COVID-19

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

Thirty-seventh report

WASHINGTON, DC

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CONTENTS

ARGENTINA

As of 31 May, 102,986,911 doses of COVID-19 vaccines had been administered to people 3 years of age and older in all of the country's 24 jurisdictions. A total of 61,708 adverse events following immunization (AEFI) were reported (59.9/100,000 doses administered). Of total reports, 69% corresponded to women, and the average age for both women and men was 41 years. Of the reported events, 4.17% were described as serious.

Using the Brighton Collaboration definition and the WHO causality algorithm, 13 cases of thrombosis with thrombocytopenia syndrome (TTS) were analyzed. Eleven of these events were classified as indeterminate or B1, while two were classified as indeterminate or B2.[1] The cases occurred in individuals between the ages of 18 and 70, of whom nine were women and four were men. All events occurred after administration of the first dose of a non-replicating viral vector vaccine. The interval between vaccination and the event was on average 10 days (range 1–24). Four of the cases resulted in death.

Source: Ministry of Health of Argentina. National COVID-19 Vaccination Campaign. 18th Vaccine Safety Surveillance Report. June 2022. Available in Spanish at: https://bancos.salud.gob.ar/sites/default/files/2022-07/informe-conaseva_18-06-2022.pdf.

[1] Manual of Surveillance of Adverse Events Following Vaccination in the Region of the Americas. Washington, DC: Pan American Health Organization; 2021. License: CC BY-NC-SA 3.0 IGO. Available in Spanish at: https://doi.org/10.37774/9789275323861.

CANADA

As of 24 June 2022, 58,112,512 doses of the Pfizer-BioNTech COVID-19 vaccine, 24,293,492 doses of the Moderna vaccine, 2,812,562 doses of the AstraZeneca and Covishield vaccine (AstraZeneca vaccine manufactured by the Serum Institute of India), and 22,022 doses of the Janssen vaccine had been administered.

As of the same date, there were 48,670 individual reports of one or more AEFI (57/100,000 doses administered). Of these, 9,878 reports involved serious events (11.6 per 100,000 doses administered).

Up to date , there have been 105 reports of TTS, of which 64 were associated with the AstraZeneca Vaxzevria/Covishield vaccine, 28 with the Pfizer-BioNTech/Comirnaty vaccine, and 12 with the Moderna/Spikevax vaccine. Among the 64 reports of TTS following administration of the AstraZeneca Vaxzevria/Covishield vaccine, the onset of symptoms was between three hours and 48 days after vaccination; median age was 57 years (age range 34 to 88 years); 55 reported cases occurred after the first dose of the vaccine; 29 had laboratory results showing the

presence of anti-platelet factor 4 (PF4) antibodies, indicating vaccine-induced immune thrombotic thrombocytopenia (VITT); and six of the cases resulted in death (these deaths are still under investigation).

As of the same date, there have been 1,097 reports of myocarditis/pericarditis, as follows:

- 657 reported cases occurred following administration of the Pfizer-BioNTech Comirnaty vaccine. The number of reports is higher than would be expected in the general population of men and women under the age of 30, and most of the reported cases occurred after the second dose.
- 414 reported cases occurred following administration of the Moderna/Spikevax vaccine. The number of reports is higher than would be expected in the general population, particularly among men and women under the age of 40, and after the second dose.
- 15 reported cases occurred after administration of the AstraZeneca Vaxzevria/Covishield vaccine.
- 11 reports did not specify the vaccine.

There were 355 reported cases of post-vaccination deaths. Following a medical review, it was determined that 110 of these deaths were unlikely to be linked to administration of a COVID-19 vaccine; 195 deaths could not be classified due to lack of information; and 50 deaths are still under investigation.

