COVID-19

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

Twenty-first report

WASHINGTON, DC

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CANADA

- As of 23 July 2021, 47,106,106 doses of COVID-19 vaccines of Pfizer-BioNTech, Moderna, AstraZeneca, and Covishield (manufactured by the Serum Institute of India) had been administered.
- A total of 10,807 individual reports of one or more adverse events (0.023% of doses administered) were received. Of these, 2,682 involved serious events (0.006% of doses administered).
- Following is information on these reported adverse events following immunization (AEFI), by vaccine and type of event:

Vaccine	Reports of adverse events					
	Number of reports of AEFI involving only non-serious events	Rate per 100,000 doses administered	Number of reports of serious AEFI	Rate per 100,000 doses administered	Total number of reports	Rate per 100,000 doses administered
Pfizer-BioNTech	4,274	13.66	1,762	5.63	6,036	19.29
Moderna	2,872	25.30	366	3.22	3,238	28.53
Covishield/ AstraZeneca	953	34.51	436	15.79	1,389	50.3
Not indicated	26	-	118	-	144	-
Total	8,125	17.27	2,682	5.67	10,807	22.94

- A total of 28,981 AEFI were reported (10,807 involving one or more events). The most frequently reported non-serious adverse events were injection-site reactions, paresthesia, itching, hives, headache, hypoesthesia, and nausea. There were 137 reported cases of anaphylaxis, of which 113 were associated with the Pfizer-BioNTech vaccine (0.36 per 100,000 doses administered) and 24 with the Moderna vaccine (0.21 per 100,000 doses administered).
- As of 23 July, there were 67 reported cases of thrombosis with thrombocytopenia syndrome (TTS), of which 56 involved individuals who had received the Covishield/AstraZeneca vaccine, 9 who had received the Pfizer-BioNTech vaccine, and 2 who had received the Moderna vaccine. In cases associated with the Covishield/AstraZeneca vaccine, onset of symptoms was between one and 34 days after vaccination. Of these cases, 23 were women (ages 44 to 88), 32 were men (ages 34 to 73), and in one case the sex of the person was not identified.

- A total of 162 post-vaccination deaths were reported. Following a medical review, it was determined that 66 of the deaths were not linked to administration of the COVID-19 vaccine; 33 are still under investigation; 6 (cases of TTS) were considered to be potentially attributable to vaccination; and in 57 cases the cause of death could not be determined due to insufficient information.
- As of 23 July, 230 cases of myocarditis/pericarditis had been reported; below is a list of the vaccines administered in these cases:

Vaccine	Total cases (per 100,000 doses administered)	Cases by sex/ median age		Doses administered		
		Women	Men	1st	2nd	Not indicated
Pfizer-BioNTech	145 (0.46)	68 (47 y.o.)	76 (30 y.o.)	83	39	23
Moderna	71 (0.62)	22 (38 y.o.)	48 (30 y.o.)	20	42	9
Covishield/ AstraZeneca	12 (0.43)	Not indicated	Not indicated	Not indicated	Not indicated	Not indicated

- As of 23 July, one case of capillary leak syndrome had been reported following administration of the first dose of the Covishield/AstraZeneca vaccine.
- In addition, 53 cases of Guillain-Barré Syndrome (GBS) were reported, of which 25 occurred after administration of the Covishield/AstraZeneca vaccine, 20 after administration of the Pfizer-BioNTech vaccine, and 8 following administration of the Moderna vaccine.

Source: https://health-infobase.canada.ca/covid-19/vaccine-safety/

CHILE

- According to official sources, between 24 December 2020 and 14 May 2021, 16,571,766 doses of COVID-19 vaccines were administered in Chile: 13,862,155 doses (83.6%) of the CoronaVac vaccine, 2,619,095 doses (15.8%) of the Pfizer-BioNTech vaccine, and 90,516 doses (0.5%) of the AstraZeneca vaccine.
- In that period, a total of 8,855 AEFI were reported:

Vaccine	Number of reports of AEFI	Rate per 100,000 doses administered	Number of reports of serious AEFI	Rate per 100,000 doses administered

