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

Minutes of the meeting held on **Tuesday 20th September 2022** at **10:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor G Dougan
Mr VI G Fenton-May
Ms S Hunneyball
Mr R Lowe
Dr S Misbah
Professor Y Perrie
Dr A Riordan
Professor K M G Taylor
Dr R Thorpe
Professor S Walsh
Mrs M Wang
Professor C Weir

Apologies

Professor J Breuer
Professor N French
Professor D Goldblatt
Professor K Hyrich
Professor H J Lachmann
Professor P J Lehner
Professor S Price
Professor C Robertson
Professor M Turner

Visiting Expert[1]

[redacted]

Observers

[redacted]

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - HQA
[redacted] - S&S

Presenters supporting specific items

[redacted] - S&S
[redacted] - S&S
Dr S Hopper - HQA
[redacted] - HQA

MHRA Observers

[redacted] - HQA
[redacted] - S&S
[redacted] - S&S
[redacted] - S&S
[redacted] - S&S
[redacted] - HQA
[redacted] - Comms

[redacted]
18th November 2022

Key

HQA = Health Quality & Access Group
S&S = Safety & Surveillance Group
Comms = Communication & Engagement

[1] Presented item 2

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 Breuer, French, Goldblatt, Hyrich, Lachmann, Lehner, Price, Robertson and Turner for this meeting.

1.5 The Chair welcomed the following visiting expert to the meeting:

<u>For Item 2: Risk of death following SARS-CoV-2 infection or COVID-19 vaccination in young people in England</u>

[redacted]
Office for National Statistics

1.6 The Chair welcomed the following observers to the meeting:

[redacted] Public Health Scotland

[redacted]
UKHSA

[redacted]
NHS England and NHS Improvement (National)

2. Risk of death following SARS-CoV-2 infection or COVID-19 vaccination in young people in England

2.1 A presentation was heard from the office for National Statistics on the risk of death following SARS-CoV-2 infection or COVID-19 vaccination in young people in England.

3. Extensive swelling of vaccinated limb and Urticaria with Spikevax COVID-19 vaccine

3.1 The EWG considered an assessment of the EU PRAC's assessment report of extensive swelling of vaccinated limb with Spikevax COVID-19 vaccine, and spontaneous reports received via the Yellow Card Scheme for Spikevax COVID-19 vaccine, with a data lock point of 12 September 2022.

3.2 The EWG also considered the Marketing Authorisation Holder's (MAH's) review of urticaria with Spikevax COVID-19 vaccine following a request by the MHRA, and spontaneous reports of urticaria received via the Yellow Card Scheme for Spikevax COVID-19 vaccine, with a data lock point of 12 September 2022.

3.3 The EWG discussed the mechanism of extensive swelling of vaccinated limb and concluded that the mechanism was unclear. However, the EWG did question whether extensive swelling of vaccinated limb was secondary to localised thrombosis, whereby it was suggested to raise this with the MAH. The EWG also noted that the evidence for extensive swelling of vaccinated limb was not particularly strong and there was only one report of extensive swelling of vaccinated limb.

3.4 The EWG discussed the proposed wording regarding extensive swelling of vaccinated limb and urticaria and agreed overall it was acceptable to align with the EU wording.

3.5 The EWG was in agreement to update the Spikevax product information to include extensive swelling of vaccinated limb and urticaria.

4. Review of Yellow Card reports of anaphylaxis with mRNA vaccines following suspension of the 15-minute observation time in 5–11-year-olds

4.1 The EWG were presented with an update on the Yellow Card reports of anaphylaxis in the 5-11 years age group following the temporary suspension of the 15-minute observation period in the 5-11 years age group. There was a total of 2 reports of anaphylaxis from over a million doses of the Pfizer/BioNTech vaccine. The EWG noted this was only a small increase in reports since this was last reviewed in January 2022, where there were no reports from a smaller exposure of 250 doses in the 5-11-year age group. For all age groups, there had not been any significant increase in the reporting of anaphylaxis since the permanent suspension of the 15-minute observation period and their remained a high proportion of reports where the individual had a previous history of allergy.

