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

Twenty-fourth report

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ARGENTINA

- As of 31 July 2021, 32,187,823 doses of COVID-19 vaccines had been administered. A total of 50,463 adverse events following immunization (AEFI) were reported to the Integrated Health Information System of Argentina (SIISA).

  Details, by vaccine, are shown in the following table:

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

Vaccine	Doses administered	AEFI reported	Reporting rate of AEFI/100,000 doses
AstraZeneca and Covishield	11,145,461	2,999	26.91
Sinopharm	9,673,401	2,384	24.64
Sputnik V	11,368,961	41,545	365.42
Unknown	-	3,535	-
Total	32,187,823	50,463	156.78

Source: Fourteenth Vaccine Safety Surveillance Report, Ministry of Health of Argentina

Of total AEFI reported, 136, or 0.3%, were considered serious events (cases requiring hospitalization), of which 46 were associated with the AstraZeneca/Covishield vaccine, 15 with the Sinopharm vaccine, and 75 with the Sputnik V vaccine.

Related serious events	Vaccine	
	Sputnik V	AstraZeneca/Covishield
Thrombosis with thrombocytopenia syndrome (TTS)	1	5
Guillain-Barré syndrome	3	1
Pericarditis	1	
Immune thrombocytopenia	3	
Thrombotic thrombocytopenic purpura	1	
Coronary thrombosis		1

Of the events classified as related events, fever and headache with myalgia and arthralgia were the most frequent diagnoses.

Source: https://www.argentina.gob.ar/coronavirus/vacuna/equipos-salud/informes-seguridad

CANADA

- As of 3 September 2021, 37,153,868 doses of the COVID-19 vaccine of Pfizer-BioNTech, 13,057,703 doses of the Moderna vaccine, and 2,784,340 doses of the AstraZeneca and Covishield vaccine (AstraZeneca manufactured by the Serum Institute of India) had been administered.
- There were 14,743 individual reports of one or more adverse events following immunization (0.027% of doses administered). Of these, 4,005 were considered serious events (0.007% of doses administered).
- A total of 39,247 AEFI were reported (of which 14,743 were for one or more events). The most frequently reported AEFI were 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 3 September 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	5,547	14.93	2,599	7.00	8,146	21.93
Moderna	3,752	28.73	681	5.22	4,433	33.95
Covishield and AstraZeneca	1,406	50.50	577	20.72	1,983	71.22
Unknown	33	-	148	-	181	-
Total	10,738	19.77	4,005	7.28	14,743	27.05

Number of reports and reporting rate (reports per 100,000 doses administered) of adverse events, by vaccine, as of 3 September 2021			
Vaccine	**Pfizer-BioNTech**	**Moderna**	**Covishield and AstraZeneca**
Anaphylaxis	132 (0.36/100,000)	30 (0.23/100,000)	0
Thrombosis with thrombocytopenia syndrome (TTS)	16 (0.04/100,000)	4 (0.03/100,000)	61 (2.19/100,000)
Guillain-Barré syndrome	30 (0.08/100,000)	15 (0.11/100,000)	30 (1.08/100,000)
Capillary leak syndrome	-	-	2 (0.07/100,000)
Myocarditis/pericarditis	384 (1.03/100,000)	276 (2.09/100,000)	16 (0.57/100,000)
Bell's palsy/facial paralysis	310 (0.83/100,000)	100 (0.76/100,000)	43 (1.54/100,000)
Fatal events	188* post-vaccination deaths		
Following a medical review of the 188 deaths, it was determined that 73 were not linked to administration of the COVID-19 vaccine, while 38 are still under investigation; 6 are considered to be potentially attributable to the vaccination (cases of TTS), and 71 could not be classified due to insufficient information.			

An analysis of 676 of the 678 cases of myocarditis/pericarditis, with indication of the vaccine administered, is shown below:

Vaccine	Total number of cases (rate per 100,000 doses administered)	By sex/median age		Number of reports, by doses administered		
		Number of women (median age)	Number of men (median age)	1st	2nd	Unknown
Pfizer-BioNTech*	384 (1.03)	145 (40 years)	235 (23 years)	173	162	49
Moderna**	276 (2.09)	70 (32 years)	202 (28 years)	57	187	32
Covishield and AstraZeneca	16 (0.57)	NA	NA	NA	NA	NA

* In five 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."

Source: Public Health Agency of Canada. Canadian COVID-19 vaccine safety report. Ottawa: Public Health Agency of Canada; September 10, 2021. https://health-infobase.canada.ca/covid-19/vaccine-safety/. Data reproduced by PAHO/WHO.

