COVID-19

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

Forty-first report

WASHINGTON, DC

Updated: 30 April 2023

OPS Organización Panamericana de la Salud
Organización Mundial de la Salud
OFICINA REGIONAL PARA LAS Américas
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OFFICIAL REPORTS ON PHARMACOVIGILANCE PROGRAMS

No significant updates have been reported in official data provided by the Region's National Pharmacovigilance Programs for the period from 29 March to 30 April 2023.

Stroke, myocardial infarction, and pulmonary embolism following bivalent vaccine booster

In January 2023, a warning was issued regarding a possible increased risk of ischemic stroke in people over 65 years of age after receiving bivalent mRNA vaccines. On 13 April, a population-based study was published to assess whether there was a difference in the risk of these events after receiving a booster dose with the bivalent Comirnaty mRNA vaccine (Original/Omicron BA.4–5), compared to the monovalent Comirnaty vaccine, in the French population. This study used data from the French National Health Data System, linked to the national COVID-19 vaccination database. All people over 50 years of age who received a booster dose with a bivalent vaccine between 6 October and 9 November 2022 were included in the study.

For each day of the study period, every person who had received a monovalent vaccine was matched with up to five randomly selected bivalent vaccine recipients. Vaccinated individuals were followed for up to 21 days following vaccination. The risks of ischemic stroke, hemorrhagic stroke, acute myocardial infarction, and pulmonary embolism associated with the bivalent vaccine, compared with the monovalent vaccine, were estimated by determining risk rates, using propensity score-weighted Cox models, which are a useful statistical technique for controlling selection bias and for obtaining more accurate and reliable results when analyzing survival data.

Of a total of 470 962 vaccinated individuals (mean age [±SD] 72.6 ±10.4 years), 97 234 (20.6%) received the monovalent vaccine, and 373 728 (79.4%) received the bivalent vaccine. At 21 days after the booster dose, there was no evidence of increased risk of cardiovascular events (simple or compound) among bivalent vaccine recipients compared to the monovalent vaccine recipients. Events assessed included ischemic stroke (hazard ratio 0.86; 95% confidence interval [CI], 0.58 to 1.27), hemorrhagic stroke (hazard ratio 0.86; 95% CI, 0.46 to 1.61), myocardial infarction (hazard ratio 0.92; 95% CI, 0.62 to 1.36), pulmonary embolism (hazard ratio 0.83; 95% CI, 0.49 to 1.40), and all four events combined (hazard ratio 0.87; 95% CI, 0.69 to 1.09).

Source: Jabagi MJ, Bertrand M, Botton J, Le Vu S, Weill A, Dray-Spira R, Zureik M. Stroke, Myocardial Infarction, and Pulmonary Embolism after Bivalent Booster. N Engl J Med. 2023 Apr 13;388(15):1431–1432. doi: 10.1056/NEJMc2302134. Epub 2023 Mar 29. PMID: 36988584; PMCID: PMC10074551.

Effectiveness of an inactivated vaccine against SARS-CoV-2 in children and adolescents: a large-scale observational study in Chile

On 20 April, a study was published that evaluated the effectiveness of the CoronaVac vaccine in preventing COVID-19 in children and adolescents in Chile. The research analyzed a prospective national cohort of approximately two million children and adolescents ages 6 to 16, and estimated the effectiveness of the inactivated SARS-CoV-2 vaccine in preventing symptomatic cases, hospitalizations, and intensive care unit admissions associated with COVID-19. The risk in individuals who received the full two-dose schedule, 28 days apart, was compared with the risk in unvaccinated individuals during the follow-up period.

The study was conducted in Chile from 27 June 2021 to 12 January 2022, when the Delta variant of SARS-CoV-2 was predominant, though other variants of concern, including the Omicron variant, were also circulating. Inverse probability-weighted survival regression models were used to estimate the relative risks of complete vaccination over non-vaccination, adjusting for relevant demographic, socioeconomic, and clinical factors. This statistical approach helps control for the effect of potential confounders, and improves the accuracy and reliability of results obtained when analyzing survival data.

