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

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OPS Organización Panamericana de la Salud
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En colaboración con Canadá

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Argentina

Dengue Vaccine

On 7 March 2024, the National Immunization Commission (CoNaIn) published an analysis of the implementation strategy for the dengue vaccine (Takeda's QDENGA®).

As of 6 February 2024, 64 ESAVIs had been recorded, 60 of which were classified as non-serious. Most of these cases were associated with symptoms of fever, retro-orbital headache, muscle pain, and skin rashes, with a smaller number of reports of allergic reactions. In addition, four serious ESAVIs were identified, with diagnoses including one case of immune thrombocytopenia in a 9-year-old patient, two cases of fever with thrombocytopenia in individuals from 47 to 83 years old, and one allergic reaction in a 16-year-old patient. These events are currently being analyzed.

As of 22 March 2024, 110 ESAVIs had been recorded, seven of which were classified as serious. The reported ESAVIs were distributed equally between the two sexes. The mean age was 36 years, with 30 events reported in minors and 21 in persons over 60 years of age; the oldest was 83 years old. No events were reported in children under 4 years of age. Thirty-six events compatible with the clinical picture of dengue were reported, characterized by fever, retro-orbital headache, muscle pain, joint pain, and rash. Sixty percent of these events occurred between six to nine days after vaccination. Two of these events were classified as serious. They occurred in individuals aged 15 and 16 years, respectively, and are currently being investigated. Thirteen allergic reactions were also reported, with no recorded cases of anaphylaxis.(*)

Additional information available from:
https://www.argentina.gob.ar/sites/default/files/2024/03/conain_presentacion_07-03-2024.pdf

*Update presented at the May session of the Regional Network of Pharmacovigilance Focal Points of the Americas with data from the Secretariat of Access and Equity in Health, Directorate for the Control of Immunopreventable Diseases, Ministry of Health of Argentina.

Respiratory Syncytial Virus (RSV) Vaccines

As of 4 April 2024, 26 898 doses of the RSV vaccine (Abrysvo®) had been administered. To date, 19 ESAVI reports have been recorded, 12 of which were classified as serious.

Source: Update presented at the May session of the Regional Network of Pharmacovigilance Focal Points of the Americas with data from the Secretariat of Access and Equity in Health, Directorate for the Control of Immunopreventable Diseases, Ministry of Health of Argentina.

COVID-19 Vaccines

Stroke Risk After COVID-19 Bivalent Vaccination Among Older Adults in the United States of America

On 19 March, a self-controlled case series was published. It is important because of a safety concern noted in January 2023 by the US Centers for Disease Control and Prevention (CDC) and the US Food and Drug Administration (FDA) for ischemic stroke among adults aged 65 years or older who received the Pfizer-BioNTech BNT162b2; WT/OMI BA.4/BA.5 COVID-19 bivalent vaccine.

The objective of this study was to evaluate stroke risk after administration of: (1) either brand of the COVID-19 bivalent vaccine; (2) either brand of the COVID-19 bivalent vaccine plus a high-dose or adjuvanted influenza vaccine on the same day (concomitant administration); and (3) a high-dose or adjuvanted influenza vaccine.

The study included 11 001 Medicare beneficiaries aged 65 years or older who experienced stroke after receiving either brand of the COVID-19 bivalent vaccine (among 5 397 278 vaccinated individuals) (mean age, 74 years [IQR, 70-80 years]; 56% were women). The study period was 31 August 2022 to 4 February 2023.

The main measures were to determine the stroke risk (nonhemorrhagic stroke, transient ischemic attack, combined outcome of nonhemorrhagic stroke or transient ischemic attack, or hemorrhagic stroke) during the 1- to 21-day or 22- to 42-day risk window after vaccination vs the 43- to 90-day control window.

Among the 11 001 beneficiaries who experienced stroke after receiving either brand of the COVID-19 bivalent vaccine, there were no statistically significant associations between either brand of the COVID-19 bivalent vaccine and the outcomes of nonhemorrhagic stroke, transient ischemic attack, nonhemorrhagic stroke or transient ischemic attack, or hemorrhagic stroke. This was evaluated during two different risk windows: 1- to 21-day or 22- to 42-day, vs the 43- to 90-day control window. The observed relative incidence rate ratio (IRR) ranged from 0.72 to 1.12, indicating the absence of a significant increase in risk.

