CONSOLIDATED REGIONAL AND GLOBAL INFORMATION ON ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI) AND OTHER UPDATES

XLIX Report

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CONTENTS

Brazil

Dengue vaccine

From 1 March 2023 to 18 June 2024, 2,162,364 doses of attenuated dengue vaccine were administered in Brazil. Of these, 1,917,041 (88.7%) were first doses and 245,323 (11.3%) were second doses. In the same period, 2270 AEFI reports were recorded, equivalent to 105 notifications per 100,000 doses administered. Of these, 1,587 (69.9%) were non-serious AEFIs. No serious AEFIs with fatal outcome were reported.

Vaccine pharmacovigilance in Brazil detected an increase in the frequency of hypersensitivity reactions and anaphylaxis following dengue vaccination. There were 442 (204.4 per million doses administered) notifications of AEFIs with terms suggestive of hypersensitivity reactions and anaphylaxis, of which 342 (77.4%) were classified as immediate hypersensitivity and 100 (22.6%) as delayed hypersensitivity. Of the cases of immediate hypersensitivity, 63 (18.4%) were anaphylactic reactions (29.1 per million doses administered). No deaths were reported.

Of the cases of anaphylaxis following dengue vaccination, 33 (52.4%) were female. Median age was 11 years (Q1: 10 and Q3: 13). Only five cases had a known history of allergies, and 11 had comorbidities. The median time between vaccination and symptom onset was 23 minutes (ranging from 3 to 240 minutes), with 25 (39.7%) cases presenting symptoms in the first 15 minutes after administration of the attenuated dengue vaccine.

Source: Departamento do Programa Nacional de Imunizações, Department of Health Surveillance and Environment, Ministry of Health. Report: Monitoramento da segurança da vacina dengue atenuada, SE 1 de 2023 à SE 25 de 2024, Brasil. 08 August 2024. Available from: https://www.gov.br/saude/pt-br/vacinacao/esavi/monitoramento-dos-eventos/2024/informe-monitoramento-da-seguranca-da-vacina-dengue-atenuada.pdf/view. Data reproduced by PAHO/WHO.

Chile

COVID-19 vaccines

In 2023, 1277 AEFIs were reported, of which 396 were related to COVID-19 vaccines. This represents a significant decrease compared to 2022, when 3170 AEFIs were recorded, of which 2583 were associated with these vaccines. This decrease can be explained by the reduction in the number of doses administered (from 19.6 million in 2022 to 3.2 million in 2023) and by reduced public concern following the end of the health emergency in May 2023.

Source: Public Health Institute, Ministry of Health of Chile. Estadísticas del Centro Nacional de Farmacovigilancia, Año 2023. September 2024. Available from: https://www.ispch.cl/newsfarmacovigilancia/24/images/parte02.pdf. Data reproduced by PAHO/WHO.

Costa Rica

COVID-19 vaccines

During 2023, 29 AEFIs related to COVID-19 vaccines were recorded in Costa Rica, 24 associated with Pfizer-BioNTech, four with AstraZeneca, and one with Moderna. As for adverse events of special interest (AESI) for Pfizer-BioNTech, 21 cases were reported, including six of seizures, and one case of atrial fibrillation with pulmonary thromboembolism, retrobulbar optic neuritis, cardioembolic stroke, reactive arthritis, acute myocardial infarction, Guillain-Barre syndrome, ventricular arrhythmia, acute cardiomyopathy with portal vein thrombosis and polyneuropathy, herpes zoster, Bell's palsy, anaphylactic reaction, thrombophlebitis, sudden death, dysgeusia/anosmia, and disseminated cutaneous herpes zoster. Two cases resulted in deaths, although only one was classified as an AESI, with multiple patient comorbidities as contributing factors.

Source: Ministry of Health of Costa Rica, National Pharmacovigilance Center. III Informe Cuatrimestral: Eventos Supuestamente Atribuibles a la Vacunación e Inmunización (ESAVI) con Vacunas contra la COVID-19, 2023. Dirección de Regulación de Productos de Interés Sanitario, 2023. February 2024. Available from: https://www.ministeriodesalud.go.cr/index.php/biblioteca-de-archivos-left/documentos-ministerio-de-salud/regulacion-de-la-salud/farmacovogilancia/informe-de-sospecha-de-reacciones-adversas-a-medicamentos/informes-acumulados-esavi-covid-19/informes-acumulados-del-2023/7235-iii-reporte-cuatrimestral-eventos-supuestamente-atribuibles-a-la-vacunacion-e-inmunizacion-esavi-con-vacunas-contra-la-covid-19/file. Data reproduced by PAHO/WHO.

Mexico

COVID-19 vaccines

As of 30 June 2024, 133,972,266 doses of COVID-19 vaccine had been administered in Mexico since the start of vaccination. To date, there have been a total of 40,213 AEFI notifications, of which 3.19% (1,284) were classified as serious.

Most serious (57%) and non-serious (71%) AEFIs occurred in women. In terms of the distribution by age group, non-serious AEFIs occurred mostly in the age group 30-39, while serious AEFIs occurred mostly in people over age 60. The main signs and symptoms in serious AEFIs were headache 43.19% (559), asthenia 37.48% (485), and dyspnea 28.90 % (374).

Source: Subsecretaría de Prevención y Promoción de la Salud, Dirección General de Epidemiología, Dirección de Vigilancia Epidemiológica de Enfermedades Transmisibles. Reporte ESAVI COVID-19 Junio 2024. 25 July 2024. Available from: https://www.gob.mx/cms/uploads/attachment/file/932840/REPORTEESAVIDVEETJUNIO2024.pdf. Data reproduced by PAHO/WHO.

