

# COVID-19

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

Thirty-fifth report

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## ARGENTINA

As of 31 January 2022, 88,232,021 doses of COVID-19 vaccines had been administered to people 3 years old and older in all 24 of Argentina's jurisdictions.

To date, there have been 59,797 reports of AEFI (67.8/100,000 doses administered). Of total reports, 69.9% were for females; the average age for both sexes was 41.5 years. Of reported events, 3.7% were reported as serious.

<i>Number of reports and reporting rate of adverse events (per 100,000 doses administered), by vaccine, as of 31 January 2022</i>			
<i>Vaccine</i>	<i>Total number of AEFI reports</i>	<i>Doses administered</i>	<i>Rate per 100,000 doses administered</i>
<b><i>Vaxzevria (AstraZeneca)/Covishield (Serum Institute of India)</i></b>	9,546	25,504,757	37.4
<b><i>CanSino(Ad5)</i></b>	64	428,862	14.9
<b><i>Spikevax (Moderna)</i></b>	1,193	4,957,529	24.1
<b><i>Comirnaty (Pfizer-BioNTech)</i></b>	1,257	10,627,861	11.8
<b><i>Inactivated SARS-COV-2 vaccine (Sinopharm)</i></b>	4,782	27,127,447	17.6
<b><i>Sputnik V (Gamaleya Institute)</i></b>	42,857	19,585,565	218.8
<b><i>Total</i></b>	<b>59,797</b>	<b>88,232,021</b>	<b>67.8</b>

Source: Argentina Ministry of Health, National COVID-19 Vaccination Campaign. Seventeenth Vaccine Safety Surveillance Report. March 2022. Available in Spanish at: <https://www.argentina.gob.ar/coronavirus/vacuna/equipos-salud/informes-seguridad>.

## CANADA

As of 15 April 2022, 55,712,970 doses of the Pfizer-BioNTech COVID-19 vaccine, 23,089,347 doses of the Moderna vaccine, 2,812,379 doses of the AstraZeneca and Covishield vaccine (AstraZeneca vaccine manufactured by the Serum Institute of India), and 20,145 doses of the Janssen vaccine had been administered.

To date, there have been 44,511 individual reports of one or more AEFI (0.54% of doses administered).

The majority of individual case reports were of non-serious adverse events. The most frequently reported adverse events were paresthesia, injection-site pain, headache, pruritus, dyspnea, fatigue, urticaria, chest pain, and fever.

Number of reports and reporting rate of adverse events (per 100,000 doses administered), by vaccine, as of 15 April 2022						
Vaccine	Number of non-serious AEFI reports		Number of serious AEFI reports		Total number of AEFI reports	
	N*	Rate per 100,000 doses administered	N*	Rate per 100,000 doses administered	N*	Rate per 100,000 doses administered
Pfizer-BioNTech	20,139	36.15	6,344	11.39	26,483	47.53
Moderna	12,067	52.26	1,798	7.79	13,865	60.05
Covishield and AstraZeneca	2,991	106.35	879	31.25	3,870	137.61
Janssen	29	143.96	20	99.28	49	243.24
Vaccine not identified	50	N/A	282	N/A	332	N/A
Total	35,276	43.21	9,323	11.42	44,599	54.63

\*N= number of reports

On 19 November 2021, Pfizer-BioNTech's Comirnaty vaccine was authorized for children between the ages of 5 and 11. Information regarding adverse events in this population and, more generally in individuals under 18 years of age, already included in the above total for Pfizer-BioNTech, is broken down in the following table:

Number of reports and reporting rate of AEFI (per 100,000 doses administered) for the Pfizer-BioNTech vaccine in the under-18-year-old population, as of 15 April 2022						
Age group (doses administered, ds)	Number of non-serious AEFI reports		Number of serious AEFI reports		Total number of AEFI reports	
	N*	Rate per 100,000 doses administered	N*	Rate per 100,000 doses administered	N*	Rate per 100,000 doses administered
Ages 12 to 17	1,118	22.93	362	7.42	1,480	30.35
4,875,965						
Ages 5 to 11	442	14.89	79	2.66	521	17.55
2,967,891						
Total	1,560	19.89	441	5.62	2,001	25.51
7,843,856						

\*N= number of reports

Note: The 5-11 age group also included reports of those born in 2017 who were not yet 5 years old at the time of vaccination.

Lastly, the following table details the number and rate (per 100,000 doses administered) of the main adverse events of special interest (AESI), by vaccine.

Number of reports and reporting rate of the main adverse events of special interest (AESI), by vaccine, in the general population, as of 15 April 2022						
AESI	Vaccine					
	Pfizer-BioNTech		Moderna		Covishield and AstraZeneca	
	N*	Rate per 100,000 doses administered	N*	Rate per 100,000 doses administered	N*	Rate per 100,000 doses administered
Anaphylaxis	610	1.09	186	0.81	29	1.03
Guillain-Barré syndrome	59	0.11	29	0.13	39	1.39
Myocardial infarction	76	0.14	25	0.11	6	0.21
Myocarditis/pericarditis	1,302	2.34	698	3.02	35	1.24
Deep vein thrombosis	168	0.30	70	0.30	72	2.56
Pulmonary embolism	234	0.42	96	0.42	132	4.69
Thrombosis with thrombocytopenia syndrome (TTS)	30	0.05	13	0.06	71	2.52
Bell's palsy/facial paralysis	599	1.08	221	0.96	55	1.96
Cerebrovascular accident	131	0.24	54	0.23	36	1.28
Acute renal injury	36	0.06	21	0.09	7	0.25
Miscarriage	59	0.11	13	0.06	1	0.04
Fatal events	331* post-vaccination deaths					
*N = number of reports **Following a medical review of the 331 deaths, 106 were determined to most likely be unrelated to administration of the COVID-19 vaccine; 56 are still under investigation, and in 169 cases the cause of death could not be classified, due to insufficient information.						