Pfizer-BioNTech	3,373	128.8	69	2.6
CoronaVac (Sinovac)	5,103	36.8	226	1.6
AstraZeneca	144	159.1	2	2.2
Not indicated	235	-	-	-
Total	8,855	53.4	297	1.8

- Of the 8,855 reports, 6,683 (75.5%) involved women, 2,101 (23.7%) involved men, and in 72 cases (0.8%) the sex of the person was not identified.
- Of these reported events, 57.7% involved adults between the ages of 16 and 39.
- For the three vaccines, the most frequently reported clinical manifestations included: pain at the injection site, headache, fever, malaise, and myalgia.
- With regard to adverse events of special interest (AESI) associated with the Pfizer-BioNTech vaccine, reports included 37 cases of anaphylaxis, 13 cases of seizures, 9 of Bell's palsy, 7 of thromboembolic events, and 3 of GBS. For the CoronaVac vaccine, there were 121 reported cases of anaphylaxis, 36 of seizures, 28 of Bell's palsy, 16 of thromboembolic events, and 4 of GBS.

Source: https://www.ispch.cl/wp-content/uploads/2021/07/Quinto-informe-ESAVI-asociados-a-la-administraci%C3%B3n-de-la-vacuna-SARS-CoV-2-en-Chile.pdf

COSTA RICA

- As of 4 July 2021, the Directorate of Epidemiological Sub-Surveillance, of the Costa Rican Social Security Fund, reported that it had administered 2,878,760 doses of COVID-19 vaccines.
- As of 4 July 2021, 4,597 AEFI associated with administration of the Pfizer-BioNTech vaccine had been reported, while there were 2,197 reports of AEFI associated with the AstraZeneca vaccine.
- From the start of the vaccination program to 4 July, there were 24 reported events that were classified as serious, all of which were associated with the Pfizer-BioNTech vaccine. Of these, 16 individuals have recovered or are in the process of recovering and 8 died.

Source: https://www.ministeriodesalud.go.cr/index.php/centro-de-prensa/noticias/746-noticias-2021/2145-vacunados-contra-covid-19-reportan-sintomas-leves-y-poco-frecuentes-despues-de-la-inmunizacion

PARAGUAY

- Between 22 February 2021 and 16 July 2021, Paraguay's Immunization Program received 1,684 reports of adverse events following administration of COVID-19 vaccines of Sputnik V, Sinovac (CoronaVac), Sinopharm, AstraZeneca, Covaxin, Hayat-Vax,* and Moderna, or 0.1% of doses administered, of which 166 cases are still under investigation.
- Of these reported AEFI, 74.2% (1,251) involved women and 25.7% (433) involved men.
- The most frequently reported clinical manifestations of AEFI were myalgias (72%), fever (61%), headache (61%), injection-site pain (58%), and fatigue (50%). Most reports involved more than one clinical manifestation.
- Notably, the reporting rate of AEFI for the Coronavac vaccine was 915.25 per 100,000 doses administered, while the rates for Sinopharm, AstraZeneca, and Sputnik V were 612.87, 237.13, and 99.31, respectively; the AEFI reporting rate for the COVAXIN vaccine was 73.04 per 100,000 doses administered.

    * Hayat-Vax is a vaccine that is the result of a joint project between Sinopharm CNBG and G42, of the United Arab Emirates, in Abu Dhabi.

Source: http://pai.mspbs.gov.py/article/vigilancia-esavi

The European Medicines Agency authorizes use of the Spikevax COVID-19 vaccine for children ages 12 to 17

On 23 July 2021, the European Medicines Agency (EMA) reported that the Committee for Medicinal Products for Human Use (CHMP) recommended granting an extension of the indication for the COVID-19 vaccine Spikevax (formerly a Moderna COVID-19 vaccine) for use in children ages 12 to 17 (the vaccine had already been licensed for use in people ages 18 and older).

Administration of the Spikevax vaccine in children ages 12 to 17 will follow the same immunization schedule as for people 18 years old and older, i.e., two doses four weeks apart.

