NOT FOR PUBLICATION

COMMISSION ON HUMAN MEDICINES

PHARMACOVIGILANCE EXPERT ADVISORY GROUP

Title of paper: COVID-19 VACCINE SAFETY SURVEILLANCE STRATEGY: UPDATE ON THE YELLOW CARD VACCINE MONITOR **Type of paper:** For advice	
Active(s) rINN	COVID-19 Vaccine AstraZeneca solution for injection COVID-19 Vaccine (ChAdOx1 S [recombinant]) BNT162b2 COVID-19 mRNA Vaccine (nucleoside modified)
Product name(s)	Pfizer-BioNTech COVID-19 vaccine Oxford-AstraZeneca COVID-19 vaccine Moderna COVID-19 vaccine
Marketing Authorisation Holder(s)	Pfizer-BioNTech AstraZeneca Moderna
Legal status	Prescription only medicines
Therapeutic classification (ATC code)	Vaccines, other viral vaccines ATC code: J07BX03
Previous assessments	NA
Assessor(s)	[redacted] Name: Katherine Donegan Email: katherine.donegan@mhra.gov.uk

COVID-19 VACCINE SAFETY SURVEILLANCE STRATEGY: UPDATE ON THE YELLOW CARD VACCINE MONITOR

Issue

1. This paper provides an update on the Yellow Card Vaccine Monitor active surveillance activity, including an overview of registered individuals and analysis of data to date. The PEAGs advice is sought on the data presented, opportunities for further use of the data, and any communications that would be appropriate at this time.

Background

2. In May 2020, the COVID-19 Vaccine Safety Surveillance Expert Working Group (EWG) advised the Medicines and Healthcare products Regulatory Agency (MHRA) on its safety monitoring strategy for COVID-19 vaccine(s). The EWG considered proposals and methodologies for MHRA-led vigilance activities and based on this advice the MHRA developed a four-stranded approach to vigilance which was endorsed by the Commission on Human Medicines[1]. One strand related to targeted active monitoring of vaccinees.

3. Through the call/recall system, which the NHS has used to invite people to register to receive a vaccine, a random selection of vaccinees have been invited to voluntarily register for follow-up via a platform called the Yellow Card Vaccine Monitor (YCVM).

4. This vigilance activity sought enrolment prior to vaccination (and thereby before any suspected side effect is experienced) and vaccinees are then contacted at set intervals (for example 7 days, 14 days, 3-6 months) to ask whether any adverse reaction occurred.

5. In comparison to spontaneous Yellow Card reporting, which helps to detect new signals, the strength of active monitoring is that it helps to estimate the frequency of common reactions and make comparisons across different sub-populations in a real world setting. Active monitoring also allows collection of data on longer term outcomes of side effects since we receive updates from individuals over time.

6. Over 82 million doses of COVID-19 vaccines have now been administered across the UK over 7 months and we have used the data captured through the methods implemented within our strategy to rapidly detect, confirm, characterise and quantify new risks, communicating on these as necessary. The YCVM has played a role in this process.

7. As the vaccination campaign potentially moves to children and adolescents with likely booster or variant vaccinations in the autumn, we will need to reflect on the YCVM activities conducted to date and consider whether any changes are needed to meet future phases of the vaccination campaign. Advice will be sought from VBR-EWG on updates to the strategy to address this need at a future meeting.

Uptake to the Yellow Card Vaccine Monitor

[1] https://www.gov.uk/government/publications/report-of-the-commission-on-human-medicines-expert-working-group-on-covid-19-vaccine-safety-surveillance/report-of-the-commission-on-human-medicines-expert-working-group-on-covid-19-vaccine-safety-surveillance

8. Up to, and including, 30th June 2021 the MHRA have invited nearly 600,000 people to the YCVM. Of these, 29,832 individuals have subsequently registered, which is an uptake rate of 4.8%. We aimed to enrol similar numbers of individuals as used in clinical trials and these numbers demonstrate that we have achieved this. Further, we are seeing a 70% response rate to follow up requests which is important in fulfilling the aims of this activity for long term data collection.