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

Number of reports and reporting rate of the main adverse events of special interest (AESI) (per 100,000 doses administered), by vaccine, in the general population, as of 24 June 2022							
Category	AESI	Vaccine					
		Pfizer-BioNTech		Moderna		Covishield and AstraZeneca	
		N*	Rate (per 100,000 doses administered)	N*	Rate (per 100,000 doses administered)	N*	Rate (per 100,000 doses administered)
Autoimmune diseases	Guillain-Barré syndrome	8	0.01	5	0.02	8	0.28
	Thrombocytopenia	95	0.16	33	0.14	51	1.81
Cardiovascular system	Myocardial infarction	84	0.14	26	0.11	9	0.32
	Myocarditis/pericarditis	657	1.13	414	1.70	15	0.53
Circulatory system	Cutaneous vasculitis	23	0.04	10	0.04	9	0.32
	Deep vein thrombosis	178	0.31	81	0.33	77	2.74
	Pulmonary embolism	258	0.44	106	0.44	137	4.87
	Thrombosis	174	0.30	46	0.19	92	3.27
	Thrombosis with thrombocytopenia syndrome (TTS)	29	0.05	12	0.05	64	2.28
Hepatic and renal system	Acute renal injury	40	0.07	24	0.10	7	0.25
	Hepatic injury	23	0.04	11	0.05	3	0.11
Nervous and central nervous system	Bell's palsy/facial paralysis	118	0.20	34	0.14	12	0.43
	Cerebrovascular accident	139	0.24	60	0.25	39	1.39
Other systems	Anaphylaxis	627	1.08	188	0.77	29	1.03
Pregnancy outcomes	Miscarriage	64	0.11	19	0.08	1	0.04
Cutaneous system	Erythema multiforme	29	0.05	18	0.07	3	0.11

*N = number of reports

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

Source: Public Health Agency of Canada. Canadian COVID-19 vaccine safety report. Ottawa: Public Health Agency of Canada; July 8, 2022. https://health-infobase.canada.ca/covid-19/vaccine-safety/. Data reproduced by PAHO/WHO.

UNITED STATES

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

Thrombosis with thrombocytopenia syndrome (TTS) after COVID-19 vaccination with the Janssen vaccine (J&J/Janssen) is rare, and has occurred in approximately four cases per million doses administered in the United States. A case series review indicates a causal relation between Janssen's COVID-19 vaccine and TTS. CDC scientists have made detailed reviews of reported cases of TTS and the results have been published in the following papers:

- U.S. Case Report of cerebral venous sinus thrombosis with thrombocytopenia after vaccination with Ad26.COV2.S, from March 2 to April 21, 2021.
- Case series of thrombosis with thrombocytopenia syndrome after COVID-19 vaccination – United States, December 2020–August 2021.
- TTS-CDC Update Document

Reports of deaths after COVID-19 vaccination are rare. Between 14 December 2020 and 6 July 2022, more than 597 million doses of COVID-19 vaccine were administered in the United States. During this time, the

Vaccine Adverse Event Reporting System (VAERS) received 15,380 preliminary reports of death (0.0026%) among people who received a COVID-19 vaccine. Subsequent follow-up identified nine deaths deemed to be causally associated with administration of the J&J/Janssen COVID-19 vaccine.

Source: Centers for Disease Control and Prevention (CDC). Selected Adverse Events Reported after COVID-19 Vaccination. Updated 7 July 2022. Note: The website is updated periodically, and the data may therefore differ at the time of publication of this newsletter. Available at: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html.

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

Efficacy and safety of the RBD-dimer-based COVID-19 vaccine ZF2001 in adults

A randomized, double-blind, placebo-controlled phase 3 trial in adults was published on 2 June 2022 to investigate the efficacy and confirm the safety of the receptor-binding domain (RBD)-based COVID-19 vaccine, ZF2001, with aluminum hydroxide as an adjuvant.

The trial was conducted at 31 clinical centers in Uzbekistan, Indonesia, Pakistan, and Ecuador. An additional center in China was included only in the safety evaluation.

Participants aged 18 years and older were randomly assigned in a 1:1 ratio to receive a total of three doses of 25 μg (30 days apart) of ZF2001 or placebo.

The primary endpoint was the onset of symptomatic COVID-19 disease (confirmed by PCR), at least seven days after receiving the third dose. Key secondary efficacy endpoints were severe-to-critical COVID-19 (including COVID-19-related death) occurring at least seven days after receiving the third dose.

Between 12 December 2020 and 15 December 2021, a total of 28,873 participants received at least one dose of ZF2001 or placebo and were included in the safety analysis; of these, 25,193 completed the three-dose regimen, with follow-up of approximately six months.

In the efficacy analysis, 158 primary endpoint cases were reported among 12,625 participants in the ZF2001 group, and 580 cases among 12,568 participants in the placebo group, for a vaccine efficacy of 75.7% (95% CI, 71.0 to 79.8).

