COVID-19

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

WASHINGTON, DC

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CANADA

- As of 19 March 2021, 3,729,312 doses of the Pfizer-BioNTech, Moderna, and Covishield vaccines had been administered.
- A total of 2,530 individual reports of one or more adverse events (0.068% of doses administered) were reported. Of these, 320 were considered serious events (0.009% of doses administered), with anaphylaxis being the most frequently reported.
- There were a total of 7,397 adverse events following immunization (AEFI) (consisting of 2,530 reports of one or more events), mostly non-serious adverse events, such as injection-site reactions, partesia, itching, hives, headache, hyposthesia, and nausea. Only 0.8% of cases corresponded to anaphylaxis (59 cases, or 15.8 cases per million doses administered).
- Most adverse events reported were among women, and in people between the ages of 18 and 49, these being the groups prioritized for vaccination
- A total of 24 reported adverse events were identified as post-vaccination deaths. After medical review, it was determined that 13 of these deaths were not linked to administration of the COVID-19 vaccine, while the other 11 are still under investigation.

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

UNITED STATES

- Nearly 126 million doses of the Pfizer-BioNTech and Moderna vaccines were administered between 14 December 2020 and 29 March 2021.
- The Vaccine Adverse Event Reporting System (VAERS) received 2,509 reports of deaths (0.0019% of doses administered) that have not been linked to the vaccine.
- Anaphylaxis following COVID-19 vaccination is very rare, with approximately two to five cases per million people vaccinated in the United States. It occurs approximately 30 minutes after vaccination, and can be immediately and effectively treated.

Link: https://espanol.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html

CARRIBEAN COMMUNITY (CARICOM)

- As of 21 March 2021, 66 cases of AEFI had been reported to VigiBase. All of these cases involved the Oxford-AstraZeneca vaccine (ChAdOx1 nCoV-19) and were reported by Barbados (53 cases), Jamaica (11 cases) and Saint Vincent and the Grenadines (2 cases).
- Six cases (9.1%) were reported as severe, with two involving patient deaths.

- The most common events reported were itching at the injection site, headache, diarrhea, and myalgia.

Link: https://carpha.org/Portals/0/Documents/VigiCarib%20News/VigiCarib%20News%20March%202021.pdf

MEXICO

- As of 23 March 2021, 5,926,967 doses of the Pfizer-BioNTech, AstraZeneca, Sinovac, and Sputnik V vaccines had been administered.
- As of that date, 12,597 cases of AEFI (0.2% of doses administered) were reported, of which 11,941 were for the Pfizer-BioNTech vaccine, 424 for the AstraZeneca vaccine, 136 for Sinovac, and 96 for Sputnik V.
- A total of 106 serious events were reported, representing 0.84% of total events reported. Of these serious events, 79 were for the Pfizer-BioNTech vaccine, 11 were for the AstraZeneca vaccine, 13 for the Sinovac vaccine, and 3 for Sputnik V. Of these serious events, 23 cases remain hospitalized.

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

UNITED KINGDOM

- As of 14 March 2021, approximately 10.9 million first doses of the Pfizer-BioNTech vaccine, 13.7 million doses of the Oxford University/AstraZeneca vaccine, and approximately 1.3 million second doses had been administered, of which the majority were the Pfizer-BioNTech vaccine. This represents an increase of 2.3 million compared with the previous week.
- By that date, 38,084 Yellow Cards were reported for the Pfizer-BioNTech vaccine, constituting 100,810 suspicious reactions, while 78,223 Yellow Cards were reported for the Oxford University/AstraZeneca vaccine, representing 228,337 suspicious reactions (for both of these vaccines, a single report could involve more than one symptom.)
- A total of 281 reports were received in which the vaccine brand was not specified.
- The overall rate of Yellow Cards reported was approximately three to six cards per 1,000 doses administered.
- For both vaccines, a detailed review of all reports found that the vast majority of reports related to injection-site reactions (such as arm pain) and generalized flu-like symptoms, headache, chills, fatigue (tiredness), nausea (discomfort), fever, dizziness, weakness, muscle aches, and tachycardia. These symptoms usually occur shortly after vaccination and are not associated with more serious or long-lasting illness.
- The Medicines and Healthcare Products Regulatory Agency (MHRA) received 237 spontaneous reports of adverse events involving anaphylaxis or anaphylactic reactions for the Pfizer-BioNTech vaccine, and 326 such reports for the AstraZeneca vaccine. The nature and frequency of these reports are consistent with previous reports, in that severe allergic reactions to these vaccines are very rare.
- With regard to Bell's Palsy (facial paralysis) events, according to the MHRA the number of cases reported to date is similar to the baseline rate, with no indication that it will increase as a result of the vaccination. These events continue to be monitored.