The results of the study indicated that the adjusted effectiveness of inactivated SARS-CoV-2 vaccine in children and adolescents ages 6 to 16 was 74.5% (95% CI, 73.8–75.2), 91.0% (95% CI, 87.8–93.4), and 93.8% (95% CI, 87.8–93.4) in preventing symptomatic COVID-19, hospitalization, and ICU admission, respectively. For the subgroup of children ages 6 to 11, vaccine effectiveness was 75.8% (95% CI, 74.7–76.8) in preventing COVID-19, and 77.9% (95% CI, 61.5–87.3) in preventing hospitalization.

There were only six children aged 6 to 11 admitted to the ICU in the unvaccinated group, and none among those who received CoronaVac. This results in an estimated vaccine efficacy of 100.0% in preventing COVID-19-related ICU admissions, though more data is likely to result in a lower estimate.

The authors conclude that if children and adolescents between the ages of 6 and 16 receive the two-dose immunization schedule of an inactivated SARS-CoV-2 vaccine, they could be effectively protected against severe COVID-19 disease.

Source: Alejandro Jara et al. Effectiveness of an inactivated SARS-CoV-2 vaccine in children and adolescents: a large-scale observational study. The Lancet Regional Health – Americas 2023;21: 100487. Published Online 20 April 2023. https://doi.org/10.1016/j.lana.2023.100487.

Safety and effectiveness of COVID-19 vaccines in children ages 5 to 11: a systematic review and meta-analysis

On 18 April, a systematic review and meta-analysis was published to assess the safety and efficacy of COVID-19 vaccines approved in the European Union in children ages 5 to 11.

This included studies of any design identified by searching the L.OVE (Living Overview of Evidence) COVID-19 platform up to 23 January 2023. Included were studies with participants ages 5 to 11 who received any COVID-19 vaccine approved by the European Medicines Agency: BNT162b2 (Pfizer-BioNTech) mRNA vaccine, bivalent BNT162b2 (against the original strain and Omicron [BA.4/A.5]), mRNA-1273 (Moderna), or mRNA-1273.214 (original and Omicron BA.1).

Efficacy and effectiveness outcomes were: SARS-CoV-2 infection (PCR-confirmed or antigen-test confirmed), symptomatic COVID-19, hospital admission due to COVID-19, COVID-19-related mortality, multisystem inflammatory syndrome in children (MIS-C), and long-term effects of COVID-19 (long COVID-19 or post-COVID-19 condition, as defined by the study investigators or per WHO definition).

Safety outcomes were: serious adverse events, adverse events of special interest (such as myocarditis), solicited local and systemic events (predefined events, for monitoring their occurrence and severity), and unsolicited adverse events (not previously identified or anticipated in clinical studies or controlled trials). The certainty of evidence was evaluated using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach.

Of the 5272 records screened, 51 studies were included. The analysis yielded the following results after vaccination with two doses of COVID-19 vaccines approved in the European Union in children ages 5 to 11:

- Efficacy against Omicron infection was 41.6% (95% CI, 28.1–52.6; eight nonrandomized studies of interventions [NRSI]; low certainty of evidence [CoE])
- against symptomatic COVID-19: 36.2% (21.5–48.2; six NRSI; low CoE)
- against COVID-19-related hospitalizations: 75.3% (68.0–81.0; six NRSI; moderate CoE)
- against MIS-C: 78% (48–90; one NRSI; very low CoE).

Efficacy against COVID-19-related mortality could not be estimated. Crude mortality rates in unvaccinated children were less than one case per 100 000 children, with no events reported in vaccinated children (four NRSI; low CoE).

No studies on the efficacy of the vaccine against long-term effects were identified.

Vaccine effectiveness after three doses was 55% (50–60; one NRSI; moderate CoE) against Omicron infections, and 61% (55–67; one NRSI; moderate CoE) against symptomatic COVID-19.

No studies reported vaccine efficacy against hospitalization after a third dose.

