

Suspected adverse reactions to COVID-19 vaccination and the safety of substances of human origin

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Key facts

- Reports of thrombosis with thrombocytopenia syndrome (TTS) within two-to-three weeks of COVID-19 vaccination have raised questions regarding the safety of SoHO donors and recipients. The pathogenesis of TTS has not yet been determined, although laboratory analyses indicate the presence of anti-PF4-polyanion auto-antibodies.
- Evidence and data currently available indicate a low likelihood of whole blood and plasma donation by asymptomatic individuals in the early phase of TTS, suggesting that the risk of venipuncture bleeding or post-transfusion thrombocytopenia with passive platelet antibody transfer is very low. Therefore, no additional blood and plasma safety measures are recommended in relation to the occurrence of suspected adverse reactions to COVID-19 vaccines.
- A routine blood count check during the selection procedure for living donors of organs, cells and tissues donated by invasive procedure will detect thrombocytopenia. Individuals with a low platelet count would not be eligible for donation of organs, cells and tissues.
- Until more information is available on the risk of TTS transfer via passenger lymphocytes, the decision to accept a deceased donor vaccinated with non-replicating viral vector COVID-19 vaccines two-to- three weeks before donation should be taken with caution.

Scope of the document

The purpose of this document is to address the safety of donors and products involving Substances of Human Origin (SoHO) and the potential risk of thrombosis with thrombocytopenia adverse events following COVID-19 vaccination of a donor. This document also supplements previous information provided on COVID-19 vaccination and supply of SoHO in the European Centre for Disease Prevention and Control (ECDC) technical report 'Coronavirus disease 2019 (COVID-19) and supply of substances of human origin in the EU/EEA - second update' [1]. ECDC will update the document and reassess the risk after consultation with relevant experts as soon as new information becomes available.

Target institutions

The document is intended for the national competent authorities for SoHO, blood and tissue establishments, plasma collection centres, organ, tissue and cell procurement organisations and transplant centres in the European Union and European Economic Area (EU/EEA) countries.

Background

The outbreak of severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection, which began in late December 2019 in China [2] and quickly escalated into a COVID-19 pandemic [3], has spurred the development of preventive and treatment options, including vaccines. New production platforms and molecular biology tools have enabled the rapid design of COVID-19 vaccine candidates, classified into two broad categories [4], gene-based vaccines and protein-based vaccines. Gene-based vaccines deliver gene sequences encoding antigens produced by host cells (e.g. recombinant viral vector or nucleic acid vaccines). Protein-based vaccines include in-vitro manufactured inactivated or live-attenuated viruses, viral protein sub-units or viral particles [4]. In December 2020, the United Kingdom, the USA, and the European Union (EU) authorised the first vaccines.

As of 28 May 2021, four gene-based COVID-19 vaccines have received conditional marketing authorisation in the EU, following evaluation by the European Medicines Agency (EMA), and are part of the EU Coronavirus Vaccines Strategy Portfolio. Two belong to the lipid nanoparticle-incapsulated nucleoside-modified mRNA type of vaccines: Comirnaty (BNT162b2, tozinameran) BioNTech/Pfizer [5] and COVID-19 Vaccine Moderna (mRNA-1273) Moderna [6]. The other two are the recombinant, non-replicating virus vector vaccine types: Vaxzevria (ChAdOx1 nCoV-19) AstraZeneca [7] and COVID-19 Vaccine Janssen (Ad26.COV.2.5) [8]. The Commission has also signed contracts with two further developers of COVID-19 vaccines: CureVac (CVnCoV, mRNA type vaccine) and Sanofi-GSK (viral protein subunit vaccine). Furthermore, EMA has initiated rolling reviews for NVX-CoV2373 developed by Novavax, CVnCoV by CureVac, COVID-19 Vaccine (Vero Cell) Inactivated by Sinovac Life Sciences Co., Ltd and Sputnik V (Gam-COVID-Vac) by Gamaleya [9-12]. According to World Health Organization (WHO) summary information from 16 April 2021, 88 vaccine products are in clinical trials and 184 in pre-clinical development worldwide [13].

Due to limited administration of the vaccines in the development and clinical trial phase, some side effects - particularly those that are very rare - only emerge during widespread use. Therefore, EMA and the national competent authorities (NCAs) in the EU Member States monitor suspected adverse reactions to COVID-19 vaccines according to a specific pharmacovigilance plan, and using the EudraVigilance system which includes the electronic reporting and analysis of suspected adverse reactions to medicines [14,15].

