COVID-19

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

WASHINGTON, DC
Update: 19 March 2021

BRAZIL

- As of 8 March 2021, 18.1 million doses of vaccine had been distributed – 14.1 million of the Sinovac vaccine and 3.9 million of the AstraZeneca vaccine, of which a total of 10,848,777 had been administered (8,159,177 first doses and 2,689,601 second doses), 63% to women and 27% to men.
- The National Health Surveillance Agency (ANVISA) reported that the most frequent adverse events following immunization (AEFI) of the COVID-19 vaccine in Brazil were non-serious and expected, and therefore do not affect the assessment of the vaccine's safety. Adverse events identified included headache, fever, and flu-like sensations.

Links:

https://localizasus.saude.gov.br/

https://agenciabrasil.ebc.com.br/saude/noticia/2021-02/anvisa-eventos-adversos-das-vacinas-estao-dentro-do-previsto

CANADA

- As of 5 March 2021, 2,255,174 doses of the Pfizer-BioNTech and Moderna COVID-19 vaccines had been administered.
- One or more adverse events were reported in 1,923 individual cases (0.085% of doses administered). Of these, 214 were considered serious events (0.009% of doses administered), with anaphylaxis being the most frequently reported.
- A total of 5,502 AEFI were reported (consisting of 1,923 cases involving one or more adverse events), with the majority being non-serious, such as reactions at the injection site, paresthesia, itching, urticaria, headache, hypoesthesia, and nausea. Only 0.9% of cases of anaphylaxis were reported (50 cases, equivalent to 22.4 cases per million doses administered).
- Among the priority groups for vaccination, the majority of adverse events reported were in women and in people between 18 and 49 years of age.
- A total of 15 reported adverse events involved post-vaccination deaths. After medical review, it was determined that nine of these deaths were not linked to administration of the COVID-19 vaccine, while the other six cases are still under review.

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

CHILE

- Between 24 December 2020 and 2 March 2021, 3,671,086 doses of the Coronavac and Pfizer-BioNTech vaccines were administered.
- The National Pharmacovigilance Center reported 62 cases of anaphylactic reactions, of which only 9 were considered to have a plausible link to the vaccine administered (three related to the Pfizer-BioNTech vaccine and six to the Coronavac vaccine). Recommendations to the community and to consulting health professionals were issued in the link below.

Link: https://www.ispch.cl/wp-content/uploads/2021/03/INF-FARMACOVIGILANCIA.pdf

SPAIN

- According to the report by the Spanish Agency of Medicines and Medical Devices (AEMPS), between 27 December 2020 and 21 February 2021, 3,058,776 doses of the Pfizer BioNTech, Moderna, and AstraZeneca vaccines were administered.
- A total of 6,266 AEFI were reported, of which 83% were among women, with people between 18 and 64 years of age, accounting for 91% of reported cases.
- Among doses of Corminaty administered, 5,736 AEFI were reported (204 reports per 100,000 doses administered), while 430 cases were reported for the Moderna vaccine (332 reports per 100,000 doses administered), and 84 cases for the AstraZeneca vaccine (69 reports per 100,000 doses administered). Overall, the most frequent events were fever or pain at the site of injection, followed by central nervous system disorders (mainly headaches and dizziness) and symptoms involving the musculoskeletal system (most commonly myalgia and arthralgia).
- Reported rates of anaphylaxis – between five and 10 cases per million doses administered – remained unchanged compared with previous reports by the agency.
- AEMPS clarified that the data presented, which reflect reports of adverse events in the country, do not provide a basis for concluding that these events were due to the vaccines administered.

Link: https://www.aemps.gob.es/informa/boletines-aemps/boletin-fv/2021-boletin-fv/3o-informe-de-farmacovigilancia-sobre-vacunas-covid-19/

UNITED STATES

- Nearly 109 million doses of the Pfizer-BioNTech and Moderna vaccines were administered between 14 December 2020 and 15 March 2021.
- The Vaccine Adverse Event Reporting System (VAERS) received 1,913 (0.0018%) reports of deaths, none of which have been linked to administration of the vaccine.

