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

Minutes of the meeting held on Friday 5th May 2023 at 13:00 in person/hybrid at 10SC

Participants Present

Members

Professor Sir M Pirmohamed (Chair)¹ Professor G Dougan² Mr VI G Fenton-May¹ Professor D Goldblatt² Ms S Hunneyball¹ Professor K Hyrich¹ Mr R Lowe³ Dr S Misbah¹ Professor S Price³ Professor C Robertson³ Professor K M G Taylor¹ Dr R Thorpe¹ Professor M Turner³ Professor S Walsh¹ Mrs M Wang¹ Professor C Weir³

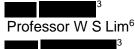
Apologies

Professor J Breuer Professor N French Professor H J Lachmann Professor P J Lehner Professor Y Perrie Dr A Riordan

Invited Experts

	4
	5

Observers





16^h January 2024

Professional Staff of MHRA Present		
- S&S		
- S&S		
- HQA		
- HQA (Principal Assessor)		
- S&S		
- HQA		
- S&S		
Dame June Raine - MHRA CEO		
- S&S		
J Singh - HQA		
- S&S (Principal Assessor)		
P Tregunno - S&S		
- HQA		
- HQA		
- S&S		

Government Legal Team



<u>Secretariat</u>



Key HQA = Health Quality & Access Group S&S = Safety & Surveillance Group MHRA CEO = Chief Executive Officer

1 Attended in person

- 2 Attended in person during item 2
- 3 Joined on line
- 4 Joined on line and presenter for item 3
- 5 Joined on line and left after item 2
- 6 Joined on line during item 2

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1. Introduction and Announcement

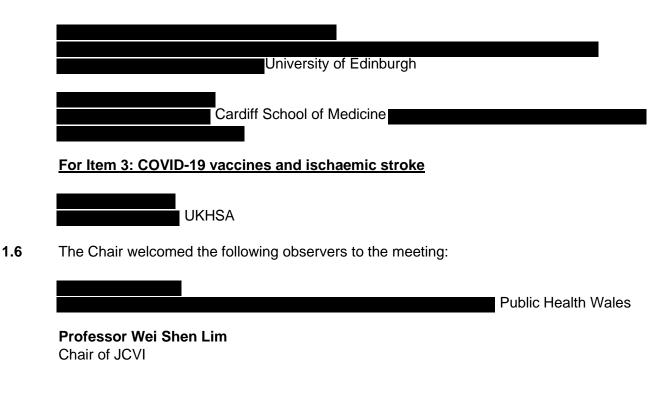
1.1 The Chair reminded Members, invited Experts and observers that the content of papers and proceeding of the meeting are strictly confidential and should be treated as 'Official – sensitive commercial' and should not be disclosed. There is no consent for members / participants to record the meeting, 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 Professor Breuer, Professor French, Professor Lachmann, Professor Lehner, Professor Perrie and Dr Riordan for this meeting.
- **1.5** The Chair welcomed the following Invited Experts to the meeting:

For Item 2: COVID-19 AstraZeneca and ADEM





NHS England and NHS Improvement (National)

