

COVID-19

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

Thirty-first report

WASHINGTON, DC

Updated: 20 December 2021

PAHO



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ARGENTINA (Special report on vaccine safety surveillance in children and adolescents)

- From 28 July 2021 when the adolescent vaccination campaign began, through 12 October 2021 when the vaccination campaign for 3- to 11-year-olds started, and until 31 October 2021, a total of 4,728,885 doses of COVID-19 vaccines were administered in this population group.
- Among the 2,796,720 doses of vaccine administered to adolescents, there were 484 reports of AEFI (17.3 reports per 100,000 doses administered); and among the 1,932,165 doses of vaccine administered to children ages 3 to 11, 153 AEFI were reported (7.9 reports per 100,000 doses administered). For children under the age of 11, the Sinopharm vaccine was used.

Vaccine	Doses administered	AEFI (N)		AEFI reporting rate/100,000 doses administered	
		Reported	Related (A1)	Reported	Related (A1)
Sinopharm	1,932,165	153	90	7.9	4.7
Moderna	1,055,244	326	243	30.9	23.0
Pfizer	1,741,476	158	107	9.1	6.1
Total	4,728,885	637	440	13.5	9.3

- The rate of reports of serious AEFI was 1.2 per 100,000 doses administered for the Sinopharm vaccine, 2.7/100,000 for the Moderna vaccine, and 1.1/100,000 for the Pfizer vaccine.
- The most common adverse events reported for the Sinopharm vaccine were mild and moderate allergic reactions, local reactions without fever, and flu-like symptoms. For the Moderna vaccine, the most common events reported were local reactions without fever, and flu-like symptoms followed by one or more of the following: headache, myalgia, arthralgia, asthenia, and chills. For the Pfizer vaccine, the most frequent adverse events reported were local reactions without fever, followed by one or more of the following: headache, myalgia, arthralgia, asthenia, and chills.
- One reported case of myocarditis following vaccination with the Pfizer vaccine, from which the patient recovered fully, is currently under investigation.

Source: Argentina Ministry of Health. Special report on vaccine safety surveillance in children and adolescents. Argentina, November 2021, available at: <https://www.argentina.gob.ar/coronavirus/vacuna/equipos-salud/informes-seguridad>.

BRAZIL (State of Santa Catarina)

- Between 18 January and 30 September 2021, 8,790,520 doses of COVID-19 vaccines were administered in the state of Santa Catarina, consisting of 3,852,286 doses of the AstraZeneca vaccine, 2,397,194 doses of Sinovac/Butantan, 2,284,348 doses of Pfizer-BioNTech, and 256,692 doses of the Janssen vaccine.
- In the same period, there were 10,251 reports of AEFI, representing 0.1% of total doses administered. According to the classification of severity, 9,638 (94%) were non-serious events and 613 (6%) were serious events. Of total events reported, 6,373 were associated with the AstraZeneca/Fiocruz vaccine, 2,528 with the Sinovac/Butantan vaccine, 1,093 with the Pfizer vaccine, and 257 with the Janssen vaccine.
- Most non-serious events involved symptoms such as fever, myalgia, injection-site pain, redness, and edema.
- A total of 242 suspected AEFI-related deaths that occurred within 30 days following vaccination were identified. Of these, the majority (75.2%) occurred in the over-65-year-old population; 227 of the deaths (93.8%) were determined to have no causal relation to the vaccine, two (0.8%) were considered to be causally related to COVID-19 vaccines, and 13 (5.4%) are still under investigation.
- The two deaths that were determined to be causally related to the vaccine were associated with the AstraZeneca vaccine, and were classified as thrombosis with thrombocytopenia syndrome (TTS).

Source: Secretary of State of Santa Catarina, Brazil. Boletim de Monitoramento de Eventos Adversos Pós-Vacinação contra a Covid-19 em Santa Catarina. Published 10 November 2021. Available at:

<https://www.saude.sc.gov.br/index.php/noticias-geral/13079-nota-secretaria-de-estado-da-saude-divulga-boletim-de-monitoramento-de-eventos-adversos-pos-vacinacao-contra-a-covid-19-em-santa-catarina>.

CANADA

- As of 26 November 2021, 42,033,351 doses of the Pfizer-BioNTech COVID-19 vaccine, 14,709,597 doses of the Moderna vaccine, and 2,798,295 doses of the AstraZeneca/Covishield vaccine (AstraZeneca vaccine manufactured by the Serum Institute of India) had been administered.
- There were 27,798 individual reports of one or more AEFI (0.046% of doses administered). Of these, 6,492 reports involved serious events (0.011% of doses administered).
- Considering all reports, there were 72,292 reported adverse events following immunization (AEFI), with 27,798 reports involving one or more events. The majority of non-serious adverse events consisted of paresthesia, injection-site pain, headache, pruritis, dyspnea, fatigue, urticaria, nausea, etc.

Number of reports and reporting rate of adverse events (per 100,000 doses administered), by vaccine, as of 26 November 2021

Vaccine	Number of reports of non-serious AEFI		Number of reports of serious AEFI		Total number of reports of AEFI	
	N	Rate/100,000 doses administered	N	Rate/100,000 doses administered	N	Rate/100,000 doses administered
Pfizer-BioNTech	11,828	28.14	4,363	10.38	16,191	38.52
Moderna	7,180	48.81	1,183	8.04	8,363	56.85
Covishield and AstraZeneca	2,261	80.80	739	26.41	3,000	107.21
Unknown	37	-	207	-	244	
Total	21,306	35.78	6,492	10.90	27,798	46.69

Number of reports and reporting rate of the main serious adverse events (per 100,000 doses administered), by vaccine, as of 26 November 2021

	Vaccine		
AESI	Pfizer-BioNTech	Moderna	Covishield and AstraZeneca
Anaphylaxis	505 (1.20/100,000)	141 (0.96/100,000)	24 (0.86/100,000)
Thrombosis with thrombocytopenia syndrome (TTS)	19 (0.05/100,000)	6 (0.04/100,000)	64 (2.29/100,000)
Guillain-Barré syndrome	44 (0.10/100,000)	22 (0.15/100,000)	37 (1.32/100,000)
Myocarditis/pericarditis	853 (2.03/100,000)	495 (3.37/100,000)	25 (0.89/100,000)
Bell's palsy/facial paralysis	462 (1.10/100,000)	152 (1.03/100,000)	48 (1.72/100,000)
Category: Autoimmune disease	63 (0.15/100,000)	31 (0.21/100,000)	77 (2.75/100,000)
Category: Cardiovascular system	960 (2.28/100,000)	536 (3.64/100,000)	40 (1.43/100,000)
Category: Circulatory system	511 (1.22/100,000)	171 (1.16/100,000)	359 (12.83/100,000)

Category: Central and peripheral nervous systems	584 (1.39/100,000)	194 (1.32/100,000)	87 (3.11/100,000)
Fatal events	243* post-vaccination deaths		
* Following a medical review of the 243 deaths, it was determined that 86 were not linked to administration of the COVID-19 vaccine; 41 deaths, of which six (cases of TTS) are considered to be potentially attributable to the vaccination, are still under investigation, while 116 deaths (one of which occurred after a report of TTS following vaccination with the Pfizer-BioNTech vaccine) could not be classified due to insufficient information.			

