

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

Minutes of the meeting held on **Friday 18th March 2022** at **11:30** via videoconference

Participants Present

Members

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

Apologies

Professor G Dougan
Sir M Jacobs
Professor P J Lehner

Invited Expert

[REDACTED] ¹

Visiting Expert

[REDACTED]

Observers

[REDACTED]
[REDACTED] ³
[REDACTED]
[REDACTED] ³
[REDACTED] ³
[REDACTED]
[REDACTED]
Professor WS Lim
[REDACTED]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea – LD

Presenters supporting specific items⁴

[REDACTED] - VRMM
[REDACTED] - VRMM
[REDACTED] - VRMM
[REDACTED] - VRMM
[REDACTED] - LD

MHRA Observers

[REDACTED] - VRMM
[REDACTED] - LD
Dr S Branch - VRMM
[REDACTED] - VRMM
[REDACTED] - MHRA-Policy
[REDACTED] - VRMM
[REDACTED] - LD
[REDACTED] a - VRMM
[REDACTED] - VRMM
Mr P Tregunno - VRMM
[REDACTED] - Comms

Secretariat

[REDACTED]
[REDACTED]

[REDACTED]

23rd June 2022

¹ participated for items 2-4
² presented item 2
³ CHM commissioners observed item 2
⁴ supported specific items

Key

LD = Licensing Division
VRMM = Vigilance & Risk Management of Medicines
Comms = MHRA Communications

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 Professors Dougan, Lehner and Sir Michael Jacobs for this meeting.

1.5 The Chair welcomed the following invited expert who joined for specific agenda items:

[REDACTED]
[REDACTED]
[REDACTED] Cambridge University Health Partners

1.6 The Chair welcomed the following visiting expert who presented item 2 - Office for National Statistics excess mortality analyses:

[REDACTED]
[REDACTED] Office for National Statistics

1.7 The Chair welcomed the following observers to the meeting:

[REDACTED]
[REDACTED] University of Birmingham

[REDACTED]
[REDACTED] NHS Lothian, Edinburgh

[REDACTED]
[REDACTED] Public Health Scotland

[REDACTED]
[REDACTED] University of London

[REDACTED]
[REDACTED]
[REDACTED] UCL Institute for Global Health
[REDACTED]
[REDACTED] Public Health Wales

[REDACTED]
NHS England [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Professor Wei Shen Lim
Chair of JCVI

[REDACTED]
[REDACTED]
[REDACTED]
NHS England and NHS Improvement (National)

2. Presentation from [REDACTED] - Office for National Statistics excess mortality analyses

- 2.1** The EWG were presented with data by the Office for National Statistics exploring the risk of death following COVID-19 vaccination in young people aged 12-29 years in England. The analyses were triggered following a perceived excess in all-cause mortality in this group against a background of emerging evidence on the potential risk of myocarditis and myopericarditis following COVID-19 vaccination.
- 2.2** ONS described a self-controlled case study that they had undertaken linking English death registrations to vaccination records. The objective of this study was to estimate the relative incidence of all-cause, and cardiac-related, deaths in 12-29 year olds in a period following vaccination compared to a baseline time period.
- 2.3** The EWG were shown the primary results of the study which showed no significant increases in risk of cardiac-related deaths, or deaths due to any cause, in the six weeks following vaccination with a COVID-19 vaccine.
- 2.4** The EWG were reassured by the data and agreed with the conclusion that COVID-19 vaccinations were not associated with an increased risk of death, from cardiac causes or otherwise in young people. It was also noted that this contrasted with data from this study, and seen elsewhere, of the risk of death, including due to cardiac-related causes, in the weeks immediately following SARS-CoV-2 infection in the same age groups. The EWG concluded that the presented evidence from this study supported a positive benefit risk balance for the COVID-19 vaccines.
- 2.5** The EWG noted the large size of the dataset used and the completeness of the vaccination record data. They agreed that the self-controlled case series design, which is a well-established method for conducting vaccine safety studies, was an appropriate study design for exploring this issue and that it had been well implemented. They also noted the sensitivity of the self-controlled case series design for detecting small changes in risk and that it accounted for time-constant confounders which strengthened confidence in their conclusions.

