COVID-19

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

Twenty-ninth report

WASHINGTON, DC

Updated: 29 October 2021

CONTENTS

ARGENTINA

- As of 31 August 2021, 43,521,623 doses of COVID-19 vaccines had been administered, and 52,649 adverse events following immunization (AEFI) had been reported to the Integrated Health Information System of Argentina (SIISA). That information, by vaccine, is shown in the following table:

Number of reports and reporting rate of adverse events (per 100,000 doses administered), by vaccine, as of 31 August 2021

Vaccine	Doses administered	AEFI reported	Reporting rate of AEFI/100,000 doses administered	Vaccine-related events*	Reporting rate of vaccination-related events/100,000 doses administered
AstraZeneca/Covishield	14,621,435	7,382	50.49	5,174	35.37
Sinopharm	13,783,959	2,841	20.61	1,436	10.3
Sputnik V	13,057,335	41,846	320.48	38,793	296.58
Moderna	2,058,894	482	23.41	351	17.0
Total	43,521,623	52,649	120.97	45,754	105.13

Source: 15th* Vaccine Safety Surveillance Report of Argentina's Ministry of Health

* Based on a causal analysis of each of the reported AEFI, events are classified as either vaccination-related, indeterminate, or serious.

- Of AEFI reported, 2.4% were considered serious events; of those classified as vaccination-related, 0.34% were considered serious (cases requiring hospitalization), of which AstraZeneca/Covishield accounted for 0.38/100,000 doses administered, Sinopharm for 0.12/100,000 doses administered, and Sputnik V for 0.65/100,000 doses administered.
- Among the events classified as vaccination-related, fever, headache with myalgia, and arthralgia were the most frequent diagnoses.
- Of adverse events of special interest (AESI) associated with the AstraZeneca/Covishield vaccine, there were: six cases of thrombosis with thrombocytopenia syndrome (TTS), one case of coronary thrombosis, and three cases of Guillain Barré syndrome (GBS); with the Sinopharm vaccine: one case of immune thrombocytopenia; and

with the Sputnik V vaccine: four cases of GBS, one case of pericarditis, three cases of immune thrombocytopenia, two cases of TTS, and one case of thrombotic thrombocytopenic purpura.

Source: Ministry of Health, Argentina, 15th Vaccine Safety Surveillance Report. Available at: https://www.argentina.gob.ar/coronavirus/vacuna/equipos-salud/informes-seguridad.

COSTA RICA

- A press release on 8 October by Costa Rica's Ministry of Health stated that, as of 3 September, 7,710 adverse events following vaccination with a COVID-19 vaccine had been reported, of which 70.4% (5,429) were in people who received the Pfizer-BioNTech vaccine and 29.6% (2,281) were in people who received the AstraZeneca vaccine.
- The age group most affected consisted of people 30–49 years old (3,803), followed by people 18–29 years old (1,449), and those 50–59 years old (1,178). Of reported AEFI, 44 were considered serous – 38 following administration of the Pfizer/BioNTech vaccine and six after administration of the AstraZeneca vaccine – and included 19 reported deaths (18 associated with the Pfizer/BioNTech vaccine and one with the AstraZeneca vaccine). Of the 19 reported deaths, nine were classified as unlikely to have been caused by the vaccination; in seven cases the cause of death was not determined, and three deaths were considered to be potentially attributable to the vaccine.

Source: The full report, in Spanish, can be found at: https://bit.ly/2YFQHNM.

PARAGUAY

- On 20 October, the 31st AEFI surveillance report of Paraguay's Ministry of Health stated that between 22 March and 8 October, 4,836,914 doses of COVID-19 vaccines had been administered to 2,836,640 people.
- Between 22 February and 8 October 2021, 2,215 reports of AEFI were received, representing 0.05% of total doses administered. Among the ESAVI reported, 71.7% (1,589) were in women; 69.4% (1,539) were in the 25- to 49-year old age group. Among all reported AEFI, 49.3% (1,094) received the AstraZeneca vaccine, 14.9% (330) the Sputnik V, 13.7% (304) the Pfizer-BioNTech, 8.2% (182) the CoronaVac, 7% (155) the Covaxin, 4.5% (101) the Moderna, and 2.2% (49) the Sinopharm vaccine.

Source: The full report, in Spanish, can be found at: https://bit.ly/3G7wCRO.