ECDC addressed the donation of SoHO by vaccinated individuals in the second update of its technical report, taking into account pre-approval safety data [1]. Following widespread use of vaccines across the EU, new data on suspected adverse reactions to COVID-19 vaccination has become available, enabling further assessment of the safety of SoHO donation in the post-vaccination period.

Suspected adverse reactions to COVID-19 vaccines

According to ECDC's COVID-19 Vaccine Tracker, from the beginning of vaccination in the EU/EEA up to 28 April 2021, a total of 133 739 633 EU-approved vaccine doses have been administered in the EU/EEA countries [16]. During the same period, 354 177 (0.2%) cases of suspected adverse reactions after vaccination were reported to EudraVigilance [15] (Table 1). The vast majority of suspected adverse reaction reports so far relate to general reactions and the administration site (e.g. 'flu-like' illness, headache, pain at the application site, chills, fatigue, nausea, fever, dizziness, weakness, myalgia, and tachycardia.) Generally, these reactions are not associated with more serious illness. Data monitoring, conducted as part of the US vaccination programme, indicates that the vast majority of non-serious adverse reactions occur within two days of vaccination, and almost all within seven days [17]. Serious reactions such as allergic and anaphylactic reactions are very rare and usually occur soon after vaccination, with a sudden onset.

Table 1. Number of administered doses of COVID-19 vaccines and selected suspected adverse reactions* by reaction type in EU/EEA, as of 28 April 2021 [15,16]

Vaccine	ADM (doses)	Adverse events (% of ADM)	Coagulopathy (% of ADM)		DIC (% of ADM)		ITP (% of ADM)		TP (% of ADM)	
			Total	Deaths	Total	Deaths	Total	Deaths	Total	Deaths
COVID-19 Vaccine Moderna	9691295	17625 (0.181864)	5 (0.000052)	1 (0.000010)	5 (0.000052)	1 (0.000010)	39 (0.000402)	2 (0.000021)	55 (0.000568)	6 (0.000062)
Comirnaty	96519666	151306 (0.156762)	44 (0.000046)	7 (0.000007)	7 (0.000007)	4 (0.000004)	85 (0.000088)	0 (0)	178 (0.000184)	15 (0.000016)
Vaxzevria	27430533	184833 (0.673822)	79 (0.000288)	2 (0.000007)	33 (0.000120)	11 (0.000040)	167 (0.000609)	6 (0.000022)	605 (0.002206)	45 (0.000164)
COVID-19 Vaccine Jansen	98139	413 (0.420832)	0 (0)	0 (0)	2 (0.002038)	0 (0)	0 (0)	0 (0)	7 (0.007133)	0 (0)
Total	133739633	354177 (0.264826)	128 (0.000096)	10 (0.000007)	47 (0.000035)	16 (0.000012)	291 (0.000218)	8 (0.000006)	845 (0.000632)	66 (0.000049)

ADM – Administered; DIC-Disseminated Intravascular Coagulation; ITP – Immune Thrombocytopenia; TP – Thrombocytopenia
* The causality between the suspected adverse reactions/adverse events and vaccines has not been assessed.

Thrombotic and thromboembolic events after vaccination

Thrombotic and thromboembolic events, including TTS, have been reported following the administration of non-replicating viral vector COVID-19 vaccines. Adverse events of this type after vaccination with Vaxzevria triggered a suspension of some batches, and even use of the vaccine in several EU/EEA countries [18]. As of 12 May 2021, some countries have resumed vaccination with Vaxzevria with age restrictions (reserved for those over 55 or 60 years old), while others have discontinued its use (Denmark, Norway)[19].

