COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Tuesday 31st August 2021** at **11:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Professor G Dougan
Mr VI G Fenton-May
Professor N French
Professor D Goldblatt
Professor K Hyrich
Professor H J Lachmann
Professor P J Lehner
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Professor S Price[1]
Dr A Riordan[2]
Professor C Robertson[3]
Professor T Solomon
Professor K M G Taylor
Dr R Thorpe
Professor M Turner
Professor S Walsh
Mrs M Wang
Professor C Weir

Apologies

Ms S Hunneyball
Sir M Jacobs

Visiting / Invited Experts

[redacted]t[4]
[redacted][5]

Observers

[redacted]
Professor W S Lim[6]
[redacted]
Dr L Squire[7]
Professor J Van-Tam

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - VRMM

Presenters supporting specific items[8]

[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM
[redacted] - VRMM
Dr N Rose - MHRA-NIBSC
[redacted] - LD

MHRA Observers

[redacted] - Government Legal Team
[redacted] - VRMM
Dr S Branch - VRMM
[redacted] - MHRA-NIBSC
Dr A Cave - Directorate
[redacted] - VRMM
[redacted] - MHRA-Policy
[redacted] - News & Digital Content
[redacted] - VRMM
[redacted] - VRMM
Dr S P Lam - LD
[redacted] – News & Digital Specialist
[redacted] - MHRA-NIBSC
[redacted] - VRMM
[redacted] - MHRA Policy
[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM
Mr P Tregunno - VRMM
[redacted] - LD
[redacted] - Government Legal Team
[redacted] - LD
[redacted] - VRMM
[redacted] - LD

Secretariat

[redacted]

[1] left during item 4
[2] joined during item 2 & left during item 4
[3] joined during item 2
[4] joined for item 4 only
[5] joined for item 2 only
[6] left during item 3
[7] left after item 4
[8] supported specific items

Key
LD = Licensing Division
VRMM = Vigilance & Risk Management of Medicines
NIBSC = National Institute for Biological Standards & Control

[redacted]

19th January 2023

1. Introduction and Announcement

1.1 The Chair reminded Members, invited Experts and observers that the content of papers and proceeding of the meeting are strictly confidential and should be treated as 'Official – sensitive commercial' and should not be disclosed. There is no consent for members / participants to record the meeting, take screenshots or photographs of presentations. The meeting was recorded by the MHRA Secretariat for minute taking purposes only. The Chair & Members including all participants gave full consent to the recording prior to the start of the meeting.

1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.4 Apologies were received from Sir Michael Jacobs and Ms Hunneyball for this meeting.

1.5 The Chair welcomed the following visiting / invited experts:

[redacted]
NIHR Senior Investigator

Who participated for item 4 - Regulation 174 request concerning 3rd Booster doses

[redacted]University of Bristol

Who participated for item 2 - Update on COVID-19 Vaccines and the risk of thromboembolic events without thrombocytopenia

1.6 The Chair welcomed the following observers:

[redacted] Public Health England

[redacted]JCVI

[redacted] Public Health Agency

[redacted] Public Health Wales

Professor Wei Shen Lim
Chair of JCVI

[redacted]
NHS England [redacted]

[redacted]
Public Health Scotland

[redacted]
Public Health England

Dr Laura Squire
DHSC

Professor Jonathan Van-Tam
Deputy Chief Medical Officer

2. Update on COVID-19 Vaccines and the risk of thromboembolic events without thrombocytopenia

2.1 The EWG was updated with new information received since the previous paper presented on 19/08/2021.

2.2 The EWG was informed that two of the draft manuscripts included in the presentation on 19/08/2021 have now been published.[1,2]

2.3 The EWG was informed of an update received from the European Medicines Agency (EMA) which confirmed that the Pharmacovigilance Risk Assessment Committee (PRAC) was currently reviewing cases of thrombosis without thrombocytopenia for the adenovirus-based vaccines within the monthly summary of safety reports submitted by the Marketing Authorisation holders (reported up to 31 July 2021).

2.4 The EWG noted the EMA's new age-stratified O/E analyses for both vaccines and EEA cases reported to EudraVigilance (DLP 31 July 2021). A marked imbalance in the O/E ratio for CVST was observed for Vaxzevria across all age groups. For Janssen, the imbalance was only seen in the 18-29 age group.