- Available evidence does not suggest that venous thromboembolism events are caused by the AstraZeneca vaccine.
- Reports in the UK of a type of rare and specific blood clots in cerebral veins (sinus vein thrombosis), which occur along with decreased platelets (thrombocytopenia), are undergoing detailed study.
- The MHRA's recommendation remains that the benefits of COVID-19 vaccines continue to outweigh the risks, and that the public should continue to receive vaccinations at the appropriate time.

Link: https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting

Due to rare thrombotic events reported in European countries, and pending the results of ongoing studies, Canada's National Advisory Committee on Immunization proposed that the Public Health Agency of Canada should discontinue use of the AstraZeneca vaccine in people under the age of 55. Six countries in Europe – Germany, Finland, France, Iceland, Lithuania and Sweden – have also imposed age-based restrictions on its use. In 12 European countries – Austria, Bulgaria, Cyprus, Slovenia, Spain, Estonia, Ireland, Italy, Luxembourg, Portugal, the United Kingdom, and Romania – the vaccine continues to be used for all adults.

Link: https://www.canada.ca/en/public-health/news/2021/03/use-of-astrazeneca-covid-19-vaccine.html

Dyer O. Covid-19: EMA defends AstraZeneca vaccine as Germany and Canada halt rollouts. BMJ 2021; 373: n883 doi:10.1136/bmj.n883

Possible explanation of rare prothrombotic events with the AstraZeneca vaccine in Europe

There are press releases and communiqués, though no published studies, stating the following: In response to reports that emerged after a few recipients of the AstraZeneca COVID-19 vaccine (AZ1222) [based on the recombinant adenovirus vector encoding the SARS-CoV-2 spike (S) glycoprotein] developed unusual thrombotic events and thrombocytopenia, a group of researchers at the University of Greifswald in Germany, together with a similar team at the University Hospital of Vienna (Austria), McMaster University (Canada), and the Paul Ehrlich Institute (Germany), investigated whether these patients might have a prothrombotic disorder caused by platelet activation due to the presence of antibodies targeting platelet proteins. A similar mechanism has been found to be caused by heparin or, sometimes, by environmental triggers.

As a result of international collaboration between scientists, doctors, regulatory authorities, physicians, and consenting patients in a brief three-day period, it was possible to:

- Identify a possible mechanism by which the vaccine induced severe thrombotic complications;
- Identify a widely available diagnostic test;
- Develop a confirmatory test that appears to be highly sensitive and specific (despite possible limitations of the sample size);
- Identify a treatment that can quickly address the catastrophic prothrombotic mechanism: IV Ig (Intravenous Immunoglobulin) is an effective treatment against HIT (Heparin-induced thromboducedcytopenia), which is similar, in clinical and laboratory settings, to the complications found in connection with the vaccine. This product, IV Ig, is approved and available in most hospitals.

Researchers even proposed a name for this syndrome, namely, VIPIT: Virus/Vaccine Induced Prothrombotic Immune Thrombocytopenia.

Source: University of Greifswald Medical School. University of Greifswald Medical School Reports Breakthrough in SARS-CoV-2 Vaccination-Related Thrombotic Complications. 2/22/2021.
Link to statement: https://gth-online.org/wp-content/uploads/2021/03/GTH_Stellungnahme_AstraZeneca_engl._3_22_2021.pdf

GACVS statement on rare thrombotic events with the AstraZeneca vaccine in Europe

The COVID-19 subcommittee of the Global Advisory Committee on Vaccine Safety (GACVS) met in March 2021 to review available data on cases of thromboembolism and thrombocytopenia reported following administration of the AstraZeneca COVID-19 vaccine. The data were obtained from clinical trials and reports on safety of the vaccines from Europe, the United Kingdom, and India, and from WHO's VigiBase reporting safety in individual cases, from which it concluded and recommended that:

- The benefits of the vaccine continue to outweigh the risks, with enormous potential to prevent SARS-CoV-2 infection and reduce mortality worldwide.

