COVID-19

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

WASHINGTON, DC
Updated 4 March 2021

OFFICIAL REPORTS ON PHARMACOVIGILANCE PROGRAMS

BRAZIL

- As of 4 February 2021, 7,768 adverse events following immunization (AEFI) against COVID-19 had been reported by the Ministry of Health.
- Of these events, 7,686 were classified as non-serious and 82 as serious. The most common events were headache, fever, muscle pain, diarrhea, nausea, and localized pain.
- Some serious adverse events were reported in older adults and are being investigated. So far, no causal association with vaccination has been demonstrated.

Link: https://www.gov.br/saude/pt-br/assuntos/noticias/saude-monitora-eventos-adversos-pos-vacinacao-da-covid-19

CANADA

- As of 19 February 2021, 1,402,139 doses of the Pfizer-BioNTech and Moderna vaccines had been administered.
- 1,235 individual reports of one or more adverse events were received (0.088% of administered doses). Of these, 167 were considered serious (0.012%), with anaphylaxis as the most frequently reported event.
- 3,303 AEFI were reported (1,235 people reported one or more events), mostly non-serious; 57% were injection site reactions and the rest were burning or prickling sensations, itching, hives, headache, numbness, and nausea. Anaphylaxis accounted for only 1.3% of reported events (43 cases, for a rate of 30 cases per one million doses administered).
- In the priority vaccination groups, most adverse events were reported in women and people between the ages of 18 and 49.
- In total, there were 10 adverse events in which death was reported after vaccination. After medical review, it was determined that seven of these deaths were not linked to administration of the COVID-19 vaccine. The other three deaths are still under investigation.

Link: http://bit.ly/3l2BKfG

UNITED STATES

- Nearly 76 million doses of Pfizer-BioNTech and Moderna vaccines were administered between December 2020 and 1 March 2021.
- The Vaccine Adverse Event Reporting System (VAERS) received 1,381 (0.0018%) reports of death among vaccinated people. Analysis showed no connection between these deaths and vaccination.

- Anaphylaxis after the COVID-19 vaccine is very rare, with approximately two to five cases per million people vaccinated in the United States. It occurs around 30 minutes after vaccination and can be treated effectively and immediately.

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

MEXICO

- As of 2 March 2021, a total of 2,583,435 doses of the Pfizer-BioNTech, AstraZeneca, and Sputnik V vaccines had been administered.
- 9,988 AEFI (0.4% of administered doses) were reported; 9,676 were reported with the Pfizer-BioNTech vaccine, 303 with AstraZeneca, and 9 with Sputnik V.
- 59 serious events were reported, comprising less than 1% of all reported events.

Link: https://www.gob.mx/salud/prensa/version-estenografica-conferencia-de-prensa-informe-diario-sobre-coronavirus-covid-19-en-mexico-265473?idiom=es

NEW STUDIES AND DEVELOPMENTS

Effectiveness of the Pfizer-BioNTech Comirnaty mRNA COVID-19 vaccine (with modified nucleosides)

The results of an observational study conducted during the mass vaccination campaign in Israel were presented in the article "BNT162b2 mRNA Covid-19 Vaccine in a Nation-wide Mass Vaccination Setting", by Dagan N. et al., published on 24 February 2021 in the New England Journal of Medicine (DOI: 10,1056/NEJMoa2101765). The study included 596,618 people in each study group (1:1 ratio between vaccinated and control groups). The following variables were studied: documented infection by SARS-CoV-2; symptomatic COVID-19; hospitalization due to COVID-19; severe and fatal cases of COVID-19.

The results of the study indicate that, at seven days after the second dose, the vaccine was 92% effective against documented infections (95% CI: 88-95); 94% effective against symptomatic illness (95% CI: 87-98); 87% effective against hospitalization due to COVID-19 (95% CI: 55-100); and 92% effective against severe COVID-19 cases (95% CI: 75-100).

The authors concluded that the Comirnaty vaccine is highly effective at preventing symptomatic COVID-19 in an uncontrolled environment, and highly effective in cases of hospitalization, serious illness, and death. In addition, they noted that the estimated benefit increases over time after vaccination.