Consolidated adverse events reported by countries of the Region, by vaccine, September 2021

Vaccine	Total doses administered in countries reporting AEFI	Total cases reported (ICSR)	Total cases/ 100,000 doses	Total serious cases reported	Total serious cases/ 100,000 doses
AstraZeneca	124,605,825	24,156	19.4	4,346	3.5
Bharat/Covaxin	194,027	157	80.9	95	49.0
CanSino/Convidencia	4,099,682	1,157	28.2	52	1.3
Gamaleya	16,242,281	42,318	260.5	107	0.7
Janssen	22,584,915	56,635	250.8	6,933	30.7
Moderna	172,509,864	293,029	169.9	24,668	14.3
Pfizer-BioNTech	364,361,148	413,082	113.4	70,161	19.3
SinoPharma	20,937,524	10,663	50.9	69	0.3
Sinovac	121,847,874	13,522	11.1	2,664	2.2
Total	**847,460,758**	**855,016**	**100.9**	**109,151**	**12.9**

Source: Dosing information from the Vaccination in the Americas dashboard (https://ais.paho.org/imm/IM_DosisAdmin-Vacunacion.asp). Accessed 17 September 2021.

- Cases: VigiBase data as of 20 September 2021, and public sources from the countries (Argentina, Epidemiological Bulletin of 31 July 2021; Canada, government website, 17 September 2021; Chile, data from July 2021; Colombia, doses administered, by vaccine, reported by the country; El Salvador, data as of 20 September 2021; Mexico, data as of 27 May 2021).
- Countries using the indicated vaccines (countries included in the table's data are in bold):
  AstraZeneca: Anguilla, Antigua and Barbuda, **Argentina**, Bahamas, **Barbados**, Belize, **Bolivia, Brazil, Canada, Chile, Colombia, Costa Rica,** Dominica, **Ecuador, El Salvador,** Grenada, Guadeloupe, Guatemala, Guyana, **Honduras, Jamaica,** Montserrat, **Mexico,** Nicaragua, **Panama, Paraguay, Peru,** Dominican Republic, Saint Kitts and Nevis, Saint Lucia, **Saint Vincent and the Grenadines,** Suriname, Virgin Islands, Trinidad and Tobago, **Uruguay.**
  Bharat Biotech: **Paraguay**
  CanSino: **Chile, Mexico**
  Gamaleya: **Argentina, Bolivia,** Guatemala, Guyana, **Honduras, Mexico,** Nicaragua, Panama, **Paraguay**, **Saint Vincent and the Grenadines, Venezuela**
  Janssen: **Bolivia, Brazil,** Colombia, Haiti, Mexico, **USA**
  Moderna: **Canada**, Guadeloupe, Guatemala, Haiti, **Honduras**, Panama, **Paraguay, USA**
  Pfizer-BioNTech: Aruba, **Bolivia**, Bonaire, **Brazil, Canada,** Cayman Islands, **Chile, Colombia, Costa Rica,** Curacao, **Ecuador, El Salvador,** Guadeloupe, **Honduras**, Martinique, **Mexico**, Nicaragua, **Paraguay, Panama, Peru,** Saint Martin, Turks and Caicos Islands, **Uruguay, USA**
  Sinopharm BBIP: **Argentina, Bolivia,** Dominica, **Paraguay, Peru,** Suriname, Trinidad and Tobago, Venezuela

Sinovac: **Brazil, Chile, Colombia, Ecuador, El Salvador, Mexico, Paraguay,** Turks and Caicos Islands, **Uruguay**

Publications on potential safety signals identified with the use of COVID-19 vaccines

ROCCA Observational Study: Early Results on Safety of Sputnik V Vaccine (Gam-COVID-Vac) in the Republic of San Marino using Active Surveillance

In August 2021, findings were published from the observational active vaccine surveillance study of the Sputnik V vaccine, conducted in the Republic of San Marino. The study was conducted nationwide between 4 March and 8 April 2021 on the 18- to 89-year-old population that received one or two doses of the Sputnik V vaccine. An e-questionnaire, conducted through emails, in person, and by telephone interviews, was used, approximately seven days after the first and second doses of vaccine had been administered. A descriptive analysis was performed to quantify the incidence of AEFI, stratifying the results by type and severity of symptoms. The mean age of the 2,558 vaccinated individuals was 66 ± 14 years. The incidence of AEFI from the first dose was 53.3% (systemic reactions at 42.2%), while the incidence of AEFI from the second dose was 66.8% (systemic reactions at 50.4%) (n = 1,288). Overall, 76.0% of two-dose recipients reported an adverse event after one of the doses of the vaccine, with 2.1% experiencing serious reactions. In people 60 to 89 years of age (n = 1,021), the incidence of AEFI was 70.0%, with 53.0% of subjects reporting systemic reactions, and 0.8% reporting severe symptoms. The most frequent symptoms were local pain, asthenia, headache, and joint pain. The authors conclude that although these results are preliminary, they suggest that the Sputnik V vaccine has a high tolerability profile in the population aged ≥60 years in terms of short-term AEFI.