Severe-to-critical COVID-19 disease occurred in six participants in the ZF2001 group, and in 43 in the placebo group, with a vaccine efficacy of 87.6% (95% CI, 70.6 to 95.7).

There were two COVID-19-related deaths among participants in the vaccine group and 12 deaths in the placebo group, with a vaccine efficacy of 86.5% (95% CI, 38.9 to 98.5).

The incidence of total adverse events and serious adverse events was similar in the two groups, and there were no vaccine-related deaths. Most adverse reactions (98.5%) were grade 1 or 2.

The authors conclude that, in a large cohort of adults, the ZF2001 vaccine was shown to be safe and effective against symptomatic and severe-to-critical COVID-19 for at least six months after full vaccination.

Source: Lianpan Dai et al. Efficacy and Safety of the RBD-Dimer–Based COVID-19 Vaccine ZF2001 in Adults. N Engl J Med 2022; 386:2097–2111 DOI: 10.1056/NEJMoa2202261. Available at: https://www.nejm.org/doi/full/10.1056/NEJMoa2202261.

Safety and immunogenicity of the FINLAY-FR-1A vaccine in COVID-19 convalescent participants: an open-label phase 2a and double-blind, randomized, placebo-controlled, phase 2b, seamless, clinical trial

On 9 June 2022, a study was published with the results of the phase 2 clinical trial, which evaluated the FINLAY-FR-1A vaccine in people convalescing from COVID-19.

The trial studied 450 convalescent participants with a history of asymptomatic, mild, or moderate COVID-19 at the National Institute of Hematology and Immunology and the National Centre for Sexual Education in Havana, Cuba.

The study included adults ages 19 to 78 who had recovered from COVID-19 and had received a negative PCR test at least two months before the initiation of the study, and with no history of COVID-19 vaccination.

Phase 2 was performed sequentially in two stages. The first stage to assess safety comprised an open, non-controlled phase 2a study in participants ages 60 to 78 who received a single dose of the FINLAY-FR-1A vaccine (50 µg of recombinant dimeric receptor binding domain [RBD]). The second stage comprised the placebo-controlled, double-blind, phase 2b trial in participants ages 19 to 78, where participants were randomly assigned (4:1) into two groups: a group vaccinated with a single dose of the FINLAY-FR-1A vaccine, and a control (placebo) group injected with vaccine excipient.

The primary outcomes were safety, evaluated 28 days after vaccination by the occurrence of serious adverse events in all participants, and successful immune response, assessed by neutralizing antibody ELISA, and defined as half-maximal surrogate virus neutralization titers ($sVNT_{50}$) of 250 or more.

All randomly assigned participants were included in the safety analysis (safety population), and immunogenicity was evaluated in participants without study interruptions (per-protocol population).

From 9 to 17 April 2021, 450 volunteers were recruited. The trial included 20 participants ages 60 to 78 in the single-group phase 2a open-label study, and 430 participants were randomly assigned to the experimental (n=344) or control (n=86) group in the phase 2b study of participants ages 19 to 78. Of phase 2a volunteers, 95% (19/20) achieved a successful immune response after vaccination.

No serious vaccine-associated adverse events were reported in the whole study population. Minor adverse events were found, the most common being pain at the injection site (105 [29%] of 364 in the intervention group; 13 [15%] of 86 in the placebo group).

A successful immune response was found in 289 (81%) of 358 participants 28 days after vaccination. However, in the control group, successful immune response was present in only four of 81 participants (5%) in the same time period.

A 31-times increase in anti-RBD IgG was detected over the pre-vaccination concentration, and the seroconversion rate was 84% (in 302 of 358 participants on day 28 after vaccination). The geometric mean titers of live-virus neutralization

test increased from 15.4 (95% CI 10.3–23.2) to 400.3 (272.4–588.1) and high response was found against Alpha, Beta, and Delta variants of interest.

The authors concluded that a single dose of the FINLAY-FR-1A vaccine against SARS-CoV-2 strengthened the pre-existing natural immunity, with excellent safety profile. The vaccine proved safe, with good tolerability, as demonstrated by the fact that most local and systemic reactions were mild. Receptor binding domain antibodies (RBD:hACE2) were induced in most volunteers after a single dose of vaccine, demonstrating their immunogenicity.

Source: Rolando Ochoa-Azze et al. Safety and immunogenicity of the FINLAY-FR-1A vaccine in COVID-19 convalescent participants: an open-label phase 2a and double-blind, randomized, placebo-controlled, phase 2b, seamless, clinical trial. Lancet Respir Med 2022 Published Online June 9, 2022. Available at: https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(22)00100-X/fulltext.