New COVID-19 variant of interest, named “Mu”

On 30 August 2021, the World Health Organization (WHO) designated variant B.1.621 as a variant of interest (VOI). It was given the WHO label "Mu," and includes the descendant Pango lineage B.1.621.1. This variant has mutations that indicate potential properties of immune escape. Preliminary data show a reduction in neutralization capacity of convalescent and vaccine sera similar to that seen for the Beta variant, but this needs to be confirmed by further studies.

Since its first identification in Colombia in January 2021, there have been a few sporadic reports of cases of the Mu variant, and some larger outbreaks have been reported from other countries in South America and in Europe. Although the global prevalence of the Mu variant among sequenced cases has declined and is currently below 0.1%, the prevalence in Colombia (39%) and Ecuador (13%) has consistently increased. The reported prevalence should be interpreted with due consideration of sequencing capacities and timeliness of sharing of sequences, both of which vary between countries. More studies are required to understand the phenotypic and clinical characteristics of this variant. The epidemiology of the Mu variant in South America, particularly with the co-circulation of the Delta variant, will be monitored for changes.

Source: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---31-august-2021

Israeli Study on safety of the Pfizer-BioNTech BNT162b2 mRNA COVID-19 vaccine

An observational case-control study conducted in Israel, based on integrated payer-provider health care records, evaluated the safety of the Pfizer-BioNTech BNT162b2 mRNA COVID-19 vaccine. Potentially serious post-immunization adverse events, including myocarditis, pericarditis, arrhythmia, deep-vein thrombosis, pulmonary embolism, myocardial infarction, intracranial hemorrhage, and thrombocytopenia, were considered in the 42 days following vaccination, compared with the risks for these events in people infected with SARS-CoV-2. The vaccinated and control groups each included a mean of 884,828 people with no previous diagnosis of the events being evaluated.

The results of the study indicate that SARS-CoV-2 infection was associated with a substantially increased risk of serious adverse events, including myocarditis, pericarditis, arrhythmia, deep-vein thrombosis, pulmonary embolism, myocardial infarction, intracranial hemorrhage, and thrombocytopenia. Administration of the Pfizer-BioNTech COVID-19 vaccine was not associated with an elevated risk of most of the adverse events examined, except for an increased risk of myocarditis (1 to 5 events per 100,000 people), which remains relatively low compared with the risk observed in cases of SARS-CoV-2 infection (11.0 events per 100,000 people).

Source: Noam Barda, Noa Dagan, Yatir Ben-Shlomo, Eldad Kepten, et al. Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. NEJM. August 25, 2021. DOI: 10.1056/NEJMoa2110475
Available at: https://www.nejm.org/doi/pdf/10.1056/NEJMoa2110475?articleTools=true

ANVISA requests information from Pfizer-BioNTech, Janssen, and Butantan on booster doses of their respective vaccines

At the end of August, ANVISA asked Pfizer-BioNTech, Janssen, and the Butantan Institute for additional information on the booster doses of their respective vaccines. This request was made in anticipation of a decision on the need, in Brazil, for an additional dose of COVID-19 vaccine.

This information includes ongoing studies on the topic, along with scientific and regulatory data to aid in decision-making.

To date, there is no conclusive data on the need to add a booster to the vaccination regimen in Brazil.

Source: https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2021/anvisa-solicita-ao-butantan-informacoes-sobre-doses-de-reforco

Resurgence of SARS-CoV-2 Infection in a Highly Vaccinated Health System Workforce

In a recent letter to the editor of the New England Journal of Medicine, SARS-CoV-2 infections in healthcare workers at the University of California San Diego Health (UCSDH) are reported to coincide with the end of California's mask mandate and the rapid dominance of the B.1.617.2 (Delta) variant, and accounted for over 95% of UCSDH isolates by the end of July. Between 1 March 31 July, 227 healthcare workers tested positive for SARS-CoV-2 by PCR assay; of these, 130 (57.3%) were fully vaccinated, and symptoms were present in 109 (83.8%) of these. Of the 90 unvaccinated individuals, 80 (88.9%) exhibited symptoms.

Of workers in the UCSDH system, 83.1% have been vaccinated with an mRNA vaccine (Pfizer-BioNTech or Moderna). In July, the case rate for symptomatic SARS-CoV-2 infection among vaccinated individuals was 5.7 per 1,000 individuals and 16.3 per 1,000 among unvaccinated individuals, indicating a vaccine effectiveness of 65.5%. Compared with the month of June, which had a vaccine efficacy rate of 94.3%, there was a 30% decline in effectiveness. The dramatic change in vaccine effectiveness from June to July is likely due to the emergence of the Delta variant and waning immunity over time, compounded by the end of masking requirements in California and the resulting increased risk of exposure in the community.

