and in phase B of the study (patients receiving placebo followed by mRNA-1273) (24), which does not match the 58 cases initially reported by the MAH. The assessor does not consider that the 7 cases reported in the placebo arm are taken into account in the 58 cases initially reported by the MAH. Nevertheless, considering the presentation of the data, it is not possible to evaluate a possible imbalance between arms.

In the other hand, the assessor acknowledges the limitations of postmarketing data, as it is already known. There are at least 38 cases reporting positive rechallenge in patients that had at least 3 doses reported. Although cases where only 2 doses are reported may also show positive rechallenge. Therefore, it is unclear why the search took into account from 3 doses onwards. The MAH considered that the majority of cases had causality “possible”, but assessed none as “certain” or “probable”. However, according to the WHO-UMC causality criteria, if rechallenge information is available and there is no information on confounders, causality can be considered “certain” or “probable/likely”. This may be the case for at least 50% of these cases since there are 60.5% of the cases with confounders and 2 considered unlikely and unassessable by the MAH. In addition, the MAH identified 21 serious cases of HMB with recurrence of HMB after subsequent vaccination and 10 cases reported as “rechallenge=yes” in the global safety database. All this make a total of 69 cases reported with positive rechallenge.

The MAH discussed the difficulty of assessing rechallenge, nevertheless there are cases in which the patient is clearly reporting the vaccine doses after which has suffered HMB (e.g., case in which patient reported HMB specifically after 1st and 3rd dose) and this information should not be undermined based on the natural background variation in menstrual cycle or lack of evidence of a full resolution of HMB prior to subsequent vaccination or incomplete data.

Furthermore, the number of cases of HMB keeps raising compared to the information previously provided by the MAH (section 3.1.1.4. of the AR). Lastly, regarding serious cases, the information is difficult to analyse. The MAH initially refers to 915 cases of which 91 were related to hospitalisation (seriousness criteria not stated for the remaining). After that, 30 are excluded due to other COVID-19 vaccine used, non-menstrual bleeding, limited information and case duplication. Of the remaining 885 cases, 350 are confounded and the other 533 serious cases are not discussed by the MAH, only the line listings and narratives are provided, precluding the analysis.

A cross-sectional study published by Baena et al that included 14 153 women who had received the full course of vaccination at least three months earlier. Of them, 11 017 (78%) reported menstrual changes. The main menstrual change reported was "more menstrual bleeding" (43%), followed by "more menstrual pain" (41.2%). "More or larger clots" was also reported (29.1%). Although self-reported, the study was conducted shortly after the second dose of the vaccine administered, so the risk of recall bias in the participants is lower compared to other similar studies. In addition, Nazir et al conducted a systematic review that included 14 observational studies (3 cohorts and 11 cross-sectional) and 78 138 vaccinated females, presented by the MAH. Of them, 39 759 women (52.05%) showed menstrual disorders. Menorrhagia, metrorrhagia and polymenorrhea were the most commonly reported problems. The author also mentions that although the studies themselves may have selection and recall bias due to the retrospective and self-reporting nature, prospective studies also provide similar insights into this phenomenon. The authors close that individuals subjected to COVID-19 vaccines may experience menstrual abnormalities, but that conclusions regarding the impact of COVID-19 vaccination on the menstrual cycle can only be drawn once more high-powered studies, such as randomized controlled trials or longitudinal prospective population-based studies, enrolling genetically and socioeconomically diverse populations, are conducted. For this reason, the MAH should also make efforts to conduct observational studies, exploring different data sources and study designs that may allow to collect data from pre and postvaccination intervals (electronic healthcare record databases where patients with vaccination data is available should also be explored), instead of only awaiting data from third parties independent investigators.

As mentioned by the co-Rapp in the report, "even though menstruation can be influenced by a wide variety of factors, the reporting women obviously noticed a marked difference after vaccination compared to before". The available post-marketing and literature data support the idea of at least a reasonable possibility of a causal relationship between HMB and Spikevax vaccination. Therefore, MS3 suggests that changes in the product information are warranted and HMB should be included in section 4.8 of the SmPC with unknown frequency. The PIL should be updated accordingly.

Comment PRAC Co-Rapporteur:

The PRAC Co-Rapporteur would like to clarify the following points: **the response from the MAH** lists a total of **67 cases** of heavy menstrual bleeding in study participants **between 20 and 66 years old**. Of these, heavy menstrual bleeding occurred in 7 participants after administration of placebo, in 31 after the 1st or 2nd administration of mRNA-1273, and in 6 after the 3rd dose of mRNA-1273. 23 individuals had received both placebo and mRNA-1273; in 12 cases, heavy menstrual bleeding occurred after the 1st or 2nd dose (unclear whether after placebo or mRNA-1273), and in the remaining 11 cases, after the 3rd dose. Since no 3rd dose of placebo was administered in study mRNA-1273-P301, these 11 cases must refer to the administration of mRNA-1273. The 58 participants in **Table 2** represent a subgroup, namely those aged **up to 55 years**. Appendix 1 also lists 58 women up to 55 years of age, so the numbers do match. The 7 placebo-treated females are included here. We noted that "However, if these 7 patients were not included in the MAH's Table 2, there were not 58 cases under 56 years of age. Presumably the MAH refers to all cases with bleeding events, including the 7 cases in which the event occurred before a vaccination with mRNA-1273". We can therefore not follow MS3 objection at this point.