Among the 4 596 beneficiaries who experienced stroke after concomitant administration of either brand of the COVID-19 bivalent vaccine plus a high-dose or adjuvanted influenza vaccine, there was a statistically significant association between vaccination and nonhemorrhagic stroke during the 22- to 42-day risk window for the Pfizer-BioNTech BNT162b2; WT/OMI BA.4/BA.5 COVID-19 bivalent vaccine. (IRR, 1.20 [95% CI, 1.01-1.42]; risk difference/100 000 doses, 3.13 [95% CI, 0.05-6.22])

and a statistically significant association between vaccination and transient ischemic attack during the 1- to 21-day risk window for the Moderna mRNA-1273.222 COVID-19 bivalent vaccine (IRR, 1.35 [95% CI, 1.06-1.74]; risk difference/100 000 doses, 3.33 [95% CI, 0.46-6.20]).

Among the 21 345 beneficiaries who experienced stroke after administration of a high-dose or adjuvanted influenza vaccine, there was a statistically significant association between vaccination and nonhemorrhagic stroke during the 22- to 42-day risk window (IRR, 1.09 [95% CI, 1.02-1.17]; risk difference/100 000 doses, 1.65 [95% CI, 0.43-2.87]).

The authors conclude that, among Medicare beneficiaries aged 65 years or older who experienced stroke after receiving either brand of the COVID-19 bivalent vaccine, there was no

evidence of a significantly elevated risk for stroke during the days immediately after vaccination.

Source: Yun Lu et al. Stroke Risk After COVID-19 Bivalent Vaccination Among US Older Adults. JAMA. 2024;331(11):938-950. doi:10.1001/jama.2024.1059

Respiratory Syncytial Virus (RSV) Vaccines

RSV Prefusion F Protein–Based Maternal Vaccine — Preterm Birth and Other Outcomes

This phase 3 trial involving pregnant women 18 to 49 years of age to assess the efficacy and safety of this RSV prefusion F protein–based maternal vaccine (RSVPreF3-Mat) was published on 14 March. The women were randomly assigned in a 2:1 ratio to receive RSVPreF3-Mat or placebo between 24 weeks 0 days and 34 weeks 0 days of gestation. The primary outcomes were any medically assessed RSV-associated lower respiratory tract disease in infants from birth to 6 months of age and safety in infants from birth to 12 months of age.

After the observation of a higher risk of preterm birth in the vaccine group than in the placebo group, enrollment and vaccination were stopped early, and exploratory analyses of the safety signal of preterm birth were performed.

The analyses included 5 328 pregnant women and 5 233 infants; the target enrollment of approximately 10 000 pregnant women and their infants was not reached because enrollment was stopped early.

A total of 3 426 infants in the vaccine group and 1 711 infants in the placebo group were followed from birth to 6 months of age; 16 and 24 infants, respectively, had any medically assessed RSV-associated lower respiratory tract disease (vaccine efficacy, 65.5%; 95% credible interval, 37.5 to 82.0), and 8 and 14, respectively, had severe medically assessed RSV-associated lower respiratory tract disease (vaccine efficacy, 69.0%; 95% credible interval, 33.0 to 87.6). Preterm birth occurred in 6.8% of the infants (237 of 3 494) in the vaccine group and in 4.9% of those (86 of 1 739) in the placebo group (relative risk, 1.37; 95% confidence interval [CI], 1.08 to 1.74; P=0.01); neonatal death occurred in 0.4% (13 of 3494) and 0.2% (3 of 1739), respectively (relative risk, 2.16; 95% CI 0.62 to 7.56; P=0.23), an imbalance probably attributable to the greater percentage of preterm births in the vaccine group. No other safety signal was observed.

The authors conclude that the results of this trial, in which enrollment was stopped early because of safety concerns, suggest that the risks of any and severe medically assessed RSV-associated lower respiratory tract disease among infants were lower with the candidate maternal RSV vaccine than with placebo but that the risk of preterm birth was higher with the candidate vaccine.

Source: Dieussaert I, Hyung Kim J, Luik S, Seidl C, Pu W, Stegmann JU, Swamy GK, Webster P, Dormitzer PR. RSV Prefusion F Protein-Based Maternal Vaccine - Preterm Birth and Other Outcomes. N Engl J Med. 2024 Mar 14;390(11):1009-1021. doi: 10.1056/NEJMoa2305478. PMID: 38477988.

Chikungunya Virus Vaccine

The following is a concise summary highlighting the most important considerations related to the epidemiology of the chikungunya virus and the vaccine available for the disease.

Global impact of the chikungunya virus: Chikungunya is an emerging global health threat with at least 5 million cases of chikungunya virus infection reported during the past 15 years. The highest risk of infection is in tropical and subtropical regions of Africa, Southeast Asia, and parts of the Americas where chikungunya virus-carrying mosquitos are endemic. However, chikungunya virus has spread to new geographical areas causing a rise in global prevalence of the disease.

