

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

Minutes of the meeting held on **Friday 22nd July 2022 at 11:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Mr VI G Fenton-May
Professor N French
Ms S Hunneyball
Professor K Hyrich
Professor H J Lachmann
Professor P J Lehner
Mr R Lowe¹
Dr S Misbah
Professor Y Perrie²
Professor S Price
Dr A Riordan³
Dr R Thorpe
Professor M Turner
Professor S Walsh
Mrs M Wang
Professor C Weir

Apologies

Professor J Breuer
Professor G Dougan
Sir M Jacobs
Professor D Goldblatt
Professor C Robertson
Professor K M G Taylor

Observers⁴

[REDACTED]
[REDACTED]
[REDACTED]

Secretariat

[REDACTED]
[REDACTED]

Key

HQA = Healthcare Quality & Access Group
S&S = Safety & Surveillance Group
NIBSC = National Institute for Biological Standards & Control
CSO = Chief Safety Officer

Professional Staff of MHRA Present

Principal Assessors

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

Presenters supporting specific items⁵

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

MHRA Observers

[REDACTED] - S&S
[REDACTED] - HQA
[REDACTED] - HQA
[REDACTED] - HQA
Dr A Cave - CSO
[REDACTED] - MHRA-Policy
[REDACTED] - S&S
[REDACTED] - HQA
[REDACTED] - MHRA-NIBSC
[REDACTED] - S&S
Mr P Tregunno - S&S
[REDACTED] - HQA
[REDACTED] - HQA

[REDACTED]

5th May 2023

¹ left during item 7
² joined during item 2
³ left after item 6
⁴ observed to the end of item 5
⁵ supported specific items

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, Dougan, Goldblatt, Robertson, Taylor and Sir Michael Jacobs for this meeting.

1.5 The Chair welcomed the following observers to the meeting:

[REDACTED]
[REDACTED]
[REDACTED] UKHSA

[REDACTED]
[REDACTED]
Public Health Scotland

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

2. A review of the latest studies on COVID-19 vaccines in pregnancy

2.1 The EWG considered the latest safety information from studies of COVID-19 vaccines comparing pregnancy outcomes in vaccinated to unvaccinated mothers, including data on ectopic pregnancy, miscarriages, stillbirth and congenital anomalies.

2.2 The EWG considered the data from 2 pre-publication manuscripts submitted *in confidence* to the MHRA from the UK Vaccination in Pregnancy (UKVIP) surveillance by the UK Health Security Agency (UKHSA) and from the COVID-19 in Pregnancy in Scotland (COPS) study, plus additional analyses from the COPS study.

2.3 The EWG noted that the UKVIP study found similar incidence rates of miscarriage prior to 14 weeks amongst women vaccinated early in pregnancy to other studies and to rates for

unvaccinated women. The study also found no evidence to suggest that miscarriage rates differed with time from vaccine exposure or by gestational age at vaccination.

- 2.4** The COPS study found no increased risk of ectopic pregnancy or miscarriage before 20 weeks associated with COVID-19 infection or with vaccinations against COVID-19 from 6 weeks prior to conception compared to uninfected and unvaccinated women respectively. The EWG noted that the rates of miscarriage for both the COVID-19 Vaccine AstraZeneca and its historical control group were higher than the corresponding groups for the Pfizer-BioNTech and Moderna vaccines; however, the study found no difference in risk of miscarriage for recipients of COVID-19 Vaccine AstraZeneca when compared with unvaccinated women who were pregnant at the same time (contemporary control group).
- 2.5** The EWG noted that this was the first information on ectopic pregnancy and concurred with the MWHEAG that this provided important and reassuring information for women receiving a COVID-19 vaccination before or during early pregnancy. The EWG considered the findings on miscarriage were reassuring overall and added to the currently available data. The EWG considered that an apparently higher risk amongst women who received the COVID-19 Vaccine AstraZeneca compared to historical controls was likely to be explained by a higher baseline risk in women who would have been eligible to receive this vaccine. The EWG considered, however, that this finding may need to be carefully conveyed to avoid misinterpretation. The EWG concurred with the MWHEAG that these findings should be included in the MHRA safety report once published.
- 2.6** Regarding new data on stillbirths, the EWG considered data from a meta-analysis by Prasad et al (2022)¹. The EWG considered that although the data from each study was reassuring that there was no increased risk of stillbirth with COVID-19 vaccines, there were however a number of methodological limitations to the meta-analysis, including inconsistency of vaccine exposure periods and lack of matching between cohorts, plus substantial heterogeneity in the data, that questioned the conclusion of a 15% reduction in stillbirths amongst women vaccinated against COVID-19 in pregnancy compared to unvaccinated women. The EWG concurred with the MWHEAG that this finding should not be included in the MHRA safety report.
- 2.7** Regarding new data on congenital anomalies, the EWG considered data from a population-based cohort study by Goldshtein et al (2022)². Amongst other pregnancy outcomes, this study compared congenital malformation rates for pregnancies exposed to COVID-19 Vaccine Pfizer/BioNTech during the 1st trimester with unvaccinated pregnancies conceived around the same time and study found similar congenital malformation rates amongst vaccinated and unvaccinated pregnancies. The EWG considered that although the data were from a single study, these data were reassuring and concurred with the MWHEAG that these early data on congenital anomalies should be reflected in the MHRA safety report.
- 2.8** The EWG considered that the data on congenital anomalies would be appropriate to include in the product information for the COVID-19 Vaccine Pfizer/BioNTech and supported seeking information on EMA's plans in this respect.