4.2 The EWG were presented analysis from NHS England from the National Reporting and Learning System (NRLS), StESI serious incident database and the SitREP vaccine centre daily reporting system. Across all three sources the number of reports of anaphylaxis was very low, with onset times occurring outside of the 15 minutes after vaccination. The EWG were reassured that the data showed that the suspension of the 15-minute observation period following vaccination had not led to an increase in the risk of harm from anaphylaxis.

4.3 The EWG were presented with international data from Japan which showed a low reporting rate of anaphylaxis in the 5-11 years age group of 0.7 cases per million doses. The EWG noted the higher number of doses administered in the 5-11-years age group in Japan compared to the UK and was reassured by the low reporting rate.

4.4 The EWG considered that the UK and international data showed that the incidence of anaphylaxis in 5-11-year-olds is low and that the suspension of the 15-minute observation period had not led to an increased risk of severe outcomes of anaphylaxis. The EWG were reassured that the Yellow Card and NHS England data on anaphylaxis since the suspension of the 15-minute observation period in all age groups did not indicate an excess risk of anaphylaxis or any evidence of harm due to the suspension. The EWG advised that the temporary suspension of the 15-minute observation period in 5–11-year-olds should become a permanent suspension, as previously advised for those aged 12 and above.

5. Comirnaty - Annual Renewal - inclusion of a booster dose in individuals aged 5-11 years, and myocarditis updates to the product information (EC reliance)

5.1 The EWG noted that there are currently 4 presentations of Comirnaty licensed in GB: 3 monovalent 'original' vaccines including a paediatric formulation for use in children aged 5 to 11 years, and the new bivalent original/omicron BA.1 vaccine.

5.2 The EWG heard that 3 procedures have been submitted via the EC decision reliance procedure: i) the second annual renewal of the conditional marketing authorisation (CMA), ii) a variation to introduce a homologous booster dose in children aged 5-11 years, and iii) a variation to update the information about the known adverse events 'myocarditis' and 'pericarditis' in the product information.

5.3 The EWG heard that no new data has emerged during the 2nd annual renewal period that alters the positive benefit/risk balance of Comirnaty. The EWG agreed with the European Medicines Agency's Committee for Medicinal Products for Human Use's conclusion that, given the substantive amount of data now available from clinical trials and real-world data, the clinical safety profile and efficacy of Comirnaty may now be considered comprehensively characterised in the sense of CMA legislation and that the CMA can be converted to a full Marketing Authorisation.

5.4 The EWG noted the positive immunogenicity data supporting the introduction of a homologous booster dose in children aged 5 to 11 years from the open label expansion of study C4591007. The EWG were reassured that the reactogenicity profile of a booster dose in this study was similar to that after dose 2 and that no new safety concerns were identified.

5.5 The EWG heard that, to reflect the current state of evidence with regards to the known adverse events 'myocarditis' and 'pericarditis', several updates have been made to the product information. In particular, the sentence '*The risk of myocarditis after a third dose of Comirnaty has not yet been characterised'* has been removed from the SmPC as this is no longer the case and the following sentence has been included in section 4.8 of the SmPC '*Limited data indicate that the risk of myocarditis and pericarditis after vaccination with Comirnaty in children aged 5 to 11 years seems lower than in ages 12 to 17 years'.*

5.6 No concerns were raised by the EWG, and it was agreed that these reliance procedures are approvable.

6. Nuvaxovid – Inclusion of a booster dose in individuals 18 years and older (EC reliance)

6.1 The EWG heard that a variation has been submitted via the EC decision reliance procedure to introduce a homologous and heterologous booster dose in individuals aged 18 years and older.