Transmission and symptomatology of chikungunya: Chikungunya virus (CHIKV) is mainly transmitted to people through the bite of an infected mosquito. The most common symptoms of chikungunya include fever and joint pain. Other symptoms may include a rash, headache, and muscle pain. Some individuals may experience debilitating joint pain that persists for months or even years. Treatment includes rest, fluids, and over-the-counter medications for pain and fever. Infection with chikungunya virus can lead to severe disease and prolonged health problems, particularly for older adults and individuals with underlying medical conditions.

Vaccine administration and composition: The first chikungunya vaccine, Ixchiq™, is administered as a single dose by injection into the muscle. It contains a live, weakened version of the chikungunya virus and may cause symptoms in the vaccine recipient similar to those experienced by people who have chikungunya disease.

Immunogenicity and efficacy: The Phase 3 immunogenicity trial demonstrated that over 98% of participants achieved an anti-CHIKV neutralizing antibody titer ≥150 at 28 days after a single dose of Ixchiq™ and the anti-CHIKV neutralizing antibody response persisted for at least 6 months after the single-dose vaccination, indicating that vaccination with Ixchiq™ is reasonably likely to prevent disease caused by CHIKV infection.

The effectiveness of Ixchiq™ is based on immune response data from a clinical study conducted in the United States in individuals 18 years of age and older. In this study, the immune response of 266 participants who received the vaccine was compared to the immune response of 96 participants who received placebo. The level of antibody evaluated in study participants was based on a level shown to be protective in non-human primates that had received blood from people who had been vaccinated. Almost all vaccine study participants achieved this antibody level.

Safety and adverse events: The safety of Ixchiq™ was evaluated in two clinical studies conducted in North America in which about 3 500 participants 18 years of age and older received a dose of the vaccine with one study including about 1 000 participants who received a placebo. The most commonly reported side effects by vaccine recipients were headache, fatigue, muscle pain, joint pain, fever, nausea, and tenderness at the injection site.

Serious adverse events in study participants: Although not commonly reported, severe chikungunya-like adverse reactions that prevented daily activity and/or required medical intervention occurred in 1.6% of Ixchiq™ recipients and no placebo recipients. Two recipients with severe chikungunya-like adverse reactions were hospitalized. In addition, some recipients had prolonged chikungunya-like adverse reactions that lasted for at least 30 days. The

Prescribing Information includes a warning to inform that the vaccine may cause severe or prolonged chikungunya-like adverse reactions.

Risks of vertical transmission of the virus: Transmission of chikungunya virus to newborn babies from pregnant individuals with viremia (virus present in the blood) at delivery has been reported and can cause severe, potentially fatal chikungunya virus disease in neonates. In one study that evaluated whether the vaccine virus was present in the blood after vaccination, most individuals had vaccine virus detected in the blood within the first week following vaccination; the vaccine virus was not detected 14 days after vaccination. The Prescribing Information includes a warning to inform that it is not known if the vaccine virus can be transmitted from pregnant individuals to newborns, nor is it known if the vaccine virus can cause any adverse effects in neonates. The warning also conveys that when considering administration to pregnant individuals, healthcare providers should take into consideration the individual's risk of exposure to chikungunya virus, gestational age and risks to the fetus or neonate from disease caused by chikungunya virus in the pregnant individual.

Regulatory initiatives and follow-up commitments:

In November 2023, the U.S. FDA approved Valneva Austria GmbH's Ixchiq™, the first chikungunya vaccine, for individuals 18 years of age and older who are at increased risk of exposure to chikungunya virus.

Ixchiq™ was granted Breakthrough Therapy and Fast Track designations by the FDA, which allow the FDA to approve certain products for serious or life-threatening conditions based on evidence of a product's efficacy that is reasonably likely to predict clinical benefit. In addition, the FDA awarded the manufacturer of Ixchiq™ a tropical disease priority review voucher, under a provision included in the Food and Drug Administration Amendments Act of 2007. This provision aims to encourage the development of new drugs and biological products for the prevention and treatment of certain tropical diseases.

In the FDA's evaluation of Ixchiq™ for accelerated approval, evidence of effectiveness is based on immune response data in clinical trial participants. As a condition for approval for Ixchiq™, the FDA is requiring confirmatory clinical studies to be conducted to verify clinical benefit, and to assess the **serious risk** of severe chikungunya-like **adverse reactions** following administration of Ixchiq™.