COVID-19 vaccines

Long-term prognosis of patients with myocarditis attributed to COVID-19 mRNA vaccination, SARS-CoV-2 infection, or conventional etiologies

On 26 August, a cohort study based on the French National Health Data System was released. Its objective was to study the long-term cardiovascular complications of post–COVID-19 mRNA vaccination myocarditis and other types of myocarditis. The study also evaluated disease management based on a study of the frequency of medical procedures and drug prescriptions during an 18-month follow-up after hospitalization. The study population included 4,635 individuals aged 12 to 49 years hospitalized for myocarditis in France between December 2020 and June 2022. Of these, 558 had postvaccine myocarditis, 298 had post–COVID-19 myocarditis, and 3,779 had conventional myocarditis.

The results indicate that patients with postvaccine myocarditis were younger than those with post–COVID-19 and conventional myocarditis (mean age of 25.9, 31, and 28.3 years, respectively).

Additionally, most of those with postvaccine myocarditis (84%), post–COVID-19 myocarditis (67%) and conventional myocarditis (79%) were men.

The vaccine group had a lower incidence of cardiovascular complications, with 32 events of a total of 558 patients, versus 497 events of a total of 3,779 patients in the conventional myocarditis group with a weighted hazard ratio of 0.55. Patients with post–COVID-19 myocarditis had 36 events of a total of 298 patients, with a weighted hazard ratio of 1.04 compared to the conventional myocarditis group.

The clinical management of patients with postvaccine or post–COVID-19 myocarditis followed a similar trend in the 18 months following hospital discharge to that of patients with conventional myocarditis.

The authors conclude that patients with post–COVID-19 mRNA vaccination myocarditis show a lower frequency of cardiovascular complications than those with conventional myocarditis. However, affected patients, mainly healthy young men, may require clinical follow-up up to several months after hospital discharge to ensure satisfactory recovery.

Source: Laura Semenzato *et al.* Long-Term Prognosis of Patients with Myocarditis Attributed to COVID-19 mRNA Vaccination, SARS-CoV-2 Infection, or Conventional Etiologies. JAMA published online on 26 August 2024. doi:10.1001/jama.2024.16380

Safety and effectiveness of COVID-19 vaccines during pregnancy: a living systematic review and meta-analysis

On 15 July, this systematic review and meta-analysis was released, with the aim of evaluating studies on the safety and effectiveness of COVID-19 vaccines administered to pregnant persons.

Searches were conducted up to October 2023 in databases and websites, without restrictions on language or publication status. Additional relevant studies were identified by hand searching the reference lists to find additional studies. An independent team selected eligible studies using the software COVIDENCE. Data extraction and risk of bias assessment were performed independently by pairs of authors. Disagreements were resolved by consensus. The study used random-effects meta-analyses of adjusted relative effects for relevant confounders of comparative studies and proportional meta-analyses to summarize frequencies from one-sample studies using the software R statistical. Certainty of evidence was evaluated with GRADE. Findings are available on an interactive living systematic review webpage, including updated evidence map and real-time meta-analyses customizable by subgroups and filters.[1]

In total, 177 studies were included involving 638 791 participants from 41 countries. Among the 11 types of COVID-19 vaccines identified, the most frequently used platforms were mRNA (154 studies), viral vector (51), and inactivated virus vaccines (17). Low to very low-certainty evidence suggests that vaccination may result in minimal to no important differences compared to no vaccination in the assessed outcomes, from 26 fewer to 17 more events per 1,000 pregnant persons, and 13 fewer to nine more events per 1,000 neonates.

Statistically significant reductions were found in emergency cesarean deliveries (9%) with mRNA vaccines, and in stillbirth (75–83%) with mRNA/viral vector vaccines.

Low to very low-certainty evidence suggests that vaccination during pregnancy with mRNA vaccines may reduce severe cases or hospitalizations in pregnant persons with COVID-19 (72%; 95% CI 42–86), symptomatic COVID-19 (78%; 95% CI 21–94), and confirmed SARS-CoV-2 infection (82%; 95% CI 39–95). Reductions were lower with other vaccine types and during Omicron variant dominance than Alpha and Delta dominance. Infants also presented with fewer severe cases or hospitalizations due to COVID-19 (64%; 95% CI 37–80) and laboratory-confirmed SARS-CoV-2 infection (66%; 95% CI 37–81).

The authors conclude that they found a large body of evidence supporting the safety and effectiveness of COVID-19 vaccines during pregnancy. This living systematic review highlights the relevance of continuous vaccine safety and effectiveness monitoring, particularly in at-risk populations for COVID-19 impact such as pregnant persons, during the introduction of new vaccines.

Source: Agustín Ciapponi, Mabel Berrueta *et al.* Safety and Effectiveness of COVID-19 Vaccines During Pregnancy: A Living Systematic Review and Meta-analysis. Drug Safety. https://doi.org/10.1007/s40264-024-01458-w

[1] https://www.safeinpregnancy.org/living-systematic-review/

Respiratory Syncytial Virus (RSV) vaccines

Nonadjuvanted bivalent respiratory syncytial virus vaccination and perinatal outcomes

On 8 July, a retrospective observational cohort study was published with the objective of evaluating the association between prenatal RSV vaccination status and perinatal outcomes among patients who delivered during the vaccination season.

The study was conducted at two New York City hospitals among patients who gave birth to singleton gestations at 32 weeks' gestation or later, from 22 September 2023 to 31 January 2024.

The exposure consisted of prenatal RSV vaccination with the RSVpreF vaccine captured from the health system's electronic health records.

The primary outcome was preterm birth (PTB), defined as less than 37 weeks' gestation. Secondary outcomes included hypertensive disorders of pregnancy (HDP), stillbirth, small-for-gestational age birth weight, neonatal intensive care unit (NICU) admission, neonatal respiratory distress with NICU admission, neonatal jaundice or hyperbilirubinemia, neonatal hypoglycemia, and neonatal sepsis. Logistic regression models were used to estimate odds ratios (ORs), and multivariable logistic regression models and time-dependent covariate Cox regression models were performed.