[1] CVD-COVID-UK consortium. Association of COVID-19 vaccines ChAdOx1 and BNT162b2 with major venous, arterial, and thrombocytopenic events: whole population cohort study in 46 million adults in England https://doi.org/10.1101/2021.08.18.21262222 Date Published: 23/08/2021 (pre-print)
[2] Julia Hippisley-Cox, Martina Patone, Xue W Mei et al. Risks of Thrombocytopenia and Thromboembolism after COVID-19 vaccination and SARS-Cov-2: self-controlled case series study https://doi.org/10.1136/bmj.n1931 Date Published: 27/08/2021

No imbalance was observed for other thromboembolic events for either vaccine, save for a slight imbalance in the 18-29 age group for Vaxzevria and mixed arterial/venous thrombosis in one of the analyses.

2.5 The EWG noted the planned PRAC action for these reviews

2.5.1 Based on the EMA O/E analysis, the MAH will be asked to include a company analysis assessing the risk of CVST without thrombocytopenia following AstraZeneca COVID-19 vaccination. This analysis is expected in the next monthly summary of safety reports submission.

2.5.2 With respect to the Janssen vaccine, PRAC is awaiting submission and review of additional MAH clinical trial data before deciding on the need for any updates to the product information to list venous thromboembolism. This proposed action was based on a continuous imbalance for observed vs expected cases in the MAH O/E analysis and a number of serious, medically confirmed case reports in young vaccinees without risk factors for venous thrombosis with a time to onset within 28 days after vaccination.

2.6 The EWG was presented with the findings of completed MHRA O/E analysis for CVST without thrombocytopenia reported within 7 days and within 42 days of vaccination with a COVID vaccine (AstraZeneca or Pfizer). The EWG was informed that a range of background incidence rates for CVST without thrombocytopenia were used in the MHRA O/E analyses to take into consideration the uncertainty around the background rate of this rare condition.

2.7 MHRA O/E analyses suggested a borderline signal for an overall risk within 42 days following a first dose of AstraZeneca using the maximum background rate. This signal was not reflected across all age groups.

2.8 The EWG noted the challenges with under-recording of thrombocytopenia in medical records and the impact the choice of background rates has on the O/E analyses.

2.9 The EWG noted the challenges faced by researchers investigating this topic via observational studies. These include the substantial heterogeneity between databases, validation of clinical diagnoses, the need to account for confounding factors and the requirement for different methodologies to help triangulate potential signals of interest.

2.10 The EWG noted that the underlying mechanisms underpinning thrombosis with thrombocytopenia syndrome (TTS) could be of relevance because there are important gaps in knowledge concerning the presentation/spectrum of that disorder, i.e. the possibility of a proportion of patients who present with thrombosis with normal platelets in comparison to those who present with low platelets but no evidence of thrombosis. The underlying mechanisms of TTS are subject to ongoing research which may inform our understanding of thrombosis cases without thrombocytopenia occurring after COVID-19 vaccination.

2.11 The EWG highlighted the absence of a recording of thrombocytopenia in the health care records used for these studies cannot be used as a reliable exclusionary criterion to confirm the platelets were normal. Studies would need access to haematological results to confirm normal platelet counts in relevant thromboembolic cases before conclusions can be drawn on whether there are increased thromboembolic events with normal platelet counts after COVID-19 vaccination.

2.12 The EWG noted that available evidence suggests there is a clinically substantial risk of thrombosis following COVID-19 infection. This should be taken into consideration when assessing the relative risk of any such events in recipients of a COVID-19 vaccine and the impact on the benefit-risk of COVID-19 vaccination.

2.13 The EWG then considered the following 3 questions:

2.13.1 Question 1: Based on the evidence presented does the EWG consider there is an association with the AZ OR Pfizer OR Moderna OR Janssen COVID-19 vaccines and the risk of thromboembolism without concurrent thrombocytopenia?

The EWG advised that whilst the observational studies provide evidence of potential association between COVID-19 vaccination and thromboembolic events, the findings are not replicated across studies/populations to consistently implicate specific vaccines to events of interest (DVT, PE, MI, Stroke, CVST) and/or to increased risk in specific age/gender groups/timeframes.

The EWG advised that observational studies and O/E analyses which demonstrate an imbalance in events of interest should be interpreted with caution owing to limitations in identifying whether thrombocytopenia was present or not. The potential for residual confounding/unmeasured variables to impact the findings must also be taken into account.

2.13.2 Question 2: If an association cannot be confirmed on the current data, what further analysis might be required to assess causality?

The EWG agreed that further research is required to corroborate the findings to date and to investigate potential associations between events of interest and different vaccines as well as how any association behaves when comparing dose 1 against booster doses. If a causal relationship is suspected there is a need to understand the biological mechanisms underpinning such potential risk and for studies to explore and assess causality.

The EWG noted that further data is expected comprising MHRA O/E analyses for non-CVST thromboembolic events, submission and review of the additional Janssen data expected by PRAC and submission and review of the additional analyses requested from AstraZeneca for inclusion in the next monthly summary of safety reports submission. The review of this data should be presented to the EWG at the next update of this topic.