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- 2.6 Finally, the EWG also noted that mortality rates in young people often fluctuated due to small numbers, that surveillance was particularly impacted upon by delays in registration of death, and that data were anticipated which would further explore causes of death during the pandemic.
3. **Update of myocarditis and pericarditis following administration of Pfizer/BioNTech, Moderna and AstraZeneca COVID-19 vaccines**
- 3.1 The EWG were presented with an update on the Yellow Card reports for myocarditis and pericarditis with the three COVID-19 vaccines in use in the UK vaccination programme as well as updated observed vs expected analysis, rapid cycle analysis and new international data and literature.
- 3.2 The EWG were presented with the UK Yellow Card data, with the EWG noting that the reporting rates seen following third/booster doses for Pfizer/BioNTech and Moderna continued to be lower than those seen for the primary dose schedule of the vaccines and that the rates were similar for both vaccines. The EWG were reassured by the lower reporting rates following third/booster doses. The EWG were presented with additional age breakdowns for the Pfizer/BioNTech vaccine for children and adolescents, with reporting rates in the 12-15 year age group being lower than those in the 16-17 age group, and with both age groups having lower reporting rates compared to adults. The EWG was reassured by the lower rates in the younger age groups. For AstraZeneca the reporting rates for first and second doses have remained similar to previous reviews and overall were lower than both of the mRNA vaccines.
- 3.3 The EWG were presented with an update to the observed vs expected and rapid cycle analyses. The EWG noted that the analysis showed signals continuing to be raised for myocarditis with the first and second dose of the Pfizer/BioNTech vaccine in the under 18 year age group. A signal continued to be raised with the third/booster dose of mRNA vaccines in the 18-49 year age group.
- 3.4 The EWG were presented international data on reports of myocarditis in children and adolescents. The EWG noted a similar reporting pattern to adults, with more reports after the second dose and more reports in males. Clinical course was reported as mild with all patients being released from hospital. The EWG considered that the available data on myocarditis in children did not raise any new concerns.
- 3.5 The EWG concluded that the benefits continued to exceed the risks overall for each vaccine and for all authorised subpopulations. No regulatory action was required based on the data presented.
4. **AstraZeneca COVID-19 Vaccine and Cardiomyopathy**
- 4.1 The EWG was presented with an assessment of the available Yellow Card data for the Pfizer/BioNTech vaccine, the AstraZeneca vaccine and the Moderna vaccine alongside other evidence from the literature and other international regulators.
- 4.2 The EWG heard that the reporting rate for Cardiomyopathy and related terms in the Standard MedDRA Query (SMQ) cardiomyopathy for each vaccine is very low.
- 4.3 The EWG noted that in a large proportion of reports, information was too limited to conduct a robust assessment, or many cases were confounded due co-morbidities.

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- 4.4 The aetiologies of different cardiomyopathy types were discussed, including stress and dilated cardiomyopathy; in view of SARS Cov-1 infection being associated with myocarditis, it was noted that past viral infections leading to myocarditis can result in cardiomyopathy years later.
- 4.5 The EWG agreed that the data did not raise a new safety concern of cardiomyopathy with any of the three vaccines and that no regulatory action was necessary at this time.
- 4.6 The EWG recommended that reports of suspected cardiomyopathy should continue to be closely monitored.
- 5. Update on COVID-19 vaccines and menstrual disorders**
- 5.1 The EWG was presented with an update on the currently available evidence regarding menstrual disorders and unexpected vaginal bleeding following vaccination against COVID-19. The available data included 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 February 2022), spontaneous data from the Netherlands, new published and pre-print studies on menstrual disorders and a new study on fertility following vaccination against COVID-19. An exploratory analysis using linked Secondary Users Service/Clinical Practice Research Datalink data in England was also presented.
- 5.2 The EWG also considered written comments received from members of the Medicines for Women's Health Expert Advisory Group.
- 5.3 The EWG agreed that there were difficulties in interpreting the findings of published/pre-print study data in relation to menstrual disorders and COVID-19 vaccines. These were at high risk of bias in some studies, the prevalence of menstrual disorders generally amongst women and the fact that there are many factors that can disrupt menstrual cycles such as stress and illness. However, the EWG concluded that there were no noteworthy trends in the study data, e.g. both heavy menstrual bleeding and delayed or light bleeding following COVID-19 vaccines were reported. Further, the EWG agreed that a potential signal of an increase in cycle length seen in a US study in people who received 2 doses of COVID-19 vaccine in the same cycle was not relevant to the UK where the interval between COVID-19 vaccine doses is at least 8 weeks.
- 5.4 The EWG considered that the lack of evidence of association between fertility issues and COVID-19 vaccines from the recent US cohort study was reassuring. The EWG considered that this was an important finding given public concerns as to whether there is a potential impact on fertility following reports of menstrual disorders after vaccination against COVID-19.
- 5.5 The EWG agreed that the currently available evidence did not support a link between changes to menstrual disorders and unexpected vaginal bleeding and COVID-19 vaccines and advised that no regulatory action was required at the current time.
- 6. For information - COVID-19 Vaccine Janssen – Booster indication (EC Reliance)**
- 6.1 The EWG noted that currently the Janssen vaccine is indicated for use in individuals aged 18 years and over for single dose primary vaccination.
- 6.2 The EWG heard that a variation has been submitted via the EC decision reliance procedure to update the relevant sections of the product information to i) introduce a homologous booster