Safety data suggested no increased risk of serious adverse events (risk ratio [RR] 0.83 [95% CI, 0·21–3.33]) in two randomized controlled trials; low CoE. Approximately 0.23 to 1.2 adverse events were reported per 100 000 vaccines administered.

Evidence on the risk of myocarditis was uncertain (RR 4.6 [0.1–156.1]; one NRSI; low CoE), with 0.13 to 1.04 events observed per 100 000 vaccines administered.

The risk of solicited local reactions was 2.07 (1.80–2.39; two RCTs; moderate CoE) after one dose, and 2.06 (1.70–2.49; two RCTs; moderate CoE) after two doses.

The risk of solicited systemic reactions was 1,09 (1.04-1.16; two RCTs; moderate CoE) after one dose, and 1.49 (1.34–1.65; two RCTs; moderate CoE) after two doses.

The risk of unsolicited adverse events after two doses (RR 1.21 [1.07–1.38]; moderate CoE) was higher in children vaccinated with an mRNA vaccine compared to unvaccinated children.

The authors conclude that, based on the results of this systematic review, in children ages 5 to 11, mRNA vaccines are moderately effective against infections with the Omicron variant, but probably protect well against COVID-19 hospitalizations. Despite being reactogenic, safety data suggest that these vaccines are generally safe. These findings may provide relevant information for public health policy, and for individual decision-making about vaccination in this age group.

Source: Vanessa Piechotta et al. Safety and effectiveness of vaccines against COVID-19 in children aged 5–11 years: a systematic review and meta-analysis. Lancet Child Adolesc Health 2023; April 18, 2023. https://doi.org/10.1016/S2352-4642(23)00078-0.

Comparative effectiveness of Pfizer-BioNTech versus Moderna COVID-19 vaccine boosting in England: OpenSAFELY-TPP

On 15 March, a cohort study was published to compare the effectiveness of BNT162b2 mRNA (Pfizer-BioNTech) and mRNA-1273 (Moderna) vaccines in preventing COVID-19-related infection and hospitalization after a booster dose, during the booster program in England. The study used a matched cohort design that emulated a comparative effectiveness trial, and used linked primary care, hospital, and COVID-19 surveillance records available on the OpenSAFELY-TPP research platform. The records covered a period when the Delta and Omicron variants of SARS-CoV-2 were predominant.

Participants consisted of 3 237 918 adults who received a booster dose of either vaccine between 29 October 2021 and 25 February 2022 as part of the national booster program in England, and who received a primary course of Pfizer–BioNTech's BNT162b2 or Oxford-AstraZeneca's ChAdOx1 vaccine. A total of 1 618 959 people were matched in each vaccine group, with a total of 64 546 391 person-weeks of follow-up.

The main outcome measures were recorded SARS-CoV-2 positive test, COVID-19-related hospital admission, COVID-19-related death, and non-COVID-19-related death at 20 weeks after receipt of the booster dose.

At 20 weeks, there was a cumulative incidence of 164.2 positive SARS-CoV-2 tests per 1000 (95% CI, 163.3 to 165.1) for BNT162b2, and 159.9 (95% CI, 159.0 to 160.8) for mRNA-1273. When comparing mRNA-1273 with BNT162b2, the hazard ratio was 0.95 (0.95 to 0.96). In terms of the risks of hospital admission with COVID-19 at 20 weeks, these were 0.75 per 1000 (0.71 to 0.79) for BNT162b2 and 0.65 (0.61 to 0.69) for mRNA-1273, with a hazard ratio of 0.89 (0.82 to 0.95).

With regard to the cumulative incidence of COVID-19-related deaths at 20 weeks, there were 0.028 deaths per 1000 (0.021 to 0.037) for BNT162b2, and 0.024 (0.018 to 0.033) for mRNA-1273, with a hazard ratio of 0.83 (0.58 to 1.19).

The comparative effectiveness of vaccines was similar in different subgroups, defined by vaccine brand, age, prior SARS-CoV-2 infection, and clinical vulnerability. The effectiveness of both vaccines was consistent across different groups and at different points during the pandemic.