Pharmacovigilance plan (PVP):

The PVP includes the following safety concerns:

- Important identified risk: Chikungunya-like adverse reactions, including vaccine-associated arthralgia.
- Important potential risks: Neutropenia and leukopenia, and cardiac events
- Missing information: Adverse pregnancy outcomes such as spontaneous abortion; Autoimmune or inflammatory disorders; Frail adults with acute or progressive, unstable, or uncontrolled clinical conditions, e.g., cardiovascular, respiratory, neurologic, psychiatric, or rheumatologic conditions; long-term safety; and Interaction with other vaccines

In addition to routine pharmacovigilance, the safety concerns of chikungunya-like adverse reactions, including vaccine associated arthralgia, cardiac events, and spontaneous abortion will be further evaluated in the postmarketing setting with enhanced pharmacovigilance

activities, which include expedited reporting (regardless of seriousness or label status), a summary and analysis in periodic safety reports, and dedicated adverse event questionnaires. Safety in pregnancy will be further evaluated in a dedicated pregnancy safety study, which will be performed in the chikungunya-endemic area of Brazil. In addition, the applicant will conduct a voluntary postmarketing safety study of 5 000 U.S. travelers for medically attended adverse events of special interest and pregnancy outcomes.

Risks of vaccination with Ixchiq™ include local and systemic reactogenicity. An additional risk includes chikungunya-like adverse reactions (12.1% of Ixchiq™ recipients developed chikungunya-like illnesses). Severe, serious, and prolonged chikungunya-like illness was reported following vaccination with Ixchiq™, including chronic disease and atypical presentations such as cardiac events. In addition, the studies demonstrated disproportionately higher incidences of spontaneous abortion in Ixchiq™ recipients compared with participants in the placebo group. Because the available evidence is insufficient to establish or exclude a vaccine-associated risk, postmarketing assessment is warranted.

Source: SBRA-IXCHIQ™ Summary Basis for Regulatory Action. December 8, 2023, available from: https://www.fda.gov/media/174693/download?attachment

FDA Approves First Vaccine to Prevent Disease Caused by Chikungunya Virus, available from: https://www.fda.gov/news-events/press-announcements/fda-approves-first-vaccine-prevent-disease-caused-chikungunya-virus

Dengue Vaccine

Brazilian Ministry of Health Strengthens Dengue Vaccine Safety

On 8 March, at a meeting with the Technical Advisory Chamber on Immunizations (CTAI) and the Interinstitutional Committee for Pharmacovigilance of Vaccines and Other Immunobiologicals (CIFAVI), the Brazilian Ministry of Health announced that the safety of the dengue vaccine had been strengthened.

The Ministry of Health indicated that out of a total of 365 000 doses of dengue vaccine applied in the country since 2023, 16 cases of severe allergic reactions had been identified, and the affected persons had fully recovered.

The Ministry of Health published the following recommendations for health professionals from the CTAI and CIFAVI:

- Observation for 30 minutes after vaccination for those with a history of allergic reactions, and 15 minutes for other recipients, regardless of the type of dose;
- In case of non-serious hypersensitivity reactions after the first dose, clinically assess each case to determine the need for assisted administration of the second dose;
- Concomitant administration with other vaccines: Inactivated vaccines can be administered 24 hours later; wait four weeks for attenuated vaccines;
- Improve adherence to hypersensitivity and anaphylaxis protocols in health facilities where vaccinations are given;
- Establish two-way communication between related organizations and institutions: ANVISA, CONASS, CONASEMS.

Additional information available from: https://www.gov.br/saude/pt-br/assuntos/noticias/2024/marco/ministerio-da-saude-reforca-seguranca-da-vacina-contra-a-dengue

Respiratory Syncytial Virus (RSV) Vaccines

ANVISA Approves Health Registration for Pfizer's Abrysvo Vaccine

On 1 April, ANVISA announced that it had approved health registration for Pfizer's Abrysvo vaccine. This vaccine is intended to combat respiratory syncytial virus (RSV) (which causes respiratory tract infections, particularly bronchiolitis in children) when administered to the mother in the second or third trimester of pregnancy.

The vaccine was also approved for the prevention of lower respiratory tract disease caused by RSV in individuals 60 years of age and older, a population also considered at risk.

The Abrysvo vaccine is a bivalent vaccine, composed of two antigens of the RSV F surface protein. It is administered into a muscle and the dosage regimen consists of application of a single dose.

ANVISA had previously authorized GlaxoSmithKline's Arexvy vaccine, intended for the prevention of diseases caused by RSV in individuals 60 years of age and older.

Additional information available from: https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2024/anvisa-registra-vacina-para-prevencao-de-bronquiolite-em-bebes

Influenza Vaccine

European Medicines Agency Issues Recommendations on Updates to Vaccines for the Prevention of 2024/2025 Seasonal Influenza

On 26 March 2024, the European Medicines Agency (EMA) issued recommendations for the influenza virus strains that vaccine manufacturers should include in vaccines for the prevention of seasonal influenza from autumn 2024, on the basis of observations by the World Health Organization.

