

COVID-19

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

Twenty-third report

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CANADA

- As of 20 August 2021, 36,004,467 doses of the COVID-19 vaccine of Pfizer-BioNTech, 12,643,463 doses of the Moderna vaccine, and 2,780,120 doses of the AstraZeneca and the Covishield vaccine (AstraZeneca manufactured by the Serum Institute of India) had been administered.
- There were 13,474 individual reports of adverse events following immunization (0.026% of doses administered). Of these, 3,549 reports were of serious events (0.007% of doses administered).
- Of total reports, 35,969 reports were of adverse events following immunization (AEFI), of which 13,474 were for one or more events; the majority of these were for non-serious events such as injection-site reactions, paresthesia, headache, pruritus, dyspnea, fatigue, nausea, etc.

Number of reports and reporting rate (reports per 100,000 doses administered) of adverse events, by vaccine, as of 20 August 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	5,225	14.51	2,262	6.28	7,487	20.79
Moderna	3,461	27.37	591	4.67	4,052	32.05
Covishield and AstraZeneca	1,210	43.52	552	19.86	1,762	63.38
Unknown	29	-	144	-	173	-
Total	9,925	18.28	3,549	6.49	13,474	24.78

Number of reports and reporting rate (reports per 100,000 doses administered) of the main serious AEFI, by vaccine,, as of 20 August 2021

Vaccine	Pfizer-BioNTech	Moderna	Covishield and AstraZeneca
Anaphylaxis	130 (0.36/100,000)	30 (0.23/100,000)	-
Thrombosis with thrombocytopenia syndrome (TTS)	15 (0.04/100,000)	3 (0.02/100,000)	60 (2.16/100,000)
Guillain-Barré syndrome	25 (0.07/100,000)	12 (0.09/100,000)	29 (1.04/100,000)
Capillary leak syndrome	-	-	2 (0.07/100,000)
Myocarditis/pericarditis	303 (0.84/100,000)	236 (1.84/100,000)	16 (0.58/100,000)
Fatal events	180* post-vaccination deaths		

**Following a medical review of the 180 deaths, it was determined that 70 were not linked to administration of the COVID-19 vaccine, while 40 are still under investigation; 6 are considered to be potentially attributable to the vaccination (cases of TTS), and 64 could not be classified due to insufficient information.*

Following is an analysis of 555 of the 557 cases of myocarditis/pericarditis, including information on the vaccine administered:

Vaccine	Total number of cases (rate per 100,000 doses administered)	By sex/median age		Number of reports per doses administered		
		Number of women (median age)	Number of men (median age)	1st	2nd	Unknown
Pfizer-BioNTech	303 (0.84)	116 (42 years)	184 (21 years)	148	117	38
Moderna**	236 (1.84)	54 (34 years)	176 (26 years)	50	161	25
Covishield/AstraZeneca	16 (0.58)	Not indicated	Not indicated	Not indicated	Not indicated	Not indicated

*In three cases, the sex of the individual was not specified.

** In three cases, the sex of the individual was not specified, and in one case the sex was given as "other."

In two cases, the name of the vaccine was not specified.

Source: Public Health Agency of Canada. Canadian COVID-19 vaccination safety report. Ottawa: Public Health Agency of Canada; 27 August 2021. <https://health-infobase.canada.ca/covid-19/vaccine-safety/>. Data reproduced by PAHO/WHO.

URUGUAY

- From 27 February to 15 July 2021, 993 people reported a total of 1,645 AEFI, out of a total of 4,466,346 doses of the three vaccines available in the country administered, with adverse events representing 0.037% of doses administered.
- For the CoronaVac vaccine, reported AEFI represented 0.02% of doses administered, while for both Pfizer-BioNTech and AstraZeneca, AEFI amounted to 0.06% of doses administered.
- The most frequently reported AEFI were injection-site pain, headache, muscle aches, malaise, diarrhea, tremor, and bronchospasm.
- As of 15 July, 9 cases of serious AEFI (mostly deep-vein thrombosis) had been confirmed, representing 0.0002% of total doses administered. Another five AEFI are still under investigation and have not yet been confirmed. These include two reports of myocarditis in adolescents; of these, one individual was discharged, while the other is in recovery and doing well.

