

COVID-19

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

Thirtieth report

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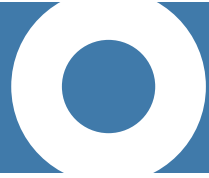
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Note to readers: As of the publication of this report, of 8 November 2021, number 30 in the series, future reports will be issued monthly. We reiterate our commitment to continue developing and sharing updates on evidence regarding consolidated regional and global information on adverse events following immunization (AEFI) against COVID-19 and other updates.



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BRAZIL (State of Rio Grande do Sul)

- In the period from 18 January to 18 September 2021, a total of 13,053,922 doses of COVID-19 vaccines were administered in the State of Rio Grande do Sul: 6,126,758 doses of Covishield (Oxford/AstraZeneca/Fiocruz), 4,125,951 doses of CoronaVac (Sinovac/Butantan), 2,500,115 doses of Comirnaty (Pfizer/Wyeth), and 301,098 doses of the Janssen-Cilag (Ad26.COV2-S [recombinant]) vaccine.
- From 18 January to 18 September 2021, there were 13,020 reports of suspected adverse events following immunization (AEFI) (0.1% of doses administered). Of these, 2,016 involved immunization errors, 1,074 reported a diagnosis of COVID-19, and 9,930 were confirmed AEFI.
- The number of reports, by producing laboratory, were: 7,009 for Covishield (Oxford/AstraZeneca/Fiocruz), 2,222 for CoronaVac (Sinovac/Butantan), 542 for Comirnaty (Pfizer/Wyeth), and 157 for the Janssen-Cilag vaccine. Incidence per 100,000 doses administered was as follows: 114.4 for Covishield, 53.9 for CoronaVac, 21.7 for Comirnaty, and 52.1 for Janssen-Cilag.
- A higher number of reported adverse events were in women (7,358) than in men (2,572).
- Among the 9,930 individuals who reported at least one adverse event, a total of 27,762 events (signs and symptoms) were reported.

AEFI	Covishield (AstraZeneca/ Fiocruz)		CoronaVac (Sinovac/ Butantan)		Comirnaty (Pfizer/Wyeth)		Janssen-Cilag		Total	
	N*	Rate**	N	Rate	N	Rate	N	Rate	N	Rate
Non-serious	19,911	325.0	5,345	129.5	1,387	55.5	415	137.8	27,058	207.3
Serious	311	5.1	328	7.9	51	2.0	14	4.6	704	5.4
Total	20,222	330.1	5,673	137.4	1,438	57.5	429	142.4	27,762	212.7

* N = number of events

** Rate per 100,000 doses administered

- In terms of the severity of the adverse events, 27,058 (97.5%) were classified as non-serious, and 704 (2.5%) as serious.
- Among the non-serious adverse events, the most common ones associated with the Covishield (AstraZeneca/Fiocruz) vaccine were fever, headache, myalgia, chills, and nausea; for CoronaVac (Sinovac/Butantan), headache, myalgia, diarrhea, fever, and sore throat; for Comirnaty (Pfizer/Wyeth), headache, myalgia, fever, cough, and nausea; and for the Janssen-Cilag vaccine, the most common adverse events were fever, headache, myalgia, fatigue, and chills.

- The highest incidence of reported serious events temporally associated with vaccination for the Covishield (AstraZeneca/Fiocruz) vaccine were headache, fever, dyspnea, death, and Guillain-Barré syndrome; for CoronaVac (Sinovac/Butantan), death, dyspnea, cerebrovascular accidents (CVA), acute myocardial infarction (AMI), and fever; for Comirnaty (Pfizer/Wyeth), headache, vomiting, myelitis, and fever; and for the Janssen-Cilag vaccine, headache, neurological disorders, dysarthria, dysphagia, and acute disseminated encephalomyelitis.
- A total of 120 thromboembolic events were reported. These included 83 cases (1.35/100,000 doses administered) after vaccination with the Covishield (AstraZeneca/Fiocruz) vaccine, 28 (0.28/100,000 doses) with CoronaVac (Sinovac/Butantan), 6 (0.24/100,000 doses) with Comirnaty (Pfizer/Wyeth), and 3 (1.00/100,000 doses) after vaccination with the Janssen-Cilag vaccine. Among the cases clinically classified as thromboembolic events were 45 cases of cerebrovascular accidents, 3 cases of acute myocardial infarction, 2 cases of pulmonary thromboembolism, 9 cases of thrombophlebitis, and 61 cases of thrombosis, including deep vein thrombosis, limb arterial thrombosis, mesenteric venous thrombosis, cerebral thrombosis, embolism and thrombosis of unspecified veins, embolism and other aortic thrombosis, and unspecified thrombosis.
- There were 190 reported deaths, of which 186 are still under investigation. Of the four deaths investigated for which causality was determined, one remains unclassifiable due to lack of supplementary data, one was temporally associated with vaccination, and two, which were inconsistent or coincident with vaccination, were determined not have a causal relationship with the vaccines, due to pre-existing or emerging conditions.