2.13.3 Question 3: Does the EWG consider there is a need for updates for the PI of the AZ, Pfizer, Moderna or Janssen vaccine?

The EWG advised no update is required at this time based on the evidence to date.

3. Pfizer Veterans database PASS – interim results

3.1 The EWG were informed that as part of the Risk Management Plan for Pfizer/BioNtech COVID-19 vaccine the company had committed to carrying out a post-authorisation safety study (PASS) in individuals receiving Pfizer/BioNtech COVID-19 vaccine in the US Veteran's Affairs Health System. The EWG heard that a draft protocol had been provided at the time of authorisation; however, the company had now provided the full study protocol for review. The company had also provided the first interim report for this study which provided a description of vaccine usage and baseline characteristics of the study population although no safety data were provided.

3.2 The EWG were presented with an overview of the study protocol including the study objectives, study design, outcomes, planned analyses and limitations of the study as well as the MHRA review of the protocol. The EWG heard that the interim report provided the baseline characteristics of over 750,000 individuals who had received at least one dose of Pfizer/BioNtech COVID-19 vaccine and a fixed cohort of over 4 million individuals in the active comparator group of historical seasonal influenza vaccine recipients.

3.3 The EWG considered that the vaccination levels among the veterans in this study at the time of the interim report were relatively low and suggested that this may have reflected vaccination policy in the US and that the individuals in this study were relatively young. The EWG discussed the lack of generalisability of this study given the predominance of males (approximately 90%) in the Veteran's Affairs Health System but noted that the company were carrying out other PASS studies on the safety of Pfizer/BioNtech COVID-19 vaccine in wider populations.

3.4 The EWG supported the MHRA's assessment conclusions regarding the PASS protocol and agreed that while the protocol was largely satisfactory, the company should be asked to provide further information on several issues for clarification identified by MHRA including confirmation that all Adverse Events of Special Interest from the MHRA core RMP for COVID-19 vaccines were included in the study and that safety data should be presented in the next interim report.

4. Regulation 174 request concerning 3rd Booster doses

4.1 The EWG heard that a paper for members was drafted based on request from DHSC with a number of questions on homologous and heterologous COVID-19 booster vaccination).

4.2 The EWG was presented with a summary of data for Pfizer and AstraZeneca vaccines on homologous booster (third) doses. The EWG was made aware that additional data are expected from COV-Boost, a study that involves combinations of seven different COVID-19 vaccines. The EWG heard a summary of the planned pharmacovigilance activities to monitor the safety of booster doses.

4.3 EWG discussion

4.3.1 The EWG heard that data are presently only available on homologous booster doses; immunogenicity data on heterologous boosting should emerge shortly from COV-Boost study.

4.3.2 The EWG noted that data on the Pfizer vaccine from Israel show that breakthrough infections are predominantly occurring in individuals vaccinated early in the vaccination campaign; however, it needs to be considered that this group included a greater proportion of higher risk individuals (elderly and clinically vulnerable people). The EWG also mentioned in the analysis of these data does not yet compute disease severity and this is not ideal because positive tests are not a primary concern which is the capability of the booster dose to prevent hospitalisation and death.

4.3.3 The EWG discussed how the immunological data correlate with immunity and mentioned that although the correlate of protection has not yet been established, thresholds identified in the immunological data could serve as a reasonable surrogate. However, until this has been robustly determined, as of now, epidemiological data is better placed to provide insights about the period when protection in the double vaccinated is expected to wane to such an extent that susceptibility to severe infection and subsequent hospitalisation become likely. The EWG concluded this point by noting that epidemiological data should

drive the policy decision on (third) booster doses. The invited expert from JCVI confirmed that vaccination data on the protection against hospitalisation, rather than immunogenicity data, will be more influential to their decision-making process.

4.3.4 The EWG noted a pre-print of study on real world effectiveness data gathered by Israel's Ministry of Health, which showed third booster dosing was associated with a 10-fold reduction in the relative risk of severe illness in those aged 60 and above.

4.3.5 The EWG commented that solid organ transplant recipients are the only source of data in the immunocompromised population. The EWG noted the need to be aware of the large group of patients who receive B-cell depleting agents and are not represented in this study, and this group of patients is unlikely to respond even to a third dose. The EWG discussed a single arm study in solid organ transplant recipients where a third dose of the Pfizer-BioNTech COVID-19 vaccine was administered approximately 2 months after they had received a second dose ([3]Kamer et al, 2021; NJEM). The invited expert from JCVI mentioned that very different strategies are being considered by JCVI to address differences in immune responses to vaccination in the general population and in immunocompromised patients. The expert continued, the role of the third dose in the immunocompromised is expected to act as a 'top up' to what is potentially an inferior response post second dose, whereas in the general population the timing of the booster dose might be comparatively delayed, to align with the point when protection afforded by the second dose is predicted to wane.