Sources:

<https://www.gub.uy/ministerio-salud-publica/sites/ministerio-salud-publica/files/documentos/noticias/Comunicado%20ESAVI%2010.8.2021%20%281%29.pdf>

Consolidated number of reported adverse events and reporting rate (reports per 100,000 doses administered), by vaccine, for countries in the Americas that reported to the UMC or publicly+ as of 31 July 2021*

Vaccine	Total doses administered	Total events	Total events/ 100,000 doses	Total serious events	Total serious events/ 100,000 doses
AstraZeneca	75,639,965	19,117	25.3	3,212	4.2
Bharat Biotech	183,119	133	72.6	68	37.1
CanSino	506,385	182	35.9	8	1.6
Gamaleya	11,065,770	41,480	374.8	83	0.8
Janssen	17,042,378	46,971	275.6	4,444	26.1
Moderna	152,450,919	202,671	132.9	17,830	12.0
Pfizer-BioNTech	269,863,200	297,040	110.1	46,790	17.3
Sinopharm	8,327,213	8,642	103.8	56	0.7
Sinovac (Coronavac)	82,662,433	9,391	11.4	1,912	2.3
TOTAL	679,227,608	636,218	93.7	75,742	11.2

+ Countries included in the table are: Argentina, Barbados, Plurinational State of Bolivia, Brazil, Canada, Chile, Colombia, Costa Rica, Ecuador, El Salvador, United States, Honduras, Jamaica, Mexico, Panama, Paraguay, Peru, Saint Vincent and the Grenadines, Uruguay, and Bolivarian Republic of Venezuela.

*Indicates doses administered by countries reporting adverse events.

Sources:

COVID-19 Vaccination in the Americas. Available at: https://ais.paho.org/imm/IM_DosisAdmin-Vacunacion.asp. Accessed 30 July 2021.

Adverse events: VigiBase database information as of 31 July; public country sources (epidemiological bulletins); and PAHO country reports.

FDA Approves First COVID-19 Vaccine

On 23 August 2021, the U.S. Food and Drug Administration (FDA) approved the first COVID-19 vaccine. The vaccine has been known as the Pfizer-BioNTech COVID-19 Vaccine, and will now be marketed as Comirnaty, for the prevention of COVID-19 disease in individuals 16 years of age and older. The vaccine also continues to be available under emergency use authorization (EUA), including for individuals 12 through 15 years of age and for the administration of a third dose in certain immunocompromised individuals.

The terms of the authorization to market the vaccine include requirements that the company conduct active surveillance studies in the U.S. and Europe related to reported cases of myocarditis and pericarditis. The company is also being required to submit prospective studies to assess the incidence of subclinical myocarditis, following administration of a second dose of Comirnaty in participants 5 to 15 years of age, and following administration of a third dose of Comirnaty in a subgroup of participants 16 to 30 years of age.

Source: <https://www.fda.gov/news-events/press-announcements/fda-approves-first-covid-19-vaccine>

Joint Statement from Health and Human Services (HHS) Public Health and Medical Experts on COVID-19 Booster Shots

On 18 August 2021, the U.S. Food and Drug Administration (FDA) released a joint statement with experts from the Department of Health and Human Services (HHS), stating that the COVID-19 vaccines authorized in the United States continue to be remarkably effective in reducing risk of serious disease, hospitalization, and death, even against the widely circulating Delta variant.

Available data indicate that protection against SARS-CoV-2 infection begins to decline over time, following the initial vaccination doses, with indications of reduced protection against mild infection and moderate disease. Current protection against serious illness, hospitalization, and death could diminish in the months ahead, especially among those who are at higher risk or were vaccinated during the earlier phases of the vaccination rollout. For that reason, they conclude that a booster dose will be needed to maximize vaccine-induced protection and prolong its durability.

The FDA and the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices will conduct an independent evaluation and determination of the safety and efficacy of a third dose of the Pfizer and Moderna mRNA vaccines, after which it will issue booster dose recommendations.