Source: <https://coronavirus.rs.gov.br/upload/arquivos/202110/18094756-boletim-eapv-04-2021.pdf>.

CANADA

As of 5 November 2021, 40,654,538 doses of the Pfizer-BioNTech COVID-19 vaccine, 14,254,199 doses of the Moderna vaccine, and 2,787,374 doses of the AstraZeneca/Covishield vaccine (AstraZeneca vaccine manufactured by the Serum Institute of India) had been administered.

A total of 22,280 individual reports of one or more AEFI (0.038% of doses administered) were received. Of these, 5,699 reports involved serious AEFI (0.010% of doses administered).

In all, 59,370 adverse events following immunization were reported (22,280 reports involving one or more events). Most of the adverse events were non-serious, and included paresthesia, injection-site reactions, headache, pruritus, fatigue, dyspnea, urticaria, erythema, etc.

Number of reports and reporting rate (per 100,000 doses administered) of adverse events, by vaccine, as of 5 November 2021

Vaccine	Number of reports of non-serious AEFI		Number of reports of serious AEFI		Total number of reports of AEFI	
	N	Rate per 100,000 doses administered	N	Rate per 100,000 doses administered	N	Rate per 100,000 doses administered
Pfizer-BioNTech	8,771	21.57	3,795	9.33	12,566	30.91
Moderna	5,690	39.92	1,016	7.13	6,706	47.05
Covishield/AstraZeneca	2,086	74.63	702	25.11	2,788	99.74
Unknown	34	-	186	-	220	
Total	16,581	28.73	5,699	9.88	22,280	38.61

Number of reports and reporting rate (per 100,000 doses administered) of adverse events, by vaccine, as of 5 November 2021

	Vaccine		
AESI	Pfizer-BioNTech	Moderna	Covishield/AstraZeneca
Anaphylaxis	406 (1.00/100,000)	111 (0.78/100,000)	21 (0.75/100,000)
Thrombosis with thrombocytopenia syndrome (TTS)	18 (0.04/100,000)	6 (0.04/100,000)	63 (2.25/100,000)
Guillain-Barré syndrome	41 (0.10/100,000)	21 (0.15/100,000)	35 (1.25/100,000)
Myocarditis/pericarditis	613 (1.51/100,000)	374 (2.62/100,000)	21 (0.75/100,000)
Bell's palsy/facial paralysis	427 (1.05/100,000)	138 (0.97/100,000)	45 (1.61/100,000)
Category: Autoimmune disease	62 (0.15/100,000)	31 (0.22/100,000)	73 (2.61/100,000)
Category: Cardiovascular system	704 (1.73/100,000)	411 (2.88/100,000)	35 (1.25/100,000)
Category: Circulatory system	467 (1.15/100,000)	152 (1.07/100,000)	350 (12.52/100,000)
Category : Central and peripheral nervous systems	534 (1.31/100,000)	177 (1.24/100,000)	84 (3.10/100,000)
Fatal events	208* post-vaccination deaths		
* Following a medical review of the 208 deaths, it was determined that 79 were not linked to administration of the COVID-19 vaccine; 47 are still under investigation, of which 7 (cases of TTS) are considered to be potentially attributable to vaccination, while 82 could not be classified due to insufficient information.			

Source: Public Health Agency of Canada. Canadian COVID-19 vaccine safety report. Ottawa: Public Health Agency of Canada. November 5, 2021. <https://health-infobase.canada.ca/covid-19/vaccine-safety/>. Data reproduced by PAHO/WHO.