From the analysis, it was observed that of 2,973 pregnant individuals (median age, 34.9 [32.4-37.7] years), 1026 (34.5%) received prenatal RSVpreF vaccination.

The vaccine was approved and recommended in the United States for pregnant individuals at 32 0/7 to 36 6/7 weeks' gestation and the analysis showed that fifteen patients inappropriately received the vaccine at 37 weeks' gestation or later and were included in the nonvaccinated group.

During the study period, 60 vaccinated patients experienced PTB vs 131 of unvaccinated patients (6.7%). Prenatal vaccination was not associated with an increased risk for PTB after adjusting for potential confounders (adjusted OR, 0.87; 95% CI, 0.62-1.20) and addressing immortal time bias (hazard ratio [HR], 0.93; 95% CI, 0.64-1.34).

There were no significant differences in pregnancy and neonatal outcomes based on vaccination status in the logistic regression models, but an increased risk of HDP in the time-dependent model was seen (HR, 1.43; 95% CI, 1.16-1.77).

The authors conclude that, in this cohort study of pregnant individuals who delivered at 32 weeks' gestation or later, the RSVpreF vaccine was not associated with an increased risk of PTB and perinatal outcomes. These data support the safety of prenatal RSVpreF vaccination, but further investigation into the risk of HDP is warranted.

Source: Moeun Son et al., Nonadjuvanted Bivalent Respiratory Syncytial Virus Vaccination and Perinatal Outcomes. JAMA Network Open. 2024;7(7): e2419268. doi:10.1001/jamanetworkopen.2024.19268

Mpox vaccine

Effectiveness of modified vaccinia ankara-bavarian nordic vaccine against mpox infection: emulation of a target trial

On 19 August, this emulation of a target trial was released with the objective of estimating the real-world effectiveness of modified vaccinia Ankara-Bavarian Nordic (MVA-BN) vaccine against mpox infection.

The linked databases in the health system of Ontario, Canada were used.

A total of 9,803 men were eligible, aged ≥18 years with a history of being tested for syphilis and a laboratory confirmed bacterial sexually transmitted infection (STI) in the previous year, or who filled a prescription for HIV pre-exposure prophylaxis in the previous year. Six hundred and fourteen individuals were excluded for various reasons.

Between 12 June 2022 and 27 October 2022, those who had been vaccinated 15 days previously were matched 1:1 with unvaccinated men by age, geographical region, past HIV diagnosis, number of bacterial STI diagnoses in the previous three years, and receipt of any non-MVA-BN vaccine in the previous year. A total of 3,204 men who received the vaccine were matched to 3,204 unvaccinated controls.

The main outcome measure was vaccine effectiveness of one dose of subcutaneously administered MVA-BN against laboratory confirmed mpox infection. A Cox proportional hazards model was used to estimate hazard ratios to compare the rate of laboratory confirmed mpox between the two groups.

The median age of matched participants was 35 years (interquartile range (IQR) 29-46 years) and more than half of the participants (66.1%) were residents of Toronto. During a median follow-up of 85 days (IQR 32-110 days) after the first dose among vaccinated individuals and 86 (31-111) days among unvaccinated individuals, we observed a total of 71 infections, with 21 in the vaccinated group (0.09 per 1,000 person days, 95% CI 0.05 to 0.13) and 50 in the unvaccinated group (0.20 per 1,000 person days, 0.15 to 0.27) over the study period of 153 days.

The hazard ratio for infection in the vaccinated group compared with unvaccinated group was 0.42 (95% CI 0.25 to 0.69), thus the estimated vaccine effectiveness for a single dose of MVA-BN against mpox infection was 58% (95% CI 31% to 75%).

The authors conclude that the findings of this study, conducted in the context of a targeted vaccination program and evolving outbreak of mpox, suggest that one dose of MVA-BN is moderately effective in preventing mpox infection.

Source: Christine Navarro *et al.* Effectiveness of modified vaccinia Ankara-Bavarian Nordic vaccine against mpox infection: emulation of a target trial. BMJ2024;386: e078243

Dengue vaccine

Efficacy and safety of butantan-dv in participants aged 2–59 years through an extended follow-up: results from a double-blind, randomized, placebo-controlled, phase 3, multicenter trial in Brazil

On 5 August, this double-blind, randomized, placebo-controlled, phase 3, multicenter trial in Brazil was released, with the objective of assessing the safety and efficacy of the live, attenuated, tetravalent Butantan-dengue vaccine (Butantan-DV) in adults, adolescents, and children through an extended follow-up period, with an average of 3.7 years of follow-up.

Healthy participants (aged 2–59 years) who had not previously received a dengue vaccine were enrolled and randomly assigned 2:1 (stratified by age 18–59 years, 7–17 years, and 2–6 years) using a central electronic randomization system to receive 0.5 mL of Butantan-DV (containing approximately 10^3 plaque-forming units of each of the four vaccine virus strains) or placebo, administered subcutaneously.

Vaccine efficacy was calculated with the accrual of virologically confirmed dengue (VCD) cases (by RT-PCR) at least 28 days after vaccination up until the cutoff (at least two years of follow-up from the last participant enrolled). The primary endpoint was vaccine efficacy against VCD after day 28 by any dengue virus (DENV) serotype regardless of dengue serostatus at baseline.

Of 16 363 participants assessed for eligibility, 16 235 were randomly assigned between 22 February 2016, and 5 July 2019, and received a single-dose of Butantan-DV (10 259 participants) or placebo (5976 participants).

At the data cutoff (13 July 2021), participants had 2–5 years of follow-up (mean 3.7 years [SD 1.0], median 4.0 years [IQR 3.2–4.5]).

A total of 356 VCD cases were captured through the follow-up (128 in the vaccine group and 228 in the placebo group). Vaccine efficacy against VCD caused by any DENV serotype was 67.3% (95% CI 59.4–73.9); cases caused by DENV-3 or DENV-4 were not observed. The proportions of participants who had serious adverse events were similar between treatment groups (637 [6.2%] in the vaccine group and 395 [6.6%] in the placebo group) up until the cutoff.