- Administration of COVID-19 vaccines does not result in an overall increase in disorders such as deep vein thrombosis or pulmonary embolism. The rates of such occurrences are consistent with the expected number of diagnoses of these disorders, which are not uncommon and occur naturally, and can also occur as a result of COVID-19 itself. The observed rates of these events have been lower than expected.
- Of the 18 cases of cerebral venous sinus thrombosis reported after more than 20 million vaccinations with the AstraZeneca vaccine in Europe, no cause-and-effect relationship has at present been established, though this remains a possibility.
- GACVS recommends that all countries continue to monitor the safety of all COVID-19 vaccines, and encourages reporting of any suspected adverse effects.

Link: https://bit.ly/3wzEM0w

Additional information concerning the events and studies being conducted on this topic can be found at:

PRAC Report, https://bit.ly/3wuI5Ga

Source: Østergaard SD, Schmidt M, Horváth-Puhó E, Thomsen RW, Sorensen HT. Thromboembolism and the Oxford–AstraZeneca COVID-19 vaccine: side-effect or coincidence? The Lancet 2021 doi: 10.1016/S0140-6736(21)00762-5

NEW STUDIES AND DEVELOPMENTS

ANVISA and Butantan discuss anti-SARS-CoV-2 equine serum tests

Technicians from the National Health Surveillance Agency (ANVISA) and the Butantan Institute in Brasil met to consider the requested authorization to research the use, in humans, of equine serum developed to combat COVID-19, also known as anti-SARS-CoV-2 hyperimmune serum.

Butantan's team indicated that it will be making adjustments in its new version of the research protocol, in order to cover important aspects of research that remain undefined. To date, no human studies have been conducted with this serum, which require the authorization of ANVISA. At this point, the only available information concerns studies with animals.

Link: https://agenciabrasil.ebc.com.br/saude/noticia/2021-03/anvisa-e-butantan-discutem-testes-com-soro-equino-anti-covid-19

New vaccine developments

Canada-based Medicago is developing the CoVLP (Coronavirus-Like-Particle) vaccine, the efficacy of which is still unknown. The proposed dose administration guideline is two doses three weeks apart by intramuscular injection. The vaccine is stable at refrigerator temperatures. The effort is being conducted using a plant called Nicotiana benthamiana, a wild species related to tobacco. Plant leaf cells infected with a virus carrying SARS-CoV-2 protein genes are used. The proteins are produced in the leaves of the plant.

In July 2020, Medicago initiated phase 1 trials of this COVID-19 vaccine, combined with adjuvants to stimulate the immune system's response to viral proteins. That study found that an adjuvant made by GSK produced promising levels of antibodies in volunteers. On 23 October, the company announced that it had reached an agreement with the Canadian government to supply 76 million doses. On 12 November 2020, a phase 2/3 trial of the vaccine began. On 16 March 2021, Medicago and GSK began a phase 3 trial.

Available at: https://www.clinicaltrials.gov/ct2/show/NCT04636697

At the same time, Cuba's Center for Genetic Engineering and Biotechnology began a test in late November using a coronavirus vaccine called Abdala, which consists of a part of the coronavirus spike protein known as the receptor-binding domain. On 1 February, the Center held a press conference to announce the start of a phase 2 trial, and on 18 March began a phase 3 trial that will recruit up to 48,000 participants.

Source: https://rpcec.sld.cu/trials/RPCEC00000363-En

Live attenuated vaccines, which are usually highly immunogenic, are also in development. They cause an immune response similar to that generated by an infection. For SARS-CoV-2, the single-dose intranasal COVI-VAC vaccine is in a phase 1 clinical trial. Its developers claim to have introduced 283 silent mutations in the gene coding for the virus's spike protein. Additional information about the clinical trial is available at: https://clinicaltrials.gov/ct2/show/record/NCT04619628

Another COVID-19 vaccine designed to prevent infection is the orally administered VXA-CoV2-1 vaccine, consisting of a non-replicating vector virus, specifically a modified adenovirus encoding the SARS-CoV-2 and nucleocapsid S protein. This vaccine is undergoing clinical evaluation in a phase 1 trial. More on this clinical trial can be found at: https://clinicaltrials.gov/ct2/show/NCT04563702

At present, it is not known whether such a wide range of next-generation COVID-19 vaccines will be needed; however, it is worth highlighting the extensive effort that has been made at the global level to develop new vaccines. The WHO COVID-19 candidate vaccine landscape and tracker indicates that, as of 16 March 2021, there were 82 vaccines under clinical evaluation and 182 in the preclinical stage. Information available at:

https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

Variants and impact on vaccination against COVID-19

COVID-19 vaccines (both those already developed and those in development) are based on inducing an immune response to the spicule glycoprotein (S) version of the initial pandemic SARS-CoV-2 virus. The central question being asked by regulators, vaccine developers, and country health authorities is how much longer the immune response to this version of S-glycoprotein will continue to be useful against new emerging variants.