COLOMBIA

- In the October bulletin of INVIMA, which covers the reporting period for adverse events following immunization (AEFI) from 17 February to 15 October 2021, there were 23,625 reports of AEFI, out of a total 44,350,661 doses of vaccines administered, representing a reporting rate of 53 per 100,000 doses administered.
- The distribution of reports, by vaccine manufacturer, as of 15 October 2021 was: 13,284 reports for the Pfizer vaccine (95.3 per 100,000 doses administered), 5,223 for SinoVac (33.4 per 100,000 doses administered), 2,385

for AstraZeneca (36.2 per 100,000 doses administered), 1,648 for Janssen (18.7 per 100,000 doses administered), 1,041 for Moderna (5.5 per 100,000 doses administered), and 44 reports for which the vaccine manufacturer was not identified.

- The distribution of events, by sex, was 71% in women and 29% in men. Of reported events, 22,675 (96%) were classified as non-serious and 950 (4%) as serious.
- The most frequently reported signs and symptoms were headache (25.1%), injection-site pain (11.1%), dizziness (9.2%), muscle pain (9.0%), fever (8.4%), and malaise (8%).

Source: <https://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/VS/ED/boletin6-farmacovigilancia-vacunas-oct2021.pdf>.

UNITED STATES

- As of 10 November 2021, following the administration of more than 401 million doses of mRNA vaccines (Pfizer-BioNTech and Moderna) in the United States, only two cases of thrombosis with thrombocytopenia syndrome (TTS), associated with the Moderna vaccine, had been reported to VAERS. Given the available information, there does not appear to be an increased risk of TTS following vaccination with mRNA COVID-19 vaccines.
- As of 27 October, more than 15.5 million doses of the J&J/Janssen COVID-19 vaccine had been administered. The Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) have identified 48 confirmed reports of people who received the J&J/Janssen vaccine and subsequently developed TTS. Women under the age of 50 should be alerted to the rare but increased risk of this adverse event. There are other COVID-19 vaccine options available for which this risk has not been seen.
- Following the administration of more than 15.5 million doses of the Janssen vaccine, approximately 244 preliminary reports of Guillain-Barré syndrome had been identified, as of 27 October 2021. These cases have mostly been reported approximately two weeks after vaccination and primarily in men, many ages 50 and older.
- As of 27 October, VAERS had received 1,784 reports of myocarditis or pericarditis among people 30 years of age or younger who had received a COVID-19 vaccine. Most cases have been reported after mRNA COVID-19 vaccination (Pfizer-BioNTech or Moderna), particularly in male adolescents and young adults.
- Reports of deaths following vaccination with COVID-19 vaccines are rare. More than 423 million doses of COVID-19 vaccines were administered in the United States between 14 December 2020 and 1 November 2021. During this time, VAERS received 9,367 reports of death (0.0022%) among people who received a COVID-19 vaccine.

Source: <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html>.

PARAGUAY

- On 29 October, the thirty-fourth AEFI surveillance report of the Paraguayan Ministry of Health indicated that, during the period from 22 March to 29 October, 5,289,784 doses of COVID-19 vaccines had been administered to 2,919,120 people.
- Between 22 February 29 October 2021, there were 2,325 reports of AEFI (0.05% of total doses administered). Of these, 379 cases were considered serious.
- Among the AEFI reported, 71.7% (1,667) were in women; 68.7% (1,610) were in people between the ages of 25 and 49. Additionally, among all AEFI reported, 49.3% (1,149) were for people who received the AstraZeneca vaccine, followed by 15.1% (352) for the Sputnik V vaccine, 14.1% (330) for the Pfizer/BioNTech vaccine, 7.8% (182) for CoronaVac, 6.7% (156) for COVAXIN, 4.6% (108) for Moderna, and 2.1% (49) for the Sinopharm vaccine.

Source: <https://pai.msps.gov.py/esavis-2021/>.

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

Anaphylactic and nonanaphylactic reactions to SARS-CoV-2 vaccines: a systematic review and meta-analysis