The recommendation for the authorization was based on a clinical trial involving 3,732 children between the ages of 12 and 17, which is part of the Spikevax pediatric research plan authorized by the EMA's Pediatric Committee. In this study, the Spikevax vaccine produced an antibody response in 12- to 17-year-olds comparable to that seen in young adults ages 18 to 25. The most common side effects in the study group were similar to those in the 18-year-old and older population.

Source: https://www.ema.europa.eu/en/news/covid-19-vaccine-spikevax-approved-children-aged-12-17-eu

Updated Brighton Collaboration case definition of myocarditis/pericarditis

On 16 July 2021, the Brighton Collaboration reported that, in order to broaden the understanding of a possible association between observed post-vaccination cases of myocarditis/pericarditis and administration of COVID-19 vaccines, the Cardiovascular Injury Working Group updated the case definition for these disorders, which is available at: https://brightoncollaboration.us/myocarditis-case-definition-update/.

Effectiveness of an inactivated SARS-CoV-2 vaccine in Chile

Chile evaluated use of the CoronaVac vaccine in its countrywide COVID-19 mass vaccination campaign, which began on 2 February 2021, using a prospective national cohort that included participants ages 16 and older who belonged to the national public health system. The evaluation attempted to estimate the effectiveness of the inactivated SARS-CoV-2 vaccine in preventing COVID-19, hospitalizations, intensive care unit (ICU) admissions, and deaths resulting from the disease. The effectiveness of the vaccine was calculated with adjustments for individual demographic and clinical factors. The cohort included approximately 10.2 million individuals.

Among people who were fully immunized, the adjusted vaccine effectiveness was 65.9% (95% confidence interval [CI], 65.2 to 66.6) in preventing COVID-19; 87.5% (95% CI, 86.7 to 88.2) in preventing hospitalizations; 90.3% (95% CI, 89.1 to 91.4) in preventing ICU admissions; and 86.3% (95% CI, 84.5 to 87.9) in preventing COVID-19-related deaths. The results suggest that the inactivated SARS-CoV-2 vaccine was effective in preventing COVID-19, including severe illness and death – a finding consistent with the results of phase 2 trials of the vaccine.

Source: Jara A, Undurraga EA, González C, et al. Effectiveness of an Inactivated SARS-CoV-2 Vaccine in Chile. N Engl J Med (2021) https://doi.org/10.1056/NEJMoa2107715.

CLARIFICATIONS/CONCLUSIONS REGARDING EVENTS PRESENTED IN PREVIOUS COMMUNICATIONS

WARNING ABOUT POSSIBLE RISK OF GUILLAIN-BARRÉ SYNDROME WITH VIRAL VECTOR COVID-19 VACCINES

- Recommendations of the COVID-19 Subcommittee of WHO's Global Advisory Committee on Vaccine Safety (GACVS)

On 13 and 20 July 2021, the COVID-19 subcommittee of the WHO Global Advisory Committee on Vaccine Safety (GACVS) met virtually to discuss rare reports of Guillain-Barré Syndrome (GBS) following vaccination with the Janssen and AstraZeneca COVID-19 vaccines, and to consider measures implemented by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

The subcommittee also reviewed preliminary data from Vigibase, the WHO global database of Individual Case Safety Reports (ICSR), which listed 164 unconfirmed cases of GBS in various countries (other than the United States) associated with the AstraZeneca (Vaxzevria and Covishield) vaccines. Fourteen of these cases were in Central and South American countries, out of a total of 19.5 million doses of AstraZeneca (Vaxzevria and Covishield) vaccines administered.