Note: Information on the Janssen vaccine was not included, due to the small number of reported cases.

Source: Public Health Agency of Canada. Canadian COVID-19 vaccine safety report. Source: Public Health Agency of Canada. April 29, 2022. <https://health-infobase.canada.ca/covid-19/vaccine-safety/>. Data reproduced by PAHO/WHO.

## ENGLISH-SPEAKING CARIBBEAN

As of 15 April 2022, the global individual case safety reports (ICSR) database, VigiBase, had received 1,457 AEFI reports from the English-speaking Caribbean, following administration of COVID-19 vaccines.

Reports came from Barbados, Jamaica, and Saint Vincent and the Grenadines, mainly in people under 65 years of age (85.3%), and in females (1,087 reports, 74.6%). As of 15 April 2022, of total events reported (n=1,457), the most frequent reactions were headache n=442 (30.3%), dizziness n=291 (20.0%), fever n=289 (19.8%), fatigue n=245 (16.8%), chills n=242 (16.6%), and myalgia n=214 (14.7%). A total of 237 ICSRs (16.3%) were classified as serious.

Individual cases reported were associated with the following COVID-19 vaccines: AstraZeneca, Covishield, Sputnik V, Pfizer-BioNTech, J&J/Janssen, Sinopharm/BIBP, Moderna, and unspecified COVID-19 vaccines.

Note: Individual case safety reports involve events that occurred following vaccination, and may include coincident events not attributable to the vaccine(s).

Source: The Caribbean Public Health Agency (CARPHA)/Caribbean Regulatory System. VigiCarib News. April 2020. Additional information can be found at: <https://carpha.org/What-We-Do/CRS/VigiCarib>.

## COLOMBIA

As of 15 April 2022, a total of 81,963,673 doses of COVID-19 vaccines had been administered. As of the same cut-off date, VigiFlow® had received 47,153 individual case reports of AEFI. An individual case report may include one or more adverse events. The nationwide reporting rate was 58 per 100,000 doses administered. Of the total number of people vaccinated, 0.05% reported AEFI.

Of individual case reports, 3.1% (1,465) were of serious AEFI; 67% (31,430) were in women. Analyzing the distribution of reports by age, the highest percentage, 12.5% (5,883), was in the 25-to-29-year-old age group, while 11.4% of reports (5,366) were for individuals between the ages of 30 and 34.

The most frequently reported signs and symptoms, without indication as to type of vaccine, were: headache (17.2%), fever (8.5%), malaise (7.5%), muscle pain (7.3%), vaccination-site pain (6.5%), and weakness (5.5%).

Source: Colombia Ministry of Health, National Institute of Food and Drug Surveillance (INVIMA), National Institute of Health (INS). Bulletin #12: April 2022. Surveillance of Adverse Events Following Vaccination (AEFI) with COVID-19 vaccines in Colombia. Reporting period: 17 February 2021 to 15 April 2022. Available in Spanish at: <https://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/VS/ED/PSP/boletin12-farmacovigilancia-vacunas-abr2022.pdf>.

## ECUADOR

As of 12 March 2022, 32,600,000 doses of COVID-19 vaccines had been administered. As of that date, 3,582 reports of AEFI had been received.

Of total reports, 3,496 were for non-serious AEFI (10.71/100,000 doses administered). The majority of reported non-serious AEFI were in individuals between the ages of 18 and 44. The most prevalent signs and symptoms were fever, headache, malaise, injection-site pain, nausea, dizziness, fatigue, redness of the skin, and diarrhea.

Of the total number of reports, 86 were for serious AEFI, of which 58 were in individuals between the ages of 18 and 64. Of the total number of serious AEFI, only 3 were related to a COVID-19 vaccine, according to the causality assessment conducted. The most prevalent signs and symptoms included allergic reaction and thrombosis with thrombocytopenia syndrome.

Source: Report published 13 April 2022 by the Ministry of Public Health of Ecuador, with data from the National Agency for Health Regulation, Control, and Surveillance (ARCSA). Available in Spanish at:

<https://www.salud.gob.ec/en-menos-del-1-por-10-millones-de-dosis-de-vacunas-se-presentaron-esavi-graves-relacionados-con-la-vacunacion-covid-19/>.

## UNITED STATES

The following is updated information from the U.S. Centers for Disease Control and Prevention (CDC) regarding serious adverse events of special interest.

Anaphylaxis following COVID-19 vaccination is rare, and has occurred at a rate of approximately five cases per million doses administered in the United States. Anaphylaxis can occur after administration of any type of vaccine.

Thrombosis with Thrombocytopenia Syndrome (TTS) after COVID-19 vaccination with the Janssen vaccine (J&J/Janssen) is rare, and has occurred in approximately four cases per million doses administered in the United States. A case series review indicated a potential causal relationship between the Janssen COVID-19 vaccine and TTS. CDC scientists have conducted detailed reviews of cases of TTS and have published the results in: [US Case Reports of Cerebral Venous Sinus Thrombosis with Thrombocytopenia after Ad26.COV2.S Vaccination, March 2 to April 21, 2021](#).

Guillain-Barré syndrome (GBS) in people who have received the J&J/Janssen COVID-19 vaccine is rare, and has largely been reported in men 50 years old and older.