The authors conclude that a single dose of Butantan-DV was generally well tolerated and efficacious against symptomatic VCD (caused by DENV-1 and DENV-2) for a mean of 3.7 years. These findings support the continued development of Butantan-DV to prevent dengue disease in children, adolescents, and adults regardless of dengue serostatus.

Source: Nogueira, Mauricio L Monteiro, Wuelton *et al.* Efficacy and safety of Butantan-DV in participants aged 2–59 years through an extended follow-up: results from a double-blind, randomised, placebo-controlled, phase 3, multicentre trial in Brazil. The Lancet Infectious Diseases, DOI: 10.1016/S1473-3099(24)00376-1

COVID-19 vaccine

FDA approves and authorizes updated mRNA COVID-19 vaccines to better protect against currently circulating variants

On 22 August, the US Food and Drug Administration approved and granted emergency use authorization (EUA) for updated mRNA COVID-19 vaccines (2024-2025 formula), manufactured by ModernaTX Inc. and Pfizer Inc., to include a monovalent component that corresponds to the Omicron variant KP.2 strain of SARS-CoV-2.

In early June, the FDA advised manufacturers of licensed and authorized COVID-19 vaccines that the COVID-19 vaccines (2024-2025 formula) should be monovalent JN.1 vaccines. Based on the further evolution of SARS-CoV-2 and a rise in cases of COVID-19, the FDA advised manufacturers to use the KP.2 strain.

The FDA assessed manufacturing and nonclinical data to support the change to include the 2024-2025 formula in these vaccines. The updated vaccines are manufactured using a similar process as previous formulas of these vaccines.

Individuals who receive the updated vaccines may experience similar side effects as those reported by individuals who received the previous formulas of this type of COVID-19 vaccine.

The updated mRNA COVID-19 vaccines include Comirnaty and Spikevax, both of which are approved for individuals 12 years of age and older. The Moderna COVID-19 Vaccine and Pfizer-BioNTech COVID-19 Vaccine are both authorized for emergency use for individuals 6 months through 11 years of age.

Additional information available from: https://www.fda.gov/news-events/press-announcements/fda-approves-and-authorizes-updated-mrna-covid-19-vaccines-better-protect-against-currently

FDA authorizes updated Novavax COVID-19 vaccine

On 30 August, the US Food and Drug Administration granted emergency use authorization (EUA) for an adjuvant COVID-19 vaccine (2024-2025 formula) from Novavax Inc. of Gaithersburg, Maryland, for use in individuals 12 years of age and older. This vaccine includes a monovalent component that corresponds to the Omicron variant JN.1 strain of SARS-CoV-2.

Individuals 12 years of age and older who have never been vaccinated with any COVID-19 vaccine are eligible to receive two doses of this updated vaccine, three weeks apart. Individuals who have been vaccinated only with one dose of any Novavax COVID-19 vaccine are eligible to receive one dose of the updated Novavax COVID-19 vaccine at least three weeks after the previous dose.

Those who have received two or more doses of a prior formula of the Novavax COVID-19 vaccine or another manufacturer's vaccine are eligible to receive a single dose of the updated Novavax COVID-19 vaccine at least two months after the last dose of a COVID-19 vaccine.

The FDA assessed manufacturing and nonclinical data to support the change to the 2024-2025 formula. The updated vaccine is manufactured using a similar process as previous formulas of

this vaccine. Individuals who receive this vaccine may experience similar side effects as those reported with previous formulas of this COVID-19 vaccine.

Additional information available from: https://www.fda.gov/news-events/press-announcements/fda-authorizes-updated-novavax-covid-19-vaccine-better-protect-against-currently-circulating

Influenza vaccine

FDA approves nasal spray influenza vaccine for self- or caregiver-administration

On 20 September, the US Food and Drug Administration approved the first vaccine for self- or caregiver-administration, the FluMist live intranasal flu vaccine from MedImmune LLC, indicated for the prevention of influenza disease caused by influenza virus subtypes A and B in individuals 2 through 49 years of age

FluMist is sprayed into the nose. It was initially approved by the FDA in 2003 for use in individuals 5 through 49 years of age, and in 2007, the FDA approved the use of FluMist to include children 2 through 5 years of age.

This vaccine contains a weakened form of live influenza virus strains. A prescription is still required to receive FluMist and it may be administered by a health care provider in a health care setting (including a pharmacy) or it may be administered by the vaccine recipient or a caregiver who is 18 years of age or older. For individuals 2 through 17, a caregiver should administer FluMist.

The most common side effects of FluMist are fever over 100°F in children 2 through 6 years of age, runny nose and nasal congestion in individuals 2 through 49 years of age and a sore throat in adults 18 through 49 years of age.

Additional information available from: https://www.fda.gov/news-events/press-announcements/fda-approves-nasal-spray-influenza-vaccine-self-or-caregiver-administration

Mpox (Monkeypox) vaccine

Brazil's National Health Surveillance Agency Renews Exceptional Authorization for Use of Two Mpox Vaccines

On 27 August, the National Health Surveillance Agency (ANVISA) announced that it had renewed the exceptional authorization for the use of two mpox vaccines, Jynneos and Imvanex, manufactured respectively by Bavarian Nordic A/S, with headquarters at Hejreskovvej 10A, 3490 Kvistgaard, Denmark, and IDT Biologika GmbH, with headquarters at Am Pharmapark 06861 Dessau-Roßlau, Germany.

The exceptional authorization applies only to the use of these vaccines by the Brazilian Ministry of Health and will be valid for six months.