Sources: Montalti M, Soldà G, Di Valerio Z, et al. San Marino Republic COVID ROCCA Group. ROCCA observational study: Early results on safety of Sputnik V vaccine (Gam-COVID-Vac) in the Republic of San Marino using active surveillance. EClinicalMedicine. 2021 Jul 8;38:101027. doi: 10.1016/j.eclinm.2021.101027. PMID: 34505029; PMCID: PMC 8413 252. https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00307-2/fulltext.

Efficacy and Safety of BNT162b2 Vaccination in Patients with Solid Cancer Receiving Anticancer Therapy: A Single Center Prospective Study

In September 2021, a prospective observational study, with a control group, conducted in Israel, was published, to evaluate the rate of seropositivity and define predictors for non-reactive immune response in patients receiving treatment for solid tumors, in addition to evaluating the frequency and severity of adverse events. The study included patients with solid tumors undergoing anticancer treatment, with immunocompetent health-care workers serving as controls. Serum titers of the receptor-binding domain (RBD) immunoglobulin G (IgG) and neutralizing antibodies were measured 2-4 weeks after each vaccine dose. The analysis included 129 patients, of which 70.5% patients were metastatic. Patients were treated with chemotherapy (55%), immunotherapy (34.1%), biological agents (24.8%), hormonal treatment (8.5%), and radiotherapy (4.6%), that were given either alone or in combination. The seropositivity rate among patients with cancer and controls was 32.4% versus 59.8% ($p < 0.0001$) after the first dose,

and 84.1% versus 98.9% ($p < 0.0001$) after the second dose. Median RBD-IgG titer was lower among patients than among controls ($p < 0.0001$). Patients who were seronegative after the second dose had significantly more comorbidities than patients who were seropositive (77.8% vs 41.1%, respectively, $p = 0.0042$). The authors conclude that, in the small number of cancer patients analyzed, adequate antibody response after BNT162b2 vaccination was achieved after two doses but not after one dose.

Source: Shmueli ES, Itay A, Margalit O, et al. Efficacy and safety of BNT162b2 vaccination in patients with solid cancer receiving anticancer therapy - a single center prospective study. Eur J Cancer. 2021 Sep 8;157:124–131. doi: 10.1016/j.eclinm.2021.101027. Preprint publication. PMID: 34508994; PMCID: PMC 8424105. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8424105/.

Maternal Outcomes After Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Vaccinated Compared With Unvaccinated Pregnant Patients

On 13 October 2021, a retrospective cohort study with a control group of all active pregnancies in the Ochsner Health System in the United States was published between 15 June 2021 and 20 August 2021. The objective was to compare SARS-CoV-2 infections in pregnant women based on their vaccination status. The vaccinated group included patients who were fully vaccinated two weeks before the start of the study period.

A total of 10,092 pregnant patients were included in the study; 1,332 vaccinated patients, along with 8,760 unvaccinated or incompletely vaccinated patients, a vaccination rate of 13.2%. Vaccinated patients had lower odds of severe or critical COVID-19 (0.08% vs 0.66%, adjusted odds ratio [aOR] 0.10, 95% CI 0.01–0.49) and COVID-19 of any severity (1.1% vs 3.3%, aOR 0.31, 95% CI 0.17–0.51). Additionally, in the unvaccinated group there was one maternal death secondary to COVID-19 complications and six stillbirths, three of which occurred in patients who had SARS-CoV-2 infection earlier in the gestation. There were no fatal cases in the group of vaccinated patients. When including all partially vaccinated patients who received any doses of the vaccine before the study, an association between vaccinated status and lower odds of severe or critical COVID-19 (0.07% vs 0.68%, aOR 0.08, 95% CI 0.004–0.40) and COVID-19 of any severity (1.1% vs 3.3%, aOR 0.30, 95% CI 0.17–0.48) remained. The study showed an association between SARS-CoV-2 vaccination and lower odds of severe or critical COVID-19 and COVID-19 of any severity in pregnant patients. This study also identified a low vaccination rate among pregnant women (13.2%). Unvaccinated status was associated with younger age, lower body mass index (BMI), current smoking, and race.

Source: Morgan JA, Biggio JR, Martin JK, et al. Maternal Outcomes After Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Vaccinated Compared With Unvaccinated Pregnant Patients. Obstet Gynecol. 2021 Oct 13. doi: 10.1097/AOG.0000000000004621. https://journals.lww.com/greenjournal/Fulltext/9900/Maternal_Outcomes_After_Severe_Acute_Respiratory.320.aspx.