According to a recent analysis of data from the Vaccine Safety Datalink, the rate of GBS within the first 21 days after administration with the J&J/Janssen COVID-19 vaccine was found to be 21 times higher than after administration of the Pfizer-BioNTech or Moderna vaccine (mRNA COVID-19 vaccines). After the first 42 days, the rate of GBS was 11



times higher following J&J/Janssen vaccination. Analysis found no increased risk of GBS after vaccination with the Pfizer-BioNTech or Moderna (mRNA) vaccine.

Cases of myocarditis and pericarditis after COVID-19 vaccination are rare. Most patients with myocarditis or pericarditis after COVID-19 vaccination responded well to medicine and rest and felt better quickly. Most reported cases were among people, particularly male adolescents and young adults, who received the Pfizer-BioNTech or Moderna COVID-19 mRNA vaccine.

A review of vaccine safety data in VAERS, from December 2020 to August 2021, found a small but increased risk of myocarditis after administration of COVID-19 mRNA vaccines. More than 350 million doses of mRNA vaccines were administered during the period analyzed. CDC scientists found that rates of myocarditis were highest following the second dose of an mRNA vaccine among males in the following age groups:

- 12 to 15 years old (70.7 cases per million doses of Pfizer-BioNTech)
- 16 to 17 years old (105.9 cases per million doses of Pfizer-BioNTech)
- 18 to 24 years old (52.4 and 56.3 cases per million doses of Pfizer-BioNTech and Moderna, respectively)

Reports of death after COVID-19 vaccination are rare. The FDA requires health care providers to notify VAERS of any deaths following COVID-19 vaccination, regardless of whether the vaccine is determined to be the cause of death. Between 14 December 2020 and 2 May 2022, more than 576 million doses of COVID-19 vaccines were administered in the United States. During this time, VAERS received 14,468 reports of deaths (0.0025%) among people who had received a COVID-19 vaccine. Clinicians at the CDC and FDA review deaths reported to VAERS, including death certificates, autopsies, and medical records.

Source: Centers for Disease Control and Prevention (CDC). Selected Adverse Events Reported after COVID-19 Vaccination. Updated 24 May 2022. Available at: <https://stacks.cdc.gov/view/cdc/117684>. Note: The website is updated weekly, and the data may differ at the time this newsletter is published.

## PARAGUAY

As of 8 April 2022, 8,521,956 doses of COVID-19 vaccines had been administered. A total of 2,701 AEFI have been reported since vaccinations began, from 22 February 2021 to 4 March 2022, representing 0.03% of doses administered. Of reported AEFI, 449 cases were considered serious (16.6% of reported cases), equivalent to 0.005% of total doses administered. The highest rate of reported AEFI is associated with the Covaxin vaccine (80.26/100,000 doses administered), followed by the AstraZeneca vaccine (63.66/100,000 doses administered) and the CoronaVac vaccine (58.07/100,000 doses administered).

Of the reports associated with these vaccines, 94% involved non-serious AEFI; 71% of AEFI reports (1,913) were in women. Reports of AEFI were mostly (1,808/2,701) in individuals between the ages of 25 and 49.



Source: Paraguay Ministry of Public Health and Social Welfare. AEFI Surveillance Information Bulletin No. 56 Regarding COVID-19 Vaccination. National Program on Immunopreventable Diseases and Expanded Program on Immunization, 8 April 2022. Available in Spanish at: <https://pai.mspbs.gov.py/wp-content/uploads/2022/02/48-Boletin-Epidemiologico-ESAVI.pdf>.

## **Publications on potential safety signals identified in the use of COVID-19 vaccines**

### **Protection by BNT162b2 against the Omicron Variant of Concern in Children and Adolescents**

On 30 March 2022, the results of a study conducted at 31 hospitals in 23 states of the United States, between 1 July 2021 and 17 February 2022, were published.

The objective of the study was to evaluate vaccine effectiveness against laboratory-confirmed COVID-19 leading to hospitalization and against critical COVID-19 (i.e., COVID-19 that requires life support or that leads to death) for patients fully vaccinated (two doses of BNT162b2) ages 12 to 18 in periods coinciding with circulation of the B.1.617.2 (delta) (July 1, 2021, to December 18, 2021) and omicron (December 19, 2021, to February 17, 2022) among patients 5 to 11 and 12 to 18 years of age. A total of 1,185 case patients were enrolled of whom were unvaccinated (88% unvaccinated), 25% of whom received life support, along with 1,627 controls who did not have COVID-19.

All patients classified as having COVID-19 had to have had a positive SARS-CoV-2 reverse-transcriptase-polymerase-chain-reaction (RT-PCR) or antigen test result within 10 days after symptom onset or within 72 hours after hospital admission. Patients classified as controls were hospitalized patients with a negative SARS-CoV-2 antigen or RT-PCR test result, with or without COVID-19-associated symptoms.

The results showed that during the Delta-predominant period, vaccine effectiveness against hospitalization among the 12-to-18-year-old age group, in the 23 to 44 weeks after full vaccination, was 92% (CI 95%, 89 to 95); 96% (95% CI 96 to 98) against critical COVID-19; and 91% (CI 95%, 86 to 94) against non-critical COVID-19.

During the Omicron-predominant period, vaccine effectiveness of the two-dose schedule among the 12-to-18-year-old age group was 40% (CI 95%, 9 to 60) against hospitalization for COVID-19; 79% (CI 95%, 51 to 91) against critical COVID-19; and 20% (CI 95%, -25 to 49) against non-critical COVID-19. Vaccine effectiveness against hospitalization in children between 5 and 11 years of age during this period was 68% (CI 95%, 42 to 82).