9. Table 1 shows that nearly 30,000 individuals have registered with the YCVM. Just over twice as many individuals registered have received the AstraZeneca vaccine compared to Pfizer despite similar numbers of first doses of the two vaccines being administered in the population. This is in the main part due to the timing of invitations being sent out. A small proportion of the cohort has received the Moderna vaccine. Approximately 5,000 individuals have registered with YCVM but have not submitted any vaccination data to date.

Table 1. Yellow Card Vaccine Monitor Registrations (as at 30th June 2021)

	Pfizer-BioNTech	**Oxford AstraZeneca**	**Moderna**	**Brand unspecified**	**Registered but no vaccine reported**	**Total**
Number of registrations	7,679	16,167	425	340	5,221	29,832

10. Table 2 compares the characteristics of individuals registered with the Yellow Card Vaccine Monitor stratified by those reporting vaccination data ("responders") compared with those who have registered but have not recorded any vaccination data to date ("non-responders"). This was carried out to see if there was a difference in individuals who are being lost to follow up.

11. Overall, there does not appear to be any particular differences in the demographics of those who register and provide data to the YCVM compared to those who register but who do not. The proportion of "responders" who are male is similar to the proportion of "non-responders". Similarly, the age distribution and proportion of those who consider themselves immunocompromised[2] are similar across the two groups.

12. With regards to ethnicity, non-white ethnicities have been grouped as a single category due to small numbers when stratified by individual ethnicity. Within both "responders" and "non-responders", participants were more likely to be of a white British, white Irish or other white ethnicity and again the distribution is similar across "responders" and "non-responders".

13. Further stratifications of participants by vaccine brand can be found in Appendix 1.

[2] List of questions: Taking regular steroid treatment (e.g. orally or rectally); Recently had treatment for cancer, leukaemia or lymphoma (radiotherapy or chemotherapy); Recently had a bone marrow transplant or taking medicines following a transplant (e.g. kidney, lung, heart, liver); Taking regular medicines for rheumatoid arthritis (or other types of arthritis except osteoarthritis); Taking medicines for inflammatory bowel disease (Crohn's disease, ulcerative colitis); Taking medicines for multiple sclerosis; Spleen has been removed; HIV-positive with symptoms or reduction in immune response; Taking other treatments or medicines, not listed above, known to lower the immune response and increase the risk of infections; Has an illness or condition, not listed above, which reduces the immune response (e.g. immunodeficiency)

Table 2. Characteristics of Individuals registered with the Yellow Card Vaccine Monitor stratified by those reporting vaccination data compared with those who have not (as at 30th June 2021).

Characteristic	Vaccination reported "responders" *	Vaccination not reported "non-responders"	Total
Total	**24,611 (100.0)**	**5,221 (100.0)**	**29,832**
Sex			
Males	10,275 (41.7)	2,317 (44.4)	12,592 (42.2)
Females	14,057 (57.1)	2,805 (53.7)	16,862 (56.5)
Unknown	279 (1.1)	99 (1.9)	378 (1.3)
Age (years)			
0-17	34 (0.1)	30 (0.6)	64 (0.2)
18-29	851 (3.5)	275 (5.3)	1,126 (3.8)
30-39	2,750 (11.2)	502 (9.6)	3,252 (10.9)
40-49	2,418 (9.8)	565 (10.8)	2,983 (10.0)
50-59	3,630 (14.7)	970 (18.6)	4,600 (15.4)
60-69	5,401 (21.9)	1,082 (20.7)	6,483 (21.7)
70-79	7,577 (30.8)	1,537 (29.4)	9,114 (30.6)
80+	1,927 (7.8)	255 (4.9)	2,182 (7.3)
Unknown	23 (0.1)	5 (0.1)	28 (0.1)
Ethnicity			
White British/Irish/Other White background	21,704 (88.2)	4,324 (82.8)	26,028 (87.2)
All other	1,279 (5.2)	433 (8.3)	1,712 (5.7)
Unknown	1,628 (6.6)	464 (8.9)	2,092 (7.0)
Immunocompromised			
Yes	2,661 (10.8)	591 (11.3)	3,252 (10.9)
No/unknown	21,950 (89.2)	4,630 (88.7)	26,580 (89.1)

* Data are: Number of participants (column percentage)

Trends in adverse reaction reporting and comparisons to patterns seen in spontaneous reports

14. Table 3 shows the proportion of individuals reporting an adverse drug reaction (ADR) following vaccination to the YCVM. 59.2% of individuals receiving the AstraZeneca vaccine have reported ADRs compared to 38.8% of individuals receiving Pfizer.