The EMA's Emergency Task Force (ETF) issued a statement recommending a transition from quadrivalent to trivalent vaccines that do not include the B/Yamagata component, as the B/Yamagata strain of the influenza B virus has not been detected in circulation since March 2020.

Taking into account the statement from the ETF and the recommendation from the WHO, the EMA has issued the following strain recommendations for the 2024/2025 season:

Live-attenuated vaccines, or egg-based trivalent vaccines:

- an A/Victoria/4897/2022 (H1N1)pdm09-like virus;
- an A/Thailand/8/2022 (H3N2)-like virus;
- a B/Austria/1359417/2021 (B/Victoria lineage)-like virus.

Cell-based trivalent vaccines:

- an A/Wisconsin/67/2022 (H1N1)pdm09-like virus;
- an A/Massachusetts/18/2022 (H3N2)-like virus;
- a B/Austria/1359417/2021 (B/Victoria lineage)-like virus.

Inactivated vaccines:

- Consider producing a quadrivalent vaccine containing two influenza B virus strains for the 2024/2025 season. In that case a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus in addition to the strains mentioned above is considered appropriate.

The Agency recommends that marketing authorization holders submit applications to change the composition of authorized seasonal influenza vaccines by 17 June 2024.

Additional information available from: https://www.ema.europa.eu/en/news/eu-recommendations-2024-2025-seasonal-flu-vaccine-composition

Pre-Pandemic Influenza Vaccination

Brazilian Health Regulatory Agency (ANVISA) Approves Pre-Pandemic Influenza Vaccines

On 6 March, the Brazilian Health Regulatory Agency (ANVISA) approved a Collegiate Board Resolution (RDC) that provides for the registration of pre-pandemic influenza vaccines, updating vaccines to a pandemic strain, and approval for use, marketing, and monitoring of the pandemic.

This standard is aligned with international regulatory best practices, already adopted by reference agencies, and provides guidelines for the development and registration of pre-

pandemic vaccines for zoonotic influenza strains (strains circulating in animals that do not yet have sustained human-to-human transmission, such as H5N1 or H7N9 strains, but have the potential to cause a public health emergency).

Pre-pandemic influenza vaccines may not be marketed, and will only be used as a basis or "matrix" for approving the vaccine for the influenza pandemic, after updating the vaccine formulation according to the strain causing the emergency.

The existence of a "matrix" that has already been evaluated and registered by ANVISA allows a specific vaccine to be approved more expeditiously in the event of a new influenza subtype, thus reducing how long it takes for the new vaccine to arrive in the country.

Additional information available from: https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2024/aprovada-resolucao-sobre-registro-de-vacinas-pre-pandemicas-contra-influenza

COVID-19 Vaccine

ANVISA Approves Updated Composition of COVID-19 (recombinant) Vaccine from Zalika Farmacéutica Ltd.

On 8 April, ANVISA approved the updated composition of the COVID-19 (recombinant) vaccine from Zalika Pharmaceuticals Ltd., manufactured by Serum Institute of India, approved by ANVISA on 8 January 2024, conditional on submission of the updated strain within 60 days from the publication of the registration.

The update consisted of changing the strain used as the source for producing the spike (S) protein antigen of SARS-CoV-2 in accordance with WHO recommendations to use the XBB.1.5 strain, which provides protection against the currently circulating forms of the virus.

As with the initial registration, this vaccine is indicated for individuals 12 years of age and older. The dosage of the vaccine in the primary immunization schedule is two doses 21 days apart. As a booster, one dose is given at least two months after administration of any COVID-19 vaccine.

Additional information available from: https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2024/anvisa-aprova-atualizacao-de-vacina-contra-covid-19

Statement from the WHO Technical Advisory Group on the Antigen Composition of COVID-19 Vaccines

On 26 April, WHO published the recommendations of the WHO Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC). This group meets regularly to assess the impact of SARS-CoV-2 evolution on the performance of approved COVID-19 vaccines, and to advise WHO on whether changes are needed to the antigen composition of future COVID-19 vaccines.

The following is a summary of the TAG-CO-VAC conclusions and recommendations on the antigen composition of COVID-19 vaccines:

- As of April 2024, nearly all circulating variants of SARS-CoV-2 genetic sequences in publicly available databases are derived from JN.1.