Unfortunately, the data provided is ambiguous, which we had already criticised in our assessment – in some cases it is not clear whether the event occurred after placebo or mRNA-1273. A clear imbalance cannot be inferred from the data, because the follow-up time was certainly longer after mRNA-1273 application than after placebo administration. Ultimately, all 58 women under 56 years

of age had received mRNA-1273, and events were attributed to the most recent intervention. For the 58 participants aged between 18 and 55 years, the MAH gives an exposure of 7,220.96 person-years. This translates into an annual incidence of 803/100,000 women, which at a median age of 40.5 years is within the range expected according to the publication by Stahlman et al. In the entire group of 67 participants who experienced heavy menstrual bleeding, the median TTO was 49 days (n = 7; range, 20-179 days; TTO > 35 days in 5 of 7 cases [71%]) for events after placebo, and 87.5 days (n = 48; range, 1-431 days; TTO > 35 days [that means apparently one normal cycle between vaccination and event] in 34 of 48 cases [71%]) for events following mRNA-1273.

For the 69 cases of a positive rechallenge, please refer to section 4.1.3.2. Even though the PRAC had asked for a WHO-UMC causality assessment, we would like to recall the criteria for the assessment of adverse events following immunisation (<https://www.who.int/publications/i/item/9789241516990>).

In the study by Baena-García L et al., “adenovirus vectored COVID-19 vaccines seem[ed] to be more associated with changes in the menstrual cycle than mRNA vaccines”. An interesting point in the study by Baena-García L et al. is that 34.5% of patients described shorter menses and 21.1% described longer menses, which is actually counterintuitive to the most commonly reported more menstrual bleeding (43.3% of respondents). Less menstrual bleeding was observed by only 22.7% of the women. We agree with the comment by Marques TA, doi.org/10.1177/17455057221129395, that the study is prone to bias and that the same objections apply as for other retrospective surveys, despite the large number of 14,153 participants.

In an observational cohort study with COVID-19 vaccine recipients who reported their health experiences to v-safe in the United States (Wong KK et al., [doi.org/10.1016/S2589-7500\(22\)00125-X](https://doi.org/10.1016/S2589-7500(22)00125-X)), 62,679 women, i.e. 1.0% of a total of 5,975,363 female respondents, reported on menstrual irregularities or vaginal bleeding. Peri- and postmenopausal bleeding after COVID-19 vaccination occurred, but, as the authors discuss, “it is unknown whether this bleeding represents a transient benign event, an event that unmasks pre-existing pathology (e.g., cancer or polyps), or a purely coincidental event”.

Results of studies on possible effects of COVID-19 vaccination on menstruation, funded by the National Institutes of Health, are not yet available.

In fact, we believe that an immune stimulus such as a vaccination in general may trigger menstrual changes – just like infections, stress and other events. However, the publications to date do not consistently show that COVID-19 is associated with menstrual changes including heavy menstrual bleeding nor that menstrual changes are a characteristic of mRNA vaccines.

In the past, reports of menstrual disorders after non-COVID vaccines triggered some investigations. But there was little discussion on this issue compared to the current situation which is characterised by extensive exposure and high media attention.

We propose to discuss heavy menstrual bleeding and the need for a change in the SmPC in the PRAC. Whether or not it will be included in the product information, it will be important to communicate that postmenopausal bleeding and longer-lasting menstrual disorders in premenopausal women must continue to be a trigger for presentation to the gynaecologist and further investigation.

4.5. Updated Rapporteurs recommendation

In the view of the PRAC Co-Rapporteur, most currently available studies are subject to multiple biases and are not capable to provide evidence of an association between heavy menstrual bleeding and Spikevax. Various menstrual disorders, not only heavy menstrual bleeding, have been reported. Besides, there is no evidence that menstrual changes occur specifically with mRNA vaccines.

The MAH is kindly asked to provide a follow-up of available data in subsequent PSURs.

We propose to discuss the issue of heavy menstrual bleeding and the need for a change in the SmPC in the PRAC. Whether or not it will be included in the product information, it will be important to communicate that postmenopausal bleeding and longer-lasting menstrual disorders in premenopausal women must continue to be a trigger for presentation to the gynaecologist and further investigation.

4.6. Adopted PRAC recommendation

Having considered all the available evidence including spontaneous case reports in EudraVigilance, data from national reviews, observational studies, and provided by the Marketing Authorisation Holder (MAH), the PRAC has agreed that the MAH for COVID-19 mRNA vaccine (nucleoside-modified) Spikevax (Moderna Biotech Spain, S.L.) should submit by 25 November 2022 a variation to amend the product information as described below (new text underlined):

Summary of Product Characteristics

Section 4.8 Undesirable effects

System Organ Class: Reproductive system and breast disorders

[Frequency] Not known: Heavy menstrual bleeding*

[Under table] * Most cases appeared to be non-serious and temporary in nature.

Package leaflet

Section 4 - Possible side effects

Not known (cannot be estimated from the available data):

- Heavy menstrual bleeding (most cases appeared to be non-serious and temporary in nature)