Source: Keehner J, Horton LE, Binkin NJ, et al. Resurgence of SARS-CoV-2 Infection in a Highly Vaccinated Health System Workforce. 2021/09/01, New England Journal of Medicine. DOI: 10.1056/NEJMc 2112 981.
https://www.nejm.org/doi/full/10.1056/NEJMc2112981

Bell's palsy following vaccination with Pfizer-BioNTech mRNA and inactivated (CoronaVac) SARS-CoV-2 vaccine

On 16 August, a study was published assessing the risk of Bell's palsy following vaccination with Pfizer-BioNTech and CoronaVac BNT162b2 vaccines, using data from the COVID-19 Vaccine Adverse Event Reporting system in Hong Kong, and a nested case-control study.

Between 23 February and 4 May 2021, 451,939 people received a first dose of the CoronaVac vaccine, and 537,205 people received a first dose of BNT162b2. There were 28 clinically confirmed reports to the Hong Kong adverse event reporting system of cases of Bell's palsy after administration of the CoronaVac vaccine, and 16 reported cases after administration of the BNT162b2 vaccine. The age-standardized incidence of clinically confirmed cases of Bell's palsy following vaccination with the CoronaVac vaccine was 66.9 cases per 100,000 people/year (95% CI 37.2 to 96.6) and 42.8 per 100,000 people/year (95% CI 19.4 to 66.1) for those who had received the BNT162b2 vaccine. The age-standardized difference for the incidence compared with the background population was 41.5 (95% CI 11·7 to 71·4) for CoronaVac and 17.0 (95% CI −6·6 to 40.6) for BNT162b2, equivalent to an additional 4.8 cases per 100,000 people vaccinated for CoronaVac and 2.0 cases per 100,000 people vaccinated for BNT162b2.

A nested case-control study using conditional logistic regression was also conducted to estimate the odds ratio (OR) for the risk of Bell's palsy and vaccination. Cases and controls were matched (1:4) by age, sex, place, and date of admission. In the nested case-control analysis, 298 cases were matched to 1,181 controls, and the adjusted ORs were 2.385 (95% CI 1.415 to 4.022) for CoronaVac and 1.755 (95% CI 0.886 to 3.477) for BNT162b2. These findings suggest an overall increased risk of Bell's palsy following vaccination with the CoronaVac vaccine. However, the beneficial and protective effects of the inactivated COVID-19 vaccine far outweigh the risk of this generally self-limiting adverse event. Additional studies are needed to confirm these findings.

Source: Bell's palsy following vaccination with mRNA (BNT162b2) and inactivated (CoronaVac) SARS-CoV-2 vaccines: a case series and nested case-control study. The Lancet. Published: 16 August 2021. https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00451-5/fulltext

Cutaneous and hypersensitivity reactions associated with COVID-19 vaccination – a narrative review

This narrative review, published on 23 August, analyzed cutaneous and hypersensitivity adverse events related to SARS-CoV-2 vaccination, from local reactions in the arm to systemic and serious reactions such as anaphylaxis. Vaccination may also induce or exacerbate pre-existing disorders such as herpes zoster infection. This review provides relevant clinical information on dermatological conditions. However, it emphasizes that there is general consensus that the benefits of SARS-CoV-2 vaccination currently outweigh the risks of possible adverse events.

Source: Wollina U, Chiriac A, Kocic H, et al. Cutaneous and hypersensitivity reactions associated with COVID-19 vaccination – a narrative review. Wien Med Wochenschr (2021).

Nervous and muscular adverse events after COVID-19 vaccination: a systematic review and meta-analysis of clinical trials

On 23 August, a systematic review and meta-analysis of clinical trials on the incidence of nervous and muscular adverse events (NMAEs) after COVID-19 vaccination, through 2 June 2021, was published. In 15 Phase 1/2 trials identified, NMAEs occurred in 29.2% of vaccinated participants, versus 21.6% in controls ($p < 0.001$), with headache and myalgia being the most frequent NMAEs. In four open-label trials, the incidence of headache, myalgia, and unsolicited NMAEs was 38.7%, 27.4%, and 1.5%, respectively. Following vaccination in Phase 3 trials, headache and myalgia were still common, with a rate of 29.5% and 19.2%, although the unsolicited NMAEs, with incidence rates of ≤ 0.7%, were not different from the control group in each study. The study concluded that after vaccination, NMAEs are common, with headache and myalgia comprising a considerable proportion of events, although life-threatening unsolicited events are rare. The authors suggest that NMAEs should be continuously monitored during the ongoing global COVID-19 vaccination program.