A systematic review and meta-analysis of anaphylactic and nonanaphylactic reactions following SARS-CoV-2 vaccines in the general adult population was published on 16 October. Its objective was to estimate the incidence rates of anaphylactic and nonanaphylactic reactions after COVID-19 vaccines and to describe the demographic and clinical characteristics, triggers, presenting signs and symptoms, treatment, and clinical course of confirmed cases. The authors searched electronic databases (Proquest, Medline, Embase, Pubmed, CINAHL, Wiley online library, and Nature) for English-language entries from 1 December 2020 to 31 May 2021. Of the 1,734 articles identified, 26 were included in the systematic review (8 case reports, 5 cohort studies, 4 case series, 2 randomized controlled trials, and one randomized cross-sectional study), while 14 articles were included in the meta-analysis (one cohort study, 2 case series, one randomized controlled trial, and one randomized cross-sectional study). Studies involving 26,337,421 vaccine recipients (Pfizer-BioNTech [n = 14,505,399] and Moderna [n = 11,831,488]) were analyzed. The overall pooled prevalence estimate of anaphylactic reactions to both vaccines was 5.0 (95% CI 2.9 to 7.2, $I^2 = 81%$, $p = < 0.0001$), while the overall pooled prevalence estimate of nonanaphylactic reactions to both vaccines was 53.9 (95% CI 0.0 to 116.1, $I^2 = 99%$, $p = < 0.0001$). Vaccination with Pfizer-BioNTech resulted in higher anaphylactic reactions compared to Moderna (8.0, 95% CI 0.0 to 11.3, $I^2 = 85%$ versus 2.8, 95% CI 0.0 to 5.7, $I^2 = 59%$). However, lower incidence of nonanaphylactic reactions was associated with Pfizer-BioNTech compared to Moderna (43.9, 95% CI 0.0 to 131.9, $I^2 = 99%$ versus 63.8, 95% CI 0.0 to 151.8, $I^2 = 98%$). Across the included studies, the most commonly identified risk factors for anaphylactic and nonanaphylactic reactions to SARS-CoV-2 vaccines were female sex and personal history of atopy. Previous history of anaphylaxis and comorbidities such as asthma, allergic rhinitis, atopic and contact eczema/dermatitis and psoriasis, and cholinergic urticaria were also found to be important. The authors

conclude that the prevalence of COVID-19 mRNA vaccine-associated anaphylaxis is very low, while nonanaphylactic reactions occur at a higher rate; cutaneous reactions, however, are largely self-limited. Neither anaphylactic nor nonanaphylactic reactions should discourage vaccination.

Source: Alhumaid S, Al Mutair A, Al Alawi Z, et al. Anaphylactic and nonanaphylactic reactions to SARS-CoV-2 vaccines: a systematic review and meta-analysis. *Allergy Asthma Clin Immunol.* 2021 Oct 16;17(1):109. doi: 10.1186/s13223-021-00613-7. PMID: 34656181; PMCID: PMC8520206. Available at:

<https://aacijournal.biomedcentral.com/articles/10.1186/s13223-021-00613-7>.

Systemic autoimmune myopathies: A prospective phase 4 controlled trial of an inactivated virus vaccine against SARS-CoV-2

On 19 October, an online pre-print cohort study, with a control group, was published, with the objective of evaluating immunogenicity and safety of an inactivated SARS-CoV-2 vaccine in systemic autoimmune myopathies (SAMs) and the possible influence of baseline disease parameters, comorbidities, and therapy on immune response. This prospective controlled study included 53 patients with SAMs and 106 non-immunocompromised individuals as a control group (CTRL). All participants received two doses of the CoronaVac-Sinovac vaccine (28-day interval). Immunogenicity was assessed by anti-SARS-CoV-2 S1/S2 IgG seroconversion (SC), anti-S1/S2 IgG geometric mean titer (GMT), factor increase GMT (FI-GMT), neutralizing antibodies (NAb) positivity, and median neutralizing activity after each vaccine dose (D0 and D28) and six weeks after the second dose (D69). Participants with pre-vaccination positive IgG serology and/or NAb and those with RT-PCR-confirmed COVID-19 during the protocol were excluded from immunogenicity analysis. Patients and CTRL were of comparable sex ($P>0.99$) and age ($P=0.90$). Immunogenicity of 37 patients and 79 CTRL-naïve participants revealed, at D69, a moderate but significantly lower SC (64.9% vs 91.1%, $P<0.001$), GMT (7.9 [95%CI 4.7–13.2] vs 24.7 [95%CI 30.0–30.5] UA/ml, $P<0.001$) and frequency of NAb (51.4% vs 77.2%, $P<0.001$). Median neutralizing activity was comparable in both groups (57.2% [interquartile range (IQR) 43.4–83.4] vs 63.0% [IQR 40.3–80.7], $P=0.808$). Immunosuppressives were less frequently used among NAb+ patients vs NAb- patients (73.7% vs 100%, $P=0.046$). Type of SAMs, disease status, other drugs, or comorbidities did not influence immunogenicity. Vaccine-related adverse events were mild, with similar frequencies in patients and CTRL ($P>0.05$). The authors conclude that, based on this study, CoronaVac-Sinovac is safe and has a moderate short-term immunogenicity in SAMs, but reduced compared with CTRL. They further identified that immunosuppression is associated with diminished NAb positivity.