¹ Prasad et al Systematic review and meta-analysis of the effectiveness and perinatal outcomes of COVID-19 vaccination in pregnancy *Nat Commun* 13, 2414 (2022). <https://doi.org/10.1038/s41467-022-30052-w>

² Goldshtein et al Association of BNT162b2 COVID-19 Vaccination During Pregnancy With Neonatal and Early Infant Outcomes *JAMA Pediatrics* (2022) doi:[10.1001/jamapediatrics.2022.0001](https://doi.org/10.1001/jamapediatrics.2022.0001)

3. Update on fatal reports of myocarditis in 2 US adolescents

3.1 This presentation to EWG provided follow-up information on two fatal cases previously presented to the EWG in February 2022

3.2 The EWG was reminded that, in February 2022, the MHRA had informed the EWG of a preprint article describing the clinical and autopsy investigations of two teenage boys in the United States, who died shortly after receiving the second dose of the Pfizer-BioNTech COVID-19 vaccine. The article concluded that the myocardial injury seen in the hearts, described as a post-vaccine reaction, was different from typical myocarditis and had an appearance most closely resembling a catecholamine-mediated stress or toxic cardiomyopathy. At that time, the EWG considered that the article contained limited detail on some aspects of the reports and appeared to lack expert cardiac histopathological input. The EWG recommended that further information should be sought from the US Food and Drug Administration and the authors.

3.3 The EWG was informed of a new pre-print article authored by the Centres for Disease Control and Prevention (CDC) which described in detail the CDC's involvement in post-mortem testing performed on the patients and which highlighted test results which had not been included in the original article. The CDC concluded that one of the patients had evidence of parvovirus B-19 infection in the heart tissue, stopping short of identifying this as the cause of death but highlighting its relevance in the differential diagnoses, while the second patient died from Clostridium septicum sepsis. The EWG was asked to comment on the latest article and offer any additional observations.

3.4 The EWG noted that the finding of Clostridium septicum sepsis was very rare in a young person but noted the high body mass index in that case, possibly indicating underlying medical conditions. The quantification of parvoviral DNA load in the other case would have been helpful in understanding the contribution of this to the sudden death but was not provided. The EWG expressed concern about the key data omitted from the initial publication and the ethical issues raised by this. The MHRA was asked to follow up with CDC on these questions. Overall, the EWG concluded there were alternative causes for cardiac pathology in both cases and that no regulatory action was warranted.

4. Fatal Yellow Card reports following COVID-19 vaccination: Proposed revised text for Coronavirus Yellow Card publication

4.1 The EWG considered a proposed revised summary of reports with a fatal outcome for inclusion in the MHRA regular publication 'Coronavirus vaccine – summary of Yellow Card reporting'. The EWG noted that the revised summary had been drafted in line with the advice from the EWG at their meeting on 29 April 2022 which had been endorsed by the CHM at their 9-10th June 2022 meeting.

4.2 The EWG noted that six key changes had been made to the revised summary of reports with a fatal outcome section to include the following additional information to that provided currently: 1) data on background weekly deaths in the UK, 2) information on the number of lives saved/hospitalisations prevented following COVID-19 vaccination, 3) information about the risk mitigation measures taken by the MHRA in relation to reports of thrombosis with concurrent thrombocytopenia, 4) reassurance that the position of the MHRA is in alignment with that of other regulators, 5) age and sex stratified data on reports with a fatal outcome following COVID-19 vaccination and 6) a summary of how the MHRA processes reports with a fatal outcome.

