COVID-19

Ad hoc update to the weekly consolidated information on adverse events following administration of immunization (AEFI) against COVID-19

WASHINGTON, DC
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Notifications of myocarditis and pericarditis following administration of COVID-19 vaccines

- In Spain, a case of acute myocarditis in a 39-year-old man was reported after administration of the second dose of the BNT162b2 vaccine, 21 days after the first dose. The individual had a history of bronchial asthma, autoimmune hypothyroidism, chronic atrophic gastritis, an isolated episode of spontaneous recurrent atrial fibrillation, and pneumothorax with left apical segmentectomy (1). Several cases of myocarditis caused by COVID-19 have been published. However, acute infection was ruled out in this patient. Case reports provide little evidence of a causal association.
- Because COVID-19-associated myocarditis and pericarditis could show a possible vaccine safety signal, a rapid disproportionality analysis was performed, based on global data from the Individual Case Safety Report (ICSR) database for drug monitoring (VigiBase), seeking possible links between myocarditis or pericarditis and COVID-19 vaccines. The odds ratios (OR) were calculated as a disproportionality measure for the two authorized mRNA vaccines (BNT162b2 and MRNA-1273) and for two most widely used "non-mRNA" vaccines (AZD1222; ChAdOx1 and JNJ-78436735; and Ad26.COV2- S). The results are shown in Table 1.
- Greater disproportionality was found between the BNT162b2 and mRNA-1273 vaccines and pericarditis. Similarly, greater disproportionality was found between the mRNA-1273 vaccine and myocarditis. BNT162b2 also showed increased disproportionality with myocarditis, but not reaching the threshold of statistical significance.
- No greater disproportionality was found between pericarditis or myocarditis and "non-mRNA" vaccines (AZD1222/ChAdOx1 and JNJ-78436735/Ad26.COV2).
- However, there are limitations with this type of analysis. Risk is not being evaluated; rather, disproportionate reporting of myocarditis and pericarditis following administration of these vaccines. Monitoring and evaluation should therefore be continued in order to establish any association.

Table 1. Odds ratio (OR) values reported for COVID-19 vaccines and myocarditis or pericarditis

	Cases/Non cases		OR (95% CI)
	Exposed	Non- exposed	
Pfizer-BioNTech (BNT162b2)			
Myocarditis	82/212422	7919/24746064	*1.21 (0.97-1.50)*
Pericarditis	107/212397	6549/24747434	**1.90 (1.57-2.30)**
Moderna (mRNA-1273)			
Myocarditis	42/40222	7959/24918264	**3.27 (2.41-4.43)**
Pericarditis	33/40231	6623/24919600	**3.09 (2.19-4.35)**
AstraZeneca (AZD1222; ChAdOx1)			
Myocarditis	33/271175	7968/24687311	0.38 (0.27-0.53)
Pericarditis	59/271149	6597/24688682	0.82 (0.63-1.05)

* No ICSR reports were found for the Janssen vaccine (JNJ-78436735; Ad26.COV2-S) and myocarditis or pericarditis.

Reference: (1) García JB, Ortega PP, Antonio Bonilla Fernández J, León AC, Burgos LR, Dorta EC. [Acute myocarditis following administration of the BNT162b2 COVID-19 vaccine]. Rev Esp Cardiol. 2021 Mar 20. Spanish. doi: 10.1016/j.recesp.2021.03.009.

FDA and CDC pause on the use of Janssen COVID-19 vaccine (updated information)

Following a thorough review of the safety of the Johnson & Johnson (Janssen) COVID-19 vaccine in the United States, including two meetings of the CDC's Advisory Committee on Immunization Practices (ACIP), the U.S. Food and Drug Administration (FDA) and the U.S. Centers for Disease Control and Prevention (CDC) have determined that the recommended pause in vaccine use should be lifted, and use of the vaccine resumed. The pause was recommended on 13 April 2021, following reports of six cases of a rare and severe type of blood clot in individuals following administration of the Janssen COVID-19 vaccine.

Beginning on 23 April 2021, medical and scientific teams from the FDA and CDC examined available data to assess the risk of cerebral venous sinus thrombosis, or CVST (thrombosis in large blood vessels in the brain), and thrombosis at other sites in the body (including but not limited to large blood vessels in the abdomen, and veins in the leg), along with thrombocytopenia, or low blood platelet counts (TTS). The two agencies confirmed that a total of 15 cases of TTS had been reported to VAERS, including the original six reported cases. All of these occurred in women between the ages of 18 and 59, with a median age of 37. Reports indicated that symptoms appeared between 6 and 15 days after vaccination.