They estimate that, beginning the week of 20 September, and starting eight months after an individual's second dose, booster shots will be offered for all Americans, prioritizing healthcare workers, nursing home residents, and other seniors. In addition, they estimate that booster shots will likely be needed for people who received the Johnson & Johnson (J&J) vaccine, and are awaiting additional data to be submitted by the company for confirmation.

In addition, the statement emphasized the urgency of vaccinating the unvaccinated in the U.S. and around the world.

Source: <https://www.fda.gov/news-events/press-announcements/joint-statement-hhs-public-health-and-medical-experts-covid-19-booster-shots>

CECMED grants emergency use authorization to the Soberana 02 and Soberana Plus vaccines

Having completed evaluation of the Soberana 02 subunit conjugate vaccine for COVID-19, and the Soberana Plus non-Thimerosal protein subunit vaccine for COVID-19, manufactured by Cuba's Finlay Institute of Vaccines, CECMED granted Emergency Use Authorization to the two vaccines, in accordance with current regulatory provisions. This approval is based on results obtained from phase I, II, and III clinical trials, as well as from the intervention study in at-risk groups and populations, and from health interventions. Preliminary analysis of results of the phase III clinical trial of the Soberana 02 vaccine candidate demonstrated that administration of a two-dose homologous regimen was 61.9% effective in preventing symptomatic disease, and 91.2% effective when administered in a heterologous regimen that included a third dose of the Soberana Plus vaccine candidate.

The approved vaccination schedule for the population over 19 years of age combines two doses of Soberana 02 and a third dose with Soberana Plus.

Source: <https://www.cecmed.cu/noticias/aprueba-cecmed-autorizo-uso-emergencia-vacunas-cubanas-soberana-02-soberana-plus>

Immune Response to Sinovac-CoronaVac Vaccine

Sinovac's CoronaVac COVID-19 vaccine was given emergency use authorization for a two-dose schedule, with an interval of 14 to 28 days between doses. As has been seen with other COVID-19 vaccines, a longer interval between doses gives a stronger antibody response.

Published results of Chile's mass vaccination campaigns, in which approximately 10.2 million people were vaccinated with two doses of CoronaVac, showed a vaccine effectiveness in the 18-year-old and older population of 65.9% against symptomatic infection, 87.5% against hospitalization, 90.3% against ICU admission, and 86.3% against death. Similar results were observed in Uruguay.

In a recent pre-print article, results of a study conducted in China with 540 participants indicate that two doses of the CoronaVac vaccine, at intervals of 14 and 28 days, produce a very strong immune response. However, levels of neutralizing antibodies against COVID-19 decline over time, and six to eight months after the second dose, the level of antibodies could be considered insufficient to maintain protection (a minimum level of protection against COVID-19 has not yet been established), though there may be protection through T-cell- and B-cell-mediated immunity. According to this study, a third dose administered six months after the second dose appears to be highly effective in replenishing

the SARS-CoV-2 specific immune response, with a significant increase in antibodies. There were fewer adverse reactions to the third dose than in previous studies.

Although it appears that there will be a need for a third dose, the timing for administering it will depend on several factors, such as the local epidemiological situation, vaccine supply, disease risk, and other relevant factors, bearing in mind that at present the priority is to vaccinate as many people as possible with the two-dose schedule.

Sources:

<https://www.minsal.cl/wp-content/uploads/2021/08/Dosis-de-refuerzo-en-la-campana-de-vacunacion-contra-SARS-CoV-2-en-Chile.pdf>

Pan H, Wu Q, Zeng G, et al. Immunogenicity and safety of a third dose, and immune persistence of CoronaVac vaccine in healthy adults aged 18–59 years: interim results from a double-blind, randomized, placebo-controlled phase 2 clinical trial. (2021) medRxiv 2021.07.23.21261026; doi: <https://www.medrxiv.org/content/10.1101/2021.07.23.21261026v1>

[Small study in Singapore appears to show that COVID-19 vaccines induce potent immune response in people who had been infected with the SARS virus](#)

People who were infected nearly two decades ago with the virus that causes severe acute respiratory syndrome (SARS) appear to generate a potent antibody response after being vaccinated against COVID-19, according to a recent publication in the New England Journal of Medicine, which reports results of a study that analyzed the immune response of eight participants in Singapore who had recovered from SARS nearly two decades ago and who were vaccinated with the Pfizer-BioNTech COVID-19 vaccine. These participants were found to produce elevated levels of neutralizing antibodies against both viruses, even after a single dose of the vaccine.