Source: Public Health Agency of Canada. Canadian COVID-19 vaccine safety report. Source: Public Health Agency of Canada; 3 December 2021. Available at: <https://health-infobase.canada.ca/covid-19/vaccine-safety/>. Data reproduced by PAHO/WHO.

MEXICO

- Vaccination against COVID-19 began in Mexico on 24 December 2020, and as of 29 October 2021, 81,842,426 doses of vaccines had been administered.
- As of 29 October 2021, 31,095 AEFI had been reported by the states' health services; of these, 97.38% (30,279) were non-serious events and 2.62% (816) were serious events.
- The highest proportion of AEFI, both serious (59.80%) and non-serious (72.50%), occurred in women. The non-serious AEFI occurred primarily in the 30- to 39-year-old age group, while the serious AEFI were mostly in the over-60-year-old age group.
- The most frequently reported non-serious AEFI signs and symptoms were headache, 64.78% (19,616), pain or tenderness at the injection site, 45.71% (13,841), and myalgia, 40.11% (12,145); while the most common serious AEFI were headache, 46.32% (378), asthenia and fatigue, 37.87% (309), and dyspnea, 31.50% (257).

Vaccine	Doses administered	Serious AEFI	Non-serious AEFI	Total AEFI	Rate per 100,000 doses
AstraZeneca	38,516,372	284	7,575	7,859	20.40
CanSino	2,979,697	61	1,351	1,412	47.39
Janssen	1,035,859	8	804	812	78.39
Moderna	2,318,057	36	274	310	13.37
Pfizer-BioNTech	16,646,623	280	17,794	18,074	108.57
SinoVac	14,532,954	108	1,641	1,749	12.03
Sputnik V	5,812,864	33	796	829	14.26
Unknown		4	21	25	
TOTAL	81,842,426	814	30,256	31,095	37.99

Source: Reporte ESAVI COVID-19 octubre 2021, Dirección de Vigilancia Epidemiológica de Enfermedades Transmisibles. Mexico City. Available at: https://www.gob.mx/cms/uploads/attachment/file/682464/REPORTE_ESAVI_2021_10.pdf.

PARAGUAY

- According to the 37th AEFI surveillance report of Paraguay's Ministry of Health, 6,060,060 doses of COVID-19 vaccines were administered to 3,344,594 people between 22 February and 26 November.
- In that same period, a total of 2,534 AEFI were reported, representing 0.04% of doses administered. A total of 413 reported cases were considered serious, representing 0.007% of doses administered.
- Among reported AEFI, 71.6% (1,815) occurred in women; 68.4% (1,734) were in the 25- to 49-year-old age group. Among the reported AEFI, 48.2% (1,221) were in people who received the AstraZeneca vaccine, 14.7% (372) the Sputnik V vaccine, 17.3% (437) the Pfizer/BioNTech vaccine, 7.2% (182) the CoronaVac vaccine, 6.2% (157) the Covaxin vaccine, 4.5% (113) the Moderna vaccine, and 2.1% (52) the Sinopharm vaccine.

Source: 37° Boletín informativo – Vigilancia de ESAVI relacionada a la vacunación contra COVID-19, 26 de noviembre de 2021. Available at: <https://pai.mspbs.gov.py/esavis-2021/>.

Consolidated reports of adverse events, by vaccine, in countries of the Region of the Americas, December 2021

As of 10 December 2021, 1,378,223,759 doses of COVID-19 vaccines had been administered in the Region of the Americas. The following table presents information provided by the countries regarding number of doses of vaccines administered, by manufacturer and number of associated AEFI:

Consolidated reports of adverse events, by vaccine, in countries of the Region of the Americas, December 2021

Vaccine	Total doses administered in countries reporting AEFI	Total reported cases	Total cases/100,000 doses	Total serious cases reported	Serious cases/100,000 doses
AstraZeneca	126,253,480	96,549*	76.5	6,097	4.8
Bharat Biotech	294,831	160	82.1	101	51.8
CanSino	3,426,234	1,415	41.3	61	1.8
Gamaleya	30,409,915	43,129	141.8	144	0.5
Janssen	26,029,900	73,995	284.3	10,870	41.8
Moderna	222,466,174	356,495	160.2	36,722	16.5
Pfizer-BioNTech	460,447,200	579,212	125.8	111,885	24.3
Sinopharm BBIP	57,558,840	13,628	23.7	1,260	2.2
Sinovac	124,633,891	37,679	30.2	4,481	3.6
TOTAL	1,051,420,465	1,202,262	114.3	171,621	16.3

* The increase in the number of total cases reported for the AstraZeneca vaccine is due to the use of country-reported adverse events compared with number of doses administered, rather than based on reports to VigiBase.

Source: Doses obtained from the Dashboard of COVID-19 Vaccination in the Americas.

(https://ais.paho.org/imm/IM_DosisAdmin-Vacunacion.asp. Accessed 10 December 2021.)

- Cases: VigiBase data as of 8 December 2021 and public sources from the countries (Argentina epidemiological bulletin, 31 August; Brazil, as of 25 October, from the epidemiological bulletin, not including the state of São Paulo; Canada country website, 3 December 2021; Colombia, doses per vaccine reported by the country; Mexico, data as of 29 October 2021).
- Countries using the indicated vaccines (countries included in the data presented in the table are in bold):
AstraZeneca: Anguilla, Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Bolivia, Brazil, Canada, Chile, Colombia, Costa Rica, Dominica, Dominican Republic, Ecuador, El Salvador, Grenada, Guadalupe, Guatemala, Guyana, Honduras, Jamaica, Montserrat, Mexico, Nicaragua, Panama, Paraguay, Peru, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Virgin Islands, Trinidad and Tobago, and 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: Argentina, Canada, Colombia, Guadeloupe, Guatemala, Haiti, Honduras, Mexico, Panama, Paraguay, USA

Publications on potential signs of problems with the safety of COVID-19 vaccines

Myocarditis following administration of COVID-19 mRNA vaccines: A case series and incidence rate determination

A cohort study was published on 3 November, its purpose was to analyze the incidence rate of myocarditis and pericarditis in the vaccinated population compared to the incidence rate in the general population. A series of retrospective cases was conducted using the COVID-19 vaccine registry of the Mayo Clinic in the United States. The myocarditis incidence rate and temporal relation to the COVID-19 mRNA vaccine were calculated, compared to the occurrence of myocarditis in a comparable population between 2016 and 2020. Clinical characteristics and outcomes of affected patients were collected. While 21 people were identified, only 7 patients ultimately met the inclusion criteria for vaccine-associated myocarditis. The overall incidence rate ratio (IRR) of COVID-19-related myocarditis was 4.18 (95% CI 1.63, 8.98), which was solely attributable to an increase in IRR among adult men (IRR 6.69, 95% CI 2.35, 15.52) compared to women (IRR 1.41, 95% CI 0.03, 8.45). All cases occurred within two weeks of administration of one dose of a COVID-19 mRNA vaccine, and most occurred within 3 days (range 1–13 days) following the second dose (6/7 patients, 86%). Overall, cases were mild, and all patients survived. The authors conclude that myocarditis is a rare adverse event associated with COVID-19 mRNA vaccines, and that its incidence rate in adult men is significantly higher than in the base population. At present, recurrence of myocarditis following subsequent doses of mRNA vaccines is unknown.