Change in COVID-19 risk over time following vaccination with CoronaVac: test negative case-control study

On 13 June 2022, a test negative case-control study was published, with the aim of estimating the change in odds of COVID-19 in the state of São Paulo, Brazil; in other words, a change in the effectiveness of the CoronaVac vaccine (Sinovac Biotech) over time following primary series completion of the inactivated whole virus vaccine.

Individual level data were collected on demographic and clinical characteristics, SARS-CoV-2 testing, and COVID-19 vaccination from four databases: the São Paulo State laboratory testing registry (GAL), national surveillance databases covering acute respiratory illness (e-SUS) and severe acute respiratory illness (SIVEP-Gripe), and the São Paulo State vaccine registry (Vacina Já) covering all people vaccinated in the state of São Paulo. Participants were adults aged 18 years and older who were residents of the state of São Paulo, had received two doses of CoronaVac, did not have a laboratory-confirmed SARS-CoV-2 infection prior to vaccination, and underwent RT-PCR testing for SARS-CoV-2 from 17 January 2021 to 14 December 2021.

Cases (confirmed infections with positive test results) were matched to test negative controls by age (in five-year bands), municipality of residence, healthcare worker status, and epidemiological week of RT-PCR test.

For the main outcome measures RT-PCR confirmed symptomatic COVID-19 and associated hospital admissions and deaths.

Conditional logistic regression was adjusted for sex, number of COVID-19-associated comorbidities, race, and previous acute respiratory illness.

Among 202,741 people with 204,137 RT-PCR tests eligible for selection as a case or control, 121,785 RT-PCR tests from 121,096 people were matched with 43,257 case-control sets for the primary analysis.

Adjusted odds ratios of symptomatic COVID-19 increased with time since completion of the vaccination series.

The adjusted odds ratios of COVID-19-related hospital admission or death significantly increased with time compared with the odds 14-41 days after series completion: from 1.25 (95% confidence interval 1.04 to 1.51) at 70-97 days up to 1.94 (1.41 to 2.67) from 182 days onwards.

Among people age ≥80 years, those vaccinated 126-153 days before their test date had increased odds of COVID-19 relative to those vaccinated 14-41 days before (odds ratio 1.58, 95% CI 1.04 to 2.42). Overall, the odds ratio of COVID-19 associated with time since vaccination was of lower magnitude among 65-79-year-olds, with a maximum odds ratio of 1.40 (1.05 to 1.86), and no increase in odds over time was observed among 40-79-year-olds.

The authors concluded that significant increases in the risk of moderate and severe COVID-19 outcomes occurred three months after primary vaccination with CoronaVac among people age 65 and older.

Moderate and severe COVID-19 outcomes increased over time following completion of a primary series of CoronaVac in older people. The authors have suggested sensitivity analyses that could be conducted to understand bias in observational studies such as this. These findings provide supportive evidence for the implementation of vaccine boosters in these populations that received this inactivated vaccine.

Source: Matt Hitchings et al. Change in COVID-19 risk over time following vaccination with CoronaVac: test negative case-control study. BMJ 2022;377: e070102. Published 13 June 2022. Available at: https://www.bmj.com/content/377/bmj-2022-070102.

Analysis of Postvaccination Breakthrough COVID-19 Infections Among Adults with HIV in the United States

On 7 June 2022, a study was published, aimed at estimating the rate and risk of breakthrough infections among fully vaccinated people with HIV (PWH) with complete COVID-19 vaccination series, and people without HIV (PWoH) in the United States.

This cohort study used the Corona-Infectious-Virus Epidemiology Team (CIVET)-II design, part of the International Epidemiology Databases to Evaluate AIDS – a collaboration of four prospective, electronic health record-based cohorts from integrated health systems and academic health centers, which contribute longitudinal data to the North American AIDS Cohort Collaboration on Research and Design.

Adult PWH who were fully vaccinated prior to 30 June 2021 were matched with PWoH on date of full vaccination, age, race and ethnicity, and sex, and were followed up through 31 December 2021.

The main outcomes were COVID-19 breakthrough infections, defined as laboratory evidence of SARS-CoV-2 infection or COVID-19 diagnosis after a patient was fully vaccinated.