Table 3. Proportion of individuals registered with the Yellow Card Vaccine Monitor reporting an ADR (as at 30th June 2021).

	Pfizer-BioNTech	Oxford AstraZeneca	Moderna	Brand unspecified	Total
Individuals reporting at least one ADR	2,980 (38.8%)	9,563 (59.2%)	252 (59.3%)	137 (40.3%)	12,932
Individuals who have not reported any ADRs	4,699 (61.2%)	6,604 (40.8%)	173 (40.7%)	203 (59.7%)	11,679

15. Table 4 compares the characteristics of individuals reporting ADRs through the YCVM compared to the Yellow Card reporting scheme.

Table 4. Characteristics of individuals reporting ADRs through the Yellow Card Vaccine Monitor compared to those reporting through the Yellow Card Scheme (as at 30th June 2021).

	Yellow Card Vaccine Monitor	**%***	**Yellow Card Scheme**	**%**
Total number of individuals reporting an ADR for a COVID-19 vaccine	12,932	100	303,203	100
Sex				
Males	4,474	34.6	71,156	23.5
Females	8,300	64.2	218,088	71.9
Unknown	158	1.2	13,959	4.6
Age (years)				
0-17	16	0.1	1,019	0.3
18-29	507	3.9	32,976	10.9
30-39	1,490	11.5	48,702	16.1
40-49	1,720	13.3	59,409	19.6
50-59	2,283	17.7	58,145	19.2
60-69	3,051	23.6	39,162	12.9
70-79	3,220	24.9	21,920	7.2
80+	636	4.9	6,494	2.1
Unknown	9	0.1	35,376	11.7
Ethnicity				
White British/Irish/Other White background	11,362	87.9	226,603	74.7
All other	720	5.6	18,085	6.0
Unknown	850	6.6	58,515	19.3
Immunocompromised				
Yes	1,357	10.5	8,303	2.7
No/unknown	11,575	89.5	294, 900	97.3

* Data are column percentage

16. For both the YCVM and Yellow Card scheme, females reported more than males, but the proportion for females compared to males is higher for the Yellow Card scheme.

    With respect to age-groups, the highest proportion of individuals reporting ADRs to the vaccine monitor is the 70-79 year old age-group (24.9%), whereas for the Yellow Card Scheme, the age is younger with the highest proportion reporting in the 40-49 year age-group (19.6%). This difference is again likely due to the timing of invitations being sent out. To date, the proportion of individuals in the youngest age-groups are low for both data sources, reflecting lower uptake and more recent deployment within these groups.

    The YCVM has a small proportion of individuals from non-white ethnic groups reporting (5.6%), which is consistent with the Yellow Card Scheme where the proportion is similar (6.0%). The Yellow Card Scheme has a larger proportion of individuals of unknown ethnicity (19.3%) compared to the YCVM (6.6%).

A previous paper presented to the VBR outlined activities we have conducted to try increase ethnic diversity in our data. Advice from the VBR has been used to help support activities for increasing diversity and engagement moving forwards.

The YCVM has a larger proportion of individuals who have reported as being immunocompromised in some way compared to the Yellow Card Scheme (10.5% vs. 2.7%).

17. Through collaboration with Public Health England (PHE) we have extended invitations to encourage pregnant women to register[3] which has contributed to 1,607 pregnant women registering (Table 5). These women will be followed up after their estimated due date to check for outcomes of their pregnancy.

Table 5. Yellow Card Vaccine Monitor Registrations by pregnancy status (as at 30th June 2021)

	Pfizer-BioNTech	**Oxford AstraZeneca**	**Moderna**	**Brand unspecified**	**No vaccine data reported**	**Total**
Individuals reporting that they are pregnant	1,197	203	120	[redacted]	86	1,607

18. Whilst pregnancy outcome for most individuals are not yet available since the estimated due date and subsequent follow-up (ten weeks post estimated due date) has not passed, this cohort will provide an important data set to monitor outcomes in due course.