4.3.6 The expert also spoke of the benefits of allowing flexibility for prescribers to immunosuppressed patients; in some cases, a shortened interval would confer better protection for example in a patient due to commence a long course of immunosuppression.

4.3.7 The EWG noted that an interval between second and third doses of at least 2 months was reasonable. In terms of homologous booster data from the Pfizer's phase I study, it was administered at 8 to 9 months post second dose; however, given some data on waning immunity at 6 months the interval may need to be shortened.

4.3.8 The EWG noted EULAR has recently had published a research letter on vaccine experience outcomes in patients with Rheumatic and Musculoskeletal diseases on immunosuppression, albeit covering a short window, the reinfection rate post vaccine (double dose) in ~5000 patients was less than 1%. The stimulated reporting aspect of the study was noted as a limitation of the data, nonetheless the data are reassuring.

4.3.9 The EWG noted that a paper[4] on outcomes of the OCTAVE trial on the Lancet pre-print server showed that humoral response is attenuated compared to healthy subjects whereas the cellular immune response to the vaccine does not appear to diminish. In the study, the majority of subjects were vaccinated with AZ or Pfizer and the tests were carried out at baseline, pre-second vaccine dose and/or 4 weeks post second dose.

[3] Three Doses of an mRNA Covid-19 Vaccine in Solid-Organ Transplant Recipients | NEJM

[4] Examining the Immunological Effects of COVID-19 Vaccination in Patients with Conditions Potentially Leading to Diminished Immune Response Capacity – The OCTAVE Trial by Pamela Kearns, Stefan Siebert, michelle willicombe, Charlotte Gaskell, Amanda Kirkham, Sarah Pirrie, Sarah Bowden, Sophia Magwaro, Ana Hughes, Zixiang Lim, Stavros Dimitriadis, Sam M. Murray, Thomas Marjot, Zay Win, Sophie L. Irwin, Georgina Meacham, Alex G. Richter, Peter Kelleher, Jack Satsangi, Paul Miller, Daniel Rea, Gordon Cook, Lance Turtle, Paul Klenerman, Susanna Dunachie, Neil Basu, Thushan I. de Silva, David Thomas, Eleanor Barnes, Carl S. Goodyear, Iain McInnes :: SSRN

4.3.10 The EWG mentioned that for vectored vaccines such as AZ it remains to be confirmed if a longer interval between second and third, or further booster doses, can impact on responses to the vector; monitoring of this area will likely be useful to guide decisions on potential further use of booster doses. The EWG noted that the third dose study on the AZ vaccine (pre-print by Oxford) did not collect data on anti-vector immune response.

4.3.11 The EWG discussed booster vaccination in children aged 12-15 years and noted that there are no data on third doses in this age range or below from Pfizer. The EWG heard the decision to deploy the vaccine to this group falls within the remit of JCVI; however, the suitability of the indication is to be determined by the MHRA. The EWG noted that if immunogenicity data might emerge on a cohort of ~100 children aged 12-15 years, these data will be of limited use, and by and large cannot inform on conclusions on safety such as peri-myocarditis. The EWG discussed the role of the Risk Management Plan (RMP); by classifying use in children aged 12-15 years as missing data, as further data would be gathered post-approval. The EWG noted that there is nothing specific in the RMP regarding the third dose, but the CMA application is anticipated to be submitted by Reliance route and is expected to include information on the third dose.

4.3.12 The EWG noted that a signal from COVID-19 vaccination has not been identified in a small cohort of patients with recurrent idiopathic myopericarditis which is reassuring, as this group are very prone to this condition.

4.4 Conclusions of the EWG on third dose (booster) Pfizer vaccine

4.4.1 Based on the available data the EWG was supportive of authorising a Pfizer vaccine third dose (homologous boosting).

4.4.2 The EWG agreed on the proposed interval of at least two months between the second and third doses (homologous boosting) for the Pfizer vaccine--as this caters to both the flexibility for immunocompromised patients and also helps to ensure that protection that could be waning in some individuals is rescued without delay.

4.4.3 The EWG discussed potential efficacy of half doses and noted that this topic needs to be revisited once full data from COV-Boost are available. The legal expert confirmed that for a Reg. 174 authorisation, off-label use cannot occur and therefore, to permit use of alternative dose/s the conditions for authorisation of the product will require amendment.