An evaluation of 113,994 patients (33,029 PWH and 80,965 PWoH) was performed, of which 70% (80,017) were 55 years or older and 92% (104,967) were male; 41% (47,098) were non-Hispanic Black, and 38% (43,218) were non-Hispanic White.

The results were as follows:

- The rate of breakthrough infections was higher in PWH vs. PWoH (55 [95% CI, 52-58] cases per 1,000 person-years vs. 43 [95% CI, 42-45] cases per 1,000 person-years).
- Breakthrough infection risk was 28% higher in PWH vs. PWoH (adjusted hazard ratio, 1.28 [95% CI, 1.19-1.37]).
- Among PWH, younger age (<45 y vs. 45-54 y), history of COVID-19, and not receiving an additional dose (aHR, 0.71 [95% CI, 0.58-0.88]) were associated with increased risk of breakthrough infections.
- There was no association of breakthrough with HIV viral load suppression, but high CD4 count (i.e., ≥500 cells/mm^3) was associated with fewer breakthroughs among PWH.

According to the study's authors, the risk of breakthrough infection was low overall (3.8%), but 28% higher in people living with HIV than in people without HIV. The higher rate and risk of infection in people with HIV observed in this study suggests comprehensive inclusion of this population in recommendations for additional primary doses in immunocompromised groups.

Source: Coburn SB, Humes E, Lang R, et al. Analysis of Postvaccination Breakthrough COVID-19 Infections Among Adults with HIV in the United States. JAMA Netw Open 2020. 2022;5(6): e2215934. doi:10.1001/jamanetworkopen.2022.15934. Available at: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2793102.

European Medicines Agency recommends authorization of Nuvaxovid COVID-19 vaccine for adolescents ages 12 to 17

On 23 June 2022, the European Medicines Agency (EMA) recommended granting an extension of indication for the COVID-19 vaccine Nuvaxovid, initially authorized for use in individuals 18 years old and older, to include use in adolescents ages 12 to 17.

The immunization schedule in adolescents is the same as in adults: two doses 3 weeks apart.

A pivotal study that included more than 2,200 adolescents ages 12 to 17 showed that the SARS-CoV-2 antibody response to Nuvaxovid was comparable to the response in young adults ages 18 to 25. The trial was carried out when the SARS-CoV-2 Delta variant was dominant, and showed that the vaccine was almost 80% effective at preventing COVID-19.

The most common side effects in adolescents ages 12 to 17 were mostly similar to those in people age 18 and above. These included: tenderness, pain, redness and swelling at the injection site; headache; muscle and joint pain; tiredness; generally feeling unwell; nausea or vomiting; and fever. Fever was seen more frequently in adolescents than in adults. These effects are usually mild or moderate and improve within a few days of vaccination.

To learn more about this recommendation, see: https://www.ema.europa.eu/en/news/ema-recommends-authorisation-nuvaxovid-adolescents-aged-12-17.

European Medicines Agency recommends authorization of Valneva's COVID-19 vaccine

On 23 June 2022, the European Medicines Agency (EMA) recommended authorization of the COVID-19 vaccine Valneva for use in the primary vaccination of people ages 18 to 50.

The vaccine, developed by Valneva Austria GmbH, contains inactivated whole particles of the original strain of SARS-CoV-2 and two types of adjuvants (aluminum and cytosine phosphoguanine). The primary immunization schedule is two doses of 0.5 mL each, with an interval of four weeks.

The immunogenicity and safety of Valneva was established in the pivotal immunobridging study VLA2001–301, phase 3, which makes it possible to compare the immune response induced by the vaccine under study versus the response induced by another vaccine, in this case Vaxzevria. This study involved 2,975 individuals age 30 and older, and 1,042 participants ages 18 to 29, who were enrolled in an open-label, non-randomized treatment group, with follow-up to be assessed up to month 12 after the first dose.

The results showed that the immunogenicity induced by Valneva in people between the ages of 18 and 50 was similar to that induced by Vaxzevria, but it was not possible to establish the immunogenicity of Valneva in people older than 50; therefore its use in this age group is not recommended.

The most common side effects seen in this study with Valneva were injection-site pain, tiredness, headache, muscle pain, nausea, and vomiting.