19. The types of ADRs being reported for YCVM as compared to the Yellow Card scheme has been reviewed to identify any differences (Table 6). A comparison of the top twenty most commonly reported ADRs at the MedDRA Higher Level Term (HLT) indicates that the ADRs reported to the Yellow Card Vaccine Monitor are broadly consistent with reports received through standard Yellow Card Reporting. However, there are some terms which are appear in the top 20 for the YCVM but not for the Yellow Card Scheme and vice vera, these are highlighted by the * in the table.

Table 6. Top 20 most common ADRs reported through the YCVM compared to standard Yellow Card Scheme reporting (as at 30th June 2021)

Top 20 reported MedDRA Higher Level Terms	**Yellow Card Vaccine Monitor**	**Standard Yellow Card Scheme reporting (COVID-19 vaccines only)**
1	Headaches Nec	Headaches NEC
2	Asthenic Conditions	Asthenic conditions
3	Musculoskeletal And Connective Tissue Pain And Discomfort	Febrile disorders
4	Feelings And Sensations Nec	Feelings and sensations NEC

[3] Yellow Card Vaccine Monitor - Invitation to pregnant women - Health Publications

5	Febrile Disorders	Nausea and vomiting symptoms
6	Muscle Pains	Musculoskeletal and connective tissue pain and discomfort
7	Pain And Discomfort Nec	Pain and discomfort NEC
8	Nausea And Vomiting Symptoms	Muscle pains
9	Joint Related Signs And Symptoms	Neurological signs and symptoms NEC
10	General Signs And Symptoms Nec	General signs and symptoms NEC
11	Neurological Signs And Symptoms Nec	Joint related signs and symptoms
12	Injection Site Reactions*	Rashes, eruptions and exanthems NEC
13	Influenza Viral Infections*	Paraesthesias and dysaesthesias
14	Disturbances In Consciousness Nec	Apocrine and eccrine gland disorders
15	Upper Respiratory Tract Signs And Symptoms*	Disturbances in consciousness NEC
16	Diarrhoea (Excl Infective)	Lymphatic system disorders NEC*
17	Paraesthesias And Dysaesthesias	Diarrhoea (excl infective)
18	Apocrine And Eccrine Gland Disorders	Pruritus NEC*
19	Rashes, Eruptions And Exanthems Nec	Gastrointestinal and abdominal pains (excl oral and throat)
20	Gastrointestinal And Abdominal Pains (Excl Oral And Throat)	Tremor (excl congenital)*

20. Table 7 shows the proportions of different sub-populations reporting an ADR to YCVM stratified by vaccine brand (Pfizer-BioNTech vs. AstraZeneca) and dose (1st vs. 2nd).

Table 7. Characteristics of individuals reporting ADRs through the Yellow Card Vaccine Monitor stratified by vaccine brand and dose (as at 30th June 2021)

Patient characteristic	**Pfizer-BioNTech**				**Oxford AstraZeneca**			
	1st dose*		**2nd dose**		**1st dose**		**2nd dose**	
Sex								
Male	831	(27.8)	176	(22.7)	3,177	(45.2)	387	(18.2)
Female	1,713	(37.3)	320	(32.5)	5,661	(63.1)	757	(28.4)
Age								
0-17	8	(42.1)	[redacted]		[redacted]		[redacted]	
18-29	242	(45.1)	12	(35.3)	191	(76.7)	16	(35.6)
30-39	768	(42.9)	41	(28.9)	542	(75.6)	38	(25.0)
40-49	206	(45.7)	33	(47.1)	1,359	(74.2)	73	(31.6)
50-59	125	(44.8)	41	(46.6)	2,017	(61.1)	261	(27.3)
60-69	341	(35.5)	109	(32.7)	2,432	(55.7)	398	(25.0)
70-79	688	(25.6)	215	(24.6)	2,062	(43.3)	325	(20.3)
80+	202	(21.4)	48	(20.5)	317	(34.5)	36	(14.3)
Ethnicity								
White	2,164	(33.0)	462	(28.9)	8,019	(55.3)	1,065	(24.0)
Non-white	237	(43.3)	18	(32.1)	411	(61.3)	42	(29.0)
Immunocompromised								
Yes	302	(33.4)	61	(30.3)	909	(53.8)	137	(28.9)
No/Unknown	2,279	(33.7)	438	(27.8)	8023	(55.4)	1011	(23.2)

* Data are: Number of participants (column percentage)

21. The highest rates of ADR reporting are seen following the first dose of the Oxford AstraZeneca vaccine. Substantially lower reporting rates are seen after dose two. The reporting rate following a first dose of the Pfizer-BioNTech vaccine is lower than that seen for the Oxford AstraZeneca vaccine with little difference seen in the rates reported after the first and second dose.

