Reassurance on bleeding and thrombotic events following second dose BNT162b2 and ChAdOx1 COVID-19 vaccines

Sue Pavord[a,*] and Will Lester[b]

[a]Department of Haematology, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom
[b]Department of Haematology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom

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We have been on a steep learning curve with recognition and understanding of rare thromboembolic, thrombocytopenic and bleeding events following first dose COVID-19 vaccines, since the start of the COVID-19 vaccination programme in early 2021. Yet still many questions remain unanswered, including whether second vaccinations hold an equivalent or lesser risk.

As the incidence of these complications is very low and, as available evidence suggests, even lower after second dose vaccine, large population-based interrogation is required. In the current issue of the journal, Joy et al. present a self-controlled case series analysis of 12.3 million individuals in England, aged 16 and over, who received two homologous doses of either BNT162b2 or ChAdOx1 vaccines, between December 8, 2020 and February 11, 2022.[1] Utilising routine primary care data linked to hospital data from the nationally representative Oxford-Royal College of General Practitioners (RCGP) sentinel network database, they determined the incidence rate ratios (IRR) within the 28-day period after 2nd vaccine, compared with the baseline period 14 days before the vaccine. Reassuringly, the IRRs indicated no significant increase in risk of bleeding, thrombosis or thrombocytopenia with the 2nd dose. A similar study using linked databases, to analyse 2 million individuals in Scotland, also found no positive correlations with BNT162b2, and a suggestive but not statistically significant link with ChAdOx1.[2]

Joy's large sample size and comprehensive adjustment for potential confounders, including age, sex, comorbidities, and deprivation, enhance the validity and reliability of the results. However diagnostic granularity is sacrificed and reliance on coding may fail to identify syndromes, whose recognition relies on detection of a constellation of features.

One such syndrome is vaccine-induced immune thrombocytopenia and thrombosis (VITT). This emerged as an unexpected, catastrophic complication of first dose adenovirus-vectored vaccines, ChAdOx1 and Ad26.COV2.S. Initial mortality rates were over 50%,[3] subsequently reduced to 22% with raised awareness and prompt management.[4] Mediated by anti-platelet factor 4 (PF4) antibodies, VITT is characterised by five clinical/laboratory features, with the likelihood of case confirmation depending on the number of features present (Table 1). Thrombosis is rapid, often widespread and most commonly involves the cerebral venous system, with secondary intracranial haemorrhage occurring in one third.[3] It is unclear why VITT predominantly affects younger adults; an incidence of 1:50,000 was observed in individuals under 50 years of age, compared to 1:100,000 in those over 50 years, and increases further with descending age.

The elevated risk of cerebral vein thrombosis after first dose ChAdOx1 was detected in a large-scale study of 11.6 million UK individuals, and not noted after BNT162b2.[5] Occasional new presentations of VITT have been reported after second dose ChAdOx1[6] although it is unclear whether they are genuine de novo cases or whether a subclinical event had occurred after the first dose.[7] It was recommended that survivors of VITT switched to mRNA vaccines for further doses, and no problems have arisen from this. A few went on to have a second dose of ChAdOx1 and interestingly none had a recurrent episode.[8]

Cases of thrombotic thrombocytopenic syndrome (TTS), not meeting the criteria for VITT, are also seen after first dose ChAdOx1 and whether these are coincidental to the vaccine or caused by it is unclear. Incidence after 2nd dose ChAdOx1 is reassuringly low and within preliminary estimates of a background unvaccinated population.[9]

De novo and relapsed cases of immune thrombocytopenic purpura (ITP) have been described after both vaccines, although a study of 2.53 million first-dose recipients in Scotland, estimated an incidence of 1.13 additional cases of ITP per 100,000 doses with ChAdOx1, but no increased incidence with BNT162b2.[10] The largest case series in patients with pre-existing ITP found post-vaccine ITP exacerbation in 13.8%.[11] Other studies have found similar or lower rates.

A key issue which worries patients and clinicians, is the risk of recurrence from a second vaccination if thrombocytopenia or thrombosis occurred after the first dose. Joy's study design does not address this and although the limited evidence available suggests that these are usually uncomplicated, many patients are understandably reluctant to take the risk of a second vaccine.

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*Corresponding author. Department of Haematology, John Radcliffe Hospital, Oxford OX3 9DU, United Kingdom.
E-mail address: sue.pavord@ouh.nhs.uk (S. Pavord).

Case definition criteria	• Onset of symptoms 5–30 post vaccine (or up to 42 days if isolated DVT/PE) • Presence of thrombosis • Thrombocytopenia (platelet count <150 × 10^9/L) • D dimer >4000 mcg/mL (FEU) • Positive anti-PF4 Abs ELISA assay
Definite VITT (D)	Meets all five criteria
Probable (P)	• D dimer >4000 FEU but one criterion not fulfilled (Timing, Thrombosis, Thrombocytopenia, anti-PF4 Abs) • Or D dimer unknown or 2000–4000 FEU with all other criteria present
Possible (S)	• D dimer unknown or 2000–4000 FEU with one other criterion not fulfilled • Or two other criteria not fulfilled (Timing, Thrombosis, Thrombocytopenia, anti-PF4 Abs)
Unlikely (U)	• Platelet count <150 × 10^9/L without thrombosis with D dimer <2000 FEU • Or thrombosis with platelet count >150 × 10^9/L and D dimer <2000 FEU, regardless of anti-PF4 Ab result • And/or alternative diagnosis more likely

Table 1: **Case definition criteria for vaccine-induced immune thrombocytopenia and thrombosis (VITT): first described in 2021 as a new syndrome seen after first dose ChAdOx1.[4]**

Nevertheless, Joy's data provide reassurance that, on a large population scale, there is no significant increase in thromboembolic, thrombocytopenia and bleeding events after second homologous dose BNT162b2 and ChAdOx1 COVID-19 vaccines[1]; the two most used vaccines in the UK during the pandemic. Further research is needed to ascertain the generalisability of these findings to other vaccine brands, and continued vigilance and monitoring of vaccine safety remain essential as new data emerge, and vaccinations are evolved to fight against new viral strains.

Declaration of interests

Neither author has conflict of interest.

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