COVID-19

CONSOLIDATED REGIONAL AND GLOBAL INFORMATION ON ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI) AGAINST COVID-19 AND OTHER UPDATES

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OFFICIAL REPORTS ON PHARMACOVIGILANCE PROGRAMS

CANADA

- As of 9 April 2021, 7,569,321 doses of Pfizer-BioNTech, Moderna, Covishield, and Oxford-AstraZeneca COVID-19 vaccines had been administered.
- A total of 3,444 individual reports of one or more adverse events (0.045% of doses administered) were received. Of these, 464 were considered serious events (0.006% of doses administered), with anaphylaxis being the one most frequently reported.
- Of the total reports, there were 1,625 non-serious and 359 serious events associated with the Pfizer-BioNTech vaccine. For the Moderna vaccine, 1,254 non-serious and 74 serious events were reported; for Covishield, 99 non-serious and 26 serious events, and for Oxford-AstraZeneca, two non-serious events.
- A total of 10,111 adverse events following administration (AEFI) were reported, including 3,444 reports of one or more events. The most frequently reported events were non-serious and mostly consistent of injection-site reactions, parestesia, itching, hives, headache, hypoesthesia, and nausea. Only 60 cases of anaphylaxis were reported.
- Most reported adverse events occurred in women (83.8% of the total) and in people between the ages of 18 and 49 (48.8% of the total), these being the groups prioritized for vaccination.
- A total of 31 reported cases of adverse events resulted in post-vaccination deaths. Following a medical review, it was determined that 16 of these deaths were not linked to the administration of the COVID-19 vaccine. The other 15 are still being investigated.

Source: https://health-infobase.canada.ca/covid-19/vaccine-safety/

UNITED STATES

- Nearly 189 million doses of vaccine were administered between 14 December 2020 and 19 April 2021.
- The Vaccine Adverse Event Reporting System (VAERS) received 3,486 (0.0016%) reports of deaths among individuals vaccinated; tests failed to establish a link between these deaths and vaccination.
- Anaphylaxis following COVID-19 vaccination remains very rare, with approximately two to five cases per million people vaccinated in the United States. When this occurs, it is around 30 minutes after vaccination, and is effectively and immediately treatable.

Source: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/mrna.html

MEXICO

- As of 19 April 2021, 14,368,074 total doses of Pfizer-BioNTech, AstraZeneca, Sinovac, Sputnik V, and CanSino vaccines had been administered.

- As of that date, 15,792 cases of AEFI (11 per 10,000 doses administered) had been reported, of which 13,619 were associated with the Pfizer-BioNTech vaccine, 1,154 with the AstraZeneca vaccine, 618 with Sinovac, 255 with Sputnik V, and 138 with the CanSino vaccine.
- A total of 227 serious events were reported, representing 1.4% of total events reported. Of these serious events, 109 occurred with the Pfizer-BioNTech vaccine, 49 with the AstraZeneca vaccine, 45 with Sinovac, 8 with Sputnik V, and 15 with the CanSino vaccine. Of these, 126 occurred in women and 101 in men; 68 cases remain hospitalized.

Source: https://www.gob.mx/salud/acciones-y-programas/versiones-estenograficas-conferencia-de-prensa

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 that the following adverse events should be added to the product information: skin pruritus and rash, uncommon (1 in 100 people); and hives and angioedema, 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 more information for evaluation from the holder of the vaccine authorization.
- With regard to thrombotic events related to the Vaxzevria vaccine, the Committee concluded that there was a plausible causal relation 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, the number of cases appears to be greater than the number in the general population. Most of these cases occur within 14 days after vaccination and in women under the age of 60. Some have resulted in death. Based on available data, no specific risk factors were 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 extravasation syndrome (in which 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 by the Committee for Medicinal Products and Human Use (CHMP) on clinical trial data, 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 for follow-up in the vaccine risk management plan, the Committee requested a review by the authorization holder and is collecting more information for analysis. No causal link has been established between this 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, no new safety update for the Moderna vaccine, following the latest update on March 25, was indicated.

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

Review of rare blood-clotting adverse events with the AstraZeneca COVID-19 vaccine (Vaxzevria and Covishield) by the World Health Organization's Global Advisory Committee on Vaccine Safety

On 16 April 2021, the World Health Organization (WHO) published conclusions of the review by the Global Advisory Committee on Vaccine Safety (GACVS) 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), which will help identify and evaluate reported TTS events and support causality assessments. With regard to the biological mechanism of TTS, they indicate that research is still underway. 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 research 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 (Janssen) COVID-19 vaccine in the United States has begun.

