

Summary of MHRA's regulatory position for specified events reported with COVID-19 Vaccine Pfizer/BioNTech, COVID-19 Vaccine AstraZeneca and COVID-19 Vaccine Moderna

Issue

The MHRA has been requested by the NHS Business Services Authority to provide an update on the current regulatory position regarding COVID-19 vaccination and:

- Major thrombo-embolic events with concurrent low platelets and the Pfizer and Moderna vaccines
- Arterial thrombosis in the absence of thrombocytopenia
- Venous thromboembolism

Background

The COVID-19 vaccines authorised and deployed in the UK since 2020 include:

- COVID-19 vaccine AstraZeneca (Vaxzevria)
- COVID-19 vaccine Pfizer/BioNTech (Comirnaty)
- COVID-19 vaccine Moderna (Spikevax)
- COVID-19 vaccine Novavax (Nuvaxovid)

The AstraZeneca vaccine is no longer used in the UK, although the conditional marketing authorisation remains valid.

Since September 2022, the main vaccines used in the UK are the bivalent versions of the Pfizer and the Moderna mRNA vaccines. The Novavax vaccine is reserved for use in a small proportion of patients who are not able to receive an mRNA vaccine. Exposure to this vaccine in the UK is very limited compared to the other 3 vaccines. Many of the major reviews undertaken by MHRA did not include Novavax as the predated approval and deployment of this vaccine in the UK.

Details of numbers of Yellow Cards received for each vaccine in the context of overall exposure, and a summary of key safety assessments can be found here

<https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions>

Major thrombo-embolic events with concurrent low platelets and the Pfizer and Moderna vaccines

By April 2021, following a review of data relating to thromboembolic events reported with concomitant low platelets following the COVID-19 vaccine AstraZeneca, a warning was added to the product information for this vaccine, on the basis that the evidence was suggestive of an association. Concurrently, these events were under close review following other types of COVID-19 vaccine. At the time, the other vaccine being used in the UK immunisation programme was Pfizer/BioNTech's mRNA COVID-19 vaccine (the Moderna mRNA vaccine started to be used in the late spring of 2021, but in much more limited numbers than for the Pfizer vaccine). The MHRA was conducting weekly monitoring of the Yellow Card data throughout 2021 and 2022 but small numbers of reports were received, despite the substantial exposure to mRNA vaccines and the evidence did not suggest a similar association as observed with the AstraZeneca vaccine. In February 2022, a review was presented to the COVID-19 vaccine benefit risk working group, which stated that up to Data Lock Point of 02/02/2022, there had been a total of 437 UK cases classified as confirmed, probable or possible for the AstraZeneca vaccine. For the Pfizer/BioNTech

vaccine, with a total of 31 cases classified as confirmed, probable or possible with 4 cases having a fatal outcome. The majority of thrombosis events were non-cerebral venous sinus thrombosis (CVST) events. For the Moderna vaccine, there were a total of 4 cases classified as probable or possible and no cases having a fatal outcome. None of the cases were CVST events.

Data provided by the vaccine manufacturers was also presented, which also did not suggest a relationship with these events. The EWG concluded that the available data do not suggest an association between thromboembolic events with concurrent thrombocytopenia and either the Pfizer/BioNTech or Moderna COVID-19 vaccines.

As of 22 November 2022, the number of Yellow Card reports of thromboembolic events with thrombocytopenia following the Pfizer and Moderna COVID-19 vaccines remains at 33 and 8 reports. To date, no signal has been identified in the UK, Europe or elsewhere for major thrombo-embolic events with concurrent low platelets and the Pfizer and Moderna vaccines. This is in the context of hundreds of millions of doses of these vaccines having been administered over the past 24 months. The product information for the Pfizer and Moderna vaccines does not include any warnings about these risks.

Arterial thrombosis & Venous thromboembolism in the absence of thrombocytopenia

The MHRA has also closely monitored thromboembolic events (CVST and at other sites) without thrombocytopenia for the COVID-19 vaccines.