Source: Perez Y, Levy ER, Joshi AY, et al. Myocarditis Following COVID-19 mRNA Vaccine: A Case Series and Incidence Rate Determination. Clin Infect Dis. 3 November 2021 Nov 3;ciab926. doi: 10.1093/cid/ciab926. Online ahead of print, available at: <https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab926/6420408>.

A systematic review of cases of central nervous system (CNS) demyelination following COVID-19 vaccination

A systematic review was published on 9 November with the aim of reviewing published cases of CNS demyelination associated with COVID-19 vaccination. The review was conducted in the PubMed, SCOPUS, EMBASE, Google Scholar, Ovid, and medRxiv databases, as of 30 September 2021, of published articles and preprints of cases of CNS demyelination associated with COVID-19 vaccines. Descriptive findings of reported cases were reviewed and stratified by demographic and clinical characteristics, diagnostic assessment, management, and overall outcome. Thirty-two cases were identified, with women accounting for the majority of cases (68.8%), and with a median age of 44 years. Eleven reported cases were in individuals who had received the Pfizer vaccine, eight who received the AstraZeneca vaccine, six the Moderna, five the Sinovac/Sinopharm, and one who received the Sputnik vaccine followed by the Johnson & Johnson vaccine. Most cases (71.8%) occurred after the first dose of vaccine, with neurological symptoms manifesting after a median of nine days. The most common presentations were transverse myelitis (12/32), and multiple sclerosis-like imaging (initial diagnosis or relapse) in another 12/32 cases, followed by disorders similar to acute disseminated encephalomyelitis (5/32) and to neuromyelitis optica spectrum disorder (3/32). In 17/32 (53.1%) of cases, a history of immune-mediated disease was reported. Demyelinating syndromes were most often reported in association

with mRNA vaccines (17/32), followed by viral vector vaccines (10/32) and inactivated vaccines (5/32). Most multiple sclerosis-like episodes reported (9/12) were triggered by mRNA-based vaccines, while transverse myelitis occurred following vaccination with viral-vector and mRNA vaccines. Treatment included high doses of methylprednisolone, plasma exchange, intravenous immunoglobulin, or a combination of these, with favorable outcomes in most cases and marked or complete improvement (25/32), with stabilization or partial recovery in the remaining cases. The authors, through this systematic review, identified few cases of CNS demyelination following any of the currently approved COVID-19 vaccines. The clinical presentation was heterogeneous, mainly after the first dose; however, half of the published cases included a history of immune-mediated disease. Most cases had a favorable outcome. Long-term post-marketing surveillance is suggested for these cases, in order to assess causation and ensure the safety of COVID-19 vaccines.

Source: Ismail II, Salama S. A systematic review of cases of CNS demyelination following COVID-19 vaccination. *J Neuroimmunol.* 2021 Nov 9;362:577765. doi: 10.1016/j.jneuroim.2021.577765. Online ahead of print. PMID: 34839149; PMCID: PMC 8577051. Available at: [https://www.jamda.com/article/S1525-8610\(20\)30371-6/fulltext](https://www.jamda.com/article/S1525-8610(20)30371-6/fulltext).

Immunogenicity and Risk of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection after Coronavirus Disease 2019 (COVID-19) vaccination in patients with cancer: a systematic review and meta-analysis

On 26 October, a systematic review and meta-analysis was published, with the aim of assessing the immune response after vaccination against COVID-19 of the population with cancer compared to the population without cancer. A search was conducted of the PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science databases from 1 March 2020 to 12 August 2021. Primary end-points were anti-SARS-CoV-2 spike protein (S) immunoglobulin G (IgG) seroconversion rates, T cell response, and documented SARS-CoV-2 infection after COVID-19 immunization. Overall effects were pooled using random-effects models. This systematic review and meta-analysis included 35 original studies. Overall, 51% (95% confidence interval, 41–62) and 73% (95% CI, 64–81) of patients with cancer developed anti-S IgG above the threshold level after partial and complete immunization, respectively. Patients with hematologic malignancies had a significantly lower seroconversion rate than those with solid tumors after complete immunization (65% vs. 94%; $P < 0.0001$). Compared with controls, patients with cancer with an incomplete vaccination schedule had a 55% reduced likelihood of achieving anti-S IgG titers above the threshold level (RR 0.45; 95% CI 0.35–0.58), whereas a 31% reduced likelihood of seroconversion was documented among those with a complete vaccination schedule (RR 0.69, 95% CI 0.56–0.84). Moreover, when compared with non-cancer controls, oncological patients had a tendency towards increased documented SARS-CoV-2 infection after partial (RR 3.21; 95% CI 0.35–29.04) and complete COVID-19 immunization (RR 2.04; 95% CI 0.38–11.10). Patients with cancer had an impaired immune response to COVID-19 vaccination compared with controls. Strategies that endorse the completion of vaccination

schedules are warranted. Future studies should aim to evaluate different approaches that enhance oncological patients' immune response.

Source: Becerril-Gaitan A, Vaca-Cartagena BF, Ferrigno AS, et al. Immunogenicity and risk of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection after Coronavirus Disease 2019 (COVID-19) vaccination in patients with cancer: a systematic review and meta-analysis. *Eur J Cancer*. 2021 Oct 26:S0959–8049(21)01168–0. doi:10.1016/j.jinf.2020.02.028. Online ahead of print. PMID: 34794855; PMCID: PMC8548030. Available at: [https://www.ejancer.com/article/S0959-8049\(21\)01168-0/fulltext](https://www.ejancer.com/article/S0959-8049(21)01168-0/fulltext).

Association between vaccination with the BNT162b2 mRNA COVID-19 vaccine and Bell's palsy: a population-based study

On 4 November, a cohort study was published examining the association between the BNT162b2 mRNA COVID-19 vaccine and Bell's palsy. Using the database of the largest healthcare provider in Israel, the authors retrieved data from different periods in 2018-2021. Observed cases of Bell's palsy occurring within 21 days after the first vaccine dose and within 30 days after the second vaccine dose were compared to the expected cases, based on the experience of the population in 2019. Standardized incidence ratios (SIRs) and attributable risks (ARs) were computed.

Overall, 132 cases of Bell's palsy were reported among 2,594,990 individuals after vaccination with a first dose, and 152 cases among 2,434,674 individuals after receiving a second dose. The age and sex weighted SIRs were 1.36 (1.14-1.61) and 1.16 (0.99-1.36) after the first and second vaccine dose, respectively. SIRs tended to be higher in older age groups after the first and second vaccine doses. The estimates were more pronounced in older females after the first vaccine dose; SIR=1.71 (1.10-2.54) at ages 45-64, and 2.51 (1.65-3.68) at age ≥ 65 years. The highest AR was 4.46 per 100,000 individuals vaccinated, detected in females aged ≥ 65 years. In patients with a previous history of Bell's palsy, only 4 cases of Bell's palsy were reported in 7,567 individuals vaccinated and 10 cases in 7,045 individuals vaccinated after the first and the second dose, respectively. The age- and sex-weighted SIRs were 1.15 (0.36-2.76) and 2.15 (1.09-3.83) after the first and second vaccine dose, respectively. The authors conclude that this study suggests that the BNT162b2 mRNA COVID-19 vaccine might be associated with increased risk of Bell's palsy. The small estimated attributable risks suggest that the impact on public health is relatively minor. The benefits of vaccinations explicitly outweigh the possible link to Bell's palsy, which has high recovery rate if timely treated with corticosteroids.