In their report, the two agencies concluded that:

- Use of the Janssen COVID-19 vaccine should be resumed in the United States.
- The FDA and CDC are confident that this vaccine is safe and effective in preventing COVID-19.
- The FDA determined that available data show that the known and potential benefits of the vaccine outweigh its known and potential risks in individuals age 18 and older.
- At present, available data suggest that the likelihood of TTS occurring is very low; however, the FDA and CDC will continue to investigate this risk.
- Health care providers who are administering vaccines should read the Janssen COVID-19 vaccine "Fact Sheet for Health Providers," and people who are to be vaccinated should read the "Fact Sheet for Recipients and Caregivers," both of which have recently been revised to include information on the risk of this syndrome, which has occurred in a very small number of people who received the Janssen COVID-19 vaccine.

Source: https://www.fda.gov/news-events/press-announcements/fda-and-cdc-lift-recommended-pause-johnson-johnson-janssen-covid-19-vaccine-use-following-thorough https://www.fda.gov/media/146304/download

In tandem with this, on 20 April 2021 the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) concluded that a warning regarding unusual blood clots with low platelet counts should be added to the product information for the Janssen COVID-19 vaccine. PRAC also determined that these events should be listed as very rare side effects of the vaccine.

Source: https://www.ema.europa.eu/en/news/covid-19-vaccine-janssen-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood

Updated WHO Interim recommendations for use of the COVID-19 ChAdOx1-S [recombinant] vaccine (AstraZeneca COVID-19 vaccine AZD1222, SII Covishield, and SK Bioscience)

On 21 April 2021, the World Health Organization (WHO) published an update to the document "Interim recommendations for use of the ChAdOx1-S [recombinant] vaccine against COVID-19 (AstraZeneca COVID-19 vaccine AZD1222, SII Covishield, SK Bioscience)," based on the recommendations issued by the Strategic Advisory Group of Experts on Immunization (SAGE) at its extraordinary meeting on 8 February 2021 (1), updated on 21 April 2021.

Under 'precautions', this update includes information on thrombosis with thrombocytopenia syndrome (TTS), which has been reported approximately 4 to 20 days after vaccination with the ChAdOx1-S [recombinant] vaccine.

The indication is that in countries with continuous transmission of SARS-CoV-2, the benefit of vaccination in protecting against COVID-19 far outweighs the risks. However, since benefit-risk assessments may differ from

country to country, countries should consider their situation, individual-level and population-level risks, availability of other vaccines, and alternatives to mitigate risk.

It has also been established that people who have had blood clots associated with low platelet levels (TTS) after their first dose should not receive a second dose.

In terms of interchangeability with other COVID-19 vaccines, this update indicates that all ChAdOx1-S [recombinant] products (AstraZeneca AZD1222, SII Covishield, and SK Bioscience) are considered equivalent and interchangeable for both doses; it is recommended that both doses be administered with ChAdOx1-S products.

These recommendations could be updated as more information becomes available from studies being conducted to assess whether COVID-19 vaccines using a different platform can be used interchangeably in the vaccination program.

Link: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-AZD1222-2021.1

Collection of information on recently reported rare and severe events

April 2021

UNITED STATES

Use of the Janssen vaccine in the United States is temporarily suspended

As of 12 April 2021, more than 6.8 million doses of the Johnson & Johnson (Janssen) vaccine had been administered in the United States. Six events involving severe clotting disorders, known as cerebral venous sinus thrombosis (CVST), were reported in combination with low blood platelet levels (thrombocytopenia), in people who had received this vaccine. In a joint statement, the U.S. Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) recommended temporarily discontinuing use of the vaccine, pending a detailed review by the Advisory Committee on Immunization Practices (ACIP) of cases under investigation, and until the Committee is able to provide a clear recommendation on how to proceed.

All six cases occurred in women between the ages of 18 and 48. Symptoms occurred 6 to 13 days after vaccination. Since this is not the typical treatment for this type of blood clotting (administration of heparin is very dangerous), health care providers have been alerted to alternative treatments. At the same time, people recently vaccinated with the Janssen vaccine have been told to be alert for possible symptoms of severe headache, abdominal pain, leg pain, or shortness of breath, and to seek immediate medical attention if they experience any of these symptoms.

Johnson & Johnson announced that it will postpone delivery of its vaccine in European Union countries.