Additional information available from: https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2024/mpox-anvisa-renova-autorizacao-excepcional-de-uso-de-duas-vacinas

ANVISA approves resolution exempting registration for the importation of Mpox medications and vaccines

On 22 August, ANVISA announced that the Collegiate Council of ANVISA had approved a resolution providing for the exemption from registration and exceptional authorization for the importation of medications and vaccines acquired by the Ministry of Health for the prevention or treatment of mpox. The measure is provisional and exceptional.

The regulation provides for a simplified, prioritized procedure for the importation of medications and vaccines, similar to the model previously adopted for imports through the COVAX Fund.

This resolution allows the Ministry of Health to ask ANVISA to exempt medications and vaccines from registration if they have already been approved for the prevention or treatment of mpox by the following international regulatory authorities: World Health Organization (WHO); European Medicines Agency (EMA); US Food and Drug Administration (USFDA); Medicines and Healthcare products Regulatory Agency of the United Kingdom (MHRA/UK); Pharmaceuticals and Medical Equipment Agency/Ministry of Health, Labor and Welfare of Japan (PMDA/MHLW/JP); and the Canadian Regulatory Agency (Health Canada).

Medications or vaccines must have the same conditions of use, manufacturing sites, and pharmaceutical forms approved and published by the regulatory authorities mentioned above.

The request for exemption from registration will be evaluated mainly by the technical areas of ANVISA and the decision must be made within seven working days.

Additional information available from: https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2024/mpox-anvisa-reedita-norma-que-simplifica-regras-para-registro-e-importacao-de-medicamentos-e-vacinas-1

Mexico's federal commission for protection against health risks implements an immediate review procedure for the regulatory approval of Mpox vaccines

On 3 September, Mexico's COFEPRIS announced that it has implemented an immediate review procedure for mpox vaccines submitted for regulatory approval.

COFEPRIS is currently evaluating the quality, safety, and efficacy of the smallpox and mpox vaccine Jynneos, submitted for regulatory approval by the company Bavarian Nordic, intended for primary vaccination or revaccination of adults 18 years of age and older at high risk of exposure to the virus.

COFEPRIS indicated that prior to the submission of this application, they maintained continuous technical communication with the Danish pharmaceutical company, and that they expect to carry out a rigorous evaluation of the quality, safety, and efficacy of the biological

product and the risk/benefit ratio within 10 days, in order to guarantee national access to this vaccine.

To date, Mexico does not have a specific vaccine or treatments for mpox virus infection. Disease management focuses primarily on relieving the symptoms, treating lesions, and preventing complications.

Additional information available from: https://www.gob.mx/cofepris/articulos/ingresa-ante-cofepris-tramite-de-registro-sanitario-para-vacuna-contra-viruela-simica-mpox?idiom=es

EMA recommended extending indication of Mpox vaccine to adolescents

On 19 September, the European Medicines Agency (EMA) recommended extending the indication of the smallpox and mpox vaccine Imvanex to adolescents from 12 to 17 years of age. This vaccine is already authorized in the European Union (EU) to protect against smallpox, mpox, and the disease caused by the vaccinia virus in adults.

Imvanex contains a live, highly weakened form of a virus called "modified vaccinia Ankara virus" (MVA-BN), which is related to the smallpox virus. EMA's Committee for Medicinal Products for Human Use (CHMP) based the recommendation to extend the use of Imvanex to adolescents on the interim results of a study that compared the vaccine's ability to generate an immune response (produce virus-specific antibodies) in 315 adolescents and in 211 adults.

The immune response in adolescents was similar to adults. Therefore, it is inferred that the vaccine will provide similar protection in adolescents to that expected in adults. According to the submitted data, the safety profile of Imvanex in adolescents was comparable to that seen in adults and no additional risk has been identified

As part of its recommendation, EMA has requested the marketing authorization holder to submit the final results of the study by 30 May 2025 to further characterize the information about safety in adolescents.

The Agency's assessment has important implications for the global response to the mpox outbreak in the Democratic Republic of the Congo (DRC) and other countries, which was declared a public health emergency of international concern (PHEIC) by the WHO on 14 August 2024.

Additional information available from: https://www.ema.europa.eu/en/news/ema-recommends-extending-indication-mpox-vaccine-adolescents#:~:text=EMA%20has%20recommended%20extending%20the,the%20vaccinia%20virus%20in%20adults

Safety of COVID-19, RSV, and Dengue vaccines

Report of the meeting of the WHO Global Advisory Committee on Vaccine Safety (GACVS), 15–17 May 2024

On 9 August, the report was published from the 47th Global Advisory Committee on Vaccine Safety (GACVS) meeting, held virtually on 15–17 May 2024. A summary of the presentations and recommendations is provided below.

Safety of COVID-19 vaccines

WHO experience related to the safety of vaccines against COVID-19 and lessons learnt were presented, highlighting challenges during the pandemic, such as largely unknown safety profiles of new vaccines, and the unprecedented high number of safety reports. Spontaneous reporting was key to signal detection, and the importance of clinical reasoning and effective communication was underlined.

In the post-pandemic phase, WHO will continue to monitor safety signals, strengthen pharmacovigilance systems, and develop tools for future pandemics. The Uppsala Monitoring Centre prioritized safety signals, with a focus on serious adverse events and adverse events of special interest, recording a huge increase in reporting VigiBase.

A review by the United States Centers for Disease Control and Prevention (CDC) found that the safety profile of the Pfizer-BioNTech, Moderna, and Janssen vaccines is largely consistent with observations in preauthorization clinical trials. The main serious adverse events include myocarditis, anaphylaxis, thrombosis, and Guillain-Barre syndrome, with preliminary data suggesting no new concerns with the updated vaccines for 2023-2024.

Safety of vaccination against respiratory syncytial virus (RSV)

A phase-3 clinical trial on the efficacy and safety of vaccination with the vaccine Abrysvo® (Pfizer) in pregnant women in 18 countries who were at 24–36 weeks of gestation was presented. Vaccine efficacy was found to be high in the 7 420 women and 7 307 infants with generally similar adverse events in the vaccine and placebo groups; this difference was not statistically significant, and geographical variation was seen in Argentina and South Africa.