They also produced a broad spectrum of neutralizing antibodies against three worrisome variants of SARS-CoV-2 prevalent in the current pandemic — Alpha, Beta, and Delta — and five bat and pangolin sarbecoviruses. No similarly potent and wide-ranging antibody response has been seen in blood samples taken from other fully vaccinated individuals, even those who had also contracted COVID-19.

Sources:

Decades-old SARS virus infection triggers potent response to COVID vaccines. Nature.

Tan C-W, Chia W-N, Young BE, Zhu F, et al. Pan-Sarbecovirus Neutralizing Antibodies in BNT162b2-Immunized SARS-CoV-1 Survivors. 2021/08/18. New England Journal of Medicine. <https://www.nejm.org/doi/full/10.1056/NEJMoa2108453>

India's National Regulatory Authority Authorizes First DNA COVID-19 Vaccine

India's national regulatory authority, the Central Drugs Standard Control Organization, granted emergency use authorization for the ZyCoV-D DNA COVID-19 vaccine, manufactured by Zydus Cadila Healthcare, in individuals aged 12 years and older, using a three-dose intradermal immunization schedule. This is the first DNA COVID-19 vaccine to be authorized for emergency use.

Source: Over 25000 people impacting lives across 4 continents. Zydus Cadila

Interim Statement on COVID-19 Vaccine Booster Doses (WHO/SAGE), 10 August 2021

WHO, with support of the Strategic Advisory Group of Experts (SAGE) on Immunization and its COVID-19 Vaccines Working Group, is reviewing the emerging evidence on the need for and timing of an additional vaccine dose (booster dose 1) for the currently available COVID-19 vaccines which have received Emergency Use Listing (EUL).

Rationale for booster doses

There are several reasons why COVID-19 vaccine booster doses may be needed:

- (i) waning protection (immunity) against infection or disease, in particular severe disease;
- (ii) reduced protection against variant(s) of concern (VOC); or
- (iii) inadequate protection from the currently recommended primary series for some risk groups for which evidence from the phase 3 clinical trials may have been lacking.

The rationale for booster doses may differ by vaccine product, epidemiological setting, risk group, and vaccine coverage rates.

Factors to consider

1. Waning immunity

Neither an immune correlate of protection nor an immune correlate for the duration of protection has been established to date. Studies suggest a correlation between the efficacy of different vaccines against symptomatic disease and mean neutralizing antibody titers induced by those vaccines (1). However, it is unclear whether declining titers over time (since vaccination) are indicative of declining vaccine effectiveness, especially against VOCs. While data on immunogenicity of some vaccines suggest that antibodies persist for at least 6 months (2), waning of neutralizing antibodies has been reported (3). Although there may be a loss of protection against infections by SARS-CoV-2, protection against severe disease is likely to be largely retained due to cell-mediated immunity (1).

2. Vaccine effectiveness

Data are currently insufficient to determine if there is a significant decline in vaccine effectiveness against any form of clinical illness from SARS-CoV-2 infection beyond 6 months after vaccination. However, some reduction in vaccine effectiveness has been reported for some VOCs. Data from Israel suggest that around 40% of breakthrough infections are in immunocompromised individuals (4). While breakthrough infections are still expected, the vast majority are less severe than those seen in unvaccinated people (5).

3. Global vaccine supply and global and national equity

National vaccination program policy decisions to add a booster dose should take into account the strength of evidence regarding the need for these doses and global availability of vaccines. Offering booster doses to a large proportion of a population when many have not yet received even a first dose undermines the principle of national and global equity. Prioritizing booster doses over speed and breadth in the initial dose coverage may also damage the prospects for global mitigation of the pandemic, with severe implications for the health, social, and economic well-being of people globally.