The authors of this study concluded that the BNT162b2 vaccination reduced the risk of Omicron-associated hospitalization by two-thirds among children 5 to 11 years of age. Although two doses provided lower protection

against Omicron-associated hospitalization than against Delta-associated hospitalization among adolescents 12 to 18 years of age, vaccination prevented serious illness caused by either variant.

Source: Ashley M. Price et al. BNT162b2 Protection against the Omicron Variant in Children and Adolescents, published 30 March 2022, at NEJM.org. DOI: 10.1056/NEJMoA 2202 826.

### Protection against SARS-CoV-2 after Covid-19 vaccination and previous infection

On 16 February 2022, a prospective multicenter cohort study was published that investigated the duration and effectiveness of immunity from infection with and vaccination against COVID-19 (BNT162b2 and ChAdOx1 nCoV-19) and the duration of acquired immunity from previous infection, in 35,768 asymptomatic healthcare workers from 135 centers in the UK, aged 18 years and older, who underwent SARS-CoV-2 PCR testing every two weeks. The study period ran from 7 December 2020 to 21 September 2021.

In this analysis, the objective was to determine the level and durability of protection against SARS-CoV-2 infection in the study group by estimating vaccine effectiveness after two doses of the COVID-19 vaccine, based on vaccine type and dosing interval, in participants without prior infection. Immunity to reinfection conferred by a previous infection plus the COVID-19 vaccine was also assessed.

Vaccine effectiveness (up to 10 months after the first dose) and infection-acquired immunity were assessed by comparing the time to PCR-confirmed infection in vaccinated persons with that in unvaccinated persons, stratified according to previous infection status.

Of 35,768 participants, 27% (9,488) had a previous SARS-CoV-2 infection. Of these participants, 95% had received two doses of vaccine: 9% with BNT162b2 vaccine, with a short interval between doses (the second dose had been administered up to 6 weeks after the first dose); 78% had received BNT162b2 vaccine with a long interval between doses (with the second dose given 6 weeks or more after the first dose); and 8% received the ChAdOx1 nCoV-19 vaccine (two doses with short and long intervals combined).

A total of 2,747 primary PCR-confirmed SARS-CoV-2 primary infections and 210 reinfections were observed.

A total of 6,169 participants in the previously infected cohort were monitored in the unvaccinated follow-up period, and up to one year after a primary infection.

Among participants without prior infection who received long-interval BNT162b2 vaccine, adjusted vaccine effectiveness decreased from 85% (CI 95%, 72 to 92) 14 to 73 days after the second dose to 51% (CI 95%, 22 to 69) at a median of 201 days (interquartile range, 197 to 205) after the second dose; this effectiveness did not differ significantly between the long-interval and short-interval BNT162b2 vaccine recipients. The adjusted vaccine effectiveness among ChAdOx1 nCoV-19 vaccine recipients was 58% (CI 95%, 23 to 77) 14 to 73 days after the second dose, considerably lower than that among BNT162b2 vaccine recipients (Table 1).

Table 1: Vaccine effectiveness among previously uninfected participants.

Vaccine schedule administered	Short-term protection 2 to 10 weeks after the second dose	Long-term protection More than 6 months after the second dose
BNT162b2 (long interval > 6 weeks)	85% (CI 95%, 72–92)	51% (IC 95%, 22 to 69)
BNT162b2 (short interval < 6 weeks)	89% (CI 95%, 78 to 94)	53% (CI 95%, 28 to 69)
AZ (combined)	58% (CI 95%, 23 to 77)	72% (CI 95%, 39 to 87)

The authors concluded that BNT162b2 vaccine administered with a short or long interval between the two doses was associated with a considerably lower short-term risk of SARS-CoV-2 infection (asymptomatic and symptomatic). However, this protection waned considerably after 6 months. The protection associated with two doses of ChAdOx1nCoV-19 vaccine was considerably lower than that associated with BNT162b2 vaccine overall.

The analysis also showed that immunity acquired by SARS-CoV-2 infection decreased after one year for unvaccinated participants, but remained consistently higher than 90% in participants subsequently vaccinated with two doses of BNT162b2, even in people infected more than 18 months previously, with an adjusted effectiveness of 95% (CI 95%, 82 to 99) in vaccinated individuals (Table 2).

Table 2: Protection against reinfection in previously infected patients.

	< 1 year after primary infection	>1 year after primary infection
Vaccinated with two doses of BNT162b2 (14 to 73 days after vaccination)	84% (CI 95%, 67 to 92)	94% (CI 95%, 75 to 99)
Vaccinated with two doses of BNT162b2 (194 to 261 days after vaccination)	86% (CI 95%, 27 to 97)	95% (CI 95%, 82 to 99)
Unvaccinated	86% (CI 95%, 81 to 89)	69% (CI 95%, 38 to 84)

Strategic use of booster doses of the vaccine to prevent decreased protection (particularly in previously uninfected people) can reduce COVID-19 infection and transmission.

Source: Protection against SARS-CoV-2 after Covid-19 Vaccination and Previous Infection. Victoria Hall et al., N Engl J Med 2022; 386:1207–1220 DOI: 10.1056/NEJMoa2118691.

### Fourth dose of BNT162b2 COVID-19 mRNA vaccine in a nationwide setting

On 13 April 2022, an observational study evaluating the effectiveness of a fourth dose of the BNT162b2 mRNA vaccine compared with a three-dose schedule (received at least four months earlier), in people 60 years of age and older in Israel was published.