4.4.4 The EWG noted that in relation to immunosuppressed patients there is an argument for giving precedence to a decision to optimise their immune response based on status or alteration of concomitant medication, rather than setting a specific interval duration. The EWG noted the advantages of making the terms as flexible as possible and agreed that the recommendation can simply state - a third dose after two months may be administered.

4.5 Conclusions of the EWG on third dose (booster) AZ vaccine

4.5.1 The EWG noted that incidents of thrombosis with thrombocytopenia syndrome (TTS) are very rare and the rate is lower at second dose compared to first; therefore, at third dose the chance of seeing an increase in the rate of this TTS was considered to be very slight. The EWG was also confident that the available data do not show an excess serious safety signal/s at second dose.

4.5.2 The EWG noted that a 2-month interval was acceptable between the second and third dose.

4.5.3 The EWG mentioned that there is no targeting to age groups in the product information and use in the under 40s of the third dose would be a deployment decision made by JCVI.

4.5.4 The EWG noted that due the paucity of data on AZ third dose the risk management plan would need to be robust, by making this a proviso, the EWG reached a consensus that AZ vaccine homologous boosting (third dose) has a positive benefit risk.

4.5.5 The EWG heard that by Monday 6th September, immunogenicity data on heterologous boosting with the Spike (S) protein maybe ready for review by this working group, or if more appropriate review by Commissioners.

4.5.6 The EWG noted that the ELISA data currently available strongly aligns with pseudo neutralisation and neutralisation assay data, and although these data are not functional per se, they represent indirect evidence of efficacy.

5. Update on Myo/pericarditis with COVID-19 Vaccines

5.1 The EWG were presented with an update on COVID-19 vaccines and myo/pericarditis which included a review of Yellow Card data (including detailed reporting rates in young people), an updated Public Health England (PHE) Secondary Uses Service (SUS) analysis, a summary of a planned UK study on myocarditis post COVID-19 vaccination, Risk Management Plan (RMP) updates for Pfizer/BioNTech COVID-19 vaccine, new literature publications and new international data.

5.2 The EWG were also informed of action taken by the MHRA in relation to a small number of positive rechallenge cases of myo/pericarditis with Pfizer/BioNTech COVID-19 vaccine. While there was limited data to support any regulatory action, it was proposed that MHRA informed PHE of the cases in case any public health actions were required. The EWG noted that PHE planned to introduce advice to vaccinators that those who experienced myo/pericarditis after the first dose should not have the second dose. The EWG also noted that four cases of recurring symptoms of myo/pericarditis after the second dose of AstraZeneca COVID-19 vaccine had been reported.

5.3 The EWG heard that the new literature publications included a report of 2 histologically confirmed cases of myocarditis within 2 weeks of receipt of mRNA COVID-19 vaccines, details of a study of COVID-19 vaccination-associated myocarditis in adolescents and a US study reporting results, consistent with other studies, that myocarditis occurred more frequently in younger males after a second dose of COVID-19 vaccine. The EWG also heard that while an additional study had found an increased risk of myocarditis following Pfizer/BioNTech COVID-19 vaccine, the risk of myocarditis was substantially higher after COVID-19 infection itself.

5.4 Regarding updated PHE SUS analysis, the EWG heard that there was no ecological indication of a rise myo/pericarditis Emergency Care Data Set (ECDS) cases as COVID-19 vaccines were introduced. However, the PHE ECDS analysis had found higher rates of myo/pericarditis in younger ages and males. In the 15 to 39 years analysis, the highest post vaccination rate rates were at 0-6 days post dose 1 of AstraZeneca and Moderna COVID-19 vaccines and 0-6 days post dose 2 Pfizer/BioNTech and Moderna COVID-19 vaccines and 7 to 27 days post dose 1 Moderna COVID-19 vaccines. However, there was likely to be some residual confounding in relation to clinically extremely vulnerable vaccine recipients.

5.5 The EWG heard that Yellow Card reports of myo/pericarditis (data lock point 23 August 2021) continued to be received with the Pfizer/BioNTech, Moderna and AstraZeneca

COVID-19 vaccines as the vaccination programme progressed. Many reports were from patients themselves and only small proportion of cases overall met the Centres for Disease Control and Prevention (CDC) case definition criteria for myo/pericarditis based on the information available in the reports. The EWG noted that while there were some fluctuations in reporting rates for each of the vaccines by age and dose since the previous EWG review of this issue, the reporting rates were based on small numbers of cases and/or relatively low vaccine exposure in some categories and the overall pattern of reporting remained broadly the same. A breakdown of Yellow Card reporting rates of myo/pericarditis by age and dose in young people was also presented. As for the Yellow Card data in all ages, the interpretation of these reporting rates was limited by low case numbers and low exposure in some groups.