Source: BNT162b2 mRNA Covid-19 Vaccine in a Nation-wide Mass Vaccination Setting. Dagan et al. New England Journal of Medicine. 24 February 2021

European research project on SARS-CoV-2 variants and vaccine development

Spain's Ministry of Science and Technology reported that the European Commission began a new initiative to improve research and management of potential SARS-CoV-2 variants. The project is called the HERA Incubator: Anticipating together the threat of COVID-19 variants. Its objectives are to promote actions to detect, analyze, and evaluate variants; accelerate vaccine development and approval; and facilitate clinical trials to include the potential influence of virus variants and vaccine prototypes in development.

The HERA Incubator initiative includes the participation of the scientific community, biotech and pharmaceutical companies, and European Union public administration institutions. It will be developed in cooperation with the World Health Organization (WHO) and other global initiatives on vaccines and COVID-19.

Hopefully, this initiative will be the starting point for the European Health Emergency Preparedness and Response Authority (HERA), a permanent institution for research and management of biomedical and public health emergencies.

Source: España participa a través del ISCIII en un proyecto europeo para la investigación en variantes del SARS-CoV-2 y el desarrollo de vacunas (Carlos III Health Institute in Spain participates in a European research project on SARS-CoV-2 variants and vaccine development). Ministry of Science and Technology, Spain. 22 February 2021. Available from: http://bit.ly/2NbPXL2

Study on Effectiveness of first dose of COVID-19 vaccines against hospital admissions in Scotland

The results of the study "Effectiveness of first dose of COVID-19 vaccines against hospital admissions in Scotland: national prospective cohort study of 5.4 million people" show that one dose of the BNT162b2 vaccine (Pfizer-BioNTech) is associated with an 85% reduction effect (95% CI: 76-91%) of COVID-19 related hospitalizations at 28-34 days after vaccination. The reduction effect was 94% for the ChAdOx1 vaccine (Oxford/AstraZeneca) over the same time interval (95% CI: 73-99%). When the test was restricted to people 80 years and older, the result of the combined effect of both vaccines on preventing COVID-19 hospitalization was 81% (95% CI: 65-90%) at 28-34 days after vaccination.

Source: Eleftheria Vasileiou, Colin R Simpson, Chris Robertson, et al. Effectiveness of first dose of COVID-19 vaccines against hospital admissions in Scotland: national prospective cohort study of 5.4 million people.

Mass vaccination in the municipality of Serrana, Riberão Preto, Brazil

On 17 February, the government of the State of São Paulo initiated a mass vaccination campaign to measure the reduction of coronavirus infection in Serrana municipality, located in the Riberão Preto region. Nearly 30,000 people over the age of 18 will receive the vaccine developed by the Butantán Institute in partnership with Sinovac.

This initiative is a clinical study to determine the efficacy of the vaccine on decreased coronavirus transmission. The municipality of Serrana was chosen due to its high case rate, among other factors. The vaccine will be given to volunteers, with a four-week interval between the two doses. The city was divided into 25 areas representing four population groups. Each of these will be vaccinated at different times according to a predetermined schedule. The groups will be compared before and after vaccination. Children under 18 years of age, pregnant or nursing women, and people who have had a fever in the previous 72 hours will not receive the vaccine.

Source: Governo de SP inicia em Serrana teste inédito de vacinação em massa (Government of São Paulo begins an unprecedented mass vaccination campaign in Serrana) 17 February 2021. Available from: https://www.saopaulo.sp.gov.br/noticias-coronavirus/governo-de-sp-inicia-em-serrana-teste-inedito-de-vacinacao-em-massa-2/

Adapting COVID-19 vaccines to SARS-CoV-2 variants: guidance for vaccine manufacturers

Currently, authorized vaccines provide protection against prevalent SARS-CoV-2 variants. However, due to ongoing mutations of the virus and the emergence of new variants, it is expected that vaccines will have to be adapted to maintain continuous protection. Current information indicates that some variants may impact the protection offered by existing COVID-19 vaccines against transmissibility and severe illness.