COVID-19 Vaccination and Non-COVID Mortality Risk in the United States (study conducted in seven integrated health care organizations from 14 December 2020 to 31 July 2021)

By 21 September 2021, an estimated 182 million people in the United States were fully vaccinated against COVID-19. Clinical trials indicate that Pfizer-BioNTech (BNT162b2), Moderna (mRNA-1273), and Janssen (Johnson & Johnson; Ad.26.COV2.S) vaccines are effective and generally well tolerated. A cohort study of 19,625 nursing home residents found that those who received an mRNA vaccine (Pfizer-BioNTech or Moderna) had lower all-cause mortality than did unvaccinated residents (1), but no studies comparing mortality rates within the general population of vaccinated and unvaccinated persons have been conducted. To assess mortality not associated with COVID-19 (non-COVID-19 mortality) after COVID-19 vaccination in a general population setting, a cohort study was conducted from December 2020 to July 2021, among approximately 11 million people enrolled at seven Vaccine Safety Datalink (VSD) sites.

After standardizing mortality rates by age and sex, this study found that COVID-19 vaccine recipients had lower non–COVID-19 mortality than did unvaccinated persons. After adjusting for demographic characteristics and VSD site, the study found that adjusted relative risk (aRR) of non-COVID-19 mortality for the Pfizer-BioNTech vaccine was 0.41 (95% confidence interval [CI] = 0.38–0.44) after dose 1 and 0.34 (95% CI = 0.33–0.36) after dose 2. The aRRs of non-COVID-19 mortality for the Moderna vaccine were 0.34 (95% CI = 0.32–0.37) after dose 1 and 0.31 (95% CI = 0.30–0.33) after dose 2. The aRR after receipt of the Janssen vaccine was 0.54 (95% CI = 0.49–0.59).

The study concluded that there is no increased risk of mortality among COVID-19 vaccine recipients. This finding reinforces the safety profile of currently approved COVID-19 vaccines in the United States.

Sources:

1. Bardenheier BH, Gravenstein S, Blackman C, et al. Adverse events following mRNA SARS-CoV-2 vaccination among U.S. nursing home residents. Vaccine 2021; 39: 3844–51. PMID:34092431 https://doi.org/10.1016/j.vaccine.2021.05.088.

2. Xu S, Huang R, Sy LS, et al. COVID-19 Vaccination and Non–COVID-19 Mortality Risk — Seven Integrated Health Care Organizations, United States, December 14, 2020–July 31, 2021. MMWR Morb Mortal Wkly Rep. ePub: 22 October 2021. DOI: http://dx.doi.org/10.15585/mmwr.mm7043e2.

European Medicines Agency (EMA) authorizes ready-to-use formulation of Pfizer-BioNTech COVID-19 vaccine

The Human Medicines Committee (CHMP) has authorized the new ready-to-use formulation of Pfizer-BioNTech's COVID-19 vaccine, which will be available in 10-vial pack size (60 doses) that can be stored at 2–8°C for up to 10 weeks. The current concentrated formulation requires dilution prior to administration, is available in a 195-vial (1,170 dose) pack size and can be stored at 2-8°C for up to one month.

The new formulation of the Pfizer-BioNTech's COVID-19 vaccine will be available in a phased rollout, starting in early 2022.

Source: https://www.ema.europa.eu/en/news/new-manufacturing-sites-new-formulation-approved-covid-19-vaccine-biontech-pfizer.

U.S. Food and Drug Administration Authorizes Change to Pfizer-BioNTech Vaccine Formulation

The U.S. Food and Drug Administration (FDA) has authorized a change to the formulation of Pfizer-BioNTech's Covid-19 vaccine that allows the use of a different buffer, called Tris, commonly used in a variety of vaccines and other FDA-approved biologics, including products for use in children. This buffer helps maintain a vaccine's pH and increases stability at refrigeration temperatures for longer periods of time, allowing vaccination providers greater flexibility.

The FDA evaluated manufacturing data to support the use of the Pfizer-BioNTech COVID-19 Vaccine containing Tris buffer and concluded that it does not present safety or effectiveness concerns. Several characteristics associated with vaccine activity, ranging from the appearance to the size of the lipid nanoparticles and the integrity of the modified mRNA, were taken into account in their evaluation.

Source: FDA, USA. FDA Authorizes Pfizer-BioNTech COVID-19 Vaccine for Emergency Use in Children 5 through 11 Years of Age. Available at: https://www.fda.gov/news-events/press-announcements/fda-authorizes-pfizer-biontech-covid-19-vaccine-emergency-use-children-5-through-11-years-aged.
https://www.fda.gov/media/150386/download.