According to the authors, the results suggest that the mRNA-1273 vaccine may offer slightly greater protection, compared to the BNT162b2 vaccine, in preventing positive SARS-CoV-2 tests and hospital admission with COVID-19 at 20 weeks after vaccination, based on a period when the Delta and Omicron variants were predominant.

Source: William J Hulme et al. Comparative effectiveness of BNT162b2 versus mRNA-1273 COVID-19 vaccine boosting in England: matched cohort study. OpenSAFELY-TPP. BMJ 2023;380:e072808.

Risk stratification in COVID-19 vaccine-associated myocarditis in young men: a systematic review.

On 3 January, a systematic review was published whose objective was to assess how the risk of myocarditis is reported in the scientific literature, and whether adequate stratification is performed for pertinent risk factors. If the risk of myocarditis is not stratified by pertinent risk factors, it may be diluted for high-risk groups and inflated for low-risk groups.

The authors conducted a systematic review of the scientific literature, following the PRISMA standards, up to March 2022, which included primary publications from PubMed, Embase, Google Scholar, and MedRxiv. A search was made for studies that estimated the incidence of myocarditis/pericarditis following administration of BNT162b2 (Pfizer), mRNA-1273 (Moderna), or Ad26COVS1 (Janssen) vaccines, and assessed whether studies adequately used relevant stratifiers such as sex, age, number of doses, and manufacturer when reporting the risk of myocarditis. The main outcome assessed was the percentage of studies using each stratifier. In addition, the incidence of myocarditis in men after the first and second doses of BNT162b2 (Pfizer) or mRNA-1273 (Moderna) vaccines was evaluated.

Of the 29 studies included in the review, from North America, Europe, Asia, and elsewhere, 28% (8/29) used all four stratifiers, while 45% (13/29) used only one or none. Studies using all four stratifiers reported an incidence of myocarditis ranging from 8.1 to 39 cases per 100 000 persons (or doses). On the other hand, six studies reported an incidence greater than 15 cases per 100 000 persons (or doses) in males ages 12–24 after dose two of an mRNA-based vaccine.

In addition, men younger than 40 years old who received a second dose of an mRNA-based vaccine were found to have the highest risk of myocarditis. These findings highlight the

importance of clear and detailed reporting on risk factors in obtaining an accurate assessment of myocarditis risk after vaccination.

Source: Benjamin Knudsen et al. COVID-19 vaccine induced myocarditis in young males: a systematic review. Eur J Clin Invest. 2023 Jan 3: e13947. doi: 10.1111/eci.13947 [Epub ahead of print] PMCID: PMC9880674 PMID: 36576362.

Safety, immunogenicity, and efficacy of the NVX-CoV2373 COVID-19 vaccine in adolescents: a randomized clinical trial.

On 26 April, a study was published to evaluate the safety, immunogenicity, and efficacy of NVX-CoV2373 in adolescents ages 12 to 17, in an expansion of the PREVENT-19 study. This multicenter, phase 3, randomized, placebo-controlled, observer-blind clinical trial is being conducted in the United States. Participant enrollment ran from 26 April to 5 June 2021, and the study is ongoing. A blinded crossover was implemented after two months of safety follow-up to offer active vaccine to all participants.

Of the 2304 participants evaluated, 57 were excluded due to prior laboratory-confirmed SARS-CoV-2 infection or known immunosuppression. The remaining 2247 participants were randomly assigned to receive NVX-CoV2373 or placebo in a 2:1 ratio, with 21 days between injections.

Main outcomes included serological non-inferiority of neutralizing antibody responses compared with those in young adults (ages 18-25) in the PREVENT-19 study, protective efficacy against laboratory-confirmed COVID-19, and assessment of reactogenicity and safety.

Of the total randomized participants, 2232 were included in the safety analysis (of whom 1487 received NVX-CoV2373 and 745 received placebo), with a mean age of 13.8; 1172 (52.5%) were male, 1660 (74.4%) were white, and 359 (16.1%) had had a previous SARS-CoV-2 infection at baseline.