- As virus evolution is expected to continue from JN.1, future formulations of COVID-19 vaccines should aim to induce enhanced neutralizing antibody responses to JN.1 and its descendent lineages.
- They recommend the use of a monovalent JN.1 lineage (GenBank: OY817255.1, GISAID: EPI_ISL_18538117, WHO Biohub: 2024-WHO-LS-001) antigen in updated vaccines.
- The continued use of the current monovalent XBB.1.5 formulation will offer protection given the neutralizing antibody responses to early JN.1 descendent lineages. However, it is expected that the ability for XBB.1.5 vaccination to protect against symptomatic disease may be less robust as SARS-CoV-2 evolution continues from JN.1.
- Other formulations and/or platforms that achieve robust neutralizing antibody responses against currently circulating variants, particularly JN.1 descendent lineages, can also be considered.
- In accordance with WHO SAGE policy, vaccination programs should continue to use any of the WHO emergency-use listed or prequalified COVID-19 vaccines and vaccination should not be delayed in anticipation of access to vaccines with an updated composition.
- The TAG-CO-VAC continues to encourage the further development of vaccines that may improve protection against infection and reduce transmission of SARS-CoV-2.

Additional information available from: https://www.who.int/news/item/26-04-2024-statement-on-the-antigen-composition-of-covid-19-vaccines

EMA's Emergency Task Force (ETF) Recommendeds Updating COVID-19 Vaccines

On 30 April, EMA's Emergency Task Force (ETF) recommended updating COVID-19 vaccines to target the new SARS-CoV-2 variant JN.1 for the 2024/2025 vaccination campaign.

In making its recommendation, the ETF consulted the World Health Organization (WHO), international partners and marketing authorization holders for COVID-19 vaccines. The ETF also considered a wide range of data, including data on the evolution of the virus and data from animal studies on the effects of candidate vaccines targeting JN.1. The evidence indicates that targeting JN.1 will help maintain the effectiveness of the vaccines as SARS-CoV-2 continues to evolve.

The EMA recommended that marketing authorization holders update the composition of their authorized vaccines in accordance with this recommendation.

Additional information available from: https://www.ema.europa.eu/en/news/etf-recommends-updating-covid-19-vaccines-target-new-jn1-variant

COVID-19 Vaccine

EMA's Safety Committee Issues Conclusion on COVID-19 Vaccines Comirnaty and Spikevax and Cases of Postmenopausal Bleeding.

On 8 March, EMA's safety committee (PRAC) concluded that there was insufficient evidence to establish a causal association between the COVID-19 vaccines Comirnaty and Spikevax and cases of postmenopausal bleeding.

The PRAC assessed all available data, including findings from literature, and available post-marketing spontaneous reports of suspected adverse reactions to the COVID-19 vaccines Comirnaty and Spikevax, concluding that the available data do not support a causal association and an update of the product information for either vaccine is not warranted.

Additional information available from: https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-4-7-march-2024

Dengue Vaccination

World Health Organization (WHO) Position Paper

On 3 May, WHO published its position on the dengue vaccine in *Weekly Epidemiological Record*, in accordance with WHO's mandate to provide normative guidance to Member States on health policy matters through the issuance of a series of regularly updated position papers on vaccines and combinations of vaccines against diseases that have an international public health impact.

Recommendations on the use of dengue vaccines were issued by the WHO Strategic Advisory Group of Experts (SAGE) in September 2023 and endorsed by the WHO thereafter. In this 3 May 2024 document, WHO issued a position paper focusing on the second licensed dengue vaccine, TAK-003 (Qdenga, Takeda). The following is a summary of the WHO position.

Vaccination against dengue should be viewed as part of an integrated strategy to control the disease, including vector control, proper case management, community education, and community engagement. TAK-003 does not prevent all cases of dengue. Comprehensive vector control must remain a critical component of dengue control programs. Furthermore, the mosquito vectors of dengue transmit other important viruses, including yellow fever, chikungunya, and Zika viruses.

WHO recommends that countries consider introducing TAK-003 into their routine immunization programs in geographical locations where high transmission intensity of dengue poses a significant public health problem. Many countries may have a heterogeneous geographical distribution of dengue transmission intensity and could consider targeted subnational introduction. Until the efficacy–risk profile for DENV3 and DENV4 in seronegative persons has been more thoroughly assessed, WHO does not recommend the programmatic use of TAK-003 vaccine in low to moderate dengue transmission settings.

To determine the extent of dengue transmission intensity, countries should consider data on age-specific seroprevalence and/or age-specific dengue hospital admissions. There is no precise age-specific seroprevalence threshold above which vaccination is indicated; the benefit of vaccination will increase with increasing seroprevalence, with better vaccine performance being expected in seropositive persons. Threshold cut-offs should be decided by countries; typically, an SP9 of >60% could be considered an indicator of high dengue transmission. In addition, a mean age of peak dengue-associated hospitalizations of <16 years could be considered an indicator of high dengue transmission.