Source: Shinjo SK, by Souza FHC, Borges IBP, et al. Systemic autoimmune myopathies: A prospective phase 4 controlled trial of an inactivated virus vaccine against SARS-CoV-2. *Rheumatology (Oxford).* 2021 Oct 19;keab773. doi: 10.1093/rheumatology/keab773. Pre-print e-pub. PMID: 34664616. Available at:

<https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keab773/6402018>.

Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine in a subgroup of healthy adults in Chile

On 19 September, an online pre-print article was published, reporting safety and immunogenicity results obtained for healthy Chilean adults aged ≥ 18 in a phase 3 clinical trial of the inactivated COVID-19 vaccine CoronaVac. Volunteers randomly received two doses of CoronaVac or placebo, separated by two weeks; 434 volunteers were enrolled, 397 aged 18-59 years, and 37 aged ≥ 60 years. Solicited and unsolicited adverse reactions were registered from all volunteers. Blood samples were obtained from a subset of volunteers and analyzed for humoral and cellular measures of immunogenicity. The primary adverse reaction in the 434 volunteers was pain at the injection site, with a higher incidence in the vaccine than in the placebo arm. Adverse reactions observed were mostly mild and local. No severe adverse events were reported. The humoral evaluation was performed on 81 volunteers. Seroconversion rates for specific anti-S1-RBD IgG were 86.67% in the 18-59 age group and 70.37% in the ≥ 60 age group, two and four weeks after the second dose. A significant increase in circulating neutralizing antibodies was detected two and four weeks after the second dose. The cellular evaluation was performed on 47 volunteers. The authors detected a significant induction of T-cell responses characterized by the secretion of IFN-gamma upon stimulation with Mega Pools of peptides from SARS-CoV-2. The authors conclude that immunization with CoronaVac in a 0-14 schedule in Chilean adults aged ≥ 18 is safe, induces anti-S1-RBD IgG with neutralizing capacity, activates T-cells, and promotes the secretion of IFN-gamma upon stimulation with SARS-CoV-2 antigens.

Source: Bueno SM, Abarca K, González PA, et al. Safety and Immunogenicity of an Inactivated SARS-CoV-2 Vaccine in a Subgroup of Healthy Adults in Chile. *Clin Infect Dis*. 2021 Sep 19:ciab823. doi: 10.1093/cid/ciab823. Pre-print e-pub. PMID: 34537835. Available at:

<https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab823/6372423>.

Reactogenicity to a third dose of mRNA vaccine (BNT162b2) in immunocompromised individuals and people over 60 years of age – a nationwide survey in Israel

On 24 September, an online pre-print retrospective cohort study, without a control group, was published. The objective of the study was to evaluate reactogenicity of the BNT162b2 vaccine, after administering a third dose to immunocompromised individuals and people 60 years old or older (approved in Israel on 13 July 2021). A retrospective cohort, using electronic surveys sent to booster vaccine recipients, between 20 July and 10 August 2021, was analyzed. A total of 17,820 people participated in the survey, with a response rate of 30.2%; 3,195 (17.9%) were immunocompromised. Fatigue, myalgia, and fever were the most frequent systemic side effects reported (19.6%, 9.2%, and 8.1%, respectively among immunocompromised; 21.3%, 9.9%, and 9.2%, respectively among seniors). 67.3% of immunocompromised and 62% of seniors reported experiencing a better or a similar response to the third dose, compared to the second. The authors conclude that local and systemic reactions after a third vaccination with SARS-CoV-2 vaccine BNT162b, reported by immunocompromised and seniors, were similar to those observed following previous vaccines and mostly self-resolved. These findings may aid in promoting confidence among vaccine providers and recipients.

Source: Shapiro Ben David S, Shamir-Stein N, Baruch Gez S, et al. Reactogenicity of a third BNT162b2 mRNA COVID-19 vaccine among immunocompromised individuals and seniors - A nationwide survey. Clin Immunol. 2021 Sep 24;232:108860. doi: 10.1016/j.clim.2021.108860. Pre-print e-pub. PMID: 34571262; PMCID: PMC8461972. Available at:

<https://www.sciencedirect.com/science/article/pii/S1521661621001972?via%3Dihub>.