Source: Shibli R, Barnett O, Abu-Full Z, et al. Association between vaccination with the BNT162b2 mRNA COVID-19 vaccine and Bell's palsy: a population-based study. *Lancet Reg Health Eur*. 2021 Dec;11:100236. doi: 10.1016/j.lanepe.2021.100236. Epub 2021 November 4. PMID: 34751262; PMCID: PMC8566165. Available at: <https://www.sciencedirect.com/science/article/pii/S2666776221002222?via%3Dihub>.

Thrombotic Events after COVID-19 Vaccination in the Over-50s: Results from a Population-Based Study in Italy

On 10 November, a cohort study was published to evaluate post-vaccination thrombotic events in patients over 50 years of age. The study mentions that several European countries suspended or changed recommendations for the use of Vaxzevria (AstraZeneca) for suspected adverse effects due to atypical blood-clotting. This research aimed to identify the number of expected thrombotic events in the Italian population over the age of 50 that received the Vaxzevria vaccine between 22 January and 12 April 2021. The venous thromboembolism (VT) and immune thrombocytopenia (IT) event rates were estimated from a population-based cohort. The overall VT rate was 1.15 (95% CI 0.93–1.42) per 1,000 person-years, and the ITP rate was 2.7 (95% CI 0.7–11) per 100,000 person-years. These figures translate into 83 VT events and 2 ITP events, in the 15 days following the first administration of Vaxzevria. The number of thrombotic events reported from the Italian Medicines Agency does not appear to have increased beyond that expected in individuals over 50 years of age. The authors conclude that these findings contribute to the ongoing discussion about vaccine safety, particularly for adenovirus-based vaccines, where the occurrence of coagulation-related disorder constitutes a significant concern.

Source: Baldi I, Azzolina D, Francavilla A, et al. Thrombotic Events after COVID-19 Vaccination in the Over-50s: Results from a Population-Based Study in Italy *Vaccines* (Basel). 2021 Nov 10;9(11):1307. doi: 10.3390/vaccines9111307. PMID: 34835237; PMCID: PMC8620372. Available at: <https://www.mdpi.com/2076-393X/9/11/1307>.

Risk-benefit analysis of the AstraZeneca COVID-19 vaccine in Australia using a Bayesian network modelling framework

On 4 November, a study was conducted using a Bayesian model, which provided a risk-benefit analysis of the AstraZeneca vaccine. This study was based on the fact that thrombosis with thrombocytopenia syndrome (TTS) has been associated with the AstraZeneca (AZ) COVID-19 vaccine (Vaxzevria). Australia has reported low TTS incidence of < 3/100,000 after the first dose, with a case fatality rate (CFR) of 5%–6%. Risk-benefit analysis of vaccination has been challenging because of rapidly evolving data, changing levels of transmission, and variation in rates of TTS, COVID-19, and CFR between different age groups. The aim of the authors was to optimize risk–benefit analysis by developing a model that enables inputs to be updated rapidly as evidence evolves. A Bayesian network was used to integrate local and international data, government reports, published literature, and expert opinion. The model estimates probabilities of outcomes under different scenarios of age, sex, low/medium/high transmission (0.05%/0.45%/5.76% of population infected over 6 months), SARS-CoV-2 variant, vaccine dose, and vaccine effectiveness. The authors used the model to compare estimated deaths from AZ vaccine-associated TTS with (i) COVID-19 deaths prevented under different scenarios; and (ii) deaths from COVID-19-related atypical severe blood clots (cerebral venous sinus thrombosis and portal vein thrombosis). For a million people aged ≥ 70 years where 70% received a first dose and 35% received two doses, the model estimated < 1 death from TTS, 25 deaths

prevented under low transmission, and > 3,000 deaths prevented under high transmission. Risks versus benefits varied significantly between age groups and transmission levels. Under high transmission, deaths prevented by AZ vaccine far exceed deaths from TTS (by 8 to > 4,500 times depending on age). Probability of dying from COVID-related atypical severe blood clots was 58–126 times higher (depending on age and sex) than dying from TTS. The authors mention that this is the first example of the use of Bayesian networks for risk–benefit analysis for a COVID-19 vaccine. The model can be rapidly updated to incorporate new data, adapted for other countries, extended to other outcomes (e.g., severe disease), or used for other vaccines.

Source: Lau CL, Mayfield HJ, Sinclair JE, et al. Risk-benefit analysis of the AstraZeneca COVID-19 vaccine in Australia using a Bayesian network modelling framework. *Vaccine*. 2021 Nov 4:S0264–410X(21)01428–6. doi: 10.1016/j.vaccine.2021.10.079. Online ahead of print. PMID: 34810000; PMCID: PMC8566665. Available at: <https://www.sciencedirect.com/science/article/pii/S0264410X21014286?via%3Dihub>.

WHO Adds Pfizer-BioNTech COVID-19 Vaccine Ready-to-Use Formulation to Emergency Use Authorization

WHO included in its emergency use authorization the new ready-to-use formulation of the Pfizer-BioNTech Comirnaty vaccine, which contains Tris/Sucrose and does not require dilution before administration.

This vaccine comes in packs of 10 or 195 vials, with a shelf life of six months when stored between -90°C and -60°C, and a shelf life of 10 weeks when stored between 2°C and 8°C within the six-month shelf life. For more information, visit:

<https://extranet.who.int/pqweb/vaccines/who-recommendation-covid-19-mrna-vaccine-nucleoside-modified-comirnaty>.

The Committee for Medicinal Products for Human Use (CHMP), of the European Medicines Agency, recommends authorization of the Pfizer-BioNTech Comirnaty vaccine in children ages 5 to 11 years

The Committee for Medicinal Products for Human Use (CHMP), of the European Medicines Agency (EMA), has recommended extending the indication for the Comirnaty vaccine to include use in children ages 5 to 11. This vaccine is currently licensed for people 12 years of age and older.

The dose of Comirnaty in children ages 5 to 11 (10 mcg) will be lower than that used in people 12 years old and older (30 mcg), while the vaccination schedule will be the same as for the older age group, i.e., two doses three weeks apart.

The CHMP indicated that the efficacy of Comirnaty was assessed based on nearly 2,000 children ages 5 to 11 with no prior signs of infection. Of the 1,305 children who received the vaccine, there were three cases of COVID-19; by comparison, among the 663 children who received a placebo, there were 16 cases of COVID-19. Thus, the vaccine was 90.7% effective in preventing symptomatic COVID-19, although CHMP indicated that the real rate could be between 67.7% and 98.3%. The Committee indicated that the most common side effects in children ages 5 to 11 were similar to those in people 12 years old and older. These include injection-site pain, tiredness, headache, redness and swelling at the injection site, muscle pain, and chills. The CHMP therefore concluded that the benefits of Comirnaty in children ages 5 to 11 outweigh the risks, especially in children with conditions that put them at increased risk of severe COVID-19.