- Anaphylaxis after receiving the COVID-19 vaccine was very infrequent, with approximately two to five cases per million people vaccinated in the United States. When this occurs, it is around 30 minutes after the vaccination, and is effectively and immediately treatable.

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

FRANCE

- Between 26 February and 4 March 2021, the French pharmacovigilance network analyzed 3,013 cases of AEFI related to the AstraZeneca vaccine, of which the majority involved flu-like symptoms (high fever, body pain, headaches).
- One case of multiple thrombosis was analyzed, but could not be determined to have been caused by the vaccine.
- With regard to the Comirnaty vaccine, 8,487 AEFI were analyzed, of which the majority were non-serious and expected.
- For this vaccine, cases of thrombocytopenia have been reported, including one case in which this event occurred after the second vaccination. Although data remain limited, this possible signal is being monitored.
- A total of 302 cases of AEFI following administration of the Moderna vaccine were analyzed and were mostly non-serious delayed local reactions. There were some reported cases of hypertension, arrhythmia, and herpes zoster, which are still being reviewed.

Link: https://ansm.sante.fr/actualites/point-de-situation-sur-la-surveillance-des-vaccins-contre-la-covid-19-11

MEXICO

- As of 15 March 2021, 4.4 million doses of the Pfizer-BioNTech, AstraZeneca, Sinovac, and Sputnik V vaccines had been administered.
- A total of 11,835 cases of AEFI (0.3% of doses administered) were reported, including 106 serious adverse events (0.7 % of total events reported) with 15 people still hospitalized.

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

PERU

- The National Center for Epidemiology, Disease Prevention, and Control, of the Ministry of Health, and the National Epidemiology Network are receiving daily reports of non-serious AEFI in the country.
- As of 19 February, 696 cases of mild AEFI and 84 moderate AEFI cases were reported. There may be a gap in the number of cases reported by the Directorate General of Medicines, Supplies, and Drugs (DIGEMID), since the pharmacovigilance units have up to 72 hours to report to the agency.

- Serious AEFI at the national level, from the time vaccinations began on 9 February are: three cases of anaphylactic reaction, two cases of acute respiratory symptoms, one case of tachycardia, one case of generalized paresthesia, and one case of syncope.
- The reported anaphylactic reactions could be related to the vaccination, if the time of presentation and the overall clinical situation are considered, though the association is, in some cases, unclear. The two cases of acute respiratory insufficiency would appear to be consistent with COVID-19. The other cases are under review.

Link: https://www.dge.gob.pe/portalnuevo/wp-content/uploads/2021/03/boletin_202106.pdf

VACCINE REGISTRY AND AUTHORIZATION

Emergency use listing (EUL/WHO): Janssen COVID-19 Vaccine

The Janssen Laboratory COVID-19 vaccine (Ad26.COV2-S [recombinant]), presented by Janssen-Cilag International NV (Belgium), was incorporated into the emergency use listing (EUL) of vaccines by the World Health Organization (WHO) on 12 March 2021, with the following general characteristics.

Characteristics of the product:

Name	**Janssen COVID-19 Vaccine (Ad26.COV2-S [recombinant])**
Date of WHO recommendation	12 March 2021
Platform/type of vaccine	Non-replicating viral vector. Replication-incompetent recombinant adenovirus type 26, encoding for the SARSCoV-2 Spike (S) glycoprotein produced in the genetically modified PER.C6® TetR cell line.
Manufacturer	Janssen
Dosage form	Suspension for intramuscular injection
Presentation	Vial of 5 doses, containing a total of 2.5 ml
Diluent	Not required
Dose/route of administration	One dose (0.5 mL) intramuscularly in the deltoid muscle of the arm, in persons over 18 years of age.
Storage temperature/length of time effective	24 months at -25°C to -15°C or 3 months stored at 2°C to 8°C. Once the vaccine is thawed, it cannot be refrozen.
Allowable time vial is open/in use	Discard a maximum 6 hours after opening.