Inclusion of an additional vaccine on the WHO Emergency Use Listing (EUL)

On 3 November 2021, the World Health Organization added the Covid-19 vaccine COVAXIN from Bharat Biotech International Limited to the Emergency Use List (EUL). Following are further details on the authorization:

COVID-19 vaccine (EUL)	Authorized site added to the WHO/EUL		
	Emergency use authorization holder	Responsible NRA*	Presentation
COVAXIN (whole inactivated virus vaccine)	Bharat Biotech International Limited, India	Central Drugs Standard Control Organization	1-, 5-, 10-, and 20-dose vials

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

Additional information on the clinical trial is available at: <https://extranet.who.int/pqweb/vaccines/who-recommendation-bharat-biotech-international-ltd-covid-19-vaccine-whole-virion>.

WHO Interim Recommendation for Use of the Bharat Biotech COVAXIN vaccine against COVID-19

The Bharat Biotech vaccine (BBV152) is a whole virion inactivated SARS-CoV-2 virus vaccine, adsorbed to alum and formulated with a toll-like receptor (TLR) 7/8 agonist (Imidazoquinoline gallamide [IMDG]), and the preservative 2-phenoxyethanol. The vaccine is given in two doses, separated by four weeks.

Inactivated vaccines have been used for diseases such as seasonal influenza, polio, and hepatitis A. Inactivated vaccines cannot replicate and therefore cannot infect individuals. IMDG and alum are adjuvants added to enhance immunogenicity. IMDG is a novel adjuvant that has not been used in any previous vaccine. Studies generally demonstrate that TLR 7/8 agonists enhance Th1 responses and inhibit Th2 responses, which is considered beneficial for COVID-19 vaccines. In addition, CD8 T-cell responses may be increased when using TLR 7/8 agonists as adjuvants.

For the phase 3 trial of the BBV152 vaccine, participants aged ≥ 18 years of age were recruited; An interim analysis was conducted including data to 17 May 2021, when the median follow-up period (14 or more days post dose 2) was 99 days. During the follow-up period, the Delta variant was the predominantly circulating virus.

Vaccine efficacy (VE) against COVID-19 vaccine of any severity, 14 or more days post dose 2, was 78% (95% CI: 65–86).

- In adults aged <60 years, VE was 79% (95% CI: 66–88); and
- in those aged ≥ 60 years it was 68% (95% CI: 8–91).

There was one case of severe COVID-19 in the vaccinated group versus 15 in the placebo group (VE 93% [95% CI: 57–99]). VE against symptomatic SARS-CoV-2 infection was 64% (95% CI: 29–82).

BBV152 vaccine demonstrated an acceptable safety and reactogenicity profile in adults aged ≥ 18 years, including those aged ≥ 60 years (and those with comorbidities associated with an increased risk of progressing to severe/critical COVID-19). In line with other inactivated vaccines, hypersensitivity reactions following immunization with BBV152 were rare and usually non-serious. Severe allergic (anaphylactic) reactions have not been reported in BBV152 clinical studies to date.

The data reviewed by WHO support the conclusion that the known benefits of BBV152 vaccine outweigh the risks that are known or considered possible. Therefore, WHO recommended the use of BBV152 in those aged ≥ 18 years.

Source: WHO. Interim recommendation for use of the Bharat Biotech BBV152 COVAXIN vaccine against COVID-19. Available at: <https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-bbv152-covaxin>.

AEFI reported to Chile's National Center for Pharmacovigilance (CNFV) since the start of the vaccination campaign in the six-to-eleven-year-old age group with inactivated SARS-CoV-2 vaccine (CoronaVac)

Between the start of the vaccination campaign on 13 September, and 7 October 2021, 643,204 doses of CoronaVac vaccine were administered in children between the ages of 6 and 11. The CNFV database recorded 71 reports of AEFI in this age group during the period. Of these, the CoronaVac vaccine was determined to be the suspected cause of 66 reported cases (representing 0.011% of total doses administered); in six cases the vaccine manufacturer was not identified.

Of reported AEFI, 42.7% were in women and 57.3% in men. Four cases were reported as severe (5.6% of the total), including one case of acute disseminated encephalomyelitis, one seizure, one case of synovitis/arthritis, and one case of anaphylaxis.

The 71 reported cases included 51 different adverse events, for a total of 157 events. The 10 most commonly reported events were vomiting (13), pruritus and erythema at the injection site (12), headache and injection-site pain (11), fever (8), urticaria (7), and seizures, syncope, and malaise (6). AEFI continue to be closely monitored.