Abrysvo® has been licensed for use in many countries, and post-marketing studies are being conducted in Argentina and the US to evaluate its safety during pregnancy. GACVS noted that the numerical imbalance in preterm births between study groups is a safety signal, but it should not preclude use of this vaccine, given its effectiveness. Post-marketing pharmacovigilance will be important to obtain more data, although it will probably take several years for definitive conclusions to be drawn owing to low uptake of the vaccine to date.

Safety of the dengue vaccine Qdenga®

The WHO position paper on dengue vaccines from May 2024 noted that, although no cases of anaphylaxis were observed during a clinical trial of the dengue vaccine Qdenga® (Takeda), 16 cases were reported after its introduction in Brazil in 2023. Post-marketing safety data on this vaccine were reviewed, and the vaccine's package insert was updated to include anaphylaxis as an adverse reaction.

Between March 2023 and May 2024 over 1.4 million doses of the vaccine were administered in Brazil, and 74 cases of serious non-fatal AEFIs were reported, of which 43 were diagnosed as anaphylaxis. Despite the higher-than-expected rate of anaphylaxis, the Ministry of Health of Brazil maintains its recommendation for use of this vaccine. PAHO also supports its use in settings with a high disease burden and recommended phase 4 studies to monitor its safety.

PAHO is working with countries to evaluate the risk of anaphylaxis and surveillance of vaccine-associated enhanced disease (VAED). It is also developing recommendations for harmonizing surveillance of arbovirus AEFIs and diagnosis of dengue in vaccinated people. GACVS congratulated Brazil on its comprehensive monitoring plan and recommended that all countries that introduce Qdenga® should have protocols for the management of anaphylaxis and continue long-term surveillance to evaluate other potential risks.

Source: World Health Organization. Weekly Epidemiological Record (WER), 9 August 2024, Vol. 99, No. 32, pp. 407-414. Available from: https://iris.who.int/handle/10665/378360

Influenza A (H5N1) vaccine

New Initiative Launched to Advance mRNA Vaccine Development Against Human Avian Influenza (H5N1)

On 29 July, WHO announced that a new project is underway aiming to accelerate the development and accessibility of human avian influenza (H5N1) messenger RNA (mRNA) vaccine candidates, with the participation of the Argentinian manufacturer Sinergium Biotech and the cooperation of the WHO mRNA Technology Transfer Program and the Medicines Patent Pool (MPP).

Avian influenza viruses, such as the H5N1 subtype, are a significant public health risk due to their widespread circulation in animals and potential to cause a future pandemic.

This development supplements ongoing work under the Pandemic Influenza Preparedness Framework. Sinergium Biotech has obtained candidate vaccines that use this technique and aims to establish proof-of-concept in preclinical models. Once the preclinical data package is concluded, the technology, materials, and expertise will be shared with other manufacturing partners, aiding the acceleration of the development of these vaccines, and bolstering pandemic preparedness efforts.

Additional information available from: https://www.who.int/news/item/29-07-2024-new-initiative-launched-to-advance-mrna-vaccine-development-against-human-avian-influenza-(h5n1)

Smallpox and Mpox vaccine

Smallpox and Mpox vaccine position paper

On 23 August, WHO published its smallpox and mpox vaccine position paper in the *Weekly epidemiological record*, in accordance with its mandate to provide normative guidance to Member States on health policy matters, by issuing a series of regularly updated position papers on vaccines against diseases that have an international public health impact. Below is a summary of the available vaccines, their safety, and recommendations.

Licensed vaccines

- MVA-BN was approved in 2013 for the prevention of smallpox in Canada and the European Union (EU) in persons 18 years of age and older. In 2019, MVA-BN was approved for the prevention of smallpox and mpox in adults in the United States and Canada extended its indication to mpox. On 22 July 2022, the EU approved the indication of MVA-BN for the prevention of mpox in adults. On 19 September, the EMA recommended extending the vaccine's indication for smallpox and mpox in adolescents from 12 to 17 years of age.
- In 2022, the United States granted emergency use authorization for the use of MVA-BN in persons under 18 years of age.
- In Japan, LC16m8 was licensed in 1975 for smallpox without age restriction and the indication was extended for the prevention of mpox in August 2022.
- ACAM2000 is approved by the FDA for immunization against smallpox and is made available for use against mpox under an Expanded Access Investigational New Drug protocol.

Vaccine safety data

- Dryvax Vaccine (discontinued)
  - Rare but serious complications documented during eradication of smallpox: generalized vaccinia, eczema vaccinatum, progressive vaccinia, post-vaccinial encephalitis (PvE), and death.
  - Highest risk of PvE among infants under 1 year of age: 6.8 cases of PvE and 3 deaths per million vaccinations.
  - Lower risk of PvE for primary vaccinees aged 1 year and older: 1.8 to 3.3 cases of PvE per million vaccinations.
  - Myopericarditis emerged as a serious adverse event with the re-introduction of Dryvax in 2002.
  - In second and third generation smallpox vaccines special attention was given to monitoring myopericarditis.

- ACAM2000 Vaccine: (second-generation, replicating)
  - Local and systemic adverse events were frequently reported in six studies involving 862 369 vaccinees.
  - 187 cases of myocarditis were reported among 900 253 vaccinees across five studies, with an incidence of 20.1 cases of myopericarditis per 100 000 vaccinees.
  - Incidence of myopericarditis in those vaccinated with ACAM2000 considerably higher than the expected background rate.
  - In studies involving over 840 000 persons vaccinated, six cases of generalized vaccinia, five cases of autoinoculation, and two deaths related to vaccination.

- MVA-BN Vaccine (third-generation, non-replicating)
  - Eight studies reported on frequent local and systemic adverse events, but no serious adverse events across 22 studies with 17 420 participants.
  - An observational study identified 4 cases of myocarditis among 839 178 doses administered, with an incidence of 4.77 cases per million doses.