Link: https://www.who.int/teams/regulation-prequalification/eul/eul-vaccines

Pfizer BioNTech and AstraZeneca Vaccines

On 23 February 2021, ANVISA granted the first marketing authorization for Pfizer BioNTech's COVID-19 vaccine in the Region. Subsequently, on 12 March 2021, the agency granted Fiocruz/AstraZeneca two different authorizations: one in the name of AstraZeneca, the other in the name of Fiocruz. This allows the two companies to adopt different distribution and marketing strategies for the product. The vaccines were registered under the names "Fiocruz Recombinant Covid-19 Vaccine," and, in the case of AstraZeneca, "Recombinant Covid-19 Vaccine."

Link: https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2021/anvisa-aprova-registro-da-vacina-da-fiocruz-astrazeneca-e-de-medicamento-contra-o-coronavirus

NEW STUDIES AND DEVELOPMENTS

The Finlay Institute (Cuba) moves forward in developing its SARS-CoV-2 vaccine

A recent publication of Cuba's Finlay Institute demonstrates that the macromolecular construction of the recombinant protein of the ACE2 receptor-binding domain (RBD) of the tetanus toxoid conjugate protein S (FINLAY-FR-2 vaccine) is capable of inducing a potent immune response in animals.

Another publication shows the results of evaluating the application of a dose of the FINLAY-FR-1A vaccine (constituted by the recombinant protein dimer of the receptor-binding domain [d-RBD] of the S protein) in COVID-19 convalescents, to test its capacity to reinforce the natural immunity conferred by the infection. The results suggest an adequate safety profile, a more than 20-fold increase in antibody response, and a four-fold increase in virus neutralizing capacity one week after vaccination.

Sources:

Valdes-Balbin Y, Santana-Mederos D, Quintero L, Fernández S, et al. RBD-Tetanus toxoid conjugate vaccine induces a strong neutralizing immunity in preclinical studies. BioRxiv 2021.02.08.430146.

Chang-Monteagudo A, Ochoa-Azze R, Climent-Ruiz Y, et al. A single dose of SARS-CoV-2 FINLAY-FR-1A dimeric-RBD recombinant vaccine enhances neutralization response in COVID-19 convalescents, with excellent safety profile. A preliminary report of an open-label phase 1 clinical trial. MedRxiv 2021.02.22.

Phase III clinical trial with the Sovereign 2 vaccine candidate

The Center for State Control of Medicines and Medical Equipment and Devices (CECMED- Cuba) authorized a Phase III clinical trial with the Sovereign 2 vaccine candidate. This is a multicenter, adaptive, in parallel-group, randomized, placebo-controlled, double-blind, Phase III study to evaluate the efficacy, safety, and immunogenicity of the SARS-CoV-2 vaccination with two doses of FINLAY- FR-2 and a booster dose of FINLAY-FR-1A. 44,010 individuals will be participating in the study, for which recruitment began on 5 March 2021.
Link: https://rpcec.sld.cu/ensayos/RPCEC00000354-Sp

Cellular immune response to COVID-19 and mRNA vaccines

Various scientific articles have appeared that relate to the evaluation of the humoral immune response to COVID-19 in convalescent and vaccinated subjects, as well as evaluations of the possible impact of SARS-CoV-2 variants on the binding and function of specific antibodies. To this end, it is important to understand the cellular immune response to COVID-19, mediated by CD4+ and CD8+ T-cell responses, and the effect of the virus variants on this type of immune response.

The group of researchers led by Alison Tarke, Center for Infectious Disease and Vaccine Research, USA, in the preliminary report entitled "Negligible impact of SARS-CoV-2 variants on CD4+ and CD8+ T cell reactivity in COVID-

19 exposed donors and vaccines," reports the results of the analysis of SARS-CoV-2 specific CD4+ and CD8+ T cell responses in COVID-19 convalescent individuals and in individuals who received COVID-19 vaccines from Moderna (mRNA-1273) and Pfizer/BioNTech (BNT162b2) against the ancestral strain and variants B.1.1.7, B.1.351, P.1, and CAL.20C.