Source: ISP. ESAVI reportados al Centro Nacional de Farmacovigilancia (CNFV) desde el inicio de la campaña de vacunación en el grupo etario de 6 a 11 años con la vacuna SARS-CoV-2 inactivada (CoronaVac) en Chile. Available at: <https://www.ispch.cl/wp-content/uploads/2021/10/20211021-Informe-estadistico-ESAVI-ninos-6-y-11-anos-VFinal.pdf>.

At present there are no additional updates to the most recent bulletin on conclusive analyses of AEFI.

WHO alert on falsified Pfizer-BioNTech COVID-19 vaccine

On 4 November 2021, the World Health Organization (WHO) published, on its website, Alert No. 6/2021, related to the falsification of Pfizer COVID-19 vaccine, identified in the Islamic Republic of Iran in October 2021. The genuine manufacturer of Pfizer-BioNTech COVID-19 vaccine has confirmed that the product listed in the Alert is falsified. The falsified product was reported at the patient level outside authorized and regulated supply chains and authorized vaccination programs in the Islamic Republic of Iran.

The products identified in the Alert were confirmed to be falsified based on: the fact that the product label and artwork are inconsistent with genuine Pfizer-BioNTech COVID-19 vaccines; and the expiration date on the labels (9/2021) is falsified and inconsistent with the expiration date on genuine Pfizer-BioNTech COVID-19 Vaccine Lot EH9899.

Summary of information on WHO falsified vaccine Alert No. 6/2021

Data indicated on the samples	
Name	Pfizer-BioNTech COVID-19
Manufacturer	Pfizer-BioNTech
N° doses	Not indicated
Lot indicated	EH9899
Date of manufacture	Not indicated
Expiration date	9/2021
Language of text and packaging	English



This alert is available at: <https://www.who.int/news/item/04-11-2021-medical-product-alert-n-6-2021-falsified-pfizer-biontech-covid-19-vaccine>.

WHO alert on falsified AstraZeneca COVID-19 vaccine

On 4 November 2021, the World Health Organization (WHO) published, on its website, Alert No. 7/2021, related to the falsification of AstraZeneca COVID-19 vaccine, identified in the Islamic Republic of Iran in October 2021. The genuine manufacturer of AstraZeneca COVID-19 (ChAdOx1-S [recombinant]) vaccine has confirmed that the product is

falsified. The falsified product was reported at the patient level outside authorized and regulated supply chains and authorized immunization programs in the Islamic Republic of Iran.

The falsified products are illicitly refilled vials of used and discarded genuine COVID-19 AstraZeneca (ChAdOx1-S [recombinant]) vaccine. The metal cap on samples of these falsified products displays evidence of tampering, indicating the metal cap was removed in order to refill the vials, and later replaced onto the vial.

Below is a summary table of the falsified vaccine data, adapted from the information published by WHO in this Alert, along with images of the identified samples.

Summary of information on WHO falsified vaccine Alert No. 7/2021

Name	COVID-19 AstraZeneca (ChAdOx1-S [recombinant]) vaccine
Manufacturer	AstraZeneca
N° doses	10 doses (5 ml)
Lot	Not indicated
Date of manufacture	Not indicated
Expiration date	Not indicated
Language of text and packaging	English



This alert is available at: <https://www.who.int/news/item/04-11-2021-medical-product-alert-n-7-2021-falsified-covid-19-vaccine-astrazeneca>.

Considerations on the falsified vaccines

Given the recent regional and global alerts issued by NRAs in the Americas, and by WHO, on incidents involving falsification of COVID-19 vaccines, WHO is issuing the following recommendations for countries' consideration.

These falsified vaccines are difficult to detect, as they may appear indistinguishable from genuine vaccine. There is therefore a risk they could be illicitly or accidentally inserted into the regulated supply chain or authorized national immunization programs.

Reused and refilled vials may sometimes be identified by physical examination. Some indicators that a vial is falsified and may have been illicitly refilled may include: labels show signs of damage; the metal cap is dented, scratched or broken; rubber seals are scratched or punctured; foreign materials/particles are visible inside the vial; visible signs that the expiration date has been changed or tampered with; the expiration date does not match the authentic batch number; and/or the product is available for private sale outside of authorized immunization programs.