5.6 The EWG were informed that the Pfizer/BioNTech RMP was being updated to include the investigation of myo/pericarditis in 3 of the pre-existing post-authorisation safety studies including investigating long-term outcomes. A new US observational study in people of any age who received Pfizer/BioNTech COVID-19 vaccine as well as a paediatric study of cases of myocarditis following COVID-19 vaccination were also planned. In addition, the EWG heard that PHE in association with Bristol University were planning a multi-centre prospective study to assess long-term cardiac outcomes in individuals aged 16 to 39 years with myocarditis following mRNA vaccination in England, and that other countries were also planning follow up studies of myo/pericarditis post COVID-19 vaccination.

5.7 In terms of new international data, the EWG were provided with the case details of a report of myocarditis with a fatal outcome from New Zealand following Pfizer/BioNTech COVID-19 vaccine. The EWG also heard information from Health Canada about higher reporting rates of myo/pericarditis for Moderna COVID-19 vaccine than for Pfizer/BioNTech and AstraZeneca COVID-19 vaccines; however, Health Canada were carrying out further analyses of these data including looking at any impact of the interval between first and second doses on reporting rates. Public Health Canada had also reported a higher reporting rate of myo/pericarditis with Moderna COVID-19 vaccine compared to Pfizer/BioNTech after the second dose, particularly in younger males.

5.8 The EWG considered that the overall pattern of reporting of myo/pericarditis after COVID-19 vaccination reported internationally since the previous EWG review of this issue had not changed. The EWG proposed that the reason the UK was not seeing the bigger signal of myo/pericarditis after the second dose of mRNA COVID-19 vaccine compared to the first dose observed in other countries such as the US and Israel may be related to the longer interval between doses in the UK compared to elsewhere. The EWG supported Health Canada's further investigation into the possible influence of dose interval on the reporting rates of myo/pericarditis following vaccination against COVID-19.

5.9 The EWG discussed that many of the reported cases of myo/pericarditis in association with COVID-19 vaccine through the UK Yellow Card Scheme lacked a clinical hospital diagnosis and may not necessarily have been true cases of myo/pericarditis. In terms of the PHE data showing higher admissions for myo/pericarditis for younger patients' post-vaccination, the EWG considered that there was a low threshold for admission of paediatric patients with suspected myo/pericarditis and therefore these data did not raise any new concerns. The EWG also considered that the new literature data available on long-term outcomes of vaccine-associated myo/pericarditis did not raise any new issues. The EWG advised that while the available data on long-term outcomes was reassuring so far, further data and studies were required and supported the planned PHE study of long-term cardiac outcomes in the UK.

5.10 The EWG discussed possible mechanisms of myo/pericarditis in association with Pfizer/BioNTech and Moderna COVID-19 vaccines and that it was important to understand these both for the COVID-19 vaccines themselves and for any future mRNA vaccines. The EWG considered that the international data currently indicating more frequent reporting of myo/pericarditis with Moderna COVID-19 vaccine compared with Pfizer/BioNTech COVID-19 vaccine may be related to the relatively higher dose and subsequent antigenic challenge with the Moderna vaccine. The EWG supported asking Moderna and Pfizer/BioNTech to conduct mechanistic studies regarding the pathogenesis myo/pericarditis in association with their vaccines.

5.11 Overall, the EWG agreed that no additional regulatory action concerning COVID-19 vaccines and myo/pericarditis was necessary at the present time, The EWG advised further close monitoring of this issue and emphasised the importance of further studies including mechanistic studies.

6. Update on Menstrual Disorders and COVID-19 Vaccines

6.1 The EWG was presented with an update on the currently available evidence regarding menstrual disorders and unexpected vaginal bleeding following vaccination against COVID-19 including an update on spontaneous reports of menstrual disorders reported via the UK Yellow Card Scheme for the AstraZeneca, Pfizer-BioNTech and Moderna COVID-19 vaccines (with a data lock point of 23 August 2021), updated data from the Yellow Card Vaccine Monitor and non-UK post-marketing data for the Janssen COVID-19 vaccine. The EWG was also informed of the recent MHRA communications, aiming to provide clear and reassuring key messages for the UK public and healthcare professionals, outlining the latest evidence on menstrual disorders, pregnancy and COVID-19 vaccination.

6.2 The EWG considered written comments received from members of the Medicines for Women's Health Expert Advisory Group.

6.3 The EWG agreed that the updated review did not identify any new signals regarding menstrual disorders and unexpected vaginal bleeding following vaccination against COVID-19. The EWG advised that it remained the case that no causal relationship between menstrual disorders and AstraZeneca, Pfizer, Moderna and Janssen COVID-19 vaccines had been established to date, and that no regulatory action was required at the current time. The EWG advised that this issue should be brought back to future EWG meetings on an ad hoc (rather than a scheduled) basis as needed; however, the MHRA should continue to keep this issue under close monitoring.