2. Update on COVID-19 vaccine AstraZeneca and acute disseminated encephalomyelitis (ADEM)

- 2.1 The EWG were presented with an updated review of the currently available evidence, regarding the risk of acute disseminated encephalomyelitis (ADEM) with the COVID-19 vaccine AstraZeneca following initial presentation of this signal in August 2022. The EWG considered Yellow Card data with a data lock point of 22nd February 2023 for the COVID-19 vaccine AstraZeneca, COVID-19 vaccine Pfizer/BioNTech and COVID-19 vaccine Moderna, statistical analyses using secondary uses services data provided by UKHSA and published literature. This review also considered data identified from other regulatory authorities and how this evidence is reflected in the associated product information within these jurisdictions.
- 2.2 The EWG were informed that since this was last reviewed, one additional Yellow Card report of ADEM following COVID-19 vaccine AstraZeneca had been received bringing the total to 15 spontaneously received UK suspected reports. The reporting rate remained below expected incidence. Previous consideration by the EWG noted the diagnostic complexity of ADEM in adult populations and that there may be an element of underreporting. To address this, additional analyses was undertaken to include the common differential diagnoses 'Neuromyelitis Optica Spectrum Disorder (NMOSD)' and 'Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD)'. The EWG were informed that the addition of these similar neurological conditions, with overlapping symptom presentation, do not directly indicate possible misdiagnosed cases due to the limited clinical detail presented in the Yellow Card reports but do suggest that there may be increased concern to the wider body of evidence underpinning occurrence of ADEM, NMOSD and MOGAD.
- **2.3** The EWG were notified that a similar data analysis was undertaken for the mRNA vaccines. Review of these reports did not indicate a signal of concern for these vaccines.
- 2.4 The EWG were informed that UKHSA had undertaken additional epidemiological review to further investigate this signal. This consisted of an observed versus expected (OvE) analysis and a self-controlled case series (SCCS) study using Secondary Uses Services data that looked at ADEM specifically. These results indicated that there was a statistically significant increase in risk of ADEM following dose 1 of COVID-19 vaccine AstraZeneca in both OvE and SCCS analyses. The EWG discussed whether this may be related to the high-risk population who received COVID-19 vaccine AstraZeneca at the time of highest use in early 2021. However, it was noted that the risk factors for ADEM are not well-defined. The EWG discussed how the SCCS design accounts for between person baseline variability and is a more robust analysis. Whilst numbers of events are still considered low

for this event, the observed signal aligns with the MHRA's analyses based on Yellow Card data, which also saw a raised signal following the first dose of COVID-19 vaccine AstraZeneca.

- 2.5 The EWG were informed that the Therapeutic Goods Administration (TGA) has included ADEM within the warnings and precautions for use section of their product information. The TGA did acknowledge that the evidence did not support a clear increase in risk, however based on biological plausibility and case assessment, concluded to make this addition as a precautionary measure. The EWG were made aware that other international regulators do not have ADEM included within the product information for COVID-19 vaccine AstraZeneca.
- 2.6 The EWG were presented with an updated literature search that identified additional case reports as well as a number of systematic reviews. Robust analytical studies were not readily available that specifically looked at the risk of ADEM following the COVID-19 vaccine AstraZeneca. It was observed that the majority of published studies considered the risk of demyelinating conditions more generally, rather than ADEM in isolation, and often considered all available COVID-19 vaccinations, rather than just COVID-19 vaccine AstraZeneca alone.
- 2.7 The EWG and invited neurological experts considered that given the link between COVID-19 vaccine AstraZeneca and other neurological events such as Guillain-Barré syndrome and transverse myelitis, an association could not be excluded based on the limited available data. The EWG noted the evidence was marginal, and it is likely that additional evidence of this association would not be available given the limited global usage of COVID-19 vaccine AstraZeneca in the ongoing vaccine rollout.
- **2.8** The EWG concluded that a precautionary approach should be pursued, and regulatory updates to the product information should be considered to reflect the potential risk of ADEM in a similar manner to that presented by the TGA.

3. Updated analysis of COVID-19 vaccines and ischaemic stroke

- **3.1** The EWG heard a presentation from the UK Health Security Agency (UKHSA) on their updated analysis of ischaemic stroke in individuals aged 50 years and older after COVID-19 Original/Omicron BA.1 bivalent booster vaccine using Secondary User Service (SUS) inpatient discharge data for admissions from 05 September 2022 to 04 December 2022. Further to the initial analysis presented to the EWG in February 2023, the updated analysis included additional information in relation to co-administration of influenza vaccine with COVID-19 BA.1 bivalent vaccine in people aged 65 years and older.
- **3.2** The EWG heard that in the cases of ischaemic stroke identified in people aged 50 years, most people were aged 65 years and older. Overall, around 15% of people had received co-administration of COVID-19 vaccine and influenza vaccine and, of these, over 85% had received an adjuvanted influenza vaccine.
- **3.3** As previously, the EAG heard that the results from SUS analysis showed no evidence of an increased risk of ischaemic stroke in the 3 weeks post vaccination in either people aged 50 years and above or 65 years and above with either Moderna or Pfizer bivalent COVID-19 vaccines compared with vaccinated people from day 22 onwards. The EWG noted that the updated analysis also showed no evidence of an increased risk of ischaemic stroke in the 3 weeks post vaccination in people aged 65 years and above who had received concomitant influenza vaccine and either Pfizer or Moderna COVID-19 BA.1 bivalent vaccine.