According to the results of this work, the sequences of the vast majority of T cell epitopes against SARS-CoV-2 appear to be unaffected by the mutations found in the variants analyzed; thus CD4+ and CD8+ T cell responses in COVID-19 convalescent individuals, or those vaccinated with COVID-19 mRNA, would not be significantly affected by the mutations found in the SARS-CoV-2 variants.

Source: Tarke Alison, et al. (Mar 1, 2021). Negligible Impact of SARS-CoV-2 Variants on CD4+ and CD8+ T Cell Reactivity in COVID-19 Exposed Donors and Vaccinees. BiorXiv. 01/03/2021

CLARIFICATIONS/CONCLUSIONS OF EVENTS PRESENTED IN PREVIOUS COMMUNICATIONS

Update on the AstraZeneca COVID-19 vaccine and thrombosis

In light of decisions made by several European Union (EU) countries (and currently reversed by most of them) to suspend the use of AstraZeneca's COVID-19 vaccine due to safety signals related to thromboembolic events, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) has been assessing the situation, and on 18 March 2021 stated the following:

PRAC confirms that:

- The benefits of the vaccine in combating COVID-19 (clotting problems that can be fatal) outweigh the risks of adverse effects;
- The vaccine is not associated with an increase in the overall risk of blood clot formation (pulmonary and venous thromboembolism events) in those receiving the vaccine;
- There is no evidence that the problems identified are related to any specific bacth of vaccine or to any specific manufacturing site;
- However, the vaccine may be associated with very rare cases of blood clots associated with thrombocytopenia with or without bleeding, including rare cases of clots in veins bringing blood from the brain (cerebral venous sinus thrombosis, CVST).

To date, 20 million people in the United Kingdom and the European Union have received the vaccine in question and EMA has reviewed seven cases of multi-vessel blood clots (disseminated intravascular coagulation, DIC) and 18 cases of CVST.

In general, the number of thromboembolic events after vaccination, both in pre-authorization clinical studies and in reports after implementation of vaccination, is lower than expected in the general population. This has led PRAC to state that there is no increased risk of blood clots.

However, the fact that usually-rare events of disseminated coagulation and CVST have occurred also in young patients remains a concern, and further observation is required, particularly in these rare cases.

Link: https://www.ema.europa.eu/en/news/covid-19-vaccine-astrazeneca-benefits-still-outweigh-risks-despite-possible-link-rare-blood-clots

As noted, several countries such as Germany, Italy, France, Spain, Portugal, and the Netherlands, resumed vaccination activities with AstraZeneca's vaccine, but since the agency could not definitively rule out a link between rare cases and the vaccine, it recommended to include the description of the cases in the vaccine inserts.

The World Health Organization had previously indicated, on 17 March 2021, that the benefits of vaccination exceeded the risks, and recommended that vaccination should continue.

Link: https://www.who.int/news/item/17-03-2021-who-statement-on-astrazeneca-covid-19-vaccine-safety-signals

This research will continue and additional information will be provided as more details about these events become available.

Surveillance should continue for potential thromboembolic events, disseminated intravascular coagulation, and cerebral venous sinus thrombosis, as well as other events that may occur after vaccination (especially if they are severe).

It is also recommended that, in case of bruising, bleeding, purple or reddish spots, and persistent severe headache or difficulty breathing within three days after vaccination, immediate medical attention should be sought.

PROGRAMMATIC ERRORS, LOGISTICS, AND RELATED ISSUES

Critical recommendations for vaccine administration

The following are some of the recommendations on administration of the COVID-19 vaccines mentioned in previous updates, due to their importance in ensuring a good outcome in the vaccination process:

- Be sure to inject the correct volume of the vaccine dose being administered.
- Use the appropriate syringes to administer all six doses of Pfizer-BioNTech vaccine.
- Comply with the storage requirements for each type of vaccine.
- Do not shake vaccines, with the exception of those vaccines that require this, e.g., those containing adjuvant formulations.
- Ensure that the second dose is administered within the recommended time frame, according to the particular vaccine administered.