Based on a careful scientific review of the available information, the GACVS subcommittee came to the following conclusions and recommendations:

- Rare cases of GBS have been reported following vaccinations with adenovirus vector COVID-19 vaccines.
- Increased reports of GBS have not been observed following mRNA COVID-19 vaccines.
- More rigorous studies using alternative data sources and robust study designs, and comparison of vaccinated and unvaccinated populations would be needed, to fully assess the significance of these events.
- The GACVS subcommittee will continue to monitor GBS and any other safety concerns and review further as more data become available.
- Healthcare professionals should monitor for and report all adverse events including GBS.
- Individuals receiving Janssen or AstraZeneca COVID-19 vaccines should be alert to signs and symptoms of GBS and should seek immediate medical attention if they develop weakness/tingling and paralysis in the extremities that may progress to other parts of the body including the chest and face. Symptoms may include difficulty in walking; difficulty with facial movements; double vision or inability to move eyes; or difficulty controlling bladder or bowel functions.
- Healthcare professionals should be aware of these signs and symptoms to allow for early diagnosis and treatment. Most people fully recover from GBS.
- Though countries should always consider their individual circumstances and benefit-risk profiles, overall the subcommittee concludes that the potential benefits of both the Janssen and AstraZeneca COVID-19 vaccines continue to outweigh any potential risk of GBS, particularly given the increase in the more transmissible Delta (B.1.617.2) variant.

Source: https://www.who.int/news/item/26-07-2021-statement-of-the-who-gacvs-covid-19-subcommittee-on-gbs

- European Medicines Agency on Janssen's COVID-19 vaccine

On 22 July 2021, the European Medicines Agency (EMA) reported that Guillain-Barré Syndrome (GBS) will be listed as a very rare side effect of Janssen's COVID-19 vaccine. The vaccine information will be updated to include, in the section on warnings and special precautions for use, that very rare cases of GBS have been reported following administration of the Janssen COVID-19 vaccine.

Health professionals should be alert to signs and symptoms of GBS to ensure correct diagnosis, to initiate adequate supportive care and treatment, and to rule out other causes. Vaccinated individuals should be advised to seek immediate medical attention if they develop signs and symptoms of GBS (such as those mentioned in the previous section).

Source: https://www.ema.europa.eu/en/news/covid-19-vaccine-janssen-guillain-barre-syndrome-listed-very-rare-side-effect

A similar measure was announced on 19 July 2021, by the EMA, for AstraZeneca's Vaxzevria COVID-19 vaccine. Additional information on this measure is available at:

- https://www.ema.europa.eu/en/documents/product-information/vaxzevria-previously-covid-19-vaccine-astrazeneca-epar-product-information_en.pdf.

Inclusions in the WHO Emergency Use Listing (EUL)

WHO has added to the Emergency Use Listing (EUL) other production sites for some of the authorized vaccines, which are summarized below:

COVID-19 vaccine (EUL)	Authorizing NRA	Authorized sites added to the EUL		
		EUL holder*	Finished product (Countries)	Authorizing NRA**
Tozinameran - COMIRNATY® - BioNTech	European Medicines Agency (EMA)	BioNTech Manufacturing GmbH	United States	Food and Drug Administration (FDA), USA
ChAdOx1-S (recombinant) AstraZeneca/SKBio	Ministry of Food and Drugs, Korea	AstraZeneca AB	Germany Spain Italy United Kingdom Republic of Korea	European Medicines Agency (EMA)
		AstraZeneca AB	Italy Japan	Ministry of Health, Labor, and Welfare (MHLW), Japan
		AstraZeneca AB	Germany Australia Italy United Kingdom	Therapeutic Goods Administration (TGA), Australia

*Authorization holder

**Authorizing NRA: The national regulatory authority (NRA) that first authorized the vaccine and that is responsible for overseeing the vaccine.

Source: https://extranet.who.int/pqweb/vaccines/covid-19-vaccines

Adverse Events of Special Interest (AESI) and related risks

In investigating adverse events—in particular, serious events of special interest—it is important to consider the possibility that the event may be associated with, or be caused by other factors, such as diseases, medications being used, or other previously administered vaccines.

In order to facilitate the evaluation of events of special interest, the following provides a summary of the main factors to consider, in this example for Guillain-Barré Syndrome (GBS):

Definition: Immune-mediated disease resulting from the production of autoimmune antibodies and/or inflammatory cells, which cross-react with epitopes of the peripheral nervous system, causing demyelination and/or axonal injury (1).