3.4 The EWG also noted that there was no evidence of a signal for haemorrhagic stroke in association with COVID-19 BA.1 bivalent vaccine in these SUS data.

4. Update on US ischaemic stroke analysis

- **4.1** The EWG was presented with follow-up to a paper presented in February 2023. The initial paper concerned a statement published by the US Centers for Disease Control and Prevention (CDC) in January 2023 which highlighted a signal for ischaemic stroke detected in patients aged 65 years and older who received the Pfizer-BioNTech Original/Omicron BA.4/5 bivalent vaccine, in the first 21 days after vaccination compared with days 22-44, based on statistical disproportionality. The follow-up involved a reanalysis of the signal by the CDC incorporating several more months of data and providing updated results.
- **4.2** The EWG was reminded that the original CDC signal assessment found an adjusted rate ratio (aRR) of 1.47 (95% confidence internal [CI] 1.11-1.95) for the risk of ischaemic stroke in days 1-21 following the Pfizer-BioNTech Original/Omicron BA.4/5 bivalent vaccine compared with days 22-44, in patients aged 65 years and older in the Vaccine Safety Datalink (VSD). This analysis used a data cut-off in January 2023. There was no signal detected in patients under 65 years of age with the same vaccine or with the Moderna Original/Omicron BA.4/5 bivalent vaccine in any age group. The signal was not detected in other US healthcare databases or by any other international regulators. At that time a supplementary analysis in the VSD also found an increased risk of ischaemic stroke in patients aged 65 years and over who received the Pfizer-BioNTech Original/Omicron BA.4/5 vaccine on the same day as a high-dose or adjuvanted influenza vaccine, in days 1-21 compared with days 22-44 (aRR 2.00, 95% CI 1.18-3.48).
- **4.3** The EWG was informed that, in the updated VSD analysis using a data cut-off in April 2023, both signals were no longer statistically significant (primary analysis: aRR 1.26, 95% CI 0.99-1.60; supplementary analysis: aRR 1.59, 95% CI 0.99-2.61). A further analysis of spontaneous reports of ischaemic stroke to the US Vaccine Adverse Events Reporting System with the bivalent mRNA vaccines did not provide evidence of a statistical signal. The CDC concluded that no safety signals had been shown in the VSD or VAERS and no regulatory action was indicated. The CDC is conducting further epidemiological analyses to investigate ischaemic stroke with the mRNA vaccines and concurrent administration of mRNA and influenza vaccines.
- **4.4** The EWG noted the updated information and recommended that monitoring of ischaemic stroke should continue, with no regulatory action warranted at this time.

5. COVID-19 Vaccines still under assessment and strain selection plans

5.1.1 An update was provided to the EWG about ongoing marketing authorisation application assessments for two new vaccines:

Bimervax (Hipra): This is a	vaccine which
	This is an ECDRP application which
will be approved as soon as possible af	ter the EMA approval.

Cosmovaxx (Vaxxinity). This is another second vaccine which second vacci

of the dossier while TGA is assessing the finished product (quality) and the nonclinical section of the dossier.

5.1.2 Furthermore, the strain selection for the upcoming booster campaign was discussed. There have been some ICMRA and Access Consortium discussions regarding the selection of the next vaccine strain, with input from FDA, EMA and WHO, but a decision has not yet been made.