Source: EMA. Comirnaty COVID-19 vaccine: EMA recommends approval for children aged 5 to 11. Available at: <https://www.ema.europa.eu/en/news/comirnaty-covid-19-vaccine-ema-recommends-approval-children-aged-5-11>.

EMA and ECDC recommendations on heterologous vaccination courses against COVID-19

On 7 December 2021, the European Medicines Agency (EMA) and the European Center for Disease Prevention and Control (ECDC) issued recommendations related to heterologous schemes for primary vaccination and boosters against COVID-19, in order to provide scientific grounds and additional flexibility to vaccination schedules in the European Union.

They point out that evidence from studies on heterologous vaccination suggests that the combination of viral vector vaccines and mRNA vaccines produces good levels of antibodies against the COVID-19 virus (SARS-CoV-2) and a higher T cell response than using the same vaccine (homologous vaccination), whether in a primary or booster schedule. The heterologous schedules were generally well tolerated. The use of a viral vector vaccine as a second dose in primary vaccination schedules, or use of two different mRNA vaccines, is less well studied.

Although the review did not consider other vaccines that are not yet authorized in the European Union, it indicated that research on heterologous combinations of those vaccines will be taken into account in the future if the vaccines are authorized.

For more information on these recommendations, visit <https://www.ema.europa.eu/en/news/ema-ecdc-recommendations-heterologous-vaccination-courses-against-covid-19>.

Update on the risk of myocarditis and pericarditis with COVID-19 mRNA vaccines

(a) EMA Pharmacovigilance Risk Assessment Committee (PRAC)

The Pharmacovigilance Risk Assessment Committee (PRAC), of the European Medicines Agency (EMA), at a meeting on 29 November to 2 December 2021, assessed the most recent data on known risk of myocarditis and pericarditis following vaccination with two mRNA-based COVID-19 vaccines – the Pfizer-BioNTech Comirnaty vaccine and the Spikevax vaccine (known previously as the Moderna vaccine). This review included two large European epidemiological studies. One study was conducted using data from the French national health system (EPI-PHARE), while the other was based on registry data from Nordic countries.

For the Comirnaty vaccine, the results of the French study indicated that, in a period of seven days after the second dose, there were approximately 0.26 extra cases of myocarditis per 100,000 vaccinated 12- to 29-year-old males, compared to unexposed persons. In the Nordic study, in a period of 28 days after the second dose, there were 0.57 extra cases of myocarditis per 100,000 vaccinated 16- to 24-year-old males, compared to unexposed persons.

In the case of Spikevax, the French study showed that in a period of seven days after the second dose there were approximately 1.3 extra cases of myocarditis per 100,000 vaccinated 12- to 29-year-old males, compared to unexposed persons. The Nordic study showed that in a period of 28 days after the second dose of Spikevax there

were approximately 1.9 extra cases of myocarditis per 100,000 vaccinated 16- to 24-year-old males, compared to unexposed persons.

Based on the data reviewed, PRAC has determined that the overall risk for both of these conditions is “very rare,” meaning that up to one in 10,000 vaccinated people may be affected. Additionally, the data show that the increased risk of myocarditis after vaccination is highest in younger males. Myocarditis and pericarditis have occurred primarily within 14 days after vaccination, and have more often been observed after the second vaccination.

The EMA confirms that the benefits of all authorized COVID-19 vaccines continue to outweigh their risks, given the risk of COVID-19 illness and related complications, and given that scientific evidence shows that they reduce deaths and hospitalizations due to COVID-19.

Source: EMA. Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 29 November – 2 December 2021 Available at: <https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-29-november-2-december-2021>.

(b) Public Health Agency of Canada

On 3 December 2021, the Public Health Agency of Canada (PHAC) released updated guidance on the use of COVID-19 vaccines licensed in Canada in people 12 years of age and older, in the context of case reports of myocarditis and pericarditis following administration of COVID-19 mRNA vaccines. These recommendations are based on current scientific evidence and the expert opinion of the National Advisory Committee on Immunization (NACI). The updated recommendations include:

- The preferential use of a complete series of an mRNA COVID-19 vaccine over the use of viral vector COVID-19 vaccines in all authorized age groups.
- In order to further minimize the rare risk of myocarditis and/or pericarditis in individuals aged 12 to 29 years, use of the Pfizer-BioNTech Comirnaty COVID-19 vaccine (30 mcg) is recommended, rather than Moderna's Spikevax vaccine (100 mcg), to initiate or complete a primary vaccination series. The second dose of a primary series should be provided eight weeks after the first dose. It was noted that emerging evidence in adults suggests that a longer interval between the first and second dose of a primary series results in a stronger immune response and higher vaccine effectiveness. New data suggest that, for mRNA vaccines, longer intervals may also be associated with a lower risk of myocarditis and/or pericarditis in adolescents and young adults.
- Based on clinical judgment, the Moderna Spikevax vaccine (100 mcg) may be considered for adolescents and adults 12 to 29 years of age who are moderately to severely immunocompromised, given new evidence that Moderna's Spikevax vaccine (100 mcg) may have a slightly higher vaccine effectiveness and may provide longer

protection against infection and severe COVID-19 outcomes, compared to the Pfizer-BioNTech Comirnaty vaccine (30 mcg).

- Booster doses: For people 18 to 29 years of age who are eligible to receive a booster dose of an mRNA vaccine, the use of the Pfizer-BioNTech booster dose (30 mcg) may be provided at least six months after the completion of a primary vaccine series.
- Everyone who is offered an mRNA COVID-19 vaccine should be informed of the rare risk of experiencing myocarditis and/or pericarditis following vaccination.

For more information on these recommendations, see: Public Health Agency of Canada. Summary of the National Advisory Committee on Immunization (NACI) Rapid Response of December 3, 2021. Available at:

<https://www.canada.ca/content/dam/phac-aspc/documents/services/immunization/national-advisory-committee-on-immunization-naci/rapid-response-recommendation-use-covid-19-vaccines-individuals-aged-12-years-older-myocarditis-pericarditis-reported-following-mrna-vaccines/summary.pdf>.

(c) UK Health Security Agency

On 29 November 2021, the UK Health Security Agency (UKHSA) published clinical guidance to support the detection and management of clinical cases of myocarditis and pericarditis associated with coronavirus (COVID-19) vaccination. It is a living document and will be reviewed and updated as further data become available.

UKHSA indicates that, as of 17 November 2021, the overall reporting rate across all age groups for myocarditis following vaccination with the Pfizer vaccine is 10 cases per million doses administered; for pericarditis, it is 7 cases per million doses administered. For Moderna, the overall reporting rate for myocarditis is 36 cases per million doses; for pericarditis, it is 21 cases per million doses. In people under 18 years of age, the reported rate for myocarditis and pericarditis is 10 cases per million doses (first or unknown dose) of the Pfizer vaccine, which is the recommended vaccine for use in this age group.