22. A consistently higher proportion of women report an ADR compared to men regardless of vaccine brand and dose. There is also a trend of decreasing ADR reporting with increasing age. There is some suggestion of higher reporting in non-white populations, but no consistent difference based on immune status.

Signal assessments supported with Yellow Card Vaccine Monitor data

23. Data from YCVM has supported signal detection analysis and is used in routine signal detection activities alongside other data sources, such as spontaneous Yellow Card reports and studies.

24. Frequency of reported headaches was reviewed in March 2021 which showed that 20% of individuals enrolled reported a headache post vaccination to the AstraZeneca vaccine. A review of lymphadenopathy was also undertaken with the YCVM helping to see how long symptoms lasted for and the numbers who had recovered. The data have been used internally at signal detection meetings to facilitate discussions on influenza-like symptoms and menstrual disorders and included in committee papers seeking advice from the group at previous meetings.

25. In July 2021, the VBR-EWG was presented with a review of the safety data for COVID-19 vaccines in pregnancy and breastfeeding. Data from YCVM, provided in Appendix 2, table 1, contributed to the overall conclusions that Yellow Card data related to COVID-19 vaccines exposure during pregnancy to date do not raise any particular safety concerns.

26. Given the volume of pregnant women enrolled in the YCVM, we have an important future data source to support continuous and long term monitoring of pregnancy outcomes and will provide an update to the VBR in due course.

27. In July 2021, the VBR-EWG were also presented with a paper on menstrual disorders, the details of which are in Appendix 3. YCVM showed a low rate of reporting of menstrual disorders (0.5%) and the available data from the YCVM does not support an increased risk of menstrual disorders with COVID-19 vaccines. This aligned with the overall assessment conclusion there is no evidence of an increased risk of menstrual disorders from either non-clinical studies or clinical trials for AstraZeneca, Pfizer, and Moderna COVID-19 vaccines.

28. Data from the YCVM has not identified any additional safety signals in isolation, which is to be expected given the size of the cohort involved. However, it has been a useful source of data to support assessments.

Future uses of the active surveillance platform

29. The YCVM platform has been, and continues to be, a helpful additional data set to support signal assessments for COVID-19 vaccines. The technology that has been

developed to support YCVM will benefit us into the future for medicine, vaccine and device safety surveillance.

30. At the time of developing YCVM, much of the system was ‘hard coded’ and required developer input to make changes to the process. However, pre-existing plans under the SafetyConnect programme to develop the platform further has been underway since the spring and further enhancements are scheduled over the coming months. These enhancements will enable MHRA to control an agile reporting and follow-up process across both the active surveillance and passive surveillance Yellow Card systems. This will provide the ability to:

    a. Build smart reporting forms which contain conditional logic that can present a reporter with questions relevant to their report. For example, if a report related to isotretinoin we could, in real time, ask questions on the patient’s psychiatric status.
    b. Automate smart follow ups to be sent to a reporter at pre-set intervals. This will be particularly helpful for possible side effects where symptoms are typically unresolved at the time of reporting and the long term outcomes may be less known e.g. SSRIs and sexual dysfunction.
    c. Send ad-hoc follow ups for retrospective data collection, for example after a signal has been raised. This would have been particularly useful when collecting follow up for individuals reporting thromboembolic events to the AZ COVID-19 vaccine or when assessing historical reports for long term outcomes.