Source: Chen J, Cai Y, Chen Y, et al. Nervous and Muscular Adverse Events after COVID-19 Vaccination: A Systematic Review and Meta-Analysis of Clinical Trials. Vaccines, 2021, 9(8), 939. Doi:10.3390/vaccines9080939. https://www.mdpi.com/2076-393X/9/8/939

Cardiovascular Adverse Events Reported from COVID-19 Vaccines: A Study Based on WHO Database

On 27 July, a study was published analyzing cardiovascular adverse events following COVID-19 vaccination reported to the global VigiBase database.

For the cardiovascular system, 4,863 AEFI were reported for BNT162b2 Pfizer, AstraZeneca, Moderna, and other COVID-19 vaccines. Common adverse events observed with vaccines under study were tachycardia (16.41%), flushing (12.17%), hypertension (5.82%), hypotension (3.60%) and peripheral coldness (2.41%). Based on disproportionality analysis (IC025 values), acute myocardial infarction, cardiac arrest, and circulatory collapse were linked to the vaccines in the >75 years age group. Hypertension, severe hypertension, supraventricular tachycardia, sinus tachycardia, and palpitations were associated with all age groups and both sexes. In addition, abnormal ECG findings and increases in C-reactive protein, D-dimer, and troponin were reported.

It should be emphasized that this is a descriptive analysis, and that causality was not analyzed. Cardiovascular events of this type need to be monitored, and studies conducted to gain an understanding of causality.

Source: Jeet Kaur R, Dutta S, Charan J, Bhardwaj P, Tandon A, Yadav D, Islam S, Haque M. Cardiovascular Adverse Events Reported from COVID-19 Vaccines: A Study Based on WHO Database. Int J Gen Med. 2021;14:3909–3927. https://doi.org/10.2147/IJGM.S324349

European Medicines Agency and the European Centers for Disease Prevention and Control highlight considerations for additional and booster doses of COVID-19 vaccines

On 2 September 2021, the European Medicines Agency (EMA) and the European Centers for Disease Prevention and Control (ECDC) published a technical report stating that, based on current evidence, there is no urgent need to administer booster doses of vaccines to fully vaccinated individuals in the general population. The report also notes that additional doses should already be considered for people with severely weakened immune systems, as part of their primary vaccination.

Evidence on vaccine effectiveness and duration of protection shows that all vaccines authorized in the EU/EEA are currently highly protective against COVID-19-related hospitalization, severe disease, and death. In the EU/EEA, approximately one in three adults over the age of 18 is not yet fully vaccinated. In this situation, the priority now should be to vaccinate all those eligible individuals who have not yet completed their recommended vaccination schedule. To complement vaccination efforts, it is also crucial to continue applying measures such as physical distancing, hand and respiratory hygiene, and using face masks where needed, in particular in high-risk settings such as long-term care facilities or hospital wards with patients at risk of severe COVID-19.

It is important to distinguish between booster doses for people with normal immune systems and additional doses for those with weakened immune systems. Some studies report that an additional vaccine dose can improve the immune response in immunocompromised individuals, such as organ transplant recipients who initially had a low response to vaccination. In such cases, the option of administering an additional dose now should be considered. Consideration could also be given to providing an additional dose, as a precautionary measure, to older frail individuals, in particular those living in closed settings such as residents of long-term care facilities.

Member States need to prepare for possible adaptations to their vaccination program should a substantial decrease in vaccine effectiveness be noted in one or more population groups.

Source: https://www.ema.europa.eu/en/news/ecdc-ema-highlight-considerations-additional-booster-doses-covid-19-vaccines

The European Medicines Agency reviews cases of multisystem inflammatory syndrome

The EMA's Safety Committee (PRAC) is assessing whether there is a risk of multisystem inflammatory syndrome (MIS) with COVID-19 vaccines, in light of a report of MIS following administration of the Pfizer-BioNTech's Comirnaty vaccine. The case occurred in a 17-year old male in Denmark who has since fully recovered.

As of 19 August, a number of cases of MIS were also reported in the EEA following vaccination with other COVID-19 vaccines: five cases associated with the Comirnaty vaccine, one with Spikevax (Moderna), and one with the Janssen vaccine.

MIS is a serious inflammatory condition affecting many parts of the body, and symptoms can include tiredness, persistent severe fever, diarrhea, vomiting, stomach pain, headache, chest pain, and difficulty breathing. Multisystem inflammatory syndrome has previously been reported following COVID-19 disease. The Danish patient, however, had no history of COVID-19. MIS is rare and its incidence rate before the COVID-19 pandemic, estimated from 5 European countries, was around 2 to 6 cases per 100,000 per year in children and adolescents below 20 years of age, and less than 2 cases per 100,000 per year in adults aged 20 years and older.