In terms of the risk of TTS with the Vaxzevria and Covishield vaccines, GACVS indicates that, according to the latest available data, the risk appears to be very low. 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 adults vaccinated. 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. Thus, 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 the research on this condition. As regards the treatment of TTS, alternative treatments such as immunoglobulins and heparin-free anticoagulants should be considered. Administration of heparin can be dangerous in these cases.

GACVS also notes that there may be a 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 database on individual-case safety reports, 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

Use of 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 related to severe clotting disorders, known as cerebral venous sinus thrombosis (CVST), were reported in combination with low blood platelet levels (thrombocytopenia) in people receiving this vaccine. The U.S. Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC), in a joint statement, recommended temporarily discontinuing use of the vaccine, pending a detailed review by the Advisory Committee on Immunization Practices (ACIP) of cases under investigation, until the Committee has 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. Because the treatment for this type of blood clotting is not the one typically used, since administering heparin is very dangerous, health care providers have been alerted to choose alternative treatments. At the same time, people who had recently been vaccinated with the Janssen vaccine were told to be alert to possible symptoms of severe headache, abdominal pain, leg pain, or shortness of breath, and to seek immediate medical attention if experiencing 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 (and will do so again on 23 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 – 52% of all Janssen doses – had been administered, and people who have been vaccinated are still in the post-vaccination time window 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

The risk of blood clots in the brain due to COVID-19: disease and vaccination. Comments that 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.

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 the incidence of CVT in patients two weeks after receiving the vaccine. 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 had been vaccinated with mRNA-based vaccines – Pfizer-BioNTech or Moderna. Patients were not paired by age or sex. The authors reported that the data did not indicate an obvious association between age and sex, and occurrences of cerebral venous thrombosis. The comparison was made with mRNA vaccines, not with viral vector vaccines.

The European Medicines Agency (EMA) has estimated the risk of CVT following administration of the AstraZeneca vaccine at 5.0 per million people (95% CI: 4.3 to 5.8 per million). 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

United States reports low rate of new infections in people who have been vaccinated

The U.S. Centers for Disease Control and Prevention has identified approximately 5,800 SARS-CoV-2 infections in the approximately 77 million people in the country who had been fully vaccinated. The 5,800 cases, representing 0.008% of those who had been fully vaccinated, included 74 patients who died of COVID-19, and 396 who required hospitalization. Just under a third (29%) of the identified cases were asymptomatic, approximately twice the rate observed in un-vaccinated patients. Close to two-thirds (65%) of the cases occurred in women, although this figure may simply reflect a greater propensity among women to be tested. Just over 40% of infections occurred in people aged 60 and older. It is important to note that the vast majority of the fully vaccinated population was considered to have been at high risk of infection from the virus. This information could confirm a high degree of effectiveness in the field, consistent with the results of clinical studies of the Pfizer-BioNTech and Moderna vaccines.

Source: Dyer O. Covid-19: U.S. reports low rate of new infections in people already vaccinated. BMJ 2021;373:n1000.

Comments on a new SARS-CoV-2 variant of interest detected in Africa, including information from a non-peer-reviewed article not yet published

The article – A novel SARS-CoV-2 variant of interest, with multiple spike mutations, detected through travel surveillance in Africa – a preprint not yet peer reviewed, reporting on Angola's first genomic surveillance results through March 2021, was developed by a group of researchers from the KwaZulu-Natal Research Innovation and Sequencing Platform, of the Nelson R. Mandela School of Medicine at the University of KwaZulu-Natal, in Durban, South Africa.

In this article, researchers note that, at the end of 2020, the Network for Genomic Surveillance in South Africa detected a SARS-CoV-2 variant of concern (501Y.V2, of the PANGO B.1.351 lineage), which is associated with increased transmissibility and resistance to neutralizing antibodies caused by natural infection and vaccination. Since then, variant 501Y.V2 has spread to more than 50 countries worldwide, and has contributed to a significant resurgence of the epidemic in southern Africa.

In March 2021, a variant of interest (VOI) was detected in three travelers from Tanzania, designated temporarily as A.VOI.V2, which has 31 amino acid substitutions (11 at spikes) and three deletions (all at spikes). Spike mutations include three substitutions in the receptor-binding domain (R346K, T478R, and E484K); five substitutions and three deletions in the N-terminal domain; and two substitutions adjacent to the S1/S2 cleavage site (H655Y and P681H).