Diseases: Autoimmune antibodies can be formed by a variety of antigenic stimuli, such as bacterial or viral infection, with a history of an infectious disease (diarrhea or respiratory disease) in the days or weeks before neurological signs appear. Among the associated infectious agents are the gastrointestinal bacterium Campylobacter jejuni, the influenza virus Mycoplasma pneumoniae, the human immunodeficiency virus, Epstein-Barr virus, cytomegaloviruses, and Zika.

In rare cases, an association with surgical procedures and with some neoplasms, particularly Hodgkin's disease and other lymphomas, has also been observed (1, 2).

Medications: GBS has most often been associated with the use of penicillin and antispasmodic medications, and less frequently with the use of oral contraceptives. Though not involving definite cause-and-effect relationships, there are reports of cases related to streptokinase, isotretinoin, danazol, captopril, gold, heroin, cyclosporin A, and fluoroquinolones (3, 4).

Vaccines: There is evidence of GBS following administration of the pH1N1 pandemic virus vaccine, with no increased risk associated with adjuvant vaccines. Studies evaluating the risk of GBS with new influenza vaccine formulations have not consistently demonstrated an increase in marginal risk. Evidence of the link between GBS and vaccines against measles, rubella, and mumps (MMR), herpes zoster (VZV), hepatitis A/B, human papillomavirus (HPV), diphtheria-tetanus, and acellular pertussis (DTaP), as well as meningococcal vaccines, may be insufficient to either confirm or rule out a causal relationship. GBS has been temporally associated with numerous vaccines; however, this temporal association must be differentiated from causation (1, 5).

Sources:

(1) Sejvar J, Kohl K, Gidudu J, et al. Guillain-Barré Syndrome and Fisher syndrome: Case definitions and guidelines for collection, analysis, and presentation of immunization safety data, Vaccine, Volume 29, Issue 3, 2011, Pages 599–612, https://doi.org/10.1016/j.vaccine.2010.06.003.

(2) Center for Disease Control and Prevention. Zika Virus. Zika and Guillain-Barré Syndrome. Available at: https://www.cdc.gov/zika/healtheffects/gbs-qa.html.

(3) Andary MT, Medscape. Zika and Guillain-Barré Syndrome. Available at: https://emedicine.medscape.com/article/315632-overview#a2.

(4) Rizawati et al. J Clin Nephrol. Guillain-Barré Syndrome Associated with Cyclosporine A. Ren Care 2016, 2:009 Volume 2 | Issue 1. https://clinmedjournals.org/articles/jcnrc/journal-of-clinical-nephrology-and-renal-care-jcnrc-2-009.pdf.

(5) Barbara Law. Safety Platform for Emergency vACcines SO2- D2.5.2.1 - AESI Case Definition Companion Guide for 1st Tier AESI Guillain-Barré and Miller Fisher Syndromes Work Package: WP2 Standards and tools V1.0 – February 9th, 2021, Nature: Report | Diss. Level: Public. https://brightoncollaboration.us/wp-content/uploads/2021/03/SPEAC_D2.5.2.1-GBS-Case-Definition-Companion-Guide_V1.0_format12062-1.pdf.

Alert on the need for sufficient syringes for vaccination

A recent opinion piece in the Washington Post, signed by, among others, Dr. Margaret Chan, former Director-General of WHO, expresses concern that the global effort to vaccinate against COVID-19 could be jeopardized if unsafe

injections are given. More than 15 billion doses will be needed to vaccinate a large proportion of the world's population. However, this may mean that in some countries, due to the lack of, or difficulty in accessing disposable syringes, syringes could end up being reused. According to the article, if this happens, more than two million lives could be lost, and more than 40 million people could be infected with blood-borne diseases. Billions of syringes are needed specifically for COVID-19 vaccines, which in turn must not hinder regular immunization programs or the regular use of syringes in health care. It is essential that vaccine donations to countries also take into account, in the planning process, the availability or donation of an adequate supply of syringes.

Source:* https://www.washingtonpost.com/opinions/2021/07/19/global-vaccine-effort-would-be-hollow-victory-if-it-leads-unsafe-injection-practices/

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