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dose, ii) introduce a heterologous booster dose after primary vaccination with an approved mRNA vaccine, iii) consequentially to add a contraindication in individuals with a history of thrombosis with thrombocytopenia syndrome (TTS) following vaccination with any COVID-19 vaccine and, iv) to update the efficacy data for primary vaccination.

- 6.3** The EWG heard that the main efficacy and safety data to support a homologous booster dose is from the large phase 3 study COV3009 in which 31300 individuals were randomised 1:1 to receive 2 doses of placebo or COVID-19 Vaccine Janssen (Janssen) 56 days apart. Vaccine efficacy against symptomatic COVID-19 from 14 days post dose 2 was 75% and 100% against severe disease. The solicited adverse reaction profile was similar to that after the first dose and no new safety signals were identified. The EWG noted that across studies where a booster dose had been given at 2, 3 or 6 months, an increase in both neutralising and binding antibodies was seen 1-month post boost.
- 6.4** The EWG heard that the main data submitted by the company in support of a heterologous booster dose was from an ongoing phase 1/2 heterologous platform study with a limited sample size, being conducted by the NIH in the United States. Adults that had completed primary vaccination with Spikevax, Janssen or Comirnaty at least 12 weeks prior to enrolment with no history of SARS-CoV-2 were randomised 1:1:1 to receive a booster with one of the 3 vaccines. A booster response to Janssen was demonstrated regardless of the primary series. Whilst the neutralising antibody titers at Day 15 after a heterologous boost with Janssen are lower than after a homologous boost by Spikevax/Comirnaty, by Day 29 the neutralising antibody titers are roughly similar between both regimens. The solicited adverse reaction profile following a heterologous booster was similar to that after the 1st dose/homologous booster dose and no new safety signals were identified.
- 6.5** The EWG heard that preliminary immunogenicity data from the ongoing dedicated booster study COV2008 also showed a similar trend, with lower antibody titers at Day 14 with heterologous boosting but broadly similar titers by Day 28.
- 6.6** The EWG noted that similar neutralising antibody results were seen at Day 28 post boost in the UK COV-Boost study in participants that had completed primary vaccination with Comirnaty and received either a homologous booster dose or heterologous booster with Janssen. Binding antibody titres were higher after homologous boosting with Comirnaty. Reactogenicity was higher after receiving heterologous booster dose of Janssen compared with a homologous booster dose of Comirnaty but no new safety signals were identified.
- 6.7** The EWG heard that longer median follow-up data (approximately 4 months) is now available from the original single dose pivotal efficacy/safety study COV3001. Whilst a drop in vaccine efficacy against symptomatic COVID-19 is seen, efficacy remains above the minimum criteria set by the WHO and this drop is considered related to the emergence of variants of concern. The EWG noted that, reassuringly, no drop in efficacy was seen against severe disease up to 6 months following a single dose of Janssen and there was less variability in terms of efficacy across the variants.
- 6.8** The EWG agreed that the proposed changes to the product information with regards to the updated efficacy information and the introduction of a homologous booster dose were approvable.
- 6.9** The EWG was satisfied with the immunogenicity data to support a heterologous booster dose following vaccination with an approved mRNA vaccine. However, a significant safety concern was raised regarding the potential risk of TTS with a first dose of an adenoviral vector vaccine when used as a heterologous booster after completing a primary series with an approved mRNA vaccine. In view of the lack of sufficient data in this setting to inform on the risk of TTS

and the difference benefit risk balance in this population when compared to use for primary vaccination, in keeping with a previous decision made for Vaxzevria, the EWG considered the benefit risk is negative in this setting.

7. For Information – Comirnaty - EC Reliance variations update

7.1 [Redacted]

7.2 [Redacted]

7.3 [Redacted]

7.4 [Redacted]

7.5 [Redacted]

7.6 [Redacted]

7.7 [Redacted]

8. Any Other Business

None.

9. Date and time of next meeting

The next meeting has been scheduled for **Tuesday 29th March 2022 at 10:30.**

The Meeting today started at 11:30 and ended at 13:29.

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

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 - 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.

Ms Hunneyball - Other relevant interest – 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 – 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.

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