The use of a pre-vaccination screening strategy to limit vaccination to seropositive persons is not recommended in settings with high dengue transmission as this would substantially reduce the public health impact of vaccination and increase programmatic costs.

Vaccine introduction should be accompanied by a well-designed communication strategy and community engagement.

Target age group for vaccination

WHO recommends the use of TAK-003 in children aged 6–16 years in settings with high dengue transmission intensity. Within this age range, the vaccine should optimally be initiated about 1–2 years prior to the age-specific peak incidence of dengue-related hospital admissions,

although programmatic alignment with the administration of other school-based vaccination and health interventions is also an important consideration. Catch-up vaccination can also be considered for other age groups within the 6–16 year age range at the time of vaccine introduction.

WHO does not currently recommend the programmatic use of TAK-003 in children aged <6 years because of the lower efficacy of the vaccine in this age group. Furthermore, the dengue seropositivity rate in this age group is generally low, even in high dengue transmission settings.

Vaccination schedule

The vaccine is recommended as a 2-dose schedule with a minimum interval of 3 months between doses. It is not advised to reduce the interval between doses. If the second dose is delayed for any reason, it is not necessary to restart the series and the second dose should be administered at the first available opportunity.

Contraindications

A history of anaphylaxis to any component of the vaccine is a contraindication to vaccination. If anaphylaxis occurs after any dose, a subsequent dose of the vaccine should not be administered.

Precautions

A history of anaphylaxis to any other vaccine or injectable therapy (i.e. intramuscular, intravenous, or subcutaneous vaccines or therapies) is not a contraindication to vaccination; however, for such persons, a risk assessment should be conducted by a health professional. It remains uncertain if there is an increased risk of anaphylaxis with the use of TAK-003, and counselling should be given about the potential risk which should be weighed against the benefits of vaccination. Such persons should be observed for 30 minutes after vaccination in health-care settings where anaphylaxis can be treated immediately.

As a small number of anaphylactic reactions have also been reported in vaccinees without a history of anaphylaxis, WHO recommends that the TAK-003 vaccine be administered only in settings where anaphylaxis can be treated. Until more data are available, all vaccinees should be observed for at least 15 minutes following vaccination.

Special populations

- **Pregnant and lactating persons:** TAK-003 is not recommended during pregnancy and pregnancy should be avoided for at least 1 month following vaccination. Inadvertent vaccination of a pregnant person is not a reason to terminate the pregnancy.
  It is unknown whether TAK-003 is excreted in human milk immediately after administration. A risk to newborn infants cannot be excluded. Until such data become available, the vaccine is contraindicated for mothers during breastfeeding.

- **Immunocompromised persons:** TAK-003 is a live attenuated vaccine. TAK-003 is contra-indicated in persons with congenital or acquired immune deficiency, including those receiving immunosuppressive therapies such as chemotherapy or high doses of systemic corticosteroids (e.g. 20 mg/day or 2 mg/kg body weight/day, of prednisone for 2 weeks or more) within 4 weeks prior to vaccination, as with other live attenuated vaccines.

The vaccine is also contraindicated in individuals with symptomatic HIV infection or with asymptomatic HIV infection associated with evidence of impaired immune function.

- **Persons with comorbidities:** Persons with comorbidities, such as sickle cell anemia, diabetes, hypertension, or underlying comorbidities that may result in bleeding tendencies (e.g. ulcerative colitis), are at higher risk of more severe disease outcomes when infected with dengue virus. Persons with such comorbidities are generally older. Persons with comorbidities who live in dengue-endemic countries could be offered vaccination, even if they fall outside the recommended age range for programmatic use (i.e. 6–16 years), provided that a substantial country-specific burden of severe dengue outcomes in these subpopulations has been documented. Such individuals need to be informed that the vaccine may not confer protection against DENV3 and DENV4 in seronegative vaccine recipients and that, with currently-available data, the potential risk of severe dengue cannot be ruled out if seronegative persons are exposed to DENV3 and DENV4. Until more data on efficacy-safety profiles become available, WHO recommends the lower age limit of 6 years, and the upper limit of 60 years for vaccination.

- **Travelers:** Persons living in non-endemic countries who have previously been infected with any of the four dengue virus serotypes following travel to dengue-endemic countries, may benefit from TAK-003 vaccination to prevent a second (and hence potentially more severe) dengue infection when travelling again to an endemic country. Frequent travelers, long-term travelers, migrants, and long-term expatriates have a higher likelihood of previous dengue infection (and are therefore more likely to be seropositive) compared to first-time or short-term travelers.
  The benefits of vaccination with TAK-003 are lower for travelers who have never experienced dengue infection (and are therefore seronegative) compared to travelers who are seropositive.
  Travelers need to be informed that the vaccine may not confer protection against DENV3 and DENV4 if they are seronegative, and that there is a potential risk of severe dengue if seronegative individuals are exposed to DENV3 and DENV4. Travelers also need to be informed that transmission of dengue is heterogeneous within countries and the circulating serotypes may vary during different periods. The highest benefit with the lowest risk is during an ongoing epidemic due to DENV2 or DENV1 at the destination.