NOT FOR PUBLICATION

- 4.3 The EWG supported the proposed revisions to the summary of reports with a fatal outcome. The EWG considered that the revised section provided additional information while maintaining consistency with the way information had previously been provided which would allow interested readers to easily pick on the information from earlier publications.
- 4.4 The EWG commented that the revised summary contained quite a lot of text. The EWG suggested that, if possible, the use of visual abstracts would make the information more accessible. The EWG discussed that MHRA may develop further tools for communicating to stakeholders, including patients and the public, in the future. MHRA informed the EWG that they would consider ways to make the revised summary of reports with a fatal outcome more readable, for example by breaking up the text.
- 4.5 The EWG also made a general comment on the overall ‘Coronavirus vaccine – summary of Yellow Card reporting’ publication that the MHRA should ensure that all hyperlinks included in the document were working correctly.
5. **Anaphylaxis, paraesthesia/hypoaesthesia and myo/pericarditis in association with Novavax COVID-19 vaccine**
- 5.1 The EWG considered a review of anaphylaxis, paraesthesia/hypoaesthesia and myo/pericarditis in association with Novavax COVID-19 vaccine including the EU Pharmacovigilance Risk Assessment Committee (PRAC) assessment of these signals. Data considered in the review included post-marketing reports of anaphylaxis, paraesthesia/hypoaesthesia and myo/pericarditis received in association with Novavax COVID-19 vaccine from outside the UK only as this vaccine is not currently deployed in the UK. Company reviews of these issues and company observed versus expected analyses were also considered.
- 5.2 The EWG noted PRAC had requested updates to the EU product information for Novavax COVID-19 vaccine to 1) amend the existing warning regarding anaphylaxis and COVID-19 vaccines to specifically state that events of anaphylaxis have been reported with Nuvaxovid and to add anaphylaxis as an adverse effect, and 2) to add paraesthesia and hypoaesthesia as adverse effects. The EWG also noted that PRAC had requested that the company provide a further analysis of myo/pericarditis in the next summary safety report.
- 5.3 The EWG supported updating the GB Novavax COVID-19 vaccine product information regarding anaphylaxis and paraesthesia/hypoaesthesia in line with the wording proposed by PRAC. The EWG also discussed that paraesthesia/hypoaesthesia had been reported in association with other COVID-19 vaccines and had subsequently been added as adverse effects to their product information. The EWG discussed that while it was unclear how many of the post-marketing reports of anaphylaxis were cases of genuine anaphylaxis, four of the cases adjudicated by the company met definite or probable anaphylaxis criteria using the Brighton Collaboration Criteria of diagnostic certainty.
- 5.4 The EWG noted that a signal of myo/pericarditis in association with Novavax COVID-19 vaccine had been observed in Australia but not in the EU. The EWG discussed potential reasons for this including possible differences in viruses or other infections circulating in the different regions and commented that COVID-19 infection levels were currently high in Australia. The EWG suggested that it would be helpful if the company were able to obtain information on any viral testing carried out in any of the cases of myo/pericarditis received from Australia and supported the PRAC request for further analyses of myopericarditis to investigate potential seasonal patterns by region.

NOT FOR PUBLICATION

- 5.5 While recognising that the deployment of vaccines is beyond the remit of the MHRA and CHM, the EWG discussed the need to consider potential differences in the use of COVID-19 vaccines in relation to the assessment of safety concerns. For example, Novavax COVID-19 vaccine may be recommended in patients who had had a previous allergic reaction to a mRNA COVID-19 vaccine in some countries. The EWG agreed that the possibility of potential differences in patient populations receiving Novavax and other COVID-19 vaccines should be taken in to account when assessing reporting rates of adverse events for individual vaccines as these may not be able to be compared directly.
- 5.6 The EWG advised that there is sufficient evidence to amend the existing warning in the Novavax COVID-19 vaccine GB product information to state that events of anaphylaxis have been reported with this vaccine and to add anaphylaxis as an adverse effect. The EWG also advised that there is sufficient evidence to add paraesthesia and hypoaesthesia as adverse effects to the GB product information for Novavax COVID-19 vaccine.
- 5.7 The EWG agreed that there is insufficient evidence to take regulatory action regarding the potential risk of myo/pericarditis in association with Novavax COVID-19 vaccine at the present time; however, this issue should continue to be kept under close review. Overall, the EWG agreed that the benefit risk balance of Novavax COVID-19 vaccine remains positive.
- 6. Nuvaxovid – Use in 12 to 17 year olds (EC reliance variation)**
- 6.1 The EWG heard that a variation has been submitted via the EC decision reliance procedure to lower the indication age from 18 years and older to 12 years and older.
- 6.2 The EWG heard that the data to support this variation is from a paediatric expansion of the Phase 3 study 2019nCoV-301 in the United States which was one of the pivotal trials in the original conditional marketing authorisation. Adolescents aged 12-17 years were randomised 2:1 to receive 2 doses of Nuvaxovid at the same dose authorised in adults, or placebo, at least 21 days apart. The safety population comprised 2,232 adolescents.
- 6.3 The EWG noted that when the neutralising antibody responses in adolescents were compared with those observed in young adults aged 18-25 years from the main adult study, all 3 non-inferiority criteria were met. The point estimate of efficacy was 79.5% in adolescents at a time when the delta variant was the dominant circulating strain. No cases of moderate or severe COVID-19 were reported.
- 6.4 The EWG were reassured that the reactogenicity profile in adolescents was similar to that in young adults, with the exception of 'fever' which was reported more frequently in adolescents post dose 2. The EWG noted that this is reflected in section 4.8 of the SmPC. No cases of pericarditis or myocarditis were reported in adolescents in the clinical trial and no new safety concerns were identified.
- 6.5 The EWG heard that an updated version of the RMP has been submitted. In this version 'Risk of anaphylaxis' has been removed from the safety concerns in-line with a request from the EMA PRAC. In addition, the company have committed to amend all post authorisation safety and effectiveness studies included in the RMP to include adolescents aged 12 to 17 years, with the exception of the pregnancy registry in adults.
- 6.6 No concerns were raised by the EWG, and it was agreed that this reliance variation is approvable.