- LC16m8 Vaccine (third generation, minimally replicating))
  - Three studies reported local adverse events such as erythema, induration and lymphadenopathy in adult vaccinees.
  - No cases of myopericarditis were found in two studies with 3346 participants.
  - One case of autoinoculation was reported with no other serious adverse events among 3488 participants.

Recommendations on vaccines and immunization against smallpox and mpox (divided into preventive vaccination and outbreak response):

1. **Smallpox vaccination:**
   - Preventive vaccination in non-outbreak settings:
     - Primary vaccination for laboratory personnel and smallpox outbreak response teams:
       - Consider periodic revaccination every 2–5 years for people at highest risk of exposure.
       - Use non-replicating or minimally replicating vaccines for individuals in close contact with vulnerable individuals.

   - Vaccination in the context of a smallpox outbreak:
     - Vaccination is recommended for contacts of cases and other persons at high risk of exposure.
     - Large-scale mass vaccination is not recommended as a first response.
     - Update smallpox outbreak response plans with a focus on timely diagnosis, timely deployment of vaccines, and contact tracing.

   Choice of vaccines in the context of a smallpox outbreak:

     - Use non-replicating, minimally replicating, or cell culture-based replicating vaccines for immunocompetent non-pregnant individuals.
     - Consider first-generation vaccines if the recommended options are not available.
     - Choice of vaccines for special populations:
       - infants, children and adolescents: Use non-replicating or minimally replicating vaccines; replicating vaccines should not be used in infants.
       - Pregnancy: Use non-replicating vaccines: Administration of MVA-BN in pregnancy constitutes “off-label” use; replicating and minimally replicating vaccines should not be used in pregnancy.
       - Immunocompromised individuals, including persons living with HIV: Use non-replicating vaccines.
     - Vaccination of previously vaccinated individuals in the context of a smallpox outbreak:

- Recommendation to vaccinate individuals previously vaccinated who are otherwise eligible, do not withhold on the grounds of prior vaccination.

Choice of vaccines for the WHO smallpox emergency reserve:

- The emergency reserve includes first-generation, second-generation (ACAM2000) and third generation (LC16m8 and MVA-BN) vaccines.
- It is recommended to add MVA-BN to the WHO physical emergency reserve.

2. Mpox vaccination

- Preventive use vaccination for laboratory personnel:
  - Primary preventive vaccination and periodic revaccination every 2–5 years is recommended for individuals who are at high risk of exposure to more virulent orthopoxviruses.

- Vaccination in the context of an mpox outbreak:
  - Vaccination is recommended for persons at high risk of exposure to mpox in an outbreak, including specific communities and health workers.

- Choice of vaccines:
  - Non-replicating vaccines (MVA-BN), minimally replicating vaccines (LC16m8), replicating cell-culture derived vaccinia-based vaccines (ACAM2000) are suggested for immunocompetent non-pregnant individuals.

- Vaccines for special populations:
  - Infants, children, and adolescents: MVA-BN or LC16m8 are recommended, ACAM2000 is contraindicated in infants.

  - Pregnancy: Use MVA-BN (off-label use); ACAM2000 and LC16m8 are contraindicated.

  - Immunocompromised individuals: MVA-BN should be used.

- Vaccination in previously vaccinated individuals:
  - Individuals who are eligible for vaccination should be vaccinated irrespective of previous smallpox vaccination.

3. **Vaccination schedules and dosing**: WHO recommends “off-label” use of a single dose or intradermal fractional dosing of MVA-BN in supply-constrained outbreak situations.
4. **Contraindications:** Replicating and minimally replicating vaccines should not be administered during pregnancy, to individuals with severe immunosuppression or skin conditions such as atopic dermatitis.
5. **Surveillance:** Strengthen mpox surveillance and laboratory testing to improve outbreak response and better characterize at risk populations.
6. **Research priorities:** Need for better understanding of modes of transmission, incidence, mortality, vaccine effectiveness, in children and in different clades of the virus.

Source: Weekly epidemiological record. Relevé épidémiologique hebdomadaire. 23 AUGUST 2024, 99th YEAR / 23 AOÛT 2024, 99e ANNÉE No 34, 2024, 99, 429–456: http://www.who.int/wer.

WHO activates procedure for inclusion in an Mpox emergency use listing

On 9 August, WHO announced that it had issued an invitation for manufacturers of mpox vaccines to submit an expression of interest for Emergency Use Listing (EUL).

The EUL procedure is an emergency use authorization process, specifically developed to expedite the availability of unlicensed medical products like vaccines that are needed in public health emergency situations. This is a time-limited recommendation, based on a risk-benefit approach.

WHO is requesting manufacturers to submit data to ensure that the vaccines are safe, effective, of assured quality, and suitable for the target populations.

Additional information available from: https://www.who.int/news/item/09-08-2024-who-invites-mpox-vaccine-manufacturers-to-submit-dossiers-for-emergency-evaluations

WHO prequalifies the first vaccine against Mpox

On 13 September, the WHO announced the MVA-BN vaccine, commercial name Imvanex®, also licensed as JYNNEOS by the US FDA and IMVAMUNE by Health Canada, as the first vaccine against mpox to be added to its prequalification list. WHO's assessment for prequalification is based on information submitted by the manufacturer, Bavarian Nordic A/S, and review by the European Medicines Agency, the regulatory agency of record for this vaccine.

The MVA-BN vaccine can be administered in people over 18 years of age as a 2-dose injection given four weeks apart. The vaccine can be kept at 2–8°C for up to eight weeks.

The WHO Strategic Advisory Group of Experts (SAGE) on Immunization recommended the use of MVA-BN vaccine in the context of an mpox outbreak for persons at high risk of exposure. While the vaccine is currently not licensed for persons under 18 years of age, this vaccine may be used "off-label" in infants, children, and adolescents, and in pregnant and immunocompromised people, where the benefits of vaccination outweigh the potential risks.