Update from the U.S. Centers for Disease Control and Prevention on Interim Clinical Considerations for the Use of COVID-19 Vaccines in Specific Populations

On 25 October 2021, the Centers for Disease Control and Prevention (CDC) updated interim clinical considerations for the use of COVID-19 vaccines licensed in the United States, including recommendations on additional and booster doses, which are summarized below:

- *mRNA vaccines:*

- People with moderate and severe immune compromise aged ≥12 years (Pfizer-BioNTech recipients) or ≥18 years (Moderna recipients) should receive an additional dose after completing the primary series of vaccinations; and a booster dose of any of the COVID-19 vaccines authorized in the United States (Pfizer-BioNTech, Moderna, or Janssen) at least six months after completing the primary series.
- People age 65 and older, residents age 18 and older in long-term care settings, and people ages 50 to 64 with certain underlying medical conditions should receive a booster dose with any of the U.S.-authorized COVID-19 vaccines (Pfizer-BioNTech, Moderna, or Janssen) at least 6 months after completing the primary series.
- People ages 18 to 49 with certain underlying medical conditions, and people ages 18 to 64 at increased risk of exposure and transmission of SARS-CoV-2 because of their occupational or institutional setting may receive a single booster dose with any of the U.S.-authorized COVID-19 vaccines (Pfizer-BioNTech, Moderna, or Janssen) at least 6 months after completing the primary vaccination series, based on their individual benefits and risks.
- Booster dose: for the Pfizer-BioNTech vaccine, the booster dose is the same dose used in the primary vaccination series, which is 30 mg in a volume of 0.3 ml. For the Moderna vaccine, the booster dose is 50 mg in a volume of 0.25 ml, or half the amount used in both the primary series and the additional dose, when applicable.

These recommendations for additional doses and booster doses for mRNA vaccines also apply to people who received two doses of different COVID-19 mRNA vaccine products for their primary immunization series.

- Janssen Vaccine: It is recommended that people age 18 and older who received a single-dose Janssen primary series can receive a booster dose with any of the U.S.-authorized COVID-19 vaccines (Pfizer-BioNTech, Moderna, or Janssen) at least 2 months after completing the primary vaccination series. The booster dose will be the same as the dose used in the primary vaccination series, i.e., 5×1010 viral particles in a volume of 0.5 ml.

Source: Centers for Disease Control and Prevention (CDC). Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Approved or Authorized in the United States. Available at: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html#considerations-covid19-vax-booster

Emergency Use Authorization (EUA) of the Pfizer-BioNTech COVID-19 vaccine to include children ages 5 to 11

The U.S. Food and Drug Administration (FDA) authorized the emergency use of the Pfizer-BioNTech COVID-19 vaccine to include children ages 5 to 11. The authorization was based on the FDA's thorough and transparent evaluation of data, which included input from independent experts on the advisory committee, who voted in favor of making the vaccine available to children in this age group.

Key points of the authorization are:

Vaccine effectiveness: The immune responses of children ages 5 to 11 were comparable to those of people ages 16 to 25. In addition, the vaccine was found to be 90.7% effective in preventing COVID-19 in children ages 5 to 11.

Vaccine safety: Vaccine safety was studied in approximately 3,100 children between the ages of 5 and 11 who received the vaccine; no serious side effects have been detected in the ongoing study.

The Pfizer-BioNTech COVID-19 vaccine for children ages 5 to 11 is given as a two-dose primary series, three weeks apart, **but in a lower dose (10 micrograms)** than is used for people 12 years old and older (30 micrograms).

The effectiveness data supporting the EUA for children down to 5 years of age are based on an ongoing randomized placebo-controlled study that recruited approximately 4,700 children 5 through 11 years of age. The study is being conducted in the United States, Finland, Poland, and Spain. Children in the vaccinated group received two doses of the Pfizer-BioNTech COVID-19 vaccine, containing 10 micrograms of mRNA per dose. The FDA analyzed data that compared the immune response of 264 participants in this study with 253 participants ages 16 to 25, who received two higher doses of the vaccine in an earlier study, which determined that the vaccine was effective in preventing COVID-19. The immune responses of the younger participants were comparable to the older participants.

The FDA also conducted a preliminary analysis of COVID-19 cases that occurred seven days after the second dose. In this analysis, among participants with no evidence of prior infection with SARS-CoV-2, three cases of COVID-19 occurred among 1,305 vaccine recipients, compared with 16 cases of COVID-19 among 663 placebo recipients; thus, the vaccine was 90.7% effective in preventing COVID-19.