As a result, the European Medicines Agency (EMA), the U.S. Food and Drug Administration (FDA), WHO, and other regulatory authorities, as an urgent public health priority, have decided to define regulatory processes to authorize adapted vaccines to protect against current and future variants of the virus, and coordinate their efforts on next steps.

The assumption is that new vaccines will be based on the same technology and platforms as existing vaccines already authorized to prevent COVID-19. The difference will lie in the specific structure (antigen) selected to induce the immune response.

Among the considerations in the EMA guide, clinical information indicates that immunogenicity studies should demonstrate effectiveness, determining the immune response induced by new vaccines against virus variants. By measuring the presence of neutralizing antibodies generated by the new variant vaccine, the goal is to verify if the immune response is equal to the immune response induced by the vaccine designed for the first virus. The effectiveness of new vaccines, if administered as a single booster dose, should also be studied in people who already received the first vaccine. Long-term effectiveness and safety will be evaluated in post-authorization studies. No additional non-clinical trials will be required. Trials conducted for the first vaccine may be used. Given that new vaccines will be produced under the same conditions as the first ones, it is expected that the same standards for processes and controls will be maintained.

Source: Adapting COVID-19 vaccines to SARS-CoV-2 variants: guidance for vaccine manufacturers. European Medicines Agency. 25 February 2021 Available from: https://www.ema.europa.eu/en/news/adapting-covid-19-vaccines-sars-cov-2-variants-guidance-vaccine-manufacturers

Meanwhile, the FDA has added an appendix on evaluating vaccines in response to new variants in its Guidance for the Pharmaceutical Industry, dated 22 February 2021. The guidance states that clinical immunogenicity studies should determine the effectiveness of vaccines. The immune response induced by the modified vaccine against the virus variant should be compared to the response induced by the prototype vaccine (the initial vaccine) against the original virus. The results of studies should be displayed using the primary vaccine series, as well as the effect of "booster" doses. The latter refers to administering the new vaccine to people who have received the complete series of the first vaccine. Studies must show non-inferiority.

Source: Emergency Use Authorization for Vaccines to Prevent COVID-19 Guidance for Industry. 22 February 2021 Available from: https://www.fda.gov/media/142749/download

CLARIFICATIONS/CONCLUSIONS OF EVENTS PRESENTED IN PREVIOUS COMMUNICATIONS

BRAZIL

On 16 February, the Amazonas Health Surveillance Foundation (Fundacao de Vigiláncia em Saúde do Amazonas, FVS-AM) reported that the death of an 83-year-old adult in Manaus on 30 January is unrelated to the AstraZeneca/Oxford vaccine dose he received on 29 January. The Reference Center for Special Immunobiologicals (Centro de Referancia de Imunobiológicos Especiais), an institution associated with FVS-AM, investigated the AEFI together with the Tropical Medicine Foundation (Fundacao de Medicina Tropical, FMT). The autopsy indicated that death resulted from acute myocardial infarction and, therefore, is not associated with the COVID-19 vaccine.

Source: FVS-AM rules out link between COVID-19 vaccine and death of elderly person in Manaus (FVS-AM descarta relação de morte de idoso em Manaus com vacina contra Covid-19). Amazonas Atual. 16 February 2021.

PROGRAMMATIC ERRORS, LOGISTICS, AND RELATED ISSUES

Vaccines on the WHO Emergency Use List (EUL)

The following is a summary of the primary characteristics of the vaccines on the list:

Name	Tozinameran - COVID-19 mRNA vaccine	AstraZeneca/SKBio COVID-19 vaccine (ChAdOx1-S [recombinant])	COVID-19 Vaccine (ChAdOx1-S [recombinant])
Commercial name	COMIRNATY®	Not applicable	COVISHIELD™
WHO recommendation date	31 December 2020 http://bit.ly/3l4vqUZ	15 February 2021 http://bit.ly/3bxiFPQ	15 February 2021 http://bit.ly/3bB1eOh
Platform/vaccine type	mRNA	Recombinant adenoviral vaccine vector ChAdOx1: encodes the SARS-CoV-2 spike protein antigen.	Recombinant adenoviral vaccine vector ChAdOx1: encodes the SARS-CoV-2 spike protein antigen.
Manufacturer	Pfizer-BioNTech	AstraZeneca/SK Bioscience Co. Ltd, Republic of Korea.	Serum Institute of India Pvt. Ltd, India.
Pharmaceutical form	Concentrate for dispersion for injection.	Solution for injection.	Solution for injection.
Presentation	6 dose vial.	10-dose vial.	2-dose and 10-dose vials.
Diluent	1.8 mL/vial of sodium chloride solution for injection at 0.9%.	Not required.	Not required.
Dosage/route of administration	0.3 mL intramuscular.	0.5 mL intramuscular.	0.5 mL intramuscular.
Storage temperature/ shelf-life	- 90°C to - 60°C for 6 months. 5 days between 2°C and 8°C or 2 hours at a temperature below 30°C before use.	2°C to 8°C for 6 months.	2°C to 8°C for 6 months.
Open/in use vial	Discard after being open for 6 hours.	Discard after being open for 6 hours.	Discard after being open for 6 hours.

Accidental overdose with COVID-19 vaccine

In Australia, five doses of the Pfizer-BioNTech COVID-19 vaccine were accidentally administered to two adults, 88 and 94 years old, who were then hospitalized for strict monitoring. The Australian authorities reported that an

investigation is underway and appropriate actions are being taken, indicating that studies of this vaccine experimented with up to four times the prescribed dose without noting serious adverse events.

In addition, it was noted that similar early reports were received from vaccination programs in residences for the elderly in Germany and the United Kingdom.

Source: COVID-19 Vaccine rollout: Australia's accidental overdose not the first in the world. 9News 24 February 2021

Comment: See suggested recommendations and precautions on the administration of COVID-19 vaccines at the end of this section.

Janssen vaccine receives Emergency Use Authorization from the FDA

On February 26, 2021, the Janssen Ad26.COV2.S vaccine against COVID-19 received Emergency Use Authorization (EUA) from the FDA. Ad26.COV2.S is a replication-incompetent adenovirus type 26 (Ad26) viral vector vaccine encoding a stabilized variant of the SARS-CoV-2 spike (S) protein. The proposal for EUA is active immunization to prevent SARS-CoV-2 in individuals 18 years and older, with a single intramuscular injection of 5×10^{10} viral particles. In support of the EUA request, Janssen submitted information on safety and efficacy from a multinational, phase 3, double-blind, randomized, placebo-controlled trial conducted with approximately 40,000 participants. The following is a summary of the information submitted:

Efficacy

The vaccine was 66.9% efficacious (95% CI: 59.0-73.4%) against moderate to severe/critical COVID-19, as defined by protocol, at 14 days after vaccination. For moderate to severe/critical COVID-19 occurring at least 28 days after vaccination, it was 66.1% efficacious (95% CI: 55.0-74.8%). The participants had no evidence of prior SARS-CoV-2 infection. The vaccine was 76.7% efficacious (95% CI: 54.6-89.1%) in preventing centrally confirmed severe/critical illness starting at least 14 days after vaccination, and 85.4% efficacious (CI95%: 54.2-96.9%) at least 28 days after vaccination.

To explore the potential impact of variants on vaccine efficacy, a subgroup analysis of efficacy was conducted against moderate to severe/critical and severe/critical COVID-19 for the United States, South Africa, and Brazil. Lower efficacy was observed against moderate to severe/critical illness variables in the following locations:

- South Africa: 52.0% efficacy (95% CI: 30.3-67.4%) 14 days after vaccination and 64.0% (95% CI: 41.2-78.7%) 28 days after vaccination, respectively.
- United States: 74.4% efficacy (95% CI: 65.0-81.6%) 14 days after vaccination and 72.0% (95% CI: 58.2-81.7%) 28 days after vaccination, respectively.
- Brazil: 66.9% efficacy (95% CI: 51.0-77.1%) 14 days after vaccination and 81.9% (95% CI: 17.0-98.1%) 28 days after vaccination, respectively.