The MHRA reviewed venous and arterial thrombosis without thrombocytopenia in August and September 2021, this followed a review by the European Medicines Agency of VTE following the Janssen COVID-19 vaccine, which although is authorised in the UK, has never been deployed. For the vaccines deployed ¹in the UK (AstraZeneca, Pfizer and Moderna) MHRA conducted observed-expected analyses for VTE and arterial embolic events without thrombocytopenia reported within 42 days of vaccination with a COVID vaccine. Analyses were conducted for PE, DVT and VTE (composite endpoint [DVT or PE], myocardial infarction, stroke, and arterial embolic event (composite endpoint [myocardial infarction or stroke])). Limitations of the analysis include the under-recording of thrombocytopenia in medical records and the point that observed cases have not been validated and medically adjudicated, and therefore observed numbers may be lower if there are misclassified cases or duplicate cases.

The MHRA concluded that the evidence does not suggest that the COVID-19 Vaccines AstraZeneca, Pfizer or Moderna increases the risk of venous thromboembolism (i.e, deep vein thrombosis/pulmonary embolism) in the absence of a low platelet count. This conclusion is in line with that reached by the European Medicines Agency (EMA). None of these vaccines include warnings in their respective product information regarding arterial or venous thromboembolism (other than CVST) without concurrent platelets

CVST

The MHRA reviewed CVST without thrombocytopenia in August and November 2021.

For the AstraZeneca vaccine, the review concluded that there was a possible link with CVST without low platelets. The product information for COVID-19 Vaccine AstraZeneca was updated to include information that CVST events not associated with low levels of blood

¹ For further detail on observed-expected analyses see [Pharmacoepidemiological considerations in observed-to-expected analyses for vaccines - PMC \(nih.gov\)](#)

platelets occurred extremely rarely. The majority of the CVST events occurred within the first four weeks following vaccination. A potential cause has not been identified.

For the mRNA vaccines (Pfizer/BioNTech and Moderna), a further review of CVST was conducted in February 2022 following a publication from the Health Sciences Authority (HSA) which is the medicines regulator for Singapore. In a safety update published on 19 January 2022², the HSA summarised the findings of its observed versus expected (O:E) analysis and self-controlled case series (SCCS) for CVST events and mRNA COVID-19 vaccines (Pfizer and Moderna). The HSA identified a small increase in incidence of CVST with mRNA COVID-19 vaccines in their O:E analysis (about 1 additional case of CVST per million doses). The SCCS analysis showed a statistically significant increased risk overall, but lower than that with COVID-19 infection itself. The HSA did not undertake any regulatory action.

The review included relevant data sources including UK vaccine usage data, clinical trial data, post-authorisation information in the form of Yellow Cards and monthly safety reports from the Marketing Authorisation Holders, literature, data from other regulators and MHRA O:E analyses of Yellow Card data. The review did not raise a signal of concern. Almost half of the Yellow Card reports exhibited confounding factors.

Expert advice was sought from the EWG who acknowledged that current literature evidence is insufficient to establish a clear causal relationship. Findings from case reports were not replicated across larger studies or populations to consistently implicate specific vaccines to the event of interest (CVST) and/or to increased risk in specific age/gender/dosing groups. Limitations in identifying whether thrombocytopenia was present or not alongside the potential for residual confounding/unmeasured variables to impact the findings must be taken into account.

The EWG noted that MHRA epidemiological analysis does not suggest a signal for an overall risk following any dose of the Pfizer or Moderna vaccine, and that O/E analyses for CVST without thrombocytopenia are very sensitive to the choice of background rate.

MHRA
February 2023

.....

Review of regulatory summary: thromboembolic events

There has been no change to the regulatory position on this condition.

MHRA
8 August 2024

² [HSA | Safety updates on COVID-19 vaccines](#)