To learn more about this recommendation, see: https://www.ema.europa.eu/en/news/ema-recommends-valnevas-covid-19-vaccine-authorisation-eu.

https://www.ema.europa.eu/en/documents/product-information/covid-19-vaccine-inactivated-adjuvanted-valneva-epar-product-information_en.pdf

Interim statement of the WHO Strategic Advisory Group of Experts on Immunization on hybrid immunity and increasing population seroprevalence rates

On 1 June 2022, WHO's Strategic Advisory Group of Experts (SAGE) on Immunization released an interim statement on hybrid immunity and increasing population seroprevalence rates. The following is a summary of the SAGE report:

Exposure to SARS-CoV-2 through infection or vaccination triggers the production of antibodies in the blood, referred to as seroconversion. Inferring the level of population-level protection against infection and/or severe outcomes from seroprevalence estimates is challenging, due to the multiple factors that can affect the level of antibodies produced by an individual. In addition, seroprevalence estimates are based only on measures of antibodies and do not incorporate measures of cell-mediated immunity, which is an important component of the overall immune protection.

Evidence suggests that hybrid immunity offers superior protection against severe outcomes due to COVID-19 compared to infection-induced or vaccine-induced immunity alone. With more evidence, integrating infection- and vaccination-induced immunity into vaccination strategies and/or schedules may provide gains, through simplified and/or more effective immunization schedules in countries or communities that have already experienced high levels of community transmission. However, basing national vaccination policies on seroprevalence rates poses several challenges, since seroprevalence rates observed in population-based studies may not be representative of the entire population or of certain subpopulations and age groups. In fact, they may also differ due to factors such as the type of environment (urban versus rural); moreover, hybrid immunity, although superior to infection- or vaccine-induced immunity alone, depends on a number of factors in complex and interrelated ways.

WHO reiterates the need for seroprevalence studies in specific at-risk populations, such as older age groups, to identify vaccination priorities and targeted efforts to be made in the future. An improved understanding of hybrid immunity will contribute to evidence-based decisions on the need for additional COVID-19 vaccine doses and provide updated recommendations on hybrid immunity to be considered in national vaccination policies.

Therefore, achieving high primary vaccine series coverage in individuals in the highest and high-risk groups remains the foremost priority, irrespective of their infection history. This is in line with the WHO SAGE Roadmap for prioritizing use of COVID-19 vaccines, while at the same time prioritizing the highest and high-priority use groups for booster doses, which are associated with enhanced protection against the Omicron variant of concern (VOC).

Additional information available at: https://www.who.int/news/item/01-06-2022-interim-statement-on-hybrid-immunity-and-increasing-population-seroprevalence-rates.

Interim statement by the WHO Strategic Advisory Group of Experts on Immunization on decision-making considerations for the use of updated COVID-19 vaccines adapted to COVID-19 variants

On 17 June 2022 , WHO's Strategic Advisory Group of Experts (SAGE) on Immunization released an interim statement on decision-making considerations for the use of vaccines adapted to COVID-19 variants, as summarized below:

- Current situation: Current COVID-19 vaccines, which are based on the ancestral strain of the SARS-CoV-2 virus, continue to exhibit strong protection against severe disease and death across all virus variants seen to date. Achieving high coverage rates with the primary series and booster doses in the highest and high priority-use groups in every country remains the priority.

  The emergence of variants of concerns, particularly Omicron, has resulted in a rapid decline of the protection against symptomatic illness. Thus, the objective of variant-updated vaccines would be to provide even greater and more durable protection against severe disease and death, and broader protection against future variants that are antigenically distant to the index virus, which could prevent spread to vulnerable people and reduce the risk of the emergence of new variants.

- COVID-19 vaccine composition and possible uses: The WHO Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC) recommended including the Omicron variant in the composition of updated vaccines. Omicron-specific monovalent vaccines used as booster doses may elicit a greater immune response than index virus-based vaccines; this will also depend on an individual's COVID-19 primary series vaccination status. An Omicron-specific monovalent vaccine, used for the primary series of vaccinations, is not likely to confer as broad protection as current index virus-based vaccine. Therefore, they are not recommended for this use at the present time.