The ACIP met on 14 April, but did not reach any conclusions, indicating that it needed more time to review information on potential health risks before voting on a recommendation. From 30 March to 1 April, 3.7 million doses of Janssen vaccine had been administered – 52% of all Janssen doses to date –, and people who have been vaccinated are still in the post-vaccination time frame for possible thrombocytopenic thrombotic events.

Sources:

https://www.fda.gov/news-events/press-announcements/joint-cdc-and-fda-statement-johnson-johnson-covid-19-vaccine

https://www.cdc.gov/vaccines/acip/meetings/slides-2021-04.html

https://emergency.cdc.gov/han/2021/han00442.asp

PRAC: Update on the safety of authorized vaccines: European Medicines Agency (EMA)

- Comirnaty: On 9 April, the Pharmacovigilance Risk Assessment Committee (PRAC), based on information from clinical trials and vaccination campaigns, requested the addition of the following adverse events to the product information: skin pruritus and rash as uncommon (1 in 100 people); and hives and angioedema as rare (1 in 1,000 people).

- Vaxzevria (previously referred to as the Oxford-AstraZeneca COVID-19 vaccine): Regarding anaphylaxis and other allergic reactions, PRAC requested that the vaccine authorization holder provide more information for evaluation.
- With regard to thrombotic events related to the Vaxzevria vaccine, the Committee concluded that there was a plausible causal connection between the vaccine and very rare cases of thrombosis in combination with thrombocytopenia, sometimes accompanied by bleeding. Thrombotic events with thrombocytopenia include venous thrombosis, which can also occur in unusual places such as veins of the cerebral venous sinus, and the splenic venous system (involving one or more veins in the abdomen), as well as arterial thrombosis. Although these events are very rare, cases appear to be more common than in the general population. Most of these cases occur within 14 days after vaccination, and in women under the age of 60. Some cases have resulted in death. Based on available data, no specific risk factors have been identified.
- PRAC agreed that the following events should be updated in the Vaxzevria product information: thrombocytopenia as a new and common adverse event (less than 1 in 10 people), and thrombosis, in combination with thrombocytopenia, as a new and very rare adverse event (less than 1 in 10,000 people).
- PRAC requested more information from Vaxzevria's authorization holder on five suspected cases of capillary leak syndrome (liquid leaks from smaller vessels, with a rapid drop in blood pressure, combined with tissue swelling) that were reported to EudraVigilance. To date, a causal association with administration of the vaccine has not been established.
- PRAC continues to update Vaxzevria's risk management plan, in connection with the review of clinical trial data by the Committee for Medicinal Products for Human Use (CHMP), in order to determine whether limb pain, abdominal pain, hives, and flu-like symptoms can occur as a result of this vaccine.
- Janssen: PRAC began an analysis of embolic and thrombotic events in a few serious and isolated cases of thrombosis combined with thrombocytopenia reported after administration of this vaccine. While these events had previously been included in the vaccine risk management plan for follow-up, the Committee requested a review by the authorization holder and is collecting more information for analysis. No causal link has been established between the event and the vaccine.
- The reports conclude that no changes in the use of the Comirnaty, Vaxzevria, and Janssen vaccines are recommended, and that they are effective in preventing COVID-19. As of 9 April, following the latest update on 25 March, there was no new safety update for the Moderna vaccine.

Link: https://bit.ly/2QT8vBg

GACVS: Review of rare adverse blood clotting events with AstraZeneca COVID-19 vaccine (Vaxzevria and Covishield)

On 16 April 2021, the World Health Organization (WHO) published conclusions from the Global Advisory Committee on Vaccine Safety (GACVS) review of the latest evidence related to reports of rare adverse events following immunization with the AstraZeneca COVID-19 vaccine (Vaxzevria and Covishield). This event, known as thrombosis

with thrombocytopenia syndrome (TTS), involves severe and unusual blood clotting events, associated with low platelet counts.

GACVS reports that the Brighton Collaboration is developing a specific case definition (a draft definition is already available) that will help identify and evaluate reported TTS events and support assessments of causal associations. With regard to the biological mechanism of TTS, they indicate that investigation is ongoing. At this stage there is no certainty that it is a "platform-specific" mechanism related to vaccines based on adenoviral vectors, though this possibility cannot be excluded. Related investigation should therefore include all vaccines that use adenoviral vector platforms. In addition, GACVS noted that an investigation into the onset of TTS following administration of the Johnson & Johnson's COVID-19 vaccine in the United States has begun.