Data needed for policy-making

The introduction of booster doses should be evidence-driven. The duration of vaccine-induced protection is likely to depend on many variables, such as the vaccine product, the primary vaccination schedule, the age and/or underlying medical conditions of the vaccinated person, risk of exposure, and circulation of specific variants. The decision to recommend a booster dose is complex and requires, beyond clinical and epidemiological data, a consideration of national strategic and programmatic aspects, and importantly an assessment of the prioritization of globally limited vaccine supply. In this context, prioritization should be given to the prevention of severe disease. Data needs can be grouped into the following categories:

1. Assessing the need for booster doses:

- Epidemiology of breakthrough cases and disease severity by age, co-morbidity, and risk groups, exposure, type of vaccine and time since vaccination, and in the context of variants of concern (VOCs).
- Efficacy, effectiveness, duration of protection of vaccines in the context of SARS-CoV-2 wild-type and VOCs from observational studies and randomized controlled trials.
- Supplementary evidence from immunological studies assessing neutralizing antibodies over time, as well as biomarkers of cellular immunity when possible.

2. Assessing the performance of booster doses:

- Immunogenicity, efficacy, effectiveness, and duration of protection of original and variant-adapted vaccine booster doses in the context of SARS-CoV-2 wild-type and VOCs.
- Safety and reactogenicity.

3. Additional considerations:

- Optimal timing of the booster dose,
- consideration of homologous versus heterologous boosters,
- possibility of smaller booster doses,

- booster needs in previously infected individuals,
- specification and prioritization of high-risk populations,
- programmatic feasibility and sustainability,
- promotion of global equity.

Conclusions

In the context of ongoing global vaccine supply constraints, the administration of booster doses will exacerbate inequities by driving up demand and consuming scarce supply while priority populations in some countries, or subnational settings, have not yet received a primary vaccination series. The focus for the time being remains on increasing global vaccination coverage with the primary series (either one or two doses for current EUL vaccines).

Introducing booster doses should be firmly evidence-driven and targeted to the population groups in greatest need. The rationale for implementing booster doses should be guided by evidence on waning vaccine effectiveness, in particular a decline in protection against severe disease in the general population or in high-risk populations, or due to a circulating VOC. To date, the evidence remains limited and inconclusive on any widespread need for booster doses following a primary vaccination series. WHO is carefully monitoring the situation and will continue to work closely with countries to obtain the data required for policy recommendations.

References:

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- (2) Emary KRW, Golubchik T, Aley PK, Ariani CV, Angus B, Bibi S et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): an exploratory analysis of a randomized controlled trial. *Lancet*. 2021;397:1351-62.
- (3) Widge AT, Roupheal NG, Jackson LA, Anderson EJ, Roberts PC, Makhene M et al. Durability of Responses after SARS-CoV-2 mRNA-1273 Vaccination. *N Engl J Med*. 2021;384:80-2. doi: 10.1056/NEJMc2032195
- (4) Whitaker H, Tsang R, Byford R, Andrews N, Sherlock J, Pillai S et al. Pfizer-BioNTech and Oxford AstraZeneca COVID-19 vaccine effectiveness and immune response among individuals in clinical risk groups. 2021.
- (5) Bergwerk M, Gonen T, Lustig Y, Amit S, Lipsitch M, Cohen C et al. Covid-19 Breakthrough Infections in Vaccinated Health Care Workers. *New England Journal of Medicine*. 2021. doi: 10.1056/NEJMoa2109072

Source: <https://www.who.int/news/item/10-08-2021-interim-statement-on-covid-19-vaccine-booster-doses>

Alert by the Public Health Institute of Chile on suspension of a lot of the CanSino COVID-19 vaccine

The Public Health Institute of Chile (ISP) published pharmaceutical alert 13/21, related to the withdrawal of lot NCOV202103009H of the CanSino COVID-19 vaccine Convidicea, expiration date 23 March 2022, once it was verified that some of the lot's units contained a lower volume of vaccine than the stated volume (0.5 ml). The ISP suspended distribution and use of the lot, and confirmed that none of the defective units had been administered to the population. According to the information provided by the manufacturer, a 0.4 ml dose contains an infectious viral titer (IFU/ml) higher than the lower limit specified for this vaccine, and its use would not affect the efficacy of the vaccine.