Electronic records from Clalit Health Services (Israel's largest health care organization) were used. A total of 182,122 people who received a fourth dose between 3 January and 18 February 2022 – when the Omicron VOC was predominant – were compared with 182,122 people who had received a third dose at least four months earlier, but had not yet received a fourth dose.

Five outcomes were examined: PCR-confirmed SARS-CoV-2 infection, symptomatic Covid-19, Covid-19–related hospitalization, severe Covid-19 (defined according to National Institutes of Health criteria), and Covid-19-related death.

Relative vaccine effectiveness of the fourth dose of BNT162b2 (on days 7 to 30 after the fourth dose) as compared with three doses of BNT162b2:

- 45% (CI 95%, 44 to 47) against PCR-confirmed SARS-CoV-2 infection;
- 55% (95% CI, 53 to 58) against symptomatic COVID-19;
- 68% (CI 95%, 59 to 74) against COVID-19-related hospitalization;
- 62% (CI 95%, 50 to 74) against severe COVID-19;
- 74% (CI 95%, 50 to 90) against COVID-19-related death.

Some limitations of the study were related to the short follow-up time, and therefore we were not yet able to assess longer-term effects, including possible waning of the effect; and, the potential for confounding, due to the observational nature of the study; and the fact that most of the participants were elderly.

The authors conclude that a fourth dose of BNT162b2 vaccine, compared with a third dose given at least four months earlier, appeared to improve short-term protection against PCR-confirmed SARS-CoV-2 infection, symptomatic illness, COVID-19-related hospitalization, severe COVID-19 illness, and COVID-19-related death.

Source: Ori Magen et al. Fourth Dose of BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting, published 13 April 2022, at NEJM.org. DOI: 10.1056/NEJMoa2201688.

## Efficacy, Safety, and Immunogenicity of the DNA SARS-CoV-2 Vaccine (ZyCoV-D): the interim efficacy results from a phase 3, randomized, double-blind, placebo-controlled study in India

On 2 April 2022, the interim analysis of a multicenter, double-blind, randomized, placebo-controlled phase 3 trial of the DNA SARS-CoV-2 vaccine (ZyCoV-D) in 49 centers in India was published.

Healthy people aged 12 years or older were enrolled and randomly assigned (1:1) to receive three doses of vaccine or placebo, intradermally via a needle-free injection system 28 days apart (at days 0, 28, and 56). Between 16 January and 23 June 2021 (data cut-off), 27,703 individuals were enrolled and randomly assigned to receive ZyCoV-D (n=13,851) or placebo (n=13,852).

The primary efficacy endpoint was the number of participants with first occurrence of symptomatic RT-PCR-positive COVID-19, 28 days after the third dose, until the targeted number of cases (interim analysis n=70, final analysis n=158) had been achieved. The interim analysis of the primary endpoint was conducted once 50% (79 cases) of the target number of cases was met.

Safety assessment included incidence and severity of solicited and unsolicited adverse events after each dose, and incidence of serious adverse events throughout the study. Immunogenicity assessment (at days 0, 56, and 84) included seroconversion rate by ELISA, geometric mean titer (GMT), geometric mean fold rise (GMFR), and neutralizing antibody titers.

The results showed that the efficacy of the ZyCoV-D vaccine was 66.6% (CI 95%, 47.6–80.7).

The occurrence of solicited adverse events was similar between the treatment groups (623 [4.49%] in the ZyCoV-D group and 620 [4.47%] in the placebo group). There were two deaths (one in each group) reported at the data cutoff, neither of which was considered related to the study treatments.

Immunogenicity assessment at day 84 yielded the following results:

- The proportion of participants achieving IgG seroconversion against the S1 antigen in the ZyCoV-D group was 93.33%, and 52.31% in the placebo group. The antibody concentration, defined by IgG-based GMT, was 952.67 EU (CI 95%, 707.94–1,282.00) in the ZyCoV-D group, and 154.82 EU (91.25–262.70) in the placebo group.
- The increase in antibody titer, as defined by GMFR, was greater in the ZyCoV-D group (136.10, CI 95%, 101.13–183.14) than in the placebo group (22.12, 13.04–37.53).
- The proportion of participants who achieved neutralizing antibody seroconversion was significantly ( $p<0.0001$ ) higher in the ZyCoV-D group (44 [88%]) than in the placebo group (20 [42.55%]).
- The neutralizing antibody concentration, defined by GMT, was higher in the ZyCoV-D group (133.9 PRNT<sub>50</sub>, CI 95%, 86.88–204.81) than in the placebo group (30.40 PRNT<sub>50</sub>, 16.35–56, 53).

- The increase in the neutralizing antibody titer, defined by GMFR, was greater in the ZyCoV-D group (26.68, CI 95%, 17.38–40.96) than in the placebo group (5.74, 3.14–10.48).
- The cellular response of IFN- $\gamma$  remained at a 9.6-times rise in median spot-forming cells per million PBMCs, compared to baseline in the vaccinated group. No significant fold change was observed in the placebo group.

The authors concluded that the ZyCoV-D vaccine was found to be effective, safe, and immunogenic in a phase 3 trial.

Source: Akash Khobragade et al. Efficacy, safety, and immunogenicity of the DNA SARS-CoV-2 vaccine (ZyCoV-D): The interim efficacy results of a phase 3, randomized, double-blind, placebo-controlled study in India. Lancet 2022; 399: 1313–21. DOI: [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(22\)00151-9/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)00151-9/fulltext).