The emergence of these variants is due to the very nature of the virus, through point mutations, recombinations, insertions, or deletions. Several of these variants have put health systems on alert. Notable among these are B.1.1.7, which emerged in the United Kingdom; B.1.351, which emerged independently in South Africa; and P1, which was

identified as coming from Brazil. These have been accumulating mutations, leading to multiple differences in the behavior of the virus that can be detected in its transmission dynamics, pathogenicity, and ability to evade antibodies developed against the initial virus. The B.1.1.7 variant, while it has been associated with a higher mortality rate and greater transmissibility, has not been shown to affect vaccine efficacy. Variant B.1.351 is associated with a 20% increase in mortality among hospitalized patients, and there are indications that S-glycoprotein mutations may affect neutralization by vaccine-generated antibodies, as well as for some monoclonal vaccines, but without loss of vaccine efficacy. For the P1 variant, it was noted that its transmissibility and antigenic profile have been affected; and with it, the ability of antibodies generated by previous infections or by vaccination to recognize and neutralize the virus.

The results of clinical studies show that although vaccine efficacy may not be as high in terms of mild or moderate COVID disease caused by variants, the vaccines are effective in preventing hospitalization and severe COVID.

What is most clear is that as long as protection levels in the population, through vaccination, are not sufficient to achieve herd immunity, the virus will continue to circulate and spread from person to person, thus incorporating mutations. Therefore, in addition to the need to continue social distancing, use of masks, and hand washing, genomic surveillance should continue, identifying variants and assessing their potential impact on vaccination.

Sources:

Rubin R. COVID-19 Vaccines vs. Variants – Determining How Much Immunity is Enough. JAMA. Published online 17 March 2021, doi:10.1001/jama.2021.3370

Darby AC, Hiscox JA. Covid-19: variants and vaccination. BMJ 2021; 372:n771 doi:10.1136/bmj.n771

Link: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---23-march-2021

LOGISTICS AND RELATED ISSUES

Gavi COVID-19 Vaccines Advance Market Commitment (COVAX AMC) Initiative

The Gavi COVID-19 Vaccines Advance Market Commitment (COVAX AMC) initiative was created to ensure that all vulnerable and high-risk people in all countries have fast, fair, and equitable access to COVID-19 vaccines, regardless of income level. In line with this goal, COVAX has sent more than 29 million COVID-19 vaccines to 46 countries. The following countries in the Americas have benefited from this program, receiving doses of the vaccine for the first time:

Country	Number of doses	Type of vaccine	Date
Peru	117,000	Pfizer-BioNTech (BNT162b2)	10 March 2021
El Salvador	33,600	AstraZeneca (AZD1222)	12-22 March 2021
	51,480	Pfizer-BioNTech (BNT162b2)	
Guatemala	81,600	AstraZeneca (AZD1222)	11 March 2021
Honduras	48,000	AstraZeneca (AZD1222)	13 March 2021
Jamaica	14,400	AstraZeneca (AZD1222)	15 March 2021
Nicaragua	135,000	SII-AstraZeneca (COVISHIELD)	16 March 2021
Ecuador	84,000	AstraZeneca (AZD1222)	18 March 2021
Paraguay	36,000	AstraZeneca (AZD1222)	20 March 2021
Colombia	244,800	SII-AstraZeneca (COVISHIELD)	1 March 2021
	117,000	Pfizer-BioNTech (BNT162b2)	20 March 2021
Brazil	1,022,400	AstraZeneca South Korea	21 March 2021
Bolivia	228,000	SII-AstraZeneca (COVISHIELD)	22 March 2021
Suriname	24,000	AstraZeneca (AZD1222)	26 March 2021

Link: https://www.gavi.org/covax-vaccine-roll-out#total-covax-deliveries-12-million

Recommendations for newly vaccinated people

Studies on the effectiveness of the Pfizer-BioNTech BNT162b2 and AstraZeneca ChAdOx1 vaccines in Israel and the United Kingdom have shown that one vaccination dose provides significant protection against the main variants of SARS-CoV-2 circulating in these countries. Studies have also shown that in the first week after vaccination there is an increase in positive test results for SARS-CoV-2. Following surveys of the adult population in the UK, it was determined that in people who had received their first dose of vaccine within three weeks of the second dose, 41% had met in enclosed environments with people who were not family members or from their support bubble, in violation of the rules on social distancing.