  In terms of administering booster doses of current vaccines, increasing vaccine coverage rates and high exposure to Omicron have led to increasing hybrid immunity in the population. However, the resulting degree and duration of protective immunity remains uncertain, so its use could initially be limited to the most vulnerable populations (as described in the WHO SAGE roadmap).
- Other considerations for the introduction of variant-updated vaccines: Having multiple products for boosters and primary series schedules will create substantial complexity for vaccinators, supply chain planning, documentation of individual vaccination status, safety monitoring, and program performance assessments, among other factors. Vaccine uptake tends to decline with every additional COVID-19 vaccine dose that is recommended as part of the schedule. However, it is possible that the availability of variant-updated vaccines that confer superior and broader immunity will change this trend.
- Conclusions: WHO will continue to review COVID-19 epidemiology, genomic surveillance, phenotypic characteristics, vaccine product development evidence, and vaccine effectiveness data, and will issue policy

recommendations for different use-case scenarios for an updated Omicron-updated vaccines, if and when they are incorporated in the emergency use listing or emergency use authorization by a stringent regulatory authority..

As we await data on variant-updated vaccines, the efficacy of existing vaccines can be optimized using additional doses in priority use groups and using heterologous immunization schedules, as previously recommended by SAGE.

Additional information available at: https://www.who.int/news/item/17-06-2022-interim-statement-on-decision-making-considerations-for-the-use-of-variant-updated-covid-19-vaccines.

Interim recommendations of the WHO Strategic Advisory Committee of Experts (SAGE) on Immunization for the use of the Janssen COVID-19 vaccine

On 6 June 2022, the WHO Strategic Advisory Group of Experts (SAGE) on Immunization issued updated recommendations for use of the Janssen COVID-19 vaccine. The following is a summary of the SAGE report:

- Administration: Results from a phase 3 trial, conducted after the inclusion of this vaccine on the emergency use listing (EUL), showed that two doses (0.5 mL each), administered two months apart, provide higher efficacy for all clinical endpoints (symptomatic infection and severe disease) compared to a single dose.
  WHO recommends the administration of two doses 2 to 6 months apart. If administration of the second dose is delayed beyond 6 months, it should be given at the earliest possible opportunity.
- Considerations for one versus two doses: In situations of limited supply or challenges in vaccine delivery, countries may consider using a single dose. WHO recommends that every effort be made to administer two doses to the highest-priority groups. In terms of the time between the two doses, it has been shown that a longer interval (six months instead of two months) substantially increases humoral immune response. Thus, countries could consider an interval of up to six months between doses.
- Interchangeability with other COVID-19 vaccines (heterologous schedule): It is currently considered standard practice to use the same product for both doses. However, WHO supports a flexible approach to homologous versus heterologous vaccination schedules, taking into account current and projected vaccine supply, considerations such as access, and the potential benefits and risks of the specific products being used.

  Evolving evidence suggests that heterologous COVID-19 vaccination schedules (using WHO EUL COVID-19 vaccines from different platforms) may be more immunogenic and effective than homologous schedules, depending on the specific platforms and order of products used. Two clinical trials have demonstrated that a single dose of the Janssen vaccine and a second dose of an mRNA vaccine (BNT162b2 or mRNA-1273) induce neutralizing antibody concentrations 4 to 22 fold higher than a second dose of the Janssen vaccine.[1,2]

As a heterologous booster, the Janssen vaccine can be administered after completing the primary vaccination series with another COVID-19 vaccine platform. In one study, it was found that the Janssen vaccine had the ability to boost antibody concentrations six months after a primary two-dose series of mRNA vaccine, with increases in antibody responses at week four following the boost comparable to a third dose of a homologous mRNA vaccine, but with higher T cell response.[3]

- People who previously received passive antibody therapy for COVID-19 (monoclonal or convalescent plasma): Vaccination does not need to be delayed in these people , the balance of benefits vs. risks favours proceeding with vaccination even considering the possibility of diminished vaccine effectiveness in this situation.
- Storage conditions: The vaccine is supplied to countries preserved at -20 °C, with a shelf life of 24 months in a multi-dose vial containing 5 doses (0.5ml each). Once thawed, the vaccine should not be re-frozen. The vials should be protected from light, and can be stored at 2°C to 8°C for 11 months. After the first dose is withdrawn, the vial should be kept at between 2 °C and 8 °C for no more than 6 hours, or at the end of the immunization session, whichever comes first.

Additional information available at: https://apps.who.int/iris/bitstream/handle/10665/355160/WHO-2019-nCoV-vaccines-SAGE-recommendation-Ad26.COV2.S-2022.1-eng.pdf?sequence=1&isAllowed=y.

[1] Sablerolles R. Immunogenicity and reactogenicity of booster vaccinations after Ad26.COV2.S priming. MedRxiv; 2021.