The following is a summary of the clinical recommendations:

- In pediatric patients recently vaccinated against COVID-19 (within the last 10 days), features of concern that may require further investigation include: significant chest pain (new onset and unexplained), tachycardia or tachypnea, dyspnea (new onset and unexplained), palpitations (new onset and unexplained), dizziness or syncope (new onset and unexplained), and general clinical concern.

In case of suspected myocarditis or pericarditis, initial investigations should include 12-lead electrocardiogram (ECG); inflammatory blood markers (C-reactive protein [CRP], full blood count [FBC], and erythrocyte sedimentation rate [ESR]); and troponin. In case of abnormal ECG or troponin, the pediatric cardiology team

should be consulted on a further management plan, including cardiac imaging (echocardiogram, cardiac magnetic resonance imaging [MRI], and rhythm monitoring [Holter 24h, stress ECG]).

- In individuals under the age of 40 who have recently been vaccinated against COVID-19 (within 10 days), features of concern that may require further investigation include: significant chest pain (new onset and unexplained), tachycardia or tachypnea, dyspnea (new onset and unexplained), palpitations (new onset and unexplained), dizziness or syncope (new onset and unexplained), and general clinical concern.

In the case of suspected myocarditis or pericarditis, initial investigations should include: 12-lead ECG and inflammatory blood markers (CRP, FBC, and ESR), and troponin. In the case of abnormal ECG or troponin, the cardiology team should be consulted on a further management plan, which may include cardiac imaging (echocardiogram, cardiac MRI) and rhythm monitoring (Holter 24h, stress ECG).

- Further follow-up: Patients that did not require referral to hospital on initial presentation or who have normal initial investigations do not require further follow-up.

All patients that did not require initial hospital care should be advised to seek medical attention if symptoms persist or worsen within 5 days.

Patients requiring outpatient follow-up should be referred to cardiology and an assessment undertaken within 4 weeks.

For more information on this guidance, see: UK Health Security Agency. Guidance: Myocarditis and pericarditis after COVID-19 vaccination: clinical management guidance for healthcare professionals. 29 Nov 2021. Available at:

<https://www.gov.uk/government/publications/myocarditis-and-pericarditis-after-covid-19-vaccination/myocarditis-and-pericarditis-after-covid-19-vaccination-guidance-for-healthcare-professionals>.

The U.S. Food and Drug Administration Expands Eligibility for Pfizer-BioNTech COVID-19 Booster Dose to 16- and 17-Year-olds

On 12 December, the U.S. Food and Drug Administration (FDA) expanded eligibility for use of a single booster dose of the Pfizer-BioNTech or Comirnaty vaccine for individuals 16 and 17 years of age at least six months after completion of a primary vaccination series with one of these vaccines.

In the time since Pfizer initially submitted safety and effectiveness data to the FDA on a single booster dose following the two-dose primary series, additional real-world data have become available on the increasing number of cases of COVID-19, in the U.S., and on the risk of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the outer lining of the heart) following vaccination with the Pfizer-BioNTech COVID-19 Vaccine.

These additional data enabled the FDA to reassess the benefits and risks of the use of the vaccine in a wider population. The FDA has determined that the benefits of a single booster dose of the Pfizer-BioNTech or Comirnaty COVID-19 vaccine, in terms of providing protection against COVID-19 and the associated serious consequences that can occur, including hospitalization and death, outweigh the risks of myocarditis and pericarditis in individuals 16 and 17 years of age.

For more information, visit: <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-expands-eligibility-pfizer-biontech-covid-19-booster-dose-16-and-17>.

SAGE/WHO interim statement on COVID-19 vaccination for children and adolescents

On 24 November, WHO's Strategic Advisory Group of Experts on Immunization (SAGE) released an interim statement examining the role of COVID-19 vaccines in adolescents and children in the global context of inequitable vaccine distribution across countries and globally limited vaccine supply. This statement analyzes aspects such as the burden of disease in children and adolescents, the role of this age group in the transmission of SARS-CoV-2, the socio-economic impact of the COVID-19 pandemic and of the pandemic response on children and adolescents, the efficacy and safety of COVID-19 vaccines in adolescents and children, global equity and public health goals, and the rationale for vaccinating adolescents and children. The group's conclusions were as follows:

- When developing their COVID-19 immunization policies and programs, countries should consider the individual and population benefits of immunizing children and adolescents given their specific epidemiological and social settings. As children and adolescents tend to have milder disease compared to adults, unless they are in a group at higher risk of severe COVID-19, it is less urgent to vaccinate them than older people, those with chronic health conditions, and health workers.
- There are benefits of vaccinating children and adolescents beyond the direct health benefits, in terms of decreasing the transmission of COVID-19. Countries' strategies related to COVID-19 control should facilitate children's participation in education and other aspects of social life, and minimize school closures. UNICEF and WHO have developed guidance on how to minimize transmission in schools and keep schools open, regardless of vaccination of school-aged children.
- Aligned and coordinated action is needed to achieve the global COVID-19 vaccination targets. Given current global inequity in vaccine access, the decision to vaccinate adolescents and children must account for prioritization to fully protect the highest-risk subgroups through primary vaccination series and, as vaccine effectiveness declines with time since vaccination, through booster doses.

Before considering implementing primary vaccination series in adolescents and children, attaining high coverage of primary series – and booster doses as needed based on evidence of waning and on optimizing vaccination impact – consideration should be given to vaccinating the highest-risk subgroups, such as older adults.

- As a matter of global equity, as long as many parts of the world are facing extreme vaccine shortages, countries that have achieved high vaccine coverage in their high-risk populations should prioritize global sharing of COVID-19 vaccines through the COVAX facility before proceeding to vaccinate children and adolescents who are at low risk for severe disease.

The full statement is available at: <https://www.who.int/news/item/24-11-2021-interim-statement-on-covid-19-vaccination-for-children-and-adolescents>.

Update on SAGE/WHO recommendations for the use of the Janssen COVID-19 vaccine

On 9 December 2021, WHO released updated interim recommendations by the Strategic Advisory Group of Experts on Immunization (SAGE) for use of the Janssen Ad26.COV2.S COVID-19 vaccine. Following is a summary of the updated recommendations.

- Second dose: The most recent results from ongoing Phase 3 studies indicate that administration of two doses increases the efficacy of the Ad26.COV2.S vaccine in all clinical endpoints compared to a single dose. WHO notes that countries can choose to use this vaccine with a single-dose or two-dose immunization schedule, taking into account that many countries face severe vaccine supply constraints combined with a high disease burden. A single dose of the vaccine is effective and facilitates rapidly increasing vaccine coverage, which in turn will reduce the burden on health care systems. A single dose may also be a preferred option for vaccinating hard-to-reach populations.

As vaccine supplies and accessibility improve, countries should consider offering a second dose, beginning with high-priority populations outlined in the WHO Prioritization Roadmap. WHO recommends an inter-dose interval of two to six months. The choice for the interval depends on the epidemiological situation and the needs of certain subpopulations.