### SARS-CoV-2 Vaccination and myocarditis in a Nordic cohort study of 23 million residents

On 20 April 2022, a population-based cohort study in four Nordic countries (Denmark, Finland, Norway, and Sweden) was published. The study used electronic records linked by a unique identifier: public, mandatory, and population-based. The study period ran from December 2020 to October 2021, and the population studied consisted of residents 12 years of age or older.

The objective was to evaluate the risks of myocarditis and pericarditis following COVID-19 vaccination by vaccine product, vaccination dose number, sex, and age.

Participants were 23,122,522 residents aged 12 years or older. They were followed up from 27 December 2020 until incident myocarditis or pericarditis, censoring, or study end (5 October 2021).

Follow-up consisted of the 28-day risk periods after administration date of the first and second doses of a SARS-CoV-2 vaccine, including BNT162b2, mRNA-1273, and AZD1222, or combinations thereof.

Outcomes of primary interest were incident events of hospitalization with a diagnostic code of myocarditis or pericarditis, while outcomes of secondary interest were incident events of myocarditis or pericarditis that caused hospitalization or that were treated on an outpatient basis.

The analysis was performed with Poisson regression, which yielded adjusted incidence rate ratios (IRRs) and excess rates with 95% CIs, comparing rates of myocarditis or pericarditis in the 28-day period following vaccination with rates among unvaccinated individuals.

Out of a total of 23,122,522 Nordic residents (81% vaccinated by study end; 50.2% women), during the periods of 28 days after vaccination and during the unvaccinated periods, 1,077 incident myocarditis events and 1,149 incident pericarditis events were observed.



Incidence rates of myocarditis during the unvaccinated period were 9.7 per 100,000 person-years for males and 4.3 per 100,000 person-years for females. Among individuals ages 16 to 24, incidence rates were 18.8 per 100,000 person-years for males and 4.4 per 100,000 person-years for females. Incidence rates of pericarditis increased with age.

During the 28-day risk period, 105 myocarditis cases following administration of the first dose of BNT162b2, and 115 myocarditis cases following the second dose were observed. There were also 15 myocarditis cases following administration of the first dose of mRNA-1273, and 60 myocarditis cases following the second dose.

Adjusted IRRs comparing the 28-day risk periods following first and second doses compared with unvaccinated periods were 1.38 (CI 95%, 1.12-1.69) for the first dose of BNT162b2, and 1.75 (CI 95%, 1.43-2.14) for the second dose, and 1.16 (CI 95%, 0.69-1.93) for the first dose of mRNA-1273 and 6.57 (CI 95%, 4.64-9.28) for the second dose.

Among males, after the first and second doses, adjusted IRRs were 1.40 (CI 95%, 1.09-1.80) for the first dose of BNT162b2 and 2.04 (CI 95%, 1.61-2.58) for the second dose, and 1.45 (CI 95%, 0.84-2.52) for the first dose of mRNA-1273 and 8.55 (CI 95%, 6.40-11.41) for the second dose.

Among females, following the first and second doses, adjusted IRRs were 1.46 (CI 95%, 1.01-2.11) for the first dose of BNT162b2 and 1.25 (CI 95%, 0.77-2.05) for the second dose, and 1.45 (CI 95%, 0.35-5.97) for the first dose of mRNA-1273 and 2.73 (CI 95%, 1.27-5.87) for the second dose.

Among males 16 to 24 years of age, the adjusted IRRs for myocarditis were 5.31 (CI 95%, 3.68-7.68) for a second dose of BNT162b2 and 13.83 (CI 95%, 8.08-23.68) for a second dose of mRNA-1273. For females, the comparative adjusted IRRs were lower.

Excess numbers of myocarditis events per 100,000 persons vaccinated in the 28-day risk periods were also estimated. Among all males, these numbers were 0.27 (CI 95%, 0.09-0.46) events after the first dose of BNT162b2 and 0.67 (CI 95%, 0.46-0.88) events after the second dose, and 0.33 (CI 95%, -0.11 to 0.78) events after the first dose of mRNA-1273 and 4.97 (CI 95%, 3.62-6.32) events after the second dose.

Among all females, the excess numbers of events per 100,000 vaccinated individuals in the 28-day risk periods were 0.15 (CI 95%, 0.02-0.28) events after the first dose of BNT162b2 and 0.09 (CI 95%, -0.09 to 0.26) events after the second dose, and 0.05 (CI 95%, -0.13 to 0.23) events after the first dose of mRNA-1273 and 0.48 (CI 95%, 0.07-0.89) events after the second dose.

Among males 16 to 24 years of age, the excess number of myocarditis events per 100,000 vaccinated individuals in the 28-day risk periods after the first dose of BNT162b2 was 1.55 (CI 95%, 0.70-2.39) events and after the second



dose was 5.55 (CI 95%, 3.70-7.39) events, and it was 1.75 (CI 95%, -0.20 to 3.71) events after the first dose of mRNA-1273 and 18.39 (CI 95%, 9.05-27.72) events after the second dose.

For a heterologous schedule (one dose with BNT162b2 and the other dose with mRNA-1273), 38 myocarditis cases (34 males) occurred following the second dose, with an excess number of events in males of 10.34 (CI 95%, 6.86-13.83) events. In males ages 16 to 24, 17 myocarditis cases occurred, with an excess number of events of 27.49 (CI 95%, 14.41-40.56) events. Estimates for pericarditis were similar.