31. These features are closely aligned to the expectations set in the IMMDSR around transformation of the surveillance system and will lead to improvements across a number of areas:
    a. Increased data quality due to asking more tailored and specific questions
    b. Increased long term data collection
    c. Reduction in resources required to manually generate follow-up requests
    d. Reduced need to follow up if all information is obtained in the first report, this will also reduce delays in assessment
    e. Increased engagement with the public

32. An exciting opportunity is the ability to pivot from a passive collection mode to a more active set up, where follow up can be scheduled into the future. Equally the system could be used to collect registry type data on a prospective basis. In time, we intend to build on these improvements to facilitate tailored communications and feedback to reporters, and to be able to present relevant news and information to users based on information within their profiles.

33. This platform will allow a wealth of data collection opportunities to support signal detection processes and we will need to carefully manage and resource these activities. This paper details some of the functionalities that are on the immediate horizon, and serves to stimulate discussion to ensure the opportunities are maximised.

Discussion

34. The Yellow Card Vaccine Monitor has, and continues to be, a helpful addition to the surveillance strategy. To date it has contributed to the assessment of several signals.

35. For any future phases of the vaccination campaign, such as booster or variant vaccinations, we intend to continue using the Yellow Card Vaccine Monitor as well to invite further individuals, through the call/recall process or else through active promotion, to overcome a potential drop off rate in responses as time goes on. For those already registered, this will lead to an extension on the follow up time beyond one year.

PEAG advice sought

36. Advice is sought from PEAG on:
    - Any comments on the data presented
    - Discussion of the future opportunities for enhanced vigilance using the platforms under development
        - What are the priority areas to focus on

VRMM

26 August 2021

Appendix 1

The appendix tables below show the characteristics of all individuals who have registered with the Yellow Card Vaccine Monitor to date.

Appendix Table 1: Yellow Card Vaccine Monitor Registrations stratified by patient sex (as at 30th June 2021)

	Pfizer-BioNTech	Oxford AstraZeneca	Moderna	Brand unspecified	No vaccine data reported	Total
Sex						
Male	2,987	7,028	122	138	2,317	12,592
Female	4,590	8,969	301	197	2,805	16,862
Unspecified	102	170	[redacted]	[redacted]	99	378

Appendix Table 2: Yellow Card Vaccine Monitor Registrations stratified by age (as at 30th June 2021)

	Pfizer-BioNTech	Oxford AstraZeneca	Moderna	Brand unspecified	No vaccine data reported	Total
Age (years)						
0-17	19	10	[redacted]	[redacted]	30	64
18-29	537	249	61	[redacted]	275	1,126
30-39	1,792	717	233	8	502	3,252
40-49	451	1,831	126	10	565	2,983
50-59	279	3,300	[redacted]	50	970	4,600
60-69	961	4,366	[redacted]	73	1,082	6,483
70-79	2,689	4,758	[redacted]	130	1,537	9,114
80+	944	920	[redacted]	63	255	2,182
Unknown	7	16	[redacted]	[redacted]	[redacted]	28

Appendix Table 3: Yellow Card Vaccine Monitor Registrations stratified by ethnicity (as at 30th June)

	Pfizer-BioNTech	Oxford AstraZeneca	Moderna	Brand unspecified	No vaccine data reported	Total
Ethnicity						
African	34	50	[redacted]	[redacted]	53	141
Any other Asian background	45	64	6	[redacted]	45	160
Any other black background	9	12	[redacted]	[redacted]	7	29
Any other ethnic group	43	52	[redacted]	[redacted]	29	128
Any other mixed group	39	47	[redacted]	[redacted]	25	116
Any other white background	456	429	73	10	196	1,164

Bangladeshi	15	9	[redacted]	[redacted]	17	42
Caribbean	18	41	[redacted]	[redacted]	16	78
Chinese	74	62	10	[redacted]	26	174
Indian	144	184	8	6	118	460
Pakistani	37	40	[redacted]	[redacted]	34	115
White & Asian	49	63	[redacted]	[redacted]	30	145
White & Black African	22	18	[redacted]	[redacted]	20	61
White & Black Caribbean	18	28	[redacted]	[redacted]	13	63
White British	6,027	13,907	269	290	4,081	24,574
White Irish	73	164	[redacted]	[redacted]	47	290
Unknown	576	997	32	23	464	2,092

Appendix 2

Yellow Card Vaccine Monitor (YCVM)

The Yellow Card vaccine monitor reports for females aged 18 to 44 years up to 30th June, included data from 203 female recipients of the Oxford-AZ vaccine, 1195 female recipients of the Pfizer-BioNTech and 119 female recipients of the Moderna vaccine. There were 565 reports of maternal exposures during pregnancy up to 9th July 2021, including data from 124 recipients of the Oxford-AZ vaccine, 383 recipients of the Pfizer-BioNTech and 58 recipients of the Moderna vaccine (Table 1).