6.4 The EWG supported the recent MHRA communications on menstrual disorders, pregnancy and COVID-19 vaccination. The EWG advised that positive messages should continue to be communicated and that current advice should be reiterated to healthcare professionals such as GPs and midwives to help ensure key messages are communicated to vaccine recipients.

7. AstraZeneca COVID-19 Vaccine Potency

7.1 The COVID-19 vaccine AstraZeneca ("AZ vaccine") was approved by the MHRA for supply under Regulation 174 (Reg174) in December 2020. A conditional Marketing Authorisation (CMA) has been in place since June 2021 for commercial stock, once it is available.

7.2 NIBSC, as the UK's OMCL, has been undertaking independent batch testing and certification of all COVID-19 vaccine batches for the UK market. The team has amassed a data set from more than 80 batches of the AZ vaccine. There is a discrepancy between the

vaccine potency assay results for the AZ vaccine obtained by the manufacturer and those obtained by the OMCL (NIBSC). All batches tested to date by NIBSC meet the Reg174 potency specification. However, the CMA potency specification is set higher and not all batches are expected to meet this specification when tested by NIBSC.

7.3 A technical investigation into this discrepancy between manufacturer's contract testing laboratories and that from NIBSC and other OMCLs is underway, but the discrepancy has implications for deployment, despite evidence from the PHE real world data that these batches (as used in the UK immunisation programme) provide good protection against COVID-19 disease.

7.4 The rationale behind the establishment of the product potency specifications was outlined:

The R174 batches are primarily dosed based on virus particle number. Clinical trial batches fully justify the release specification for this parameter. It was noted that other regulatory authorities also dose the vaccine based on viral particle number. In the EU, however, dosing is based on infective particle number instead. The UK also adopted this unit for dosing in the CMA to ensure parity with the EU to allow straightforward access of this product into NI. During iterative rounds of assessment, the EU raised the specification limit for infectious units from 3.2×10^8 ifu/mL (i.e. the R174 limit) to 7.0×10^8 ifu/mL. This higher limit for the CMA means that batches for use under R174 may not conform to the more stringent specification in force for products released under the CMA.

7.5 A summary of NIBSC potency data was presented. The test performs within expected limits, though an assay control material shows a lower, but within acceptable limits, potency trend. Overall, the final drug product potency for individual batches are lower than those reported by the company contract testing laboratory. Batches of vaccine tested by NIBSC are all derived from one drug substance manufacturer.

7.6 Coincidentally, a number of batches tested by NIBSC have also been assessed by another National Control Laboratory in the EU corroborating NIBSC data. A NIBSC internal review of its assay performance has resulted in some modifications to optimise the assay but this is not expected to result in all batches meeting the CMA specification.

7.7 The company is undertaking an investigation, considering results from more than one National Control Laboratory.

7.8 The purpose of the presentation was to make EWG aware of the following:

a. The potency differences noted are most profound for one DP site;
b. Assuming no changes are made to the Drug Product production process, the refinement of the assay at NIBSC alone may not result in all future batches meeting the CMA specification;
c. The manufacturer-led investigation may not identify the root cause for the differences in potency results between OMCLs and CTLs;
d. The move from Reg174 to CMA may result in a number of batches identified as Out of Specification for the potency value;
e. If legal advice agrees, NIBSC will need to approach the EWG for guidance on Batch Specific Variation for those batches that do not meet the CMA specification, but which are deemed critical for vaccination campaign use.

8. <u>Any Other Business</u>

None.

9. Date and time of next meeting

The next scheduled meeting is to take place on **Friday 10th September** at **10:30**.

The Meeting today started at 11:38 and ended at 16:12.

Members are reminded that the content of papers and proceeding of the meetings are to be treated as 'Official – sensitive commercial'. Members are also reminded that, in accordance with the Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members must also declare any other matter which could reasonably be perceived as affecting their impartiality. Detailed guidance is set out in the Code of Practice

Annex I

Conflict of Interest Policy for CHM COVID-19 Vaccine Benefit Risk EWG

Chair and Members

- May not hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May not currently be or have previously been involved in the development of COVID-19 vaccines

Invited to all meetings, receives all papers and presentations and is permitted full participation in discussion, including drawing up conclusions and recommendations

Invited experts

- May hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May currently be or have previously been involved in the development of COVID-19 vaccines

May be invited to all relevant meetings, receives all papers and presentations and is permitted to participate in discussions when invited by the Chair. Does not contribute to conclusions and recommendations

Observers

Are invited to attend all meetings. Will not participate in drawing up conclusions and recommendations.