6.2 The EWG noted the positive immunogenicity data from 2 studies in support of heterologous booster dosing: Study 2019nCoV-101, part 2, and Study 2019nCoV-501. The EWG heard that solicited reactogenicity data was only collected in study 101 and that in this study solicited adverse reactions occurred at higher frequencies and with higher grades after a booster dose compared with after the primary series. The EWG noted that this is reflected in the updated SmPC and were reassured by the fact that the majority of reactions remained mild to moderate with a median duration of 1 to 3 days and that the reactogenicity profile remained within that seen with some other COVID-19 vaccines, e.g., dose 2 of Spikevax. The EWG heard that, based on limited data, participants that experienced a severe reaction following the second dose of Nuvaxovid are more likely to experience a severe reaction following the third dose and that this is reflected in the SmPC. The EWG highlighted that it will be important to monitor whether a potentiation of reactogenicity with subsequent doses continues beyond the third dose.

6.3 The EWG noted the positive immunogenicity data from the COV-BOOST study in support of heterologous booster dosing after another mRNA vaccine or adenoviral vector vaccine. The EWG were reassured that the reactogenicity profile after a heterologous booster dose was similar to that seen following the control vaccine in the study (MenACWY) and that no new safety concerns were identified.

6.4 The EWG heard that the Risk Management Plan has been updated with this variation to include data on booster doses and that there are no changes to the current important identified/potential risks or missing information. The EWG noted that a separate variation is being submitted to update the product information and RMP to include the new adverse events 'myocarditis' and 'pericarditis' (as presented at the VBR EWG meeting on 25 August 2022). The EWG highlighted that in view of the increased reactogenicity seen with a 3rd dose of Nuvaxovid, the RMP updates with respect to 'myocarditis' and 'pericarditis', should capture characterisation of whether there is any increased risk of myocarditis/pericarditis with a 3rd dose.

6.5 The EWG agreed that this reliance variation is approvable.

7. ECDRP variation application - Spikevax dispersion for injection - PLGB 53720/0002 – 0087
National variation application - Spikevax bivalent Original / Omicron 0.1 mg/mL dispersion for injection - PLGB 53720/0004 – 0006

7.1 These variation applications are to extend the use of Spikevax and Spikevax bivalent as [redacted] booster doses to the adolescent population aged 12 to 17 years. At its meeting on 01 September 2022, CHM advised that data from Study mRNA-1273-P203 Part C should be evaluated prior to the grant of the Spikevax variation (PLGB 53720/0002 – 0087).

7.2 The EWG heard a summary of the clinical immunogenicity data from study P203. Part C investigated a single [redacted] booster dose of Spikevax in adolescent participants who had received a primary series of Spikevax. The EWG was reassured by the adolescent

data and considered that the immune response to the [redacted] booster dose was acceptable, based on a cross-trial comparison of the immune response of young adults to a primary series of Spikevax.

7.3 The EWG also heard summary of the safety and reactogenicity data from Part C. The local and systemic reactogenicity profile after a single [redacted] booster dose of Spikevax were favourable when compared to the reactogenicity profile after Dose 2, in the adolescent participants of Study P203. No new safety concerns were identified. The EWG was reassured by the adolescent data and considered that the reactogenicity and safety profile of a booster dose of Spikevax were acceptable in the adolescent population.

7.4 Overall, the EWG considered that the submitted data were reassuring, and recommended approval of the Spikevax variation. Furthermore, the EWG considered that the data from Study mRNA-P203 Part C could be extrapolated to Spikevax bivalent, and recommended approval of the Spikevax bivalent variation.

8. Any Other Business

8.1 None.

9. Date and time of next meeting

The next meeting has been scheduled for **Friday 7th October 2022** at **11:30**.

The Meeting today started at 10:31 and ended at 11:47.

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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 - 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).

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.

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

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).

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.

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; some of the COPS paper are based in the same institute as Professor Weir (Usher Institute, University of Edinburgh). Other relevant interest arising from his department collaborates with Imperial College on a number of clinical trials.

Observers

[redacted] - 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.