The EMA's safety committee, the Pharmacovigilance Risk Assessment Committee (PRAC)¹, performed a signal assessment on 'embolic and thrombotic events' following vaccination with Vaxzevria in March 2021 [18,20]. A total of 269 cases (258 serious and 45 fatal) reported to EudraVigilance were analysed. At the time of the assessment, over 5.5 million doses of the AstraZeneca vaccine had been administered in EU/EEA countries (source: ECDC COVID-19 Tracker) and approximately 9.7 million doses in the UK, as of 28 February 2021 (source: weekly summary of Yellow Card reporting). Reported cases were individuals healthy at the time of vaccination who developed moderate to severe thrombocytopenia and thrombotic complications at unusual sites, such as cerebral venous sinus thrombosis, or thrombosis in the portal, splanchnic, or hepatic veins, one-to-two weeks after vaccination. Some patients developed deep venous thromboses, pulmonary emboli, or acute arterial thromboses. The patients had low platelet counts at diagnosis, but the onset and rate of platelet decrease preceding the thrombotic event are unknown. The pathogenesis of this syndrome, known as TTS but also referred to as vaccine-induced immune thrombotic thrombocytopenia (VITT), has not yet been determined. At least three studies have detected high levels of antibodies to platelet factor 4 (PF4)-polyanion complexes by enzyme-linked immunosorbent assay (ELISA), as well as by assays based on platelet activation which, when tested, was enhanced by the addition of PF4 [21-23]. These findings indicate that TTS resembles heparin-induced thrombocytopenia (HIT). Cases of TTS after vaccination with COVID-19 Vaccine Janssen have been reported in the US. Following a thorough safety review of rare and severe cases of blood clots after receiving the Janssen COVID-19 Vaccine, the US Food & Drug Administration (FDA) lifted the recommended pause on vaccine use. The FDA also amended the emergency use authorisation for COVID-19 Vaccine Janssen to include information about possible very rare and serious blood clots in people who receive the vaccine [24,25]. PRAC found a possible link to very rare cases of unusual blood clots with low blood platelets after vaccination with Vaxzevria and COVID-19 Vaccine Janssen and concluded that these events should be listed as very rare side effects of the vaccines [18,26]. A laboratory study among healthy persons showed that 7% of the participants tested positive for anti-PF4/polyanion antibodies post vaccination with mRNA- or adenoviral vector-based vaccines [27]. The positive PF4-polyanion samples did not induce platelet activation in the presence of PF4. The authors concluded that anti-PF4-polyanion antibodies detected after vaccination probably have minor (if any) clinical relevance [27].

¹ More information on PRAC: www.ema.europa.eu/en/glossary/prac

Thrombocytopenic events without thrombosis presented with petechiae, bruising or mucosal bleeding (gingival, vaginal, epistaxis) and onset of symptoms between 1–23 days (median five days) following Comirnaty and Moderna vaccines have also been reported to the US Vaccine Adverse Event Reporting System (VAERS) [28]. VAERS is not designed to determine if a vaccine caused or contributed to an adverse event. A report to VAERS does not mean the vaccine caused the event [29].

The occurrence of thrombosis with thrombocytopenia following COVID-19 vaccination has raised questions concerning the safety of SoHO donation by vaccinated donors and the potential risk that the resultant SoHO products could pose to patients.

COVID-19 vaccination and the donation of substances of human origin

Current recommendations

In its technical report [1], ECDC indicates that according to EU Directives, after vaccination with attenuated viruses (e.g. replication competent virus vector-based vaccines, live-attenuated virus vaccines) SoHO donors must be deferred for four weeks. Individuals vaccinated with inactivated/killed viruses or vaccines that do not contain live agents (i.e. mRNA vaccines, non-replicating/replication-deficient virus vector-based vaccines and protein sub-unit vaccines) may be accepted as SoHO donors if they feel well [30-32]. In situations where information about vaccine type is missing or the vaccination is experimental, a four-week deferral period should be applied. Given that COVID-19 vaccines are newly developed and the effects on SoHO donation are unknown, Member States may take a precautionary approach and defer donors who develop clinical symptoms directly after receiving a SARS-CoV-2 vaccine for up to seven days after symptoms have resolved. In addition, vaccinated donors need to comply with the same general requirements for donation as non-vaccinated donors.

In February 2021, WHO updated interim guidance on maintaining a safe and adequate blood supply and collecting convalescent plasma in the context of the COVID-19 pandemic. WHO also suggested that a precautionary deferral period of up to seven days could be considered following vaccination to minimise the impact of call-backs from donors who develop symptoms following donation soon after vaccination [33].

A review of national guidelines for post-vaccination blood donation (Table 2) showed that most EU countries (18/26; 69%) do not recommend a seven-day waiting period after vaccination with registered mRNAs and non-replicative viral vector vaccines. However, more than half of the countries have opted for a shorter waiting period of 24–48 hours, similar to that usually implemented for other non-live vaccines. In six countries, the waiting period after vaccination is seven days. In one country, this period is 14 days and in another 28 days. However, seven countries opted for different waiting periods depending on the type of vaccine. A deferral from donation for seven days after the cessation of any signs of vaccination side effects is required in 12 countries (46%).