In terms of the risk of TTS with the Vaxzevria and Covishield vaccines, GACVS has stated that the risk appears to be very low, according to the latest available data. UK data suggest that the risk is approximately four cases per million adults receiving the vaccine (one case per 250,000), while the estimated rate in the European Union (EU) is approximately one per 100,000 vaccinated adults. Countries assessing the risk of TTS following COVID-19 vaccination should conduct a risk-benefit analysis that takes into account local epidemiology (including incidence and mortality from COVID-19 disease), the age groups being targeted for vaccination, and the availability of alternative vaccines.

With regard to TTS risk factors, GACVS notes that while available data suggest an increased risk in younger adults, more research is needed to understand age-related risk. In terms of sex, though more cases have been reported in women than in men, GACVS points out that more women have been vaccinated, and that some cases of TTS have been reported in men. More analysis is required to determine risk factors. The Committee encourages countries to investigate and report all cases of TTS that occur following COVID-19 vaccination. Thrombosis at specific sites, such as the brain and abdomen, appears to be a key characteristic of TTS. Doctors should watch for any new, severe and persistent headaches or other major symptoms, such as severe abdominal pain and shortness of breath, that begin 4 to 20 days after administration of adenovirus-based COVID-19 vaccines. In addition, it is important that, in cases of thrombosis, doctors measure platelet levels and conduct appropriate radiological studies as part of investigating this condition. Alternative treatments such as immunoglobulins and heparin-free anticoagulants should be considered for the treatment of TTS. Administration of heparin can be dangerous in these cases.

GACVS also notes that there may be geographical variation in the risk of these rare adverse events. They therefore recommend that all countries monitor the safety of all COVID-19 vaccines and provide data to their local authorities and to WHO's global ICSR database, so that evidence is available to support recommendations on these vaccines.

Sources: https://bit.ly/3gCnR7O

https://brightoncollaboration.us/draft-case-definition-of-thrombosis-and-thromboembolism/

https://emergency.cdc.gov/han/2021/han00442.asp

Risk of blood clots in the brain due to COVID-19: disease and vaccination. Comments include information from a non-peer-reviewed study that has not yet been published

According to research from the University of Oxford, COVID-19 disease is associated with a much higher risk of cerebral venous thrombosis than the risk from the COVID-19 vaccination with the Pfizer-BioNTech and Moderna vaccines. Researchers used electronic records from large U.S. databases to compare the incidence of cerebral venous thrombosis (CVT) in patients two weeks after being diagnosed with COVID-19, with patients two weeks after receiving the vaccination. In 513,284 patients diagnosed with COVID-19, the incidence of CVT was 39.0 per million people (confidence interval 95%: 25.2 to 60.2 per million). In the 489,871 patients receiving the vaccine, the incidence was 4.1 per million (95% CI: 1.1 to 14.9 per million), for an adjusted relative risk of 6.36, with $P<0.001$. The patients were vaccinated with the mRNA-based Pfizer-BioNTech or Moderna vaccine. Patients were not paired by age or sex. The authors reported that the data did not indicate an obvious association between age/sex and occurrences of CVT. It should be noted that the comparison was made with mRNA vaccines, not with viral vector vaccines.

Thrombocytopenia associated with an immune response has been considered to be associated with occurrences of CVT following vaccination with the AstraZeneca vaccine, specifically with antibodies to platelet factor 4, which causes blood clotting and consumes platelets. These antibodies have been identified in patients who have experienced blood clots. Thirty percent of cases of CVT due to COVID-19 occurred in patients under the age of 30.

Sources:

Torjesen I. Covid-19: Risk of cerebral blood clots from disease is 10 times that from vaccination, study finds. BMJ 2021; 373 :n1005 doi: 10.1136/bmj.n1005

Taquet M, Husain M, Geddes JR, Luciano S, Harrison PJ. Cerebral venous thrombosis: a retrospective cohort study of 513 284 confirmed COVID-19 cases and a comparison with 489 871 people receiving a COVID-19 mRNA vaccine. OSF. doi: 10.17605/OSF. IO/H2MT7

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- Informe técnico: Vacuna SARS-CoV-2 ChAdOx1-s recombinante de AstraZeneca y casos de eventos trombóticos combinados con trombocitopenia [Technical report: AstraZeneca recombinant SARS-CoV-2 ChAdOx1-s vaccine and cases of thrombotic events combined with thrombocytopenia.] (Chile) https://www.ispch.cl/wp-content/uploads/2021/04/20210419-INFORME-TECNICO-VACUNA-ASTRAZENECA-1.pdf