7. Spikevax bivalent Original / Omicron 0.10 mg/mL dispersion for injection - MODERNA BIOTECH SPAIN SL - PLGB 53720/0004 - 0001

7.1 The Expert Working Group (EWG) heard a summary of the preclinical data presented by the company to support the bivalent vaccine, comprising 3 reports of pharmacology studies in mice, 1 report of pharmacology studies in monkeys, 2 reports of pharmacokinetic studies and 1 general toxicity study. The group heard that the pharmacokinetic studies indicated fast clearance of SMT-102 and also routes of metabolism of SMT-102, a component of the nanolipid particle. The general toxicity study, in compliance with GLP, with a monovalent vaccine indicated changes expected of a vaccine but no untoward toxic events.

7.2 [REDACTED]

7.3 Written comments from additional members of the group who were not able to attend the meeting on 22 July 2022 were requested. Pending these responses, the Expert Working Group advised that these data suffice to support clinical use of the bivalent vaccine.

7.4 The EWG heard a summary of clinical immunogenicity and safety data from study mRNA-1273-P205. Adult participants received a second booster dose of mRNA-1273.214 (bivalent vaccine) or mRNA-1273 (original vaccine). No methodological issues were raised. Results were presented for an interim Day 29 analysis. mRNA-1273.214 was associated with a superior neutralising antibody response against Omicron BA.1 and BA.4/5 and a non-inferior neutralising antibody response against ancestral SARS-CoV-2, compared to mRNA-1273. [REDACTED] At a median safety follow-up of 43 days, the safety/reactogenicity profile of mRNA-1273.214 was comparable to that of mRNA-1273 when used as a first or second booster. No new safety concerns were raised. The results in participants over 65 years of age were comparable to the overall population. The submitted risk management plan (RMP) was in line with that of the original vaccine.

7.5 [REDACTED] The EWG discussed whether mRNA-1273.214 would provide clinically relevant protection against Omicron BA.4/5, although the similarities in the spike proteins of BA.1 and BA.4/5 were noted. Written advice should be sought from the relevant experts who were unable to attend the meeting.

7.6



7.7

The EWG considered that if the original vaccine received approval for use as a booster in adolescents, the bivalent vaccine could be indicated as a booster dose in individuals aged 12 years and older by extrapolation. Otherwise, the indication should be restricted to individuals aged 18 years and older. In addition, the EWG considered that the bivalent vaccine could be used as a first booster dose, and for heterologous boosting, by extrapolation from the original vaccine. The bivalent vaccine should be recommended for use in pregnancy and when breastfeeding, in line with the original vaccine. The MHRA guidance to remove the 15-minute observation period for the original vaccine should also apply to the bivalent vaccine.

8.

Minutes of the following meetings for review & approval

- **Monday 12 April 2021**
- **Monday 21 June 2021**
- **Friday 29 April 2022**

8.1

All the above minutes have been endorsed as a true and accurate record of the meetings.

9.

Any Other Business

9.1

None.

10.

Date and time of next meeting

The next meeting has been scheduled for **Friday 12th August 2022 at 11:30.**

The Meeting today started at 11:32 and ended at 13:57.

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 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 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.

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).

NOT FOR PUBLICATION

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.

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.

Observer

██████████ - NPS – was part of an expert working group (██████████) with ██████████ conducting the initiative on behalf of ██████████ to discuss strategies to improve 'vacceptance'. ██████████ has not received any form of payment or other remuneration as described above but a paper is expected to be published.