According to the authors, the results showed that both first and second doses of mRNA vaccines were associated with increased risk of myocarditis and pericarditis. For individuals receiving two doses of the same vaccine, risk of myocarditis was highest among young males (ages 16-24) after the second dose. These findings are compatible with between four and seven excess events in 28 days per 100,000 vaccinated individuals after BNT162b2, and between 9 and 28 excess events per 100,000 people vaccinated after mRNA-1273 vaccination. This risk should be balanced against the benefits of protecting against severe COVID-19 disease.

Source: Karlstad Ø, Hovi P, Husby A, et al. SARS-CoV-2 Vaccination and Myocarditis in a Nordic Cohort Study of 23 Million Residents. JAMA Cardiol. Published online 20 April 2022. doi:10.1001/jamacardio.2022.0583.

## Joint statement by the European Center for Disease Prevention and Control and the European Medicines Agency on the administration of a fourth dose of COVID-19 mRNA vaccines

On 6 April 2022, the COVID-19 task force of the European Medicines Agency (EMA) and the European Center for Disease Prevention and Control (ECDC) issued a joint statement noting that it is too early to consider using a fourth dose of mRNA COVID-19 vaccines (Pfizer's Comirnaty and Moderna's Spikevax) in the general population. In this regard, the following recommendations were presented:

- **Individuals 80 years of age or older:** A fourth dose (or second booster) can be given to adults 80 years of age and older, given the higher risk of severe COVID-19 in this age group and the protection provided by a fourth dose.
- **Adults between 60 and 79 years of age with normal immune systems:** There is currently no clear evidence in the EU that vaccine protection against severe disease is waning substantially in adults with normal immune systems aged 60 to 79 years, and thus no clear evidence to support the immediate use of a fourth dose in this population.
- **Individuals under 60 years of age with normal immune systems:** There is currently no conclusive evidence that vaccine protection against severe disease is waning or that there is an added value of a fourth dose in this population.
- **Immunocompromised individuals:** The administration of a fourth dose of mRNA vaccines to immunocompromised persons had already been recommended, and should be a part of vaccination campaigns. There are currently no data on immunogenicity, safety, or efficacy of additional doses in this population.

The ECDC and EMA will continue to review available evidence on the effectiveness of COVID-19 vaccines and will update their recommendations accordingly.

Additional information is available at: <https://www.ema.europa.eu/en/news/ecdc-ema-issue-advice-fourth-doses-mrna-covid-19-vaccines>.

### Meeting highlights from the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) meeting of 4-7 April 2022

**COVID-19 mRNA vaccines:** Based on PRAC's review of the very rare cases of autoimmune hepatitis (AIH) spontaneously reported in the EudraVigilance database, assessment of data from the medical literature, and further data and analyses provided by the marketing authorization holders, the committee concluded that available evidence does not support a causal link between COVID-19 vaccines Comirnaty and Spikevax and very rare cases of autoimmune hepatitis (AIH).

AIH is a serious chronic inflammatory condition in which the immune system attacks and damages the liver. Signs and symptoms of autoimmune hepatitis vary from person to person and may include yellowing of the skin (jaundice), build-up of fluid in the legs (edema) or belly (ascites), and gastrointestinal symptoms.

EMA will continue to closely monitor any new reports of the condition and take appropriate measures if necessary. Additional information available at: <https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-4-7-april-2022>.

### Plenary meeting of the WHO Strategic Advisory Group of Experts (SAGE) on Immunization

Following is a summary of highlights of the WHO Strategic Advisory Group of Experts on Immunization meeting, on **infection- and vaccination-induced immunity to SARS-CoV-2 (hybrid immunity)**, held from 4 to 7 April 2022:

- Globally, the seroprevalence of SARS-CoV-2 is rising rapidly globally, on the basis of both infection and vaccination.
- The protective effect of infection-induced immunity, alone or in combination with vaccination, needs to be understood, particularly relating to possible modifications to the COVID-19 vaccine schedule.
- More evidence is required on duration of protection for both hybrid immunity and vaccine-induced immunity, by severity of disease outcome, taking into consideration scientific principles, uncertainties, and the varied seroprevalence rates in populations across countries.
- SAGE emphasizes the need to continue to protect high-priority use groups, as outlined in the SAGE/WHO roadmap for prioritizing the use of COVID-19 vaccines.
- Additional information is available at: [https://cdn.who.int/media/docs/default-source/immunization/sage/sage-pages/sage\\_april2022meetinghighlights\\_11apr2022\\_final.pdf?sfvrsn=c2bd9f68\\_1](https://cdn.who.int/media/docs/default-source/immunization/sage/sage-pages/sage_april2022meetinghighlights_11apr2022_final.pdf?sfvrsn=c2bd9f68_1).

### WHO recommends the use of nirmatrelvir and ritonavir in patients with mild to moderate COVID-19 at high risk of hospitalization

On 22 April 2022, WHO issued a statement recommending the use of nirmatrelvir and ritonavir, marketed as Paxlovid, for the treatment of patients with mild to moderate COVID-19 at highest risk of hospitalization, calling it the best therapeutic choice for high-risk patients to date.

This recommendation is based on new data from two randomized controlled trials involving 3,078 patients. The data show that the risk of hospitalization is reduced by 85% following this treatment in high-risk groups (over 10% risk of hospitalization). This translates to 84 fewer hospitalizations per 1,000 patients.

WHO advises against its use in patients at lower risk, as the benefits were found to be negligible.

This medicine can only be administered while the disease is in its early stages; prompt and accurate testing is therefore essential for a successful outcome with this therapy. For the global distribution of nirmatrelvir and ritonavir, access to testing and early diagnosis in primary health care settings will be key.