The Yellow Card vaccine monitor reports for females aged 18 to 44 years up to 30th June, included data from 203 female recipients of the Oxford-AZ vaccine, 1195 female recipients of the Pfizer-BioNTech and 119 female recipients of the Moderna vaccine. There were 1366 reports of maternal exposures during pregnancy up to 30th June 2021, including data from 187 recipients of the Oxford-AZ vaccine, 1003 recipients of the Pfizer-BioNTech and 95 recipients of the Moderna vaccine. Of these, 565 participants reported suspected ADRs following vaccination up to 9th July 2021. Thus, 66% (n= 124) of recipients of the Oxford-AZ vaccine, 38% (n=383) of recipients of the Pfizer-BioNTech and 61% (n=58) of recipients of the Moderna vaccine reported suspected ADRs and were included in the analysis (Table 1).

Appendix 2, Table 1 Yellow Card Vaccine Monitor reports for Maternal exposures to COVID Vaccines in pregnancy received up to 9/7/21

Timing of vaccination	total	ns	pre-pregnancy	1st TM	2nd TM	3rd TM
Oxford-AZ vaccine	**124**		[redacted]	**52**	**50**	**19**
Presumed ongoing, no problems	116		[redacted]	47	49	17
Presumed ongoing,	[redacted]			[redacted]	[redacted]	

obstetric complications						
miscarriage (< 22wk)	[redacted]			[redacted]		
Live births	[redacted]					[redacted]
Pfizer-BioNTech vaccine	**383**		[redacted]	**79**	**209**	**93**
Presumed ongoing, no problems	369		[redacted]	74	206	87
Presumed ongoing, obstetric complications	[redacted]			[redacted]	[redacted]	[redacted]
miscarriage (< 22wk)	[redacted]			[redacted]		
Live births	[redacted]				[redacted]	[redacted]
Moderna vaccine	**58**		[redacted]	**11**	**31**	**15**
Presumed ongoing, no problems	56		[redacted]	10	31	14
miscarriage (< 22wk)	[redacted]			[redacted]		
Live births	[redacted]					[redacted]

A small number of 1st trimester miscarriages have been reported following 1st trimester vaccinations with each of the vaccines, corresponding to rates of about 10% for the Oxford-AZ and Moderna vaccines and about 5% for the Pfizer-BioNTech vaccine. The Moderna case reported subchorionic bleeding at 6 weeks and that a subchorionic hematoma was found at 8 week scan (both prior to vaccination).

[redacted]

Appendix 3

As of 30th June 2021, there were a total of 16,862 women registered with the Yellow Card Vaccine Monitor (YCVM) (8969 AZ; 4590 Pfizer; 301 Moderna; 3002 unspecified). As of 30th June 2021, a total of 74 women (n=37 AstraZeneca; n=35 Pfizer; n= 2 Moderna) in the YCVM reported a total of 77 PTs related to menstrual disorders, suggesting the reporting rate is very low and these events are only reported in 0.5% of women registered.

The majority of women reporting reactions after receiving the Pfizer (60%) and Moderna (100%) vaccines were in the age range 30-39 years and almost 50% of the women reporting a reaction after the AstraZeneca vaccine were in the age range 40-49 years. This pattern may reflect the age dependent deployment of the vaccines in the vaccination program.

The majority of reporters were of a white ethnic background (AstraZeneca 84%, Pfizer 71%, Moderna 100%). Where specified, the majority of reactions were reported after the first vaccine dose (84%), with a mean time to onset of 4-13 days (median 4-7 days). Of the 77 reactions, 21 were reported as recovered and the mean time to recovery was 5-18 days (median 4 days). The majority of reports relate to cycle irregularity (29 reports), reduced bleeding (23 reports) and painful bleeding (12 reports). Duration and onset times for the different categories could not be estimated due to missing information and small numbers of reports.