As different types of vaccines are purchased or received by the countries' immunization programs, greater caution will be required in the handling and logistics of vaccine administration, mainly to ensure that, for vaccines with two-dose schedules, both doses are administered using the same product. At the moment, though studies are currently underway, there is no evidence or study that confirms the interchangeability of vaccines. Until the results are available and have been authorized by the regulatory authorities, vaccines of different types or manufacturers should not be interchanged.

To avoid confusion and reduce possible errors, the following is recommended:

- Assign different vaccines to different geographical locations;
- Allocate different vaccines to different populations, e.g., health care workers, by age group, by work activity (emergency response workers, essential workers, military, police, etc.);
- Although some vaccines can be differentiated by their conservation and storage conditions, all vaccines are kept in refrigerators at temperatures between +2° and +8°C prior to administration; therefore, they must be clearly identified and kept separate.
- It is recommended that the technical specifications of the vaccines in use, or a summary table of their characteristics, be placed in visible locations cited in the previous update, to facilitate compliance with the conditions of use of each type of vaccine.
- Ensure availability of the second dose and its timely distribution.

Link: https://www.health.gov.on.ca/en/pro/programs/publichealth/coronavirus/docs/vaccine/vaccine_storage_handling_pfizer_moderna.pdf

Preliminary information from a pre-publication (non-peer-reviewed) study: Distribution of reconstituted mRNA vaccines in the United States.

One of the current recommendations on the handling of reconstituted vials of Pfizer-BioNTech and Moderna vaccines, or the product already in syringes, is that they should not be transported in order to avoid unnecessary movement, since this could alter the integrity of the mRNA. This represents a limitation to prompt and rapid vaccination; therefore, in order to identify whether vaccines could be reconstituted centrally and then distributed to vaccination sites, an analysis was performed to determine the integrity of reconstituted mRNA vaccines under different conditions of movement.

It was confirmed that moderate movement of the reconstituted vaccines for 180 minutes at room temperature (simulating land transportation), does not affect the quality of the mRNA. These results allow for improving the efficiency of vaccine distribution, since this would allow terrestrial transport of the vaccine at room temperature, within a period of three hours, to centers that are not close or that do not have the right conditions to reconstitute the vaccine. Thus, it would be possible to reach different locations and obtain uniform vaccination coverage of the population in a short period of time.

Source: Grau S, Ferrandez O, Martin-Garcia E, Maldonado R. May we overcome the current serious limitations for distributing reconstituted mRNA vaccines? MedRxiv. 12/03/2021

Destruction of used vials to avoid counterfeiting

Since 2013, WHO launched the Global Surveillance and Monitoring System to encourage countries to report cases of substandard and falsified medical products, and to increase surveillance in the supply chains of countries and regions that may be affected by these products. This problem affects all regions of the world; increased surveillance should therefore include hospitals, clinics, health centers, wholesalers, distributors, pharmacies, and any other supplier of medical products.

In addition, the high demand for vaccines by countries and the anxiety created in the population increases the incentive for and risk of counterfeiting.

Improper disposal of empty, damaged, or expired vaccine vials can create opportunities for them to be reconditioned, refilled, and used for counterfeit versions. Given this risk, it is essential to ensure that the label on the vials is defaced or destroyed before disposal, and ensure that they are then incinerated. It is equally important to remember that all medical products must be obtained from authorized/licensed and reliable suppliers. The authenticity and physical condition of incoming products should be carefully verified.

It is important to emphasize this issue since different types of waste are generated in the cold chain. The handling, segregation, collection, treatment, transport, and final disposal of these wastes deserve special attention, both because of the health risks involved and because of the legal regulations in force in each country.

Sources:

https://www.who.int/es/news-room/fact-sheets/detail/substandard-and-falsified-medical-products

https://www.europol.europa.eu/early-warning-notification-vaccine-related-crime-during-covid-19-pandemic-0

Wright, Louisa. Officials warn of fake COVID-19 vaccines. DW. 04/01/2021 Available at:

http://bvsms.saude.gov.br/bvs/publicacoes/manual_rede_frio4ed.pdf