Researchers consider this finding to be a new VOI, due to the diversity of mutations with known or suspected biological significance, specifically in relation to neutralizing antibody resistance and potentially increased transmissibility. In addition, the authors point out that urgent research is needed to prevent the spread of the virus inside and outside the country.

Source: De Oliveira T, et al. A novel variant of interest of SARS-CoV-2 with multiple spike mutations detected through travel surveillance in Africa. Medrxvid. 4/4/2021.

Risk of falsified vaccines linked to inadequate disposal of vials

It is important to remember that improper disposal of used vials of COVID-19 vaccines can lead to a high risk of falsified vaccines, as empty vials could be reused.

As indicated in the 30th WHO Regulatory Update in 2019, falsified meningitis vaccines were identified in the Africa Region, with improperly discarded vials being reused, refilled and presented as genuine products.

With regard to COVID-19 vaccines, WHO, in Medical Product Alert No. 2/2021, reported the presence of a falsified vaccine, identified as "BNT162b2," detected in Mexico in February 2021, which was administered to patients in settings that were not a part of authorized vaccination programs.

Due to the high risk of discarded vials being recovered, it is essential that they be safely disposed of at the site where they are used. Consideration should also be given to the possibility of reverse logistics if the handing and safe disposal of vaccine waste cannot be ensured, so that they can be transferred to a location established for this purpose. Failing this, the possibility of crushing empty vials should be considered, provided that a safe way of doing this is available.

Tracking activities at each stage of vaccine distribution and use will be essential in preventing falsified products from being introduced. It is important to keep the vaccines in their original secondary packaging during storage and transport, in order to protect QR codes and barcodes, which make it possible to verify vaccine information.

Sources:

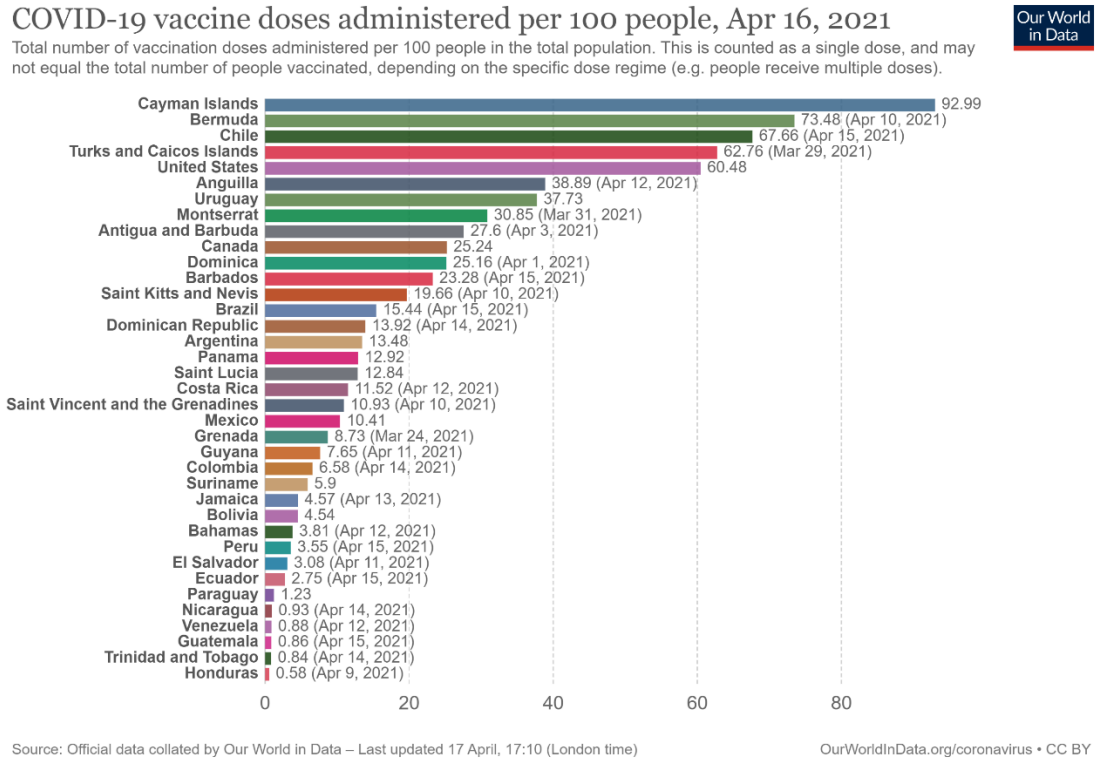
World Health Organization (WHO). 30th WHO Regulatory Update on COVID-19. Available at: https://cdn.who.int/media/docs/default-source/medicines/regulatory-updates/covid-19/30th-who-regulatory-update-on-covid-19_05mar2021.pdf?sfvrsn=f9cfcefe_3&download=true