[2] Atmar RL. Heterologous SARS-CoV-2 Booster Vaccinations – Preliminary Report. medRxiv; 2021.

[3] Tan CS. Ad26.COV2.S or BNT162b2 Boosting of BNT162b2 Vaccinated Individuals. medRxiv; 2021.

The EMA publishes a new version of guidance for variant strains update to COVID-19 vaccines

On 8 June 2022, the European Medicines Agency (EMA) published the second revision of the guide for updated vaccines for COVID-19 variant strains, which contemplates the procedure for requesting a change in composition of COVID-19 vaccines authorized in the European Union. This change is considered a type II variation, and includes the replacement or addition of a serotype, strain, antigen, or coding sequence, or the combination of serotypes, strains, antigens, or coding sequences.

Where the change in composition consists of the addition of one or more active substances to the original vaccine, different versions of the vaccine may coexist under the same authorization, with each version of the vaccine having separate product information and instructions for use.

The name of the modified vaccine should take into account the provisions of the WHO document, international common names for the active substances of the variant COVID-19[1] vaccine, and incorporation of the qualifiers/abbreviations, such as those used by WHO for designating COVID-19 variants of concern and interest, so as to ensure adequate differentiation between the different authorized versions. The use of the qualifiers/abbreviations, in addition to batch numbers, will also facilitate traceability.

Additional information available at:

https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/procedural-guidance-variant-strains-update-vaccines-intended-protection-against-human-coronavirus_en.pdf

https://cdn.who.int/media/docs/default-source/international-nonproprietary-names-(inn)/21-520_inn_for_vocs.pdf?sfvrsn=9b14f30_6&download=true

https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/

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Decisions of Regional Regulatory Authorities

The FDA releases a memorandum with recommendations for COVID-19 vaccine strain selection

On 30 June, the U.S. Food and Drug Administration (FDA) released a memorandum with recommendations for COVID-19 vaccine strain selection, indicating the procedure for requesting to modify the composition of the licensed vaccine, considered a type II change, which may consist of a substitution or addition of a serotype, strain, antigen, or coding sequence, or a combination of serotypes, strains, antigens, or coding sequences.

Regarding the composition of the updated vaccines, the FDA recommended that manufacturers develop a bivalent COVID-19 vaccine, based on the original strain and the Omicron BA.4/5 strain, for use as a booster dose in the United States.

Additional information available at: https://www.fda.gov/media/134922/download.

Chile's Institute of Public Health (ISP) updates the factsheets for the Moderna and Pfizer-BioNTech COVID-19 vaccines

In June 2022, the ISP released the third version of the Moderna Spikevax COVID-19 vaccine factsheet, along with the sixth version for the Pfizer-BioNTech COVID-19 vaccine. The following are some aspects of the update:

- Moderna COVID-19 vaccine: Information on authorization for use in children 6 to 11 years of age was included. The primary vaccination schedule in this age group includes two doses of 50 micrograms (0.25 mL), which is half the dose of the primary schedule for people 12 years of age and older, administered with a 28-day (four week) interval
- Severely immunocompromised persons 6 years of age and older: A third dose may be given at least 28 days (four weeks) after the second dose to those 12 years of age and older (0.5 mL, 100 micrograms), and to children 6 to 11 years of age (0.25 mL, 50 micrograms) who are severely immunocompromised.
- Pfizer-BioNTech COVID-19 vaccine: Included information regarding authorization for use in children age 5 and older, with authorized presentations according to age range.
    - Individuals 12 years old and older (30 µg mRNA/0.3 mL):
        - Concentrate formulation: Multidose vial (six doses) with purple cap, to be diluted before administration with 1.8 mL of 0.9% sodium chloride injectable solution.
        - Ready-to-use formulation (no prior dilution required): Multidose vial (six doses), lid and label with gray border.
    - Ages 5 to 11 (10 µg mRNA/0.2 mL):
        - Pediatric concentrate formulation: Multidose vial (10 doses) with orange border cap and label, to be diluted before administration with 1.3 mL of 0.9% sodium chloride injectable solution.

Additional information available at: https://www.ispch.cl/wp-content/uploads/2022/06/FIV-PfizerV06-20062022A.pdf.

https://www.ispch.cl/wp-content/uploads/2022/06/FIV-ModernaV03-20062022A.pdf.