It should be noted that, in the United States, 96.4% of sequenced cases were identified as the SARS-CoV-2 Wuhan-H1 D614G variant. In South Africa, 94.5% of sequenced cases were identified as the 20H/501Y, Variant V2 (B.1.351). In Brazil, 69.4% were identified as a variant of the P.2 lineage and 30.6% were identified as the Wuhan-H1 D614G variant.

Safety

43,783 people participated in the phase 3 safety study; 21,895 received the vaccination and 21,888 received the placebo. A subset of participants (N = 6,736) were monitored for reported reactions within seven days of vaccination and unsolicited events within 28 days. In this group, mild to moderate injection site reactions and systemic events were the most common. The most common solicited adverse reactions were injection site pain (48.6%), headache (38.9%), fatigue (38.2%), and muscle pain (33.2%); 0.7% and 1.8%, respectively, of local and systemic solicited adverse reactions were reported as Grade 3. In general, solicited reactions were most often reported in younger participants.

An imbalance was observed in the number of reported events involving urticaria in the vaccine group (N = 5) and the placebo group (N = 1) within seven days of vaccination, which could possibly be related to the vaccine. Disparities in thromboembolic events and in tinnitus were reported between vaccine and placebo groups (15 to 10, and 6 to 0, respectively). Based on currently available information, the vaccine could not be ruled out as a contributing factor to these events. The FDA will recommend further evaluation of thromboembolic events once the vaccine is administered to more people.

As of 5 February 2021, 25 total deaths had been reported in the study (5 in the vaccine group, 20 in the placebo group). These deaths are indicative of events and rates that occur in these age groups in the general population and include seven deaths in the placebo group due to COVID-19 infection.

Clarifications on indications for use and recommendations for COVID-19 vaccine administration

Age groups authorized to receive COVID-19 vaccines

In accordance with Emergency Use Authorizations:

- Pfizer-BioNTech: people ≥16 years old
- Moderna: people ≥18 years old
- AstraZeneca: people ≥18 years old
- Moderna: people ≥18 years old

Children and adolescents outside these age ranges should not receive COVID-19 vaccines at this time.

Administration

- Pfizer-BioNTech: two doses (30 µg, 0.3 ml each) three weeks apart (21 days)

- Moderna: two doses (100 µg, 0.5 ml each) 28 days apart
- AstraZeneca: two doses (no less than 2.5×10^8 IU, 0.5 ml each) 28 to 84 days apart
- Sinovac: two doses (600 SUof inactivated virus, 0.5 ml each) 28 days apart

People should not receive their second dose of mRNA vaccine earlier than recommended (three weeks between doses for Pfizer-BioNTech or one month for Moderna). In any case, administration of the second dose up to four days before the scheduled date is considered valid. If the second dose is inadvertently administered before the recommended period has elapsed, it should NOT be repeated.

The second dose should be administered as close to the recommended time interval as possible. If this is not possible, the second dose of the Pfizer-BioNTech and Moderna vaccines may be administered up to six weeks (42 days) after the first dose. There is currently little evidence on the effectiveness of these vaccines if administered after this window.

To date, there is no evidence regarding the interchangeability of COVID-19 vaccines. There are no data available on the safety and efficacy of a mixed vaccine series. The series must be completed with the same vaccine.

Strategies should be defined to ensure that the vaccinated person receives the second dose after the appropriate interval. To this end, the following measures are recommended, among others:

- Provide a vaccination card with the relevant information, and request that it be brought to the appointment for the second dose.
- Make the appointment for the second dose before the vaccinated person leaves, to ensure that they return to the same vaccination site.

Studies on vaccine interchangeability are about to start, but until results and evidence on the safety and effectiveness of different strategies emerge, the same vaccine should be used.

Source: Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Authorized in the United States. Centers for Disease Control and Prevention. 3 March 2021 Available from:

https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fvaccines%2Fcovid-19%2Finfo-by-product%2Fpfizer%2Fclinical-considerations.html