World Health Organization (WHO). COVID-19 vaccination: supply and logistics guidance, interim guidance. Available at: https://cdn.who.int/media/docs/default-source/medicines/regulatory-updates/covid-19/30th-who-regulatory-update-on-covid-19_05mar2021.pdf?sfvrsn=f9cfcefe_3&download=true

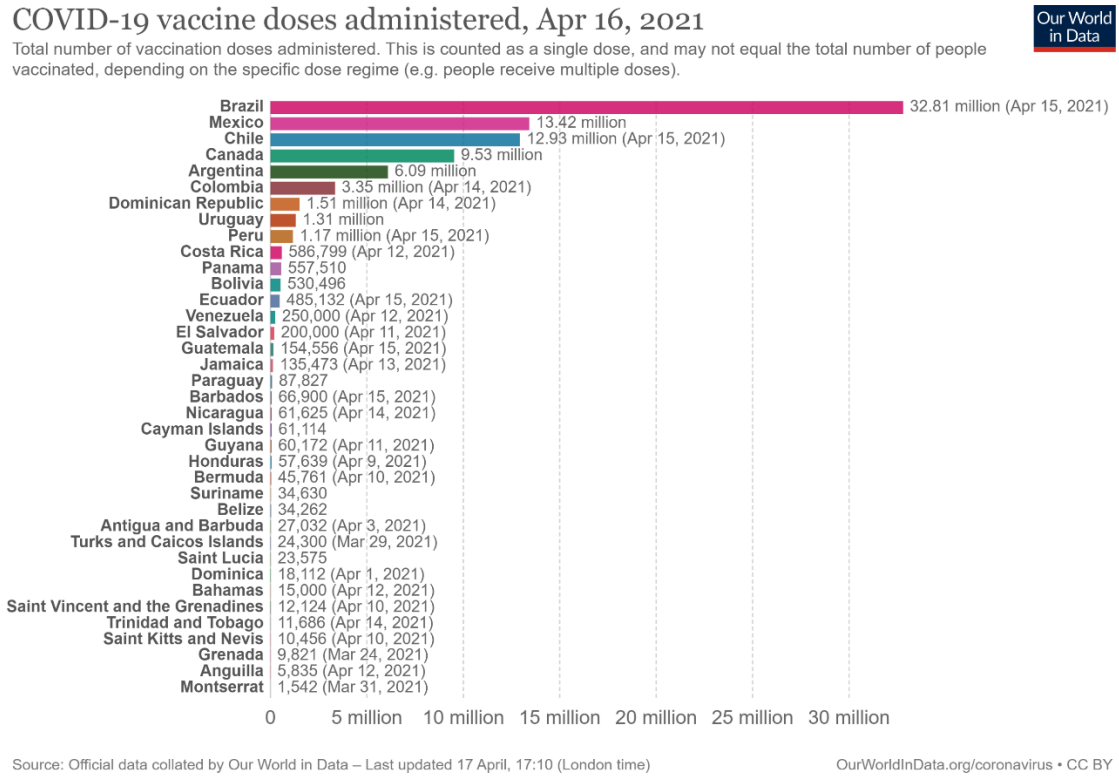
World Health Organization (WHO). Medical Product Alert No. 2/2021: Falsified COVID-19 Vaccine BNT162b2. Available at: https://apps.who.int/iris/rest/bitstreams/1332203/retrieve

Use of the COVID-19 vaccine in the Region of the Americas as of 16 April 2021

The following are consolidated data on the doses administered per 100 people in the total population, by country and total doses administered, as of 16 April 2021. The count represents single doses, and may not match the number of people vaccinated, depending on the specific dosing regimen (i.e. some people receive multiple doses). The United States, with 202.28 million doses administered as of 16 April 2021, in the second graph was excluded.



Source: Our World in Data. Available at: https://ourworldindata.org/



Source: Our World in Data. Available at: https://ourworldindata.org/

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