6. <u>Minutes of the meetings held on:</u>

- Friday 23rd April 2021
- Friday 14th May 2021
- Wednesday 6th October 2021
- Tuesday 9th November 2021
- Wednesday 17th November 2021
- Tuesday 13 December 2022
- Friday 4th February 2022
- **6.1** All minutes listed above were approved as true and accurate record of the proceedings, subject to some minor amendments, typos and grammatical errors, which have been resolved.

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

7.1 Verbal update on COVID-19 vaccine ADR data publication

- **7.1.1** The EWG were presented with an update on the plans for transition to routine data publication and communication of safety concerns for COVID-19 vaccines after March 2023. The Group were reminded that in June 2022 they endorsed the proposal to reduce the frequency of the weekly publication on COVID-19 vaccine ADR data in a phased approach, starting with a monthly publication from August 2022 reducing to quarterly from the end of 2022.
- **7.1.2** The EWG noted that monthly reports had continued throughout the duration of the Autumn 2022 COVID-19 vaccine booster programme, during which over 20 million doses of bivalent mRNA vaccines had been administered in the UK. The EWG heard that the Autumn 2022 booster programme had now concluded, and the MHRA's ongoing surveillance of the Moderna and Pfizer (Original/BA.1) bivalent vaccines had not revealed any new safety concerns, with the nature of the suspected adverse events being in line with that seen with the monovalent mRNA vaccines.
- **7.1.3** The EWG noted that the departure from the June 2022 proposal to move to a quarterly narrative publication from the end of 2022 to stopping regular narrative publication after March 2023 was proportionate to the established safety profile of the main COVID-19 vaccines used in the UK immunisation programme to date and the lack of any new safety signals concerning bivalent COVID-19 vaccines. Moreover, the proposal is in alignment with other major regulators who no longer publish regular narrative information concerning COVID-19 vaccines.
- **7.1.4** The EWG noted that regular publication of Adverse Drug Reaction (ADR) data will continue, including the new interactive analysis prints, in line with approaches for other medicinal products. The EWG also noted that robust safety monitoring and surveillance

of COVID-19 vaccines will continue along with prompt communication on any updated safety advice.

7.1.5 The EWG endorsed the approach and suggested that it would be important to provide signposting for patients to previous versions of the narrative publication on COVID-19 vaccine Yellow Card data.

7.2 Closing Remarks

- **7.2.1** Chair and Members of the COVID-19 Therapeutics EWG were invited to join this part of the meeting as both COVID-19 Vaccines Benefit Risk EWG (92 meetings) and COVID-19 Therapeutics EWG (32 meetings) draws to a close. Dame June Raine took this opportunity to express her deepest gratitude to the Chairs and Members and all other participants for their significant personal contribution and dedication as their advice has enabled MHRA to carry out robust regulation of medicines and ensured that the UK and international populations were able to benefit from safe and effective COVID-19 vaccines at the earliest opportunity. The Agency is greatly indebted to the significant contribution of the Expert Working Groups.
- 8. The Meeting today started at 13:03 and ended at 14:49.

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

The following participants declared interests and other relevant interests at the meeting today:

Professor Sir Munir Pirmohamed - <u>NPNS</u> AstraZeneca - Research grant to UOL to support PhD in drug interactions.

<u>Other relevant interests</u> 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).

Ms Hunneyball - <u>Other relevant interest</u> – writes articles published in the Chemist and Druggist magazine, a trade magazine for pharmacists, but receives no payment for these articles. The information referred to in the articles is in the public domain. Ms Hunneyball makes it clear that these are her personal views and reflections and references all sources of information used.

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

Professor 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.

Dr Misbah - <u>NPNS</u> - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust.

Professor Price - <u>NPNS</u> 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 Ramsay - Other relevant interest 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.

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Mrs Wang - <u>Other relevant interests</u> 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 - <u>NPNS</u> - Imperial College and <u>Other relevant interest</u> arising from his department collaborates with Imperial College on a number of clinical trials.