WHO also recommends single-dose use in supply-constrained outbreak situations. WHO emphasizes the need to collect further data on vaccine safety and effectiveness in these circumstances.

Available data shows that a single-dose MVA-BN vaccine given before exposure has an estimated 76% effectiveness in protecting people against mpox, with the 2-dose schedule achieving an estimated 82% effectiveness. Vaccination after exposure is less effective than pre-exposure vaccination.

Good safety profile has been consistently demonstrated in clinical studies, as well as in real-world use during the ongoing global outbreak since 2022. In light of the changing epidemiology and emergence of new virus strains, it remains important to collect as much data as possible on vaccine safety and effectiveness in different contexts.

Additional information available from: https://www.who.int/news/item/13-09-2024-who-prequalifies-the-first-vaccine-against-mpox

COVID-19 treatment

Mexico's Federal Commission for Protection against Health Risks (COFEPRIS) Authorized the Registration of the Medication Nirmatrelvir/Ritonavir for the Treatment of COVID-19 in Adults

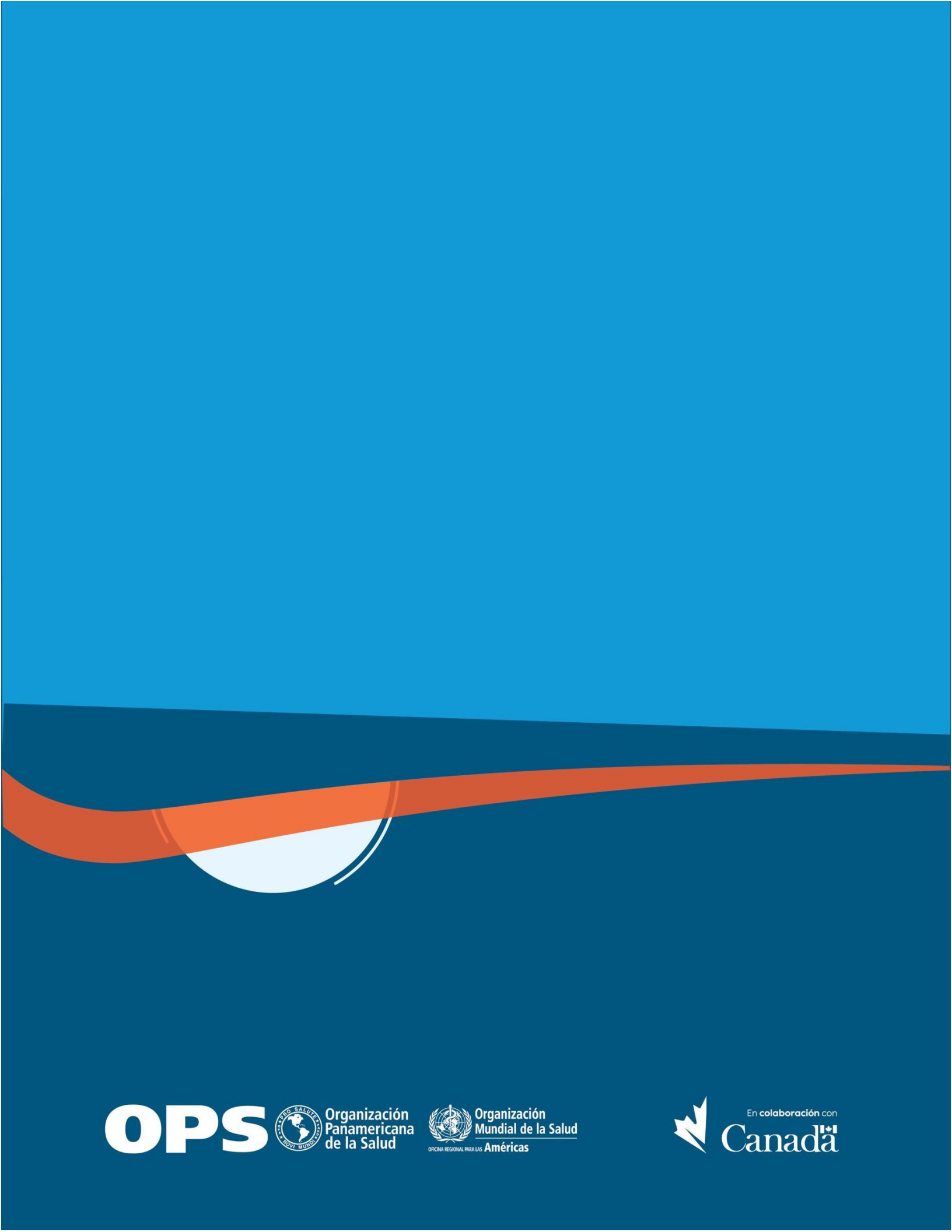
On 1 August, COFEPRIS announced that it had authorized the registration of the medication nirmatrelvir/ritonavir (Paxlovid®) from Pfizer, indicated for the treatment of COVID-19 in adults who do not require supplemental oxygen and who present a higher risk of progression to severe COVID-19. This is a prescription-only medication.

The decision was based on the evaluation carried out by the New Molecules Committee and the specialized technical team of COFEPRIS, who determined that the medication meets the quality, safety, and efficacy requirements to provide marketing authorization for this medication to prevent hospitalizations and mortality from COVID-19.

This medication is also authorized for sale in the private sector in the Region by the US Food and Drug Administration (FDA), Health Canada, and the National Health Surveillance Agency of Brazil (ANVISA).

Additional information available from: https://www.gob.mx/cofepris/es/articulos/cofepris-se-convierte-en-una-de-las-primeras-agencias-regulatorias-en-autorizar-comercializacion-abierta-de-paxlovid?idiom=es

https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2022/anvisa-aprova-venda-do-medicamento-paxlovid-em-farmacias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