Additional information is available at: <https://www.who.int/news/item/22-04-2022-who-recommends-highly-successful-covid-19-therapy-and-calls-for-wide-geographical-distribution-and-transparency-from-originator>.

## Decisions of the Region's Regulatory Authorities

### Brazil

#### Janssen COVID-19 Vaccine

On 5 April 2022, Brazil's National Health Surveillance Agency (ANVISA) published definitive registration of the Janssen-Cilag COVID-19 (recombinant) vaccine. The vaccine was approved by ANVISA for emergency use on 31 March 2021. This marketing authorization is for the vaccine's use as primary vaccination and as a booster dose.

Additional information is available at: <https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2022/anvisa-aprova-registro-definitivo-da-vacina-covid-19-da-janssen>.

#### CoronaVac COVID-19 vaccine for children 3 to 5 years of age

On 14 April 2022, ANVISA reported that, after evaluating the views of the medical associations and studies provided by the Butantan Institute, the data presented were insufficient to reach a decision on the use of the CoronaVac vaccine in children 3 to 5 years of age. They, therefore, concluded that additional data from ongoing studies need to be provided in order to assess the benefit of the vaccine in this age group, under current epidemiological conditions.

Additional information is available at: <https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2022/coronavac-para-criancas-de-3-a-5-anos-processo-de-analise-na-anvisa-entra-em-exigencia>.

## Canada

### Initial guidance on a second booster dose of COVID-19 vaccines in Canada

On 5 April 2022, the National Advisory Committee on Immunization (NACI) published a document titled "Initial Guidance on a Second Booster Dose of COVID-19 Vaccines in Canada," in light of decreasing protection over time—after the first booster dose—against severe disease and/or the risk of immune evasion from highly communicable VOCs capable of causing severe illness. On this topic, NACI issued the following recommendations:

- Jurisdictions should prepare for rapid deployment of a second COVID-19 vaccine booster dose program over the coming weeks, prioritizing the following populations:
  - Adults 80 years of age and older living in the community (Strong NACI Recommendation)
  - Residents of long-term care or other congregate living settings for seniors (Strong NACI Recommendation)
  - While the greatest benefit is expected in adults 80 years of age and older, jurisdictions may also consider offering a second COVID-19 booster dose to adults 70 to 79 years of age living in the community (Discretionary NACI Recommendation)
  - NACI recommends providing a second booster dose six months after the previous booster dose; however, this six-month interval may need to be balanced with local and current epidemiological conditions.

Additional information is available at: <https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/guidance-second-booster-dose-covid-19-vaccines.html>.

## Chile

### Chile's Public Health Institute authorizes use of the Moderna vaccine in children between the ages of 6 and 11

On 12 April 2022, Chile's Public Health Institute (ISP) authorized an expansion of the age range for Moderna's Spikevax mRNA-1273 COVID-19 vaccine, to begin at age 6. Emergency use authorization for this vaccine was granted by the ISP on 2 February 2022 for individuals ages 12 and older.

The ISP did this expansion after analyzing the quality, safety, and efficacy record of the vaccine in this new age range, along with authorization of the vaccine by the EMA.

Additional information is available in Spanish at: <https://www.ispch.cl/noticia/isp-autoriza-uso-de-vacuna-moderna-en-ninos-entre-los-6-y-11-anos-de-edad/>.

## Peru

### Ministry of Health: Administration of a fourth dose of the Moderna vaccine is safe and effective

On 23 April 2022, Peru's Ministry of Health (MoH) published an official statement on administration of a fourth dose of Moderna's COVID-19 vaccine in people over 50 years of age, immunocompromised individuals, and health personnel, five months after administration of the third dose of a COVID-19 vaccine.

The bulletin informs the public that Moderna vaccine immunization schedules of 50- and 100-microgram doses for adults are safe and effective.

The MoH reaffirmed that doses greater than 100 micrograms have never been administered, and that SAGE recommends a dose of 50 micrograms (0.25mL) as a fourth dose of the Moderna COVID-19 vaccine. To date, while active surveillance continues, no severe adverse effects have been reported in relation to administration of the Moderna vaccine in Peru.

Additional information is available in Spanish at: <https://www.gob.pe/institucion/minsa/noticias/601787-minsa-aplicacion-de-cuarta-dosis-con-vacuna-moderna-es-segura-y-eficaz-comunicado-oficial-n-931>.

<https://www.gob.pe/institucion/minsa/noticias/608307-covid-19-peru-supero-el-medio-millon-de-personas-vacunadas-con-la-cuarta-dosis>.

According to recommendations by SAGE/WHO for use of the Moderna COVID-19 vaccine, the vaccination schedule is as follows:

Individuals 12 years of age and older: Two doses of 100 micrograms (0.5 mL), with an interval of four to eight weeks – preferably eight weeks, in order to reduce the risk of myocarditis (primary series); and a dose of 50 micrograms (0.25 mL) four to six months after the second dose (booster dose).

Moderately or severely immunocompromised individuals: An extended primary series, including a complete third dose of 100 micrograms (0.5 mL), is recommended one to six months after the second dose, with a booster (fourth) dose of 50 micrograms (0.25 mL) three to six months after the additional (third) dose.

Heterologous booster: A 50-microgram (0.25 mL) dose of the Moderna vaccine can be used as a booster dose, after a complete primary series of COVID-19 vaccines from another platform included in the WHO Emergency Use Listing (EUL).

Additional information is available at: <https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-mRNA-1273-2021.3>.

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