  Although pre-vaccination screening to determine serostatus is not required, where available its use could be considered to inform the assessment of risks and benefits.
  Protection starts 14 days after the first dose and has been demonstrated between the first and second dose; hence, the first dose can be given up to 14 days before travel to a dengue-endemic country. To ensure the durability of the protection, a second dose is needed after a minimum interval of 3 months. Until more data become available on efficacy-safety profiles, WHO recommends a lower age limit of 6 years and an upper limit of 60 years for travelers.

- **Health workers:** Health workers are generally not at greater risk of dengue. All health-care workers should be up to date with vaccinations as recommended in their national immunization schedules.

Special settings

- **Outbreak response:** Dengue transmission in dengue-endemic countries is characterized by cyclical patterns, typically peaking every 3–5 years, with varying serotype dominance. An increase in the frequency and magnitude of outbreaks has been observed in recent decades.
  A preventive strategy through routine vaccination is more impactful than a reactive campaign in response to an outbreak.

Research priorities

WHO proposes the following research priorities to further evaluate the safety, efficacy, and effectiveness of TAK-003, as well as related programmatic issues:

- Conducting post-marketing studies to generate more precise estimates of the effectiveness/risk profile against DENV3 and DENV4 in seronegative persons.
- Monitoring rates of hospitalized dengue in countries implementing vaccination, including capturing vaccination status, age, serotype, and severity of disease.
- Monitoring pregnancy and birth outcomes following inadvertent vaccination during pregnancy.
- Assessing safety and immunogenicity in immunocompromised persons, including HIV-positive persons, and persons aged >60 years.
- Monitoring vaccine effectiveness against asymptomatic and mild infections to better understand the effect of the vaccine on dengue transmission.
- Monitoring vaccine effectiveness in individuals with co-morbidities that increase the risk of severe dengue.
- Evaluating the immunogenicity and efficacy/effectiveness of a heterologous prime-boost approach to vaccination to increase a more balanced tetra-valent response – i.e. mix-and-match with other live-attenuated dengue vaccines.
- Optimizing vaccination schedules, such as the effectiveness of single-dose vaccination, or a longer interval between 2 doses.
- Establishing the need for and timing of booster doses as well as correlates of protection to facilitate the approval of future dengue vaccines.
- Evaluating cost–effectiveness in settings with different levels of transmission intensity.
- Monitoring co-administration of TAK-003 with flavivirus vaccines and other live attenuated vaccines.
- Strengthening risk communication, community engagement and vaccine confidence.
- Monitoring the impact of the vaccine on antimicrobial resistance.

Source: WHO. Weekly Epidemiological Record, 3 MAY 2024, 99th YEAR / 3 MAI 2024, 99e ANNÉE No 18, 2024, 99, 203–224, available from: https://iris.who.int/bitstream/handle/10665/376641/WER9918-eng-fre.pdf

Cholera Vaccine

WHO Prequalifies New Oral Simplified Vaccine for Cholera

A new oral vaccine for cholera has received prequalification by the World Health Organization (WHO) on 12 April. The inactivated oral vaccine Euvichol-S has a similar efficacy to existing vaccines but a simplified formulation, which will enable a rapid increase in production and supply in communities battling with cholera outbreaks.

There were 473 000 cholera cases reported to WHO in 2022 - double the number from 2021. Further increase of cases by 700 000 was estimated for 2023. Currently, 23 countries are reporting cholera outbreaks with most severe impacts seen in the Comoros, Democratic Republic of the Congo, Ethiopia, Mozambique, Somalia, Zambia, and Zimbabwe.

The WHO list of prequalified vaccines includes the oral cholera vaccines: Shanchol, from Sanofi Healthcare India Private Limited; Dukoral, from Valneva Sweden AB; Euvichol and Euvichol-Plus, from EuBiologicals Co., Ltd, which also produces the new vaccine Euvichol-S, recently added to this list.

The Euvichol-S vaccine contains two formalin-inactivated components, V. cholerae O1 Inaba El Tor strain Phil 6973 and O1 Ogawa classical strain Cairo 50, compared to the other inactivated oral cholera vaccines which contain five different components.

Additional information available from: https://www.who