After vaccination, the ratio of geometric mean titers of neutralizing antibodies in adolescents compared with young adults was 1.5 (95% CI, 1.3–1.7). Twenty mild COVID-19 cases occurred after a median of 64 (IQR, 57-69) days of follow-up. Of these, six occurred among NVX-CoV2373 recipients, with an incidence of 2.90 (95% CI, 1.31-6.46) cases per 100 person-years, and 14 occurred among placebo recipients, with an incidence of 14.20 (95% CI, 8.42-23.93) cases per 100 person-years, yielding a vaccine efficacy of 79.5% (95% CI, 46.8%-92.1%).

The vaccine showed 82.0% efficacy (95% CI, 32.4%-95.2%) against the Delta variant, which was the only viral variant identified by sequencing (11 out of 20 cases [55%] yielded sequencing

results). Reactogenicity was largely mild to moderate and transient, with a trend toward greater frequency after the second dose of NVX-CoV2373. Serious adverse events were rare and were evenly distributed across treatment groups. No adverse events led to study discontinuation.

According to the authors, the results obtained in this randomized clinical trial indicate that the NVX-CoV2373 vaccine is safe, immunogenic, and effective in preventing COVID-19, including the predominant Delta variant, in adolescents. Children and adolescents represent an important segment of the population that must be vaccinated to achieve herd immunity and control the pandemic.

Source: Áñez G, Dunkle LM, Gay CL et al. Safety, Immunogenicity, and Efficacy of the NVX-CoV2373 COVID-19 Vaccine in Adolescents: A Randomized Clinical Trial. JAMA Netw Open. 2023;6(4): E239135. doi:10.1001/jamanetworkopen.2023.9135. https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2804216.

U.S. Food and Drug Administration (FDA) Authorizes Changes to Simplify Use of Moderna and Pfizer-BioNTech Bivalent mRNA COVID-19 Vaccines

On 18 April, the FDA amended the emergency use authorizations (EUAs) for the Moderna and Pfizer-BioNTech (Original and Omicron BA.4–5) COVID-19 mRNA vaccines to include their use for all doses administered to persons six months of age and older, including for an additional dose or doses for certain populations in the United States.

The Moderna and Pfizer-BioNTech monovalent COVID-19 vaccines are no longer licensed for use in the United States. The FDA will authorize their export under certain conditions.

Additional information available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-takes-key-action-approving-second-covid-19-vaccine.

The European Medicines Agency (EMA) recommends granting an extension of indication for the bivalent Spikevax COVID-19 vaccine

The EMA's Committee on Medical Products for Human Use, at its meeting on 24-26 April, recommended granting an extension of indication for Moderna's bivalent Spikevax (Original/Omicron BA.4–5) COVID-19 vaccine to include its use as a booster in children ages 6 to 11.

Additional information available from: https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-4-7-april-2022.

U.S. FDA extends indication for Pfizer-BioNTech bivalent COVID-19 vaccine for children with certain types of immunocompromise

On 28 April, the FDA authorized use of the Pfizer-BioNTech bivalent COVID-19 vaccine for persons 6 months to 4 years of age with certain types of immunocompromise who have previously received three 0.2 mL doses of the monovalent (Original) Pfizer-BioNTech COVID-19 vaccine or the bivalent (Original/Omicron BA.4-5) Pfizer-BioNTech COVID-19 vaccine.

A fourth dose should be administered at least one month following the most recent dose; additional doses may be administered at the discretion of the healthcare provider, taking into consideration the individual's clinical circumstances.

Additional information available from: https://www.fda.gov/news-events/press-announcements/fda-roundup-april-28-2023?utm_medium=email&utm_source=govdelivery.