Annex II

Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UOL to support PhD in drug interactions.
Other relevant interests in Pfizer, Janssen, Sanofi – Sir Munir is part of an EU-funded IMI consortium on gene therapy, and these companies are partners in the project. The University of Liverpool will get funding from the EU (but not from the partners), this IMI project commences on 3rd November 2020.
AGILE – this is a Liverpool early phase trial platform (between University of Liverpool and Liverpool School of Tropical Medicine). It is funded by the Wellcome Trust and UKRI/DHSC/NIHR. It is NOT evaluating vaccines, but only drugs to treat COVID-19. Sir Munir is not on the trial management group, and he is not directly involved in choosing the compounds for the study. Sir Munir has no involvement with any of the developers of the compounds to be studied (academic or industrial).
Sir Munir is a member of the UK COVID Therapeutics Advisory Panel (UK-CTAP), which is advising the CMO on which compounds need to be prioritised for the RECOVERY+ trial (RECOVERY is funded via NIHR/DHSC).

Professor Breuer– NPNS – Professor Breuer is on the data safety monitoring committee, DSMB, a study looking at combining vaccines being run by Matthew Snape in Oxford. There does not appear to be any involvement of the vaccine manufacturers and is for already licensed vaccines. The study is funded by the NIHR (Dec 2020).

Professor French - Other relevant interest - Provides clinical care when in covering the acute medical wards where patients with COVID-19 are cared. NPNS in GSK - In September 2020 a sub-contract was signed with the Liverpool School of Tropical Medicine to undertake work evaluating the safety and effectiveness of GSK's RTS's malaria vaccine in Malawi. GSK are the primary funders to the LSTM.

Professor Hyrich – NPNS - Professor Hyrich was co-I on an investigator-initiated research grant exploring predictors of outcome in rheumatoid arthritis. NPNS Pfizer- she is a Co-I on a grant exploring adherence to JAK inhibitors in rheumatoid arthritis. NPNS in Abbvie, Professor Hyrich gave some lectures at an education conference on effectiveness of treatment for rheumatoid arthritis.

Professor Lachmann – Other relevant interest as a volunteer participant in the Oxford vaccine study and no other involvement in the study.

Professor Lehner - Other relevant interest – Professor Lehner previously held a DPAC (Discovery Partnership with Academia) agreement with GSK, but this has been completed. Professor Lehner's participation in his local hospital D and T governance committee deliberations would form the normal activity and professional responsibility in his post and does not interfere with the EWG considerations (Sept 2020).

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust. Other relevant interest in AstraZeneca arising from being part of a collaboration in which the epidemiology and therapeutic approaches to Vaccine associated Thrombosis-Thrombocytopenia (VITT).

Professor Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019).

Professor Price - NPNS in GSK and AstraZeneca – which relates to donations provided by both companies to the British Toxicology Society (BTS) to support their Annual Congress and Education and Training of which Professor Price is currently President of the Society (2020-2022).

Dr Riordan - Other relevant interests - Participant in Oxford University's ChAdOx1 nCoV-19 clinical trial –received immunisation 27/8/2020. NPNS - Postgraduate External Examiner for Oxford University (Postgraduate Diploma in Paediatric Infectious Diseases). Member of the independent Data Safety Monitoring Board for COV-BOOST trial.

Professor Solomon - Other relevant interests – Professor Solomon provides clinical care for patients with Covid-19; chaired the MRC/NIHR committee which awarded funding for development of the Oxford Vaccine.

Mrs Wang – Other relevant interests arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, as recorded on Mrs Wang's medical records. The family of Mrs Wang lives with several rare diseases and conditions, some of which result in epileptic fits.

Professor Weir - NPNS - Imperial College and Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials

Observers

[redacted] University of Oxford employee [redacted] JCVI

Professor Wei Shen Lim - NPNS arises from the institution (Nottingham University Hospitals NHS Trust) where Professor Lim works has received unrestricted investigator-initiated research funding from Pfizer for an unrelated prospective population-based cohort study of pneumococcal pneumonia in which Professor Lim is the Chief Investigator.

[redacted] - Lapsed and NPNS - Regarding companies to declare interests for, prior to joining Public Health Scotland, [redacted] worked for a company that provided epidemiological services to the pharmaceutical industry. Whilst working there, [redacted] supported respiratory vaccine development activities at [redacted] has now left that role.

[redacted] - Other relevant interests in Pfizer & GSK- The Immunisation and Countermeasures Division has provided vaccine manufacturers (including Pfizer and GSK) with post-marketing surveillance reports on pneumococcal and meningococcal infection which the companies are required to submit to the UK Licensing authority in compliance with their Risk Management Strategy. A cost recovery charge is made for these reports.