The concern is that people who have been vaccinated mistakenly assume that one dose of the vaccine provides them with immediate protection, and therefore comply less with the protection practices they had been practicing up to that point. Although the results are from limited studies in Israel and the United Kingdom, it is reasonable to conclude that they are applicable to other countries as well, since the vast majority of the population are weary of confinement one year after the start of the pandemic.

Given that a mere two weeks after completing the vaccination schedule a person can be considered fully vaccinated, the Centers for Disease Control and Prevention (CDC) recommends reminding people, at the time of the vaccination, that it is their personal responsibility to continue these practices:

- Social distancing
- Wearing a mask
- Careful and frequent hand washing until fully vaccinated.

Two weeks after receiving the second dose of the vaccine, people may, among things:

- Meet indoors with people who are fully vaccinated without wearing a mask.
- Meet indoors with unvaccinated people outside of their family environment (e.g. relatives living separately from the vaccinated person) without a mask, as long as none of the people or their close friends have an increased risk of severe COVID-19 disease.
- If a person has been near someone with COVID-19, they do not need to have a diagnostic test unless they have symptoms.

Source: Are people letting down their guard too soon after covid-19 vaccination? The BMJ Opinion. 18 March 2021
Link: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html

Traceability and information on COVID-19 vaccines

It is important to establish measures to enable countries to protect themselves from possible counterfeiting, fraud, and misdirected doses by implementing an appropriate tracking system, and following WHO traceability guidelines as set forth in the document "COVID-19 vaccination: supply and logistics guidance," dated 12 February 2021.

WHO recommends establishing rigorous and efficient management throughout the supply chain. In some cases, COVID-19 vaccines will have a QR code or barcode on secondary and tertiary packaging, which may provide information and facilitate product tracking. The QR code contains real-time information on product shelf life, thermal stability, and new information on vaccine profiles, while the barcode contains manufacturer information, lot number, and expiration date.

Countries should consider strengthening training for the staff involved, as well as establishing supply chain information management systems. To avoid the introduction of counterfeit products in the immunization supply chain, strengthening the following distribution best practices is recommended:

- Authorization of the actors involved in the different aspects of the distribution process;

- Establishment of requirements and procedures on the receipt and shipment of vaccines, as well as for the management of subcontracted services, with duties and responsibilities delegated only to duly authorized entities, in accordance with national law;
- Ensuring product traceability from the manufacturer to immunization service delivery sites;
- Requesting that manufacturers of COVID-19 vaccines place a QR/bar code on each pack. This will allow the vaccine information to be verified once this code is scanned, and verify that it is not a counterfeit vaccine.

For more information on this and related topics, we recommend reviewing the above-referenced WHO document, which can be found at: https://apps.who.int/iris/rest/bitstreams/1332203/retrieve

Falsified COVID-19 vaccine alert in Mexico

WHO, through medical product alert No. 2/2021, reported the existence of a falsified COVID-19 BNT162b2 vaccine, identified in Mexico in February 2021. The counterfeit product was supplied and administered to patients outside of authorized vaccination programs.

Information on the falsified product

Product Name	**COVID-19 Vaccine BNT162b2**
Stated manufacturer	Pfizer BIONTECH
Lot number	783201
Exp date	AUG 24
Packaging language	English
Identified in	Mexico

Source: Medical Products Alert No. 2/2021: COVID-19 BNT162b2 Falsified Vaccine

Laboratory analysis of the contents of the falsified vaccine is in process. Results will be reported when they become available. However, the genuine manufacturer of the COVID-19 BNT162b2 vaccine has confirmed that it did not manufacture the product involved in this alert, and that the lot number and expiration date are forged. In addition, the glass vials and label are different from the authentic vials of the COVID-19 BNT162b2 vaccine (see image).

Source: Medical Products Alert No. 2/2021: COVID-19 BNT162b2 Falsified Vaccine

It is important to disclose this information and take appropriate action, as this falsified COVID-19 vaccine could continue to circulate in the Region and continue to be offered to patients outside authorized vaccination programs. It is also important to increase surveillance at the different levels of distribution, including hospitals, clinics, health centers, wholesalers, distributors, pharmacies, and other medical product providers.

For more information on this alert, visit:
https://www.who.int/es/news/item/26-03-2021-medical-product-alert-n-2-2021-falsified-covid-19-vaccine-bnt162b2