Australia's Therapeutic Goods Administration (TGA) announces that the product information for the Pfizer COVID-19 vaccine and for the bivalent vaccines have been updated

The most recent edition of the WHO Pharmaceuticals Newsletter, No. 1, 2023, stated that the Australian TGA had reported changes to the product information for the following vaccines, to include a warning about:

Pfizer-BioNTech mRNA vaccine (monovalent and bivalent): Potential risk of non-sexually acquired genital ulceration. However, the causal association between the vaccine and this event has not been definitively established.

Oxford/AstraZeneca Vaxzevria: Potential risks of acute disseminated encephalomyelitis (ADEM). However, the causal association between the vaccine and this event has not been definitively established. Health professionals should be alert to signs and symptoms of demyelinating disorders to ensure a correct diagnosis, in order to initiate supportive care and appropriate treatment and rule out other possible causes.

Additional information available from: https://www.who.int/publications/i/item/9789240070240.

Updated COVID-19 vaccine recommendations from the World Health Organization's Strategic Advisory Group of Experts (SAGE)

On 28 April, PAHO published the following resources related to updating the WHO/SAGE roadmap for prioritizing the use of COVID-19 vaccines, included in the 40th edition of this Report.

Available resources are as follows:

- **Technical note:** Available from: https://iris.paho.org/handle/10665.2/57425
- **Infographic:** Available from: https://www.paho.org/en/documents/update-who-recommendations-vaccination-against-covid-19-infographic
- **Summary table:** Available from: https://www.paho.org/en/documents/update-who-recommendations-vaccination-against-covid-19-abstract-table

Conclusions of the Meeting of the WHO Technical Advisory Group on COVID-19 Vaccine Composition

On 16–17 March, the meeting of the WHO Technical Advisory Group on the Composition of COVID-19 Vaccines (TAG-CO-VAC) was held. Based on a review of available data on administration of booster doses of new COVID-19 vaccines containing descendant lineages of the Omicron variant, they concluded:

Booster doses of index virus-based vaccines continue to confer high levels of protection against severe disease and death caused by all SARS-CoV-2 variants, including contemporary Omicron descendent lineages.

Protection from severe disease and symptomatic infection induced by index virus-based vaccines and BA.1- or BA.4/5-containing bivalent mRNA vaccines declines over time. However, protection from severe disease is maintained longer than protection from symptomatic infection.

As compared to index virus-based vaccines, booster doses of BA.1- or BA.4/5-containing bivalent mRNA vaccines may modestly increase vaccine effectiveness against symptomatic disease.

Both BA.1- and BA.4/5-containing bivalent mRNA vaccines enhance the magnitude and elicit greater breadth of cross-reactive immune responses to SARS-CoV-2 variants when used as a booster dose, as compared to the index virus-based vaccines.

Given that the SARS-CoV-2 virus is continuously evolving, it is desirable to have vaccines that confer broader cross-reactivity.

It is essential to ensure equitable access worldwide to all vaccines with an updated antigen composition.

The Group continues to encourage the further development of vaccines that enhance mucosal immunity because they may improve protection against infection and transmission of SARS-CoV-2.

In the coming months, the Group will continue to meet to assess the available evidence and make recommendations on the composition of COVID-19 vaccines.

Additional information available from: https://www.who.int/news/item/14-04-2023-report-of-the-meeting-of-the-who-technical-advisory-group-on-covid-19-vaccine-composition-(tag-co-vac)-held-on-16-17-march-2023.

Inclusions in the WHO Emergency Use Listing (EUL)

On 17 April, WHO added the bivalent Comirnaty COVID-19 vaccine (Original/Omicron BA.4–5) to the Emergency Use Listing (EUL). Following are additional details on the authorization:

COVID-19 vaccine (EUL)	Emergency use authorization holder	Responsible NRA*	Presentation
COMIRNATY Original /Omicron BA.4–5 (5/5 mcg)	BioNTech Manufacturing GmbH	European Medicines Agency (EMA)	1.3 mL vial

*The NRA that first authorized the vaccine and that is responsible for supervision of the vaccine.

Additional information available from: https://extranet.who.int/pqweb/vaccines/comirnaty-originalomicron-ba4-5-57-mcg.