At this stage, there is no change to the current EU recommendations for the use of COVID-19 vaccines. The PRAC recommends that all health professionals report any cases of MIS and other adverse events in people receiving these vaccines.

Source: https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-30-august-2-september-2021

Update on SARS-CoV-2 Variants of Concern

In the Weekly Epidemiological Update on COVID-19, Issue 54, published on 24 August 2021, the World Health Organization included an update on emerging evidence of the phenotypic impact of Variants of Concern (VOCs) of SARS-CoV-2, as it relates to their transmissibility, severity of disease, risk of reinfection, and effect on diagnosis. The following table presents, in adapted form, the information included in the above report.

Summary of the phenotypic impact* of WHO variants of concern (VOCs)

	Alpha	Beta	Gamma	Delta
Transmissibility	Increased transmissibility and secondary attack rate	Increased transmissibility	Increased transmissibility	Increased transmissibility and secondary attack rate. Similar transmissibility between vaccinated and unvaccinated individuals.
Disease severity	Increased risk of hospitalization, and possible increased risk of severity and mortality	Not confirmed: possible increased risk of hospital mortality	Not confirmed: possible increased risk of hospitalization	Increased risk of hospitalization
Risk of reinfection	Neutralizing activity is preserved; risk of reinfection remains similar	Reduction in neutralizing activity; T cell response triggered by D614G virus remains effective	Report of moderate reduction in neutralizing activity	Report of moderate reduction in neutralizing activity
Effect on diagnosis	Limited impact: S gene target failure (SGTF); no impact on the overall outcome of multitarget	No impact on RT-PCR or Ag-RDT has been observed	None reported to date	None reported to date

	RT-PCR; no impact was observed in the Ag-RDT			

* Generalized findings as compared to previous/co-circulating variants. Based on emerging evidence, including non-peer-reviewed preprint articles and reports, all subject to ongoing investigation and revision.

Source: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---24-august-2021

Chile's Institute of Public Health Expands CoronaVac Vaccine Age Group to Include Children Age 6 and Older

On 6 September 2021, Chile's Public Health Institute (ISP) reported that it was expanding the age range of the emergency use authorization for the CoronaVac vaccine, initially authorized for individuals age 18 and older, to include children 6 years old and older. According to the ISP, existing data indicate a good immune response to the vaccine in this age group, and reported AEFI for the pediatric population in clinical studies, and in emergency use in China, have been mostly non-serious and consistent with the known information on this vaccine.

In regard to the authorization for children between ages 3 and 5, the ISP indicated that the experts convened to assess such an authorization agreed on the need for additional data, which they anticipate will be provided by the Phase III studies being conducted in Chile, led by the Pontifical Catholic University of Chile.

Source: https://www.ispch.cl/noticia/isp-aprueba-ampliacion-del-rango-etario-para-administrar-la-vacuna-coronavac-en-menores-desde-los-6-anos-de-edad/

Update to the Alert on Falsified Covishield COVID-19 vaccine

On 31 August 2021, the World Health Organization (WHO) issued an update on its website to Alert No. 5/2021, regarding falsification of the Covishield COVID-19 vaccine made by the Serum Institute of India Pvt. Ltd, identified in Africa and Asia, between July and August 2021. The update includes information on a batch of 5 ml (10-dose) vaccine, identified in Myanmar, in which the name appears, misspelled, as "Covisheld," rather than Covishield. Below is a table summarizing the falsified batches, adapted from information published by WHO in the alert, along with images of the samples identified in Myanmar.

Summary of information on falsified batches -- WHO alert No. 5/2021

Information on the samples of the falsified product			
Name	**COVISHIELD ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant)**		**COVISHELD ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant)**
Manufacturer	Serum Institute of India Pvt. Ltd.		
N° doses	10 doses (5 ml)	4 doses (2 ml)	10 doses (5 ml)
Batch	4121Z040	Not indicated	4126Z079
Date of manufacture	Not indicated	Not indicated	08.05.2021
Expiration date	10.08.2021	Not indicated	07.11.2021
Text and packaging language	English	English	English
Identified in	Uganda	India	Myanmar
Comment	The expiration date has been falsified	The manufacturer does not produce Covishield in 4-dose (2- ml) quantities	The batch has been falsified and the name of the product does not match the original

Source: https://www.who.int/news/item/31-08-2021-medical-product-alert-n-5-2021-falsified-covishield-vaccine

Source: https://www.who.int/news/item/31-08-2021-medical-product-alert-n-5-2021-falsified-covishield-vaccine