Table 2. Waiting period for blood donation following COVID-19 vaccination and deferral period after suspected adverse reaction in EU by country (30 April 2021)

Country	Waiting period following COVID-19 vaccination	Deferral period after suspected adverse reaction
Austria	48 hours	7 days
Belgium	48 hours	7 days
Bulgaria	28 days	-
Croatia	48 hours (Co,Mo,Cv) or 28 days (Va)	7 days
Czechia	48 hours (Co,Mo,) or 28 days (Va)	-
Cyprus	48 hours (Co,Mo,) or 28 days (Va,JJ)	-
Denmark	No waiting period	14 days after fever
Estonia	No waiting period (Co,Mo) or 28 days (Va)	-
Finland	No waiting period	-
France	No waiting period	-
Germany	No waiting period	-
Greece	No waiting period	7 days
Hungary	No waiting period	A few days
Ireland	7 days	-
Italy	48 hours	7 days
Latvia	7 days	-
Lithuania	No waiting period	Symptom-free
Luxembourg*	7 days	7 to 14 days after fever
Malta	7 days	7 days
Netherlands	7 days	-
Portugal	48 hours	7 days
Poland	48 hours (Co,Mo) or 14 days (Va,JJ)	7 days
Romania	7 days (Co,Mo) or 28 days (Va,JJ)	-
Slovakia	14 days (Co,Mo) or 28 days (Va,JJ)	-
Slovenia	24 hours	7 days
Spain	48 hours	7 days or 14 days after fever
Sweden	7 days	14 days

Co – Comirnaty vaccine; Mo – COVID-19 Moderna vaccine; Cv – CuraVax vaccine; Va – Vaxzevria vaccine; JJ – COVID-19 Janssen vaccine, * personal communication.

Currently, the US FDA recommends no waiting period for blood donors who have received non-replicating, inactivated, or mRNA-based COVID-19 vaccines and a short waiting period (e.g. 14 days) for those who have received live-attenuated viral COVID-19 vaccines [34].

To ensure donor and donation safety, the Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC) has implemented seven-day deferral for blood, tissues and cells of donors vaccinated with COVID-19 vaccines licensed in the UK, including the AstraZeneca, Moderna and Pfizer/BioNTech COVID-19 vaccines. This measure will also reduce the risk of a donation being discarded if a vaccine recipient develops symptoms directly related to the vaccine in the week following donation [35].

At the time of writing, there are no published reports of complications in SoHO donation or SoHO recipients due to adverse effects of COVID-19 vaccination in a donor.

Suspected adverse reactions to COVID-19 vaccines and SoHO donations

Most COVID-19 side effects reported to date have been general events, such as 'flu-like' conditions and application site pain. These events occur within seven days of vaccination and are not associated with serious illness. A donor with this type of side effect will be detected during the donor selection process. Blood and plasma donors will be rejected, while living organ, tissue and cell donors will undergo individual risk assessments.

The occurrence of TTS following administration of some non-replicating viral vector COVID-19 vaccines may have consequences for the safety of SoHO donors and SoHO supply and therefore poses the following risks:

- risk of bleeding from the venepuncture site in asymptomatic whole blood and plasma donors in the early phase of TTS;
- risk of passive transfer of platelet antibodies from a donor with TTS to transfusion recipient leading to thrombocytopenia;
- risk of transmitting passenger leukocytes through the transplanted organ donated by a deceased donor with TTS. Such passenger lymphocytes can trigger immune thrombocytopenia in the recipient.

A routine blood count check during the selection procedure for living donors of organs, cells and tissues donated by invasive procedure will detect thrombocytopenia. Individuals with a low platelet count would not be eligible for donation of organs, cells and tissues. Nevertheless, special attention should be paid to hematopoietic stem cell donors who have recently received the COVID-19 vaccine. Although a rare occurrence, the use of growth factors to mobilise hematopoietic stem cells can cause a transient hypercoagulable state in some donors [36]. This effect could be augmented in donors with TTS. To avoid TTS augmentation in hematopoietic stem cell donors stimulated with growth factors following vaccination, the European Society for Blood and Marrow Transplantation (EBMT) [37] and the World Marrow Donor Association (WMDA) [38] recommend a waiting period for stimulation after vaccination and also for vaccination following donation.

Donation of whole blood and plasma

According to current guidelines, individuals with thrombocytopenia should not be accepted as blood or plasma donors because of the risk of bleeding at the venepuncture site. The quality and clinical efficacy of the blood components produced will also be affected [39].

Post-vaccination immune thrombocytopenia is not an unexpected event. Secondary immune thrombocytopenia has been reported in children following the measles-mumps-rubella (MMR) vaccine (estimated prevalence 1:40 000 children) [40], varicella vaccine [40] and other types of vaccines [41]. In children, it is generally a mild disease with few clinically serious episodes or long-term sequelae, despite the low platelet counts found [42]. A case-controlled study of adult recipients of all types of vaccines indicated no discernible increase in immune thrombocytopenia within a year post-vaccination [43]. The prevalence of post-COVID-19 vaccination thrombocytopenia is unknown, but preliminary data show that this is a rare event. The estimated incidence following the Vaxzevria vaccine in the UK is 9.3 cases per million doses [44]. The link between TTS and vaccines (Vaxzevria and COVID-19 Vaccine Janssen) is characterised as possible [18,26]. The timing of the onset and the dynamics of platelet depletion before the thrombotic event are unknown. However, clinically manifested cases of TTS in the EU/EEA occurred 0–16 days after vaccination with Vaxzevria [20]. No cases of bleeding from the venepuncture site due to post-vaccination thrombocytopenia in blood or plasma donors have been reported. Given the above evidence and the increased public awareness of TTS, which allows for earlier identification and treatment, the likelihood of whole blood and plasma donation by asymptomatic individuals in the early phase of TTS is estimated to be very low.