- Interchangeability with other vaccines and platforms: When a second dose of the Ad26.COV2.S vaccine is given, use of the same vaccine is considered standard practice. However, WHO supports a flexible approach to vaccination schedules, taking into account current vaccine supply and other access considerations, along with the potential benefits and risks of the specific products being used. Evolving evidence suggests that heterologous COVID-19 vaccination schedules, using WHO Emergency Use Listing (EUL) vaccines from different platforms, may be more immunogenic and effective than homologous schedules, depending on the specific platforms and the order of the products used. Two clinical trials have demonstrated that a single dose of the Ad26.COV.S vaccine and a second dose of an mRNA vaccine (BNT162b2 or mRNA-1273) induce neutralizing antibody concentrations 4 to 22 times higher than a second dose of the Ad26.COV2.S vaccine (1,2). Ad26.COV.S also has the ability to boost antibody concentrations six months after a primary two-dose series of mRNA vaccine, with increases in antibody responses at week four following the boost comparable to a homologous third dose of mRNA vaccine, but with higher T cell responses (3). No major safety concerns have been identified regarding the use of Ad26.COV2.S in heterologous schedules, although the overall study size is limited.

- Safety: As of 31 August 2021, an estimated 33.5 million doses of Ad26.COV2.S vaccine had been administered worldwide. Based on post-marketing safety surveillance, the following safety concerns were identified:
 - Guillain-Barré syndrome (GBS): The incidence of GBS is estimated at 4.15 per 100,000 people vaccinated, based on a 42-day risk window.
 - Thrombosis with thrombocytopenia syndrome (TTS): TTS was reported as approximately 2 cases per million doses administered. The majority of the cases were in people under 65 years of age (83%), with 55% of cases in women and 45% in men. The mean and median times to onset of the event were 16.5 days and 12 days, respectively.
 - Capillary leak syndrome (CLS): Very rare cases of CLS (0.21 per million doses administered) have been reported, some in persons with a prior history of CLS, and some with fatal outcomes. The mean and median times to onset of the event were 1.3 days and 1 day, respectively.
 - In countries with ongoing SARS-CoV-2 transmission, the benefit of vaccination with the Ad26.COV2.S vaccine in protecting against COVID-19 far outweighs the risks of TTS, GBS, and CLS. However, benefit–risk assessments may differ from country to country, and countries should consider their epidemiological situation, individual and population-level risks, availability of other vaccines, and alternate options for risk mitigation. The benefit–risk ratio is greatest in older age groups, as the risk of severe COVID-19 disease outcomes, including COVID-19-related thromboembolic events, increases with age.
- Pregnant and breastfeeding women: WHO recommends the use of the Ad26.COV2.S vaccine in pregnancy only if the benefits of vaccination outweigh the potential risks. WHO does not recommend pregnancy testing prior to vaccination. WHO also does not recommend delaying pregnancy or terminating pregnancy because of vaccination.

In the case of breastfeeding women, WHO recommends the use of this vaccine, and does not recommend discontinuing breastfeeding because of vaccination.

- Immunocompromised persons (ICPs): WHO recommends a second dose for moderately or severely immunocompromised ICPs aged 18 years and older one to three months after the first dose. The most appropriate time for the second dose should be discussed with the treating physician, and may vary depending on the epidemiological setting and the extent and timing of immune suppressive therapy. There are no data available to determine the need and timing of a third dose.

- Co-administration with inactivated influenza vaccines: It is acceptable to co-administer Ad26.COV2.S with an inactivated influenza vaccine. Different arms for injection should be used when both vaccines are delivered during the same visit.

For more information on this update, visit: <https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-Ad26.COV2.S-2021.1>.

- (1) Sablerolles R. Immunogenicity and reactogenicity of booster vaccinations after Ad26.COV2.S priming. medRxiv. 2021. doi: <https://doi.org/10.1101/2021.10.18.21264979>.
- (2) Atmar RL. Heterologous SARS-CoV-2 Booster Vaccinations – Preliminary Report. MedRxiv. 2021. doi: <https://doi.org/10.1101/2021.10.10.21264827>.
- (3) Tan CS. Ad26.COV2.S or BNT162b2 Boosting of BNT162b2. Vaccinated Individuals. MedRxiv. 2021. doi: <https://www.medrxiv.org/content/10.1101/2021.12.02.21267198v1>.

Recommendations of the WHO Strategic Advisory Group of Experts on Immunization on heterologous schedules

On 16 December 2021, WHO published interim recommendations of the Strategic Advisory Expert Group on Immunization (SAGE) regarding heterologous COVID-19 vaccine schedules, for vaccines included in the WHO Emergency Use Listing (EUL) (Ad26.COV2.S, BBV152, BNT162b2, ChAdOx1-S [recombinant], mRNA-1273, Sinopharm-BIBP, and Sinovac CoronaVac).

These recommendations note that, due to the multiplicity of possible heterologous vaccine combinations, the limited direct evidence on the benefits of specific heterologous combinations against the primary outcome of interest (i.e., the level of protection conferred against severe COVID-19), and the lack of an established immune-correlate of protection against COVID-19, the available body of evidence was deemed not to lend itself to formal GRADEing of evidence (Grading of Recommendations, Assessment, Development and Evaluation). Nevertheless, SAGE considered these indirect data from multiple sources as sufficient to proceed with issuing this good practice statement, which is summarized below.

- Homologous schedules are considered standard practice based on substantial safety, immunogenicity, and efficacy data available for each WHO EUL COVID-19 vaccine. However, WHO supports a flexible approach to vaccination schedules, and considers that two heterologous doses of any WHO EUL COVID-19 vaccine constitute a complete primary series.
- Heterologous vaccination should only be implemented with careful consideration of current vaccine supply, vaccine supply projections, and other access considerations, alongside the potential benefits and risks of the specific products being used.
- Rapidly achieving high vaccination coverage with a primary vaccination series in priority-use groups, as defined in the WHO Prioritization Roadmap, should continue to be the focus while vaccine supply remains constrained.

Either homologous or heterologous immunization schedules should be utilized. This process should not be delayed over considerations regarding the potential benefits of heterologous schedules.

- For countries considering heterologous schedules, WHO makes the following recommendations on the basis of equivalent or favorable immunogenicity or effectiveness for heterologous versus homologous schedules:
- Recommendations on the relative risks and benefits of homologous versus heterologous primary and booster doses will be reviewed as additional data become available.
- WHO emphasizes the need for key gaps in the evidence to be addressed, including:
 - Effectiveness and duration of protection of heterologous versus homologous schedules for specific WHO EUL product combinations, especially for heterologous schedules involving inactivated vaccines, given the relative lack of data available for these.
 - Long-term safety of heterologous schedules for specific WHO EUL product combinations, including surveillance for rare adverse events.
 - Influence of the order of products and platforms on the safety, immunogenicity, and effectiveness of heterologous vaccination.
 - Effectiveness of heterologous vaccination in relation to the time interval between the first and second doses, and between the primary series and booster dose.
 - Correlates of initial protection or duration of protection for homologous and heterologous schedules.
 - Safety, immunogenicity, and effectiveness of fractional doses in the context of heterologous vaccination.
 - Relative immunogenicity and effectiveness of heterologous versus homologous vaccination schedules against variants of concern, including the Omicron variant.