Due to the high risk of discarded vials being recovered, it is essential that they be safely disposed of at the site where they are used. Applying reverse logistics as a possible alternative, if the safe treatment and disposal of vaccine residues cannot be guaranteed, they could be transferred to a location established for that purpose. Failing that, consideration could be given to the possibility of discarded vaccine vials being crushed, if a safe way to do so is available. WHO requests increased vigilance within the supply chains of countries and regions likely to be affected by these falsified products. Increased vigilance should include hospitals, clinics, health centers, wholesalers, distributors, pharmacies, and any other suppliers of medical products, as they could be affected by the introduction of falsified products.

It is important to remind health professionals and the general public that all medical products, including COVID-19 vaccines, must be obtained from authorized providers and from national immunization programs. The products' authenticity and physical condition should be carefully checked.

National regulatory health authorities are advised to immediately notify WHO if these falsified products are discovered in their country. Any information concerning the manufacture, distribution, or supply of these products should be reported by contacting rapidalert@who.int.

Sources:

1. World Health Organization. Medical Product Alert N°7/2021: Falsified COVID-19 Vaccine AstraZeneca. Available at: <https://www.who.int/news/item/04-11-2021-medical-product-alert-n-7-2021-falsified-covid-19-vaccine-astrazeneca>.

- World Health Organization. COVID-19 vaccination: supply and logistics guidance: interim guidance, 12 February 2021. Available at: <https://www.paho.org/en/documents/covid-19-vaccination-supply-and-logistics-guidance-interim-guidance-12-february-2021>.

Adverse Events of Special Interest (AESI) and related risks: Vaccine-associated enhanced disease (VAED)

Vaccine-associated enhanced disease (VAED) falls within the immunological category of AESI. VAED occurs when an individual who has received a vaccine develops a more severe presentation of that disease when subsequently exposed to the virus, compared to when infection occurs without prior vaccination. This assumes that the vaccine recipient has not previously been exposed to the disease and is seronegative at the time of immunization. In particular, vaccine-associated enhanced respiratory disease (VAERD or simply ERD) refers to disease with predominant involvement of the lower respiratory tract, or as part of a systemic process.

The case definition for VAED presents three levels of diagnostic certainty:

- Level 1 (definitive case): A definitive case of VAED cannot be ascertained with current knowledge of the mechanisms of pathogenesis of VAED.
- Level 2 (probable): Ascertainment is based on confirmed infection, with known criteria of previous serological status (2A, highest level of certainty) or without previously known (2B, lower certainty) serostatus, clinical and epidemiologic criteria, and available histopathology.
- Level 3 (possible): Ascertainment is based on confirmed or suspected infection, known (3A higher level of certainty) or unknown (3B lower level of certainty) serostatus, clinical and epidemiologic criteria, but no histopathology findings.

VAED risk factors:

Diseases and other factors: Severe disease has been documented resulting from infection in individuals primed with non-protective immune responses against the respective wild-type viruses. VAED typically presents with symptoms related to the target organ of the infection pathogen.

Vaccines in general: VAED or VAERD may occur at any time after vaccination. The timing of occurrence of clinical manifestations of VAED or VAERD after vaccination will be dependent on the mechanism or pathophysiologic pathway leading to disease enhancement after natural infection. VAED or VAERD may present within 2–4 weeks of natural infection, if the expected initial antibody responses are inadequate; or may present at a later time (>1 month or longer) after natural infection if antibody waning is noted or if the mechanism is not exclusively antibody mediated. Classic examples of VAED are atypical measles and enhanced respiratory syncytial virus (RSV) occurring after administration of inactivated vaccine for these pathogens. No single or combination of specific confirmatory tests is available to

diagnose VAED. As the clinical manifestations of VAED lies within the spectrum of natural disease – occurring more frequently and/or severely in vaccinated individuals – it is also difficult to separate vaccine failure (also called breakthrough disease) from VAED in vaccinated individuals. All cases of vaccine failure should be investigated for VAED. Vaccine failure is defined as the occurrence of the specific vaccine-preventable disease in a person who is appropriately and fully vaccinated, taking into consideration the incubation period and the normal delay for the protection to be acquired as a result of immunization.

Sources:

Brighton Collaboration. Vaccine-associated enhanced disease: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data [Internet]. BC; 2020 [cited 29 Oct 2021]. Available at: <https://brightoncollaboration.us/vaed/>.

Munoz FM, Cramer JP, Dekker CL, et al. Vaccine-associated enhanced disease: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine*. 2021;39(22): 3053–3066. <https://doi.org/10.1016/j.vaccine.2021.01.055>.

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