Source: <https://www.ispch.cl/wp-content/uploads/2021/07/Scan13-07-2021-161212.pdf>

Additions to the WHO Emergency Use Listing (EUL)

WHO has added the following additional production sites for Moderna's COVID-19 vaccine to the Emergency Use Listing (EUL):

COVID-19 vaccine (EUL)	Authorizing NRA	Authorized sites added to the EUL list		
		EUL holder*	Manufacturers of finished product	Authorizing NRA
mRNA (nucleoside- modified)	European Medicines Agency (EMA)	ModernaTX, Inc.	Baxter Pharmaceutical Solutions LLC, U.S.A. Catalent Indiana, LLC, U.S.A.	Food and Drug Administration (FDA), U.S.A.

*Authorization holder

Authorizing NRA: The National Regulatory Authority that first authorized the vaccine and is responsible for its oversight.

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

Adverse Events of Special Interest (AESI) and related risks: Thrombosis with thromboembolism syndrome (TTS)

Definition

Refers to the formation of a blood clot in one of the body's large veins. Most often this formation occurs in the lower limb. The blood clot (thrombus) can block some or all of the blood flow. Thrombosis is a serious condition, due mainly to the high risk of developing a pulmonary thromboembolism, which occurs in a third of patients with thrombosis and has a high mortality rate.

Risk factors and diseases

Risk factors: Acquired (vitamin K deficiency, liver disease, disseminated intravascular coagulation, and severe liver disease); hereditary (antithrombin deficiency, dysfibrinogenemia, factor V Leiden mutation, protein C deficiency, protein S deficiency, prothrombin mutation 20210A); clinical (advanced age, hospitalization for acute medical illness, long-haul flights [duration >4 hr.], obesity, pregnancy [including the postpartum period]; surgical (central venous access, major surgery, orthopedic surgery, trauma or fracture).

Diseases: Antiphospholipid syndrome, congestive heart failure, inflammatory bowel disease, malignancy, myeloproliferative disorders, myocardial infarction, polycythemia vera, previous venous thromboembolism (VTE), sepsis, stroke, and varicose veins.

Medications: Drug-induced: oral contraceptive pills, administration of intravenous immunoglobulin, antipsychotic drugs; antiestrogens, chemotherapy, heparin-induced thrombocytopenia, high-dose progestogen therapy, hormone replacement therapy, oral contraceptives, vaginal ring for birth control, strontium ranelate, thalidomide, and lenalidomide.

Vaccines: In acute viscerotropic disease associated with yellow fever vaccine, disseminated intravascular coagulation (increased prothrombin time or activated partial thromboplastin time with increased fibrinogen degradation products) and bleeding have been observed.

Sources:

Miriam Sturkenboom, Tuur Egbers, Carlos Durán. Coagulation Disorders Event Definition Form, Access vACCine COVID-19. https://docs.google.com/document/d/1a_omRtQjNcHOsT55ctE3KNBT2VgMA5eZ/edit#

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Associação Portuguesa de Hemofilia e outras Coagulopatias Congênitas. Boletim Hemophilia. <http://aphemofilia.pt/medicamentos-indicacoes/>

Chris Parker, Carol Coupland, Julia Hippisley-Cox. Antipsychotic drugs and risk of venous thromboembolism: nested case-control study. BMJ 2011; 342 doi: <https://doi.org/10.1136/bmj.d112> (published 10 January 2011)

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Brazil: Ministry of Health Manual de vigilância epidemiológica de eventos adversos pós-vacinação, 2020. http://bvsms.saude.gov.br/bvs/publicacoes/manual_vigilancia_epidemiologica_eventos_vacinacao_4ed.pdf

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