For more information on these recommendations and the evidence considered by SAGE/WHO, please refer to the full document available at:

<https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-heterologous-schedules>.

Inclusions in the WHO Emergency Use Listing (EUL)

WHO has added the following COVID-19 vaccines to the Emergency Use Listing (EUL):

Name	COVOVAX™ COVID-19 vaccine (SARS-CoV-2 rS Protein Nanoparticle [recombinant])	NUVAXOVID™ COVID-19 vaccine (SARS-CoV-2 rS [Recombinant, adjuvanted])
EUL holder	Serum Institute of India Pvt. Ltd. (SIPL)	Novavax CZ a.s.
NRA of record*	Central Drugs Standard Control Organization, India.	European Medicines Agency (EMA)
WHO/EUL recommendation issued	17 December 2021	20 December 2021
Platform/Type of vaccine	Protein subunit (recombinant)	Protein subunit (recombinant)
Presentation	1- and 10-dose vials	10-dose vial
Diluent	Not required	Not required

* NRA of record: The NRA that first authorized the vaccine and that is responsible for supervision of the vaccine.

For more information on these vaccines, visit: <https://extranet.who.int/pgweb/vaccines/vaccinescovid-19-vaccine-eul-issued>.

Update to PAHO's COVID-19 Vaccine Pharmacovigilance Dashboard

On 12 December 2021, the new version of PAHO's COVID-19 vaccine pharmacovigilance dashboard was published. Among the main changes in this new version is the incorporation of a new section of consolidated information on the different COVID-19 vaccines, with tables summarizing the general characteristics of these vaccines, their efficacy, efficacy against variants, and recommendations of the main reference entities. These tables can be downloaded as a PDF file.

In addition, the efficacy-effectiveness and safety sections for each vaccine were modified, using summary tables of the main clinical studies conducted, making it possible to view their characteristics, the results obtained, and the corresponding interpretation, while also maintaining the extended version of the information, giving details of the various available studies. For each vaccine, information was also included on major reference entities, additional doses, booster doses, and heterologous vaccination schedules, as applicable.

In the storage and logistics sections for each vaccine, images were incorporated to complement and facilitate the use of the information, highlighting the appropriate conditions and warnings to consider in each stage of COVID-19 vaccine preservation and use.

PAHO's COVID-19 Vaccine Pharmacovigilance Dashboard is available at: <https://covid-19pharmacovigilance.paho.org/>.

Decisions of the Region's Regulatory Authorities

National Administration of Drugs, Foods, and Medical Devices (ANMAT): On 3 December, Argentina's Ministry of Health, through Resolution 3451/2021, authorized emergency use of the Sputnik Light vaccine, of the Russian Federation Ministry of Health's Gamaleya National Research Center for Epidemiology and Microbiology.

This information is available at: <https://www.boletinoficial.gob.ar/detalleAviso/primera/253978/20211206>

Center for State Control of Drugs and Medical Equipment and Devices (CECMED): On 7 December, CECMED, in granting Emergency Use Authorization (EUA) of the Cuban vaccine Soberana Plus®, whose holder is the Finlay Institute of Vaccines (IFV), extended its indication to children convalescing from COVID-19 who were discharged from hospital or home medical care at least two months before, making it available for all patients age 2 years and older recovering from COVID-19, pursuant to the regulations and provisions in force in the country.

This authorization can be viewed at: <https://www.cecmed.cu/noticias/aprueba-cecmed-autorizo-uso-emergencia-vacuna-cubana-soberana-plus-poblacion-pediatrica>.

Adverse Events of Special Interest (AESI) and Related Risks: Anosmia, Ageusia

Anosmia and ageusia are considered neurological disorders, according to the list of events prioritized by SPEAC as potentially relevant to COVID-19 (1).

These are included because their effects are very common in cases of acute COVID-19 infection, and this has led to their being proposed as a way to screen for the disease. They are also known to occur in other respiratory viral infections such as influenza. According to ACCESS, ageusia is the loss of the taste functions of the tongue, while anosmia is the loss of the ability to detect one or more smells. The case definition of the ACCESS authors is as follows:

Anosmia: Absent smell function. There are two possible causes for anosmia: (i) conductive and/or traumatic; and (ii) sensorineural.

Ageusia: Absent taste function. A scale that ranges from 0, which refers to no taste, to 4, which refers to total taste loss, is used.

Risk factors:

- Diseases and other factors:

Anosmia: Nasal obstructive disorders such as chronic rhinosinusitis, nasal polyposis, allergic rhinitis, and nasal masses can obstruct the flow of nasal air to olfactory clefts and cause decreased smell. Chronic rhinosinusitis can occur following vaccination. Approximately 20% to 30% of patients who have experienced head trauma develop

some degree of olfactory dysfunction, with 5% experiencing anosmia. Thus, recent trauma should be excluded. In 20% to 30% of patients with olfactory dysfunctions, there is a recent history of upper respiratory infection. Damage to the olfactory bulb can occur from neurodegenerative diseases such as Alzheimer's and Parkinson's. Anosmia as part of another disease should be excluded.

Ageusia: Damage to taste nerves, dietary deficiencies, systemic conditions such as hypothyroidism, diabetes mellitus, pernicious anemia, Sjogren's syndrome and Crohn's disease, cranial nerve injuries (neuritis due to herpes zoster, meningioma or neurinomas), skull base tumors, etc. Patients with cancer of any part of the head or neck who are receiving radiation therapy. Inflammation from burns, lacerations, surgery, and local anesthesia. Local anti-plaque medications and certain dental infections, dentures, dental restorations, etc. In addition, factors associated with aging can affect the gustatory system.

- Medications:

Anosmia: Many drugs, such as antihypertensives and antihyperlipidemics, can be associated with smell disorders. Angiotensin converting enzyme inhibitors, diuretics, calcium channel blockers, and statins; amphetamines, enalapril, estrogen, phenothiazines, reserpine, and prolonged use of decongestants.

Ageusia: Use of certain medications, such as antibiotics (ampicillin, macrolides, metronidazole, quinolones, tetracycline), antineoplastic agents, drugs to treat neurological disorders (anti-parkinsonian drugs, central nervous system stimulants, migraine medications), cardiovascular medications, antipsychotics, tranquilizers, tricyclic antidepressants, antihistamines, bronchodilators, antifungals, and antivirals have reported ageusia as an adverse event.

- Vaccines in general: There is no reference to events associated with vaccines, except for influenza vaccine (2). Possible risk with COVID-19 vaccines.

Sources:

- (1) ACCESS vACCines. COVID-19 – Monitoring Readiness: Anosmia, ageusia event definition Form CD. <https://docs.google.com/document/d/1ktG7HrP1Kie-SpmVgyQpij5KiVUi9qx5/edit>.
- (2) Doty RL, Berman AH, Izhar M, et al. Influenza vaccinations and chemosensory function. Am J Rhinol Allergy. 2014 Jan-Feb;28(1):50–3. doi: 10.2500/ajra.2014.28.3987. <https://pubmed.ncbi.nlm.nih.gov/24717882/>. PMID: 24717882.

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