Source: FDA, USA. FDA Authorizes Pfizer-BioNTech COVID-19 Vaccine for Emergency Use in Children 5 through 11 Years of Age. Disponible en: https://www.fda.gov/news-events/press-announcements/fda-authorizes-pfizer-biontech-covid-19-vaccine-emergency-use-children-5-through-11-years-age

Safety data available in support of the EUA include more than 4,600 participants (3,100 vaccines, 1,538 placebos) ages 5 to 11 enrolled in the ongoing study. In this trial, a total of 1,444 vaccine recipients were monitored for safety for at least two months after the second dose. Adverse events commonly reported in the clinical trial included injection site pain (arm pain), redness and swelling, fatigue, headache, muscle and/or joint pain, chills, fever, swollen

lymph nodes, nausea, and decreased appetite. More children reported side effects after the second dose than after the first dose. Side effects were generally of mild to moderate severity and occurred within two days of vaccination, and most symptoms disappeared within a day or two.

Source: FDA, USA. FDA Authorizes Pfizer-BioNTech COVID-19 Vaccine for Emergency Use in Children 5 through 11 Years of Age. Available at: https://www.fda.gov/news-events/press-announcements/fda-authorizes-pfizer-biontech-covid-19-vaccine-emergency-use-children-5-through-11-years-age. https://www.fda.gov/media/150386/download.

Update on recommendations of the WHO Strategic Advisory Committee of Experts (SAGE) on Immunization for the use of Sinovac and Sinopharm COVID-19 vaccines

On 21 and 28 October 2021, the World Health Organization (WHO) Strategic Advisory Group of Experts (SAGE) on Immunization published an update to its provisional recommendations for use of the Sinovac-CoronaVac and Sinopharm vaccines. These recommendations are presented below.

- Additional dose: Additional doses may be needed as part of a primary vaccination series, in populations where the immune response to the standard primary series is considered likely to be insufficient. In this regard, they recommend:
    - For immunocompromised individuals 18 years old and older: Administer a third dose one to three months after the second dose of the standard primary series. If more than three months have elapsed since the second dose, the third dose should be administered at the first possible opportunity, taking into account the epidemiological setting and the administration of immunosuppressive therapy.
    - People age 60 years old and older: In countries that have achieved high two-dose vaccination coverage, administration of a third dose is recommended in individuals ages 60 years old and older, with an interval of 3 to 6 months between the second and third doses; if more than 6 months have elapsed since the second dose, the third dose should be given as soon as possible.
- Heterologous schedule: The benefit of an additional dose has been assessed using the same vaccine for the first two doses (homologous schedule). Evolving evidence suggests that a heterologous series (using a different vaccine platform for the third dose) may be more immunogenic than a homologous series. However, data on safety, immunogenicity, and effectiveness of the vaccine using additional heterologous doses compared to homologous doses is still too limited to issue recommendations on this. However, in situations of interrupted vaccine supply for the primary series, or for countries with access to COVID-19 vaccines from another platform included in the WHO emergency use listing (EUL), a heterologous third dose can be considered.
- Booster doses: Booster doses are administered to a vaccinated population that has completed a primary vaccination series when, with time, vaccine effectiveness has fallen below a rate deemed sufficient in that population (6). For the COVID-19 vaccine BIBP, the need for, and timing of, booster doses is being assessed. Recommendations with regards to booster doses will be updated as data become available..
- Coadministration with other vaccines: COVID-9 vaccines can be co-administered with inactivated influenza vaccines.

Updated WHO/SAGE interim recommendations for use of the COVID-19 vaccines, Sinovac-CoronaVac and Sinopharm, are available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-Sinovac-CoronaVac-2021.1.

https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-BIBP.

Incorporation of conservation and use guidelines to the pharmacovigilance dashboard of COVID-19 vaccines

In October 2021, guidelines on the conservation and use of COVID-19 vaccines were incorporated into PAHO's COVID-19 vaccine pharmacovigilance dashboard, in Spanish and English, and are available on the main page of the dashboard, as well as in the storage and handling section for each vaccine.

In these illustrated guides, the specific storage conditions for each vaccine are summarized in a clear and simple way, as well as warnings and precautions for conserving, preparing, and administering the vaccines, handling of vails during use, and disposal of used vials and supplies. These guides can be downloaded, in pdf format for ease of reference and dissemination.

The COVID-19 vaccine pharmacovigilance dashboard is available at https://covid-19pharmacovigilance.paho.org/index.php.

Interim Recommendations by the U.S. Centers for Disease Control and Prevention on COVID-19 Vaccine Administration Errors and Deviations

The following table shows the main interim recommendations of the U.S. Centers for Disease Control and Prevention (CDC), according to the type of error or deviation in the administration of COVID-19 vaccines authorized in the U.S.