Passive transfer of platelet antibodies through blood and blood components can cause severe post-transfusion reactions, including thrombocytopenia, haemorrhages, and death [45-47]. In most cases, the passively transferred antibodies are anti-HPA-1a and anti-CD-36 [48]. Passive transmission of anti-PF4-polyanion antibodies by

transfusion of blood from a donor in the early phase of TTS is theoretically possible. However, at present there is a lack of evidence for assessing whether such antibodies will destroy recipient platelets.

Available data and evidence indicate that it is unlikely that asymptomatic individuals in the early phase of TTS will donate whole blood and plasma. Furthermore, there is no data to indicate a possibility of post-transfusion thrombocytopenia through the passive transfer of anti-PF4-polyanion antibodies. Therefore, no additional blood and plasma safety measures are recommended in relation to the occurrence of COVID-19 vaccines adverse events.

Organs and tissues from deceased donors

Passenger lymphocytes can trigger immune thrombocytopenia in the organ transplant recipient, as reported in cases of transplant-mediated immune thrombocytopenia [49-57]. Therefore, there is a theoretical possibility of immune cells being transmitted via transplanted organs with a high passenger leukocyte burden (e.g. liver, lung, small intestine, and pancreas) from deceased donors with TTS to the transplant recipient. Blood vessels grafts, bone, tendons, meniscus, skin and cornea/sclera are not considered to pose a risk of passenger lymphocyte syndrome. The UK National Health Service (NHS) is monitoring 26 patients who have received kidney (15), simultaneous pancreas & kidney (1), liver (7), lung (1), islet (1), or heart (1) transplants from confirmed TTS donors for outcomes [58]. The results will offer an insight into the risk associated with organ transplantation from deceased donors experiencing TTS.

Until more information on the risk of TTS transfer via passenger lymphocytes is available, the decision to accept a deceased donor, vaccinated with non-replicating viral vector COVID-19 vaccines two or three weeks before donation, should be taken with caution. Careful assessment of risks versus benefits and informed patient consent are recommended before organ retrieval. Currently, the UK NHS recommends that liver, lung, whole pancreas, or small bowel transplantation should only be carried out in the most urgent situations and with clear documentation on the decision and the consent processes [58]. The organs collected from deceased donors suffering severe thromboembolic and thrombosis symptoms associated with thrombocytopenia need to be rigorously scrutinised to check the lack of microthrombi. Assessments of organ functionality (presence or not of multi-organ failure) and clotting (presence of disseminated intravascular coagulation) need to be performed before transplantation.

Conclusion

The evidence and data currently available indicate that it is unlikely that asymptomatic individuals in the early phase of TTS will donate whole blood and plasma, suggesting that the risk of venipuncture bleeding or post-transfusion thrombocytopenia with passive platelet antibody transfer is very low. Therefore, no additional blood and plasma safety measures are recommended in relation to the occurrence of suspected adverse reactions to COVID-19 vaccines.

Until more information is available on the risk of TTS transfer via passenger lymphocytes, the decision to accept a deceased donor, vaccinated with non-replicating viral vector COVID-19 vaccines two to three weeks before donation, should be taken with caution.

Consulted experts

This document was drafted and coordinated by Dragoslav Domanović and reviewed by the European Medicines Agency and an ad hoc panel of experts from the national competent authorities: Sophie Lucas Samuel – France, Kostas Stamoulis – Greece, Beatriz Dominguez-Gil – Spain; Vincenzo de Angelis – Italy and Fewzi Teskrat – MDH-MFH-Malta. Experts: Sheila MacLennan (Consultant in Transfusion Medicine/Director of JPAC, UK) and the following SoHO stakeholder associations: the European Blood Alliance (Ryenne Lieshout – Krikke), the International Plasma and Fractionation Association (Leni von Bonsdorff) and the World Marrow Donors Association (Mirjam Fetcher).

Disclaimer

All data published in this report is correct to the best of our knowledge at the time of publication.

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