Vaccine	Administration error/deviation	Description	Recommendation
Pfizer-BioNTech and Janssen COVID-19 Vaccines	Site and route of administration	Site of administration other than the deltoid muscle or anterolateral thigh	First dose: Administer the second dose at the recommended interval. Second dose: Do not administer additional doses. Inform the vaccinated person of potential local and systemic adverse events.
		Incorrect route of administration (e.g., subcutaneous)	
	Age	Unauthorized age group	In children under 12 years of age: Do not administer an additional dose. Between ages 12 and 17: If the Moderna vaccine was administered as the first dose, administer the second dose of this vaccine at the recommended interval. If the Janssen vaccine was administered, do not repeat the dose.
	Dose level	Higher-than-authorized dose volume	Do not repeat the dose. Administer the second dose at the recommended interval. If serious adverse events occur after the first dose, the decision to administer a second dose should be assessed on a case-by-case basis.
		Lower-than-authorized dose volume	If more than half the dose was administered, do not repeat that dose; if it is the first dose, administer the second dose at the recommended interval. If less than half the dose was administered or the dose ratio cannot be estimated, immediately administer the authorized dose in the opposite arm; if it is the first dose, the interval for the second dose should be estimated from the date of administration of the correct dose.
	Storage and handling	Deviation in storage temperature, time of use of open vial	Consult the manufacturer for guidance. If the dose needs to be repeated, this should be done as soon as possible, in the opposite arm.
		Dose administered after the expiration date	
	Interval between vaccinations	Second dose given earlier than recommended	Less than 17 days after the first dose for the Pfizer-BioNTech vaccine, or less than 24 days for Moderna: Do not repeat the dose.
		Second dose given later than recommended	More than 42 days after the first dose: Do not repeat the dose.
	Mixing vaccines:	Administration of a vaccine other than an mRNA vaccine	Do not repeat the dose.
Pfizer-BioNTech COVID-19	Diluent	ONLY the diluent was administered (0.9% sterile sodium chloride)	Inform the person that no vaccine was administered and proceed as soon as possible to administer vaccine in the opposite arm.

Vaccine		Administration of the vaccine with no diluent	Inform the vaccinated person of potential local and systemic adverse events. The second dose should be administered at the recommended interval; if serious adverse events occur after the first dose, the decision to administer a second dose should be assessed on a case-by-case basis.
		Incorrect diluent	Consult the manufacturer for guidance. If the dose needs to be repeated, this should be done as soon as possible, in the opposite arm.
		Incorrect diluent volume	For doses administered with a diluent volume of less than 1.8 ml, inform the vaccinated person of potential local and systemic adverse events. The second dose should be administered at the recommended interval; if serious adverse events occur after the first dose, the decision to administer a second dose should be assessed on a case-by-case basis. For doses administered with a diluent volume greater than 1.8 ml, do not repeat the dose. Administer the second dose at the recommended interval.

Source: Centers for Disease Control and Prevention (CDC). COVID-19 Vaccine Administration Errors and Deviations. Available at: https://www.cdc.gov/vaccines/covid-19/downloads/covid19-vaccine-errors-deviations.pdf.

Delta subvariant of the novel Coronavirus has been circulating with increasing intensity in Belém, Pará

The information was confirmed by the Municipal Department of Health (SESMA), after sequencing 16 samples of the SARS-CoV-2 virus obtained from patients in Belém, the capital of the state of Pará, Brazil. In its analyses, SESMA detected a Delta subvariant, AY.33, circulating in Belém, which may be undetectable by rapid tests and by standard RT-qPCR protocols. In view of the finding, the city's local government is ordering anyone exhibiting symptoms consistent with COVID-19 to remain in social isolation for 14 days. In the note released by SESMA, the results of analyses carried out since July were presented, which revealed a reversal in the trend of the identified variants.

In July and August, of the 1,612 COVID-19 cases reported in Belém, 72 samples (4%) from symptomatic patients whose RT-qPCR tests were positive were sent for sequencing. Of these cases, 84.7% were caused by the Gamma variant, while cases of the Delta variant accounted for 9.7%.

Of the 332 cases of symptomatic patients reported in September, RT-qPCR tests for 24 (7%) were positive. Of these, 50% were cases caused by the Delta variant, while 50% of the patients had been infected by the Gamma variant of the SARS-CoV-2 virus.

In the first 20 days of October, 152 cases were reported. The 20 genotyped samples (13%) revealed a reversal in the trend, with a predominance of the Delta variant, accounting for 75% of the cases, while the Gamma variant was identified in 25% of samples analyses.

Source: https://agenciabrasil.ebc.com.br/saude/noticia/2021–10/covid-19-aumenta-circulacao-de-subvariante-delta-em-belem-do-para?amp.

Adverse Events of Special Interest (AESI) and Related Risks: Acute myelitis

Acute myelitis falls within the neurological category of adverse events of special interest (AESI), and has a proven association with immunization with several different vaccines (1). There are numerous underlying causes of acute myelitis, including infectious, toxic, neoplastic, autoimmune, and metabolic etiologies (2).

Definition: There are three important levels of certainty, based on clinical and laboratory characteristics. The characteristic findings of spinal cord biopsy for myelitis are sufficient to establish level 1, but this is considered rare. In order to establish level 2 or 3, it is essential to document at least one feature of myelopathy in addition to evidence of spinal cord inflammation (fever, CSF pleocytosis, CT/MRI findings characteristic of myelitis), and the absence of alternative diagnoses. If features of encephalitis or ADEM (acute disseminated encephalomyelitis) are present, in addition to myelitis, the level of certainty for myelitis should be determined, and should include an evaluation of the tools used in the particular case to diagnose encephalitis/ADEM. Myelitis can occur in combination with encephalitis. If this is the case, and if there is the same level of certainty for both, the diagnosis is encephalomyelitis.

Diseases and other factors: Autoimmune/connective tissue disease, Bechet's disease, Sjogren's syndrome, neoplastic, thyroid, mixed connective tissue disease; systemic lupus erythematosus; antiphospholipid antibody syndrome; systemic sclerosis; urticarian vasculitis; systemic vasculitis; perinuclear ANCA (anti-neutrophil cytoplasmic antibodies); nutritional deficiency: vitamin B12, vitamin E, copper; conditions causing spinal cord compression; spinal cord tumors; abscesses or post-transplant conditions ; graft-versus-host disease; common variable immunodeficiency; conditions that resulted in spinal cord radiation therapy, which would be important in assessing causality.

Bacterial infections caused by the mycobacterium tuberculosis bacterium; Borrelia burgdorferi (Lyme disease); Treponema pallidum (neurosyphilis); Mycoplasma pneumoniae, Campylobacter jejuni, Chlamydia species, Legionella pneumoniae, brucellosis, groups A and B beta hemolytic streptococcus, Salmonella paratyphi B, Acinetobacter baumanii, orientia tsutsugamushi (scrub typhus).

Parasitic infections: Toxocara species; species of Schistosoma, Gnasthostoma spinigerum, Echinococcus granulosus, Toxoplasma gondii, species of Acanthamoeba, Trypanosoma brucei, Taenia solium, Gnasthostoma spinigerum, Paragonimus westermani, Neurocysticercosis.

Fungal infections: Actinomyces species, Blastomyces species, Coccidioides immitis, Aspergillus species, Cryptococcus species, Cladophialophora bantiana vaccine (3).

Medications: TNF-alpha inhibitors, sulfasalazine, epidural anesthesia, chemotherapeutic agents, heroin, benzene, brown recluse spider toxin (3).

Vaccines in general: Evidence for the link between MMR, VZV, influenza, hepatitis A/B, HPV, DTaP, meningococcal vaccines, and ADEM has been reviewed, and the overall evidence was insufficient to either accept or reject a causal relationship. It should be noted that immune-mediated mechanisms include autoantibodies, T cells, and molecular mimicry.

Window of risk for myelitis as a vaccine-related reaction:

- Inactivated or subunit vaccines: Immune-mediated mechanism for myelitis, probably as ADEM, where the recommended window of risk for people is 2 to 42 days, and for epidemiological studies, 5 to 28 days for primary analysis and 2 to 42 days for secondary analysis.
- Live attenuated vaccines: This should be based on the incubation period of the vaccine strain, adding, as stated above, 5 to 28 days after the end of the incubation period for primary analysis, and 2 to 42 days after the end of the incubation period for secondary analysis (3).

Sources:

1 Safety Platform for Emergency Vaccines (SPEAC) - D2.3 Priority List of Adverse Events of Special Interest: COVID-19 - Authors: Barbara Law, Miriam Sturkenboom,V2.0, Date: May 25, 2020.

2 SPEAC - Work Package: WP2 Standards and tools, V1.0 – February 15, 2021, Author: Barbara Law. Nature: Report | Diss. level: Public https://brightoncollaboration.us/wp-content/uploads/2021/03/SPEAC_D2.5.2.1_Generalised-Convulsion-Case-Definition-Companion-Guide-V1.0_format12068-1.pdf.

3 Barbara Law. Safety Platform for Emergency Vaccines SO2- D2.5.2.1 - AESI Case Definition Companion Guide for 1st Tier AESI. Acute Myelitis Work Package: WP2 Standards and tools, V3.0, February 13, 2021, Nature: Report | Diss. level: Public. https://brightoncollaboration.us/wp-content/uploads/2021/03/SPEAC_D2.5.2.1_Myelitis-Case-Definition-Companion-Guide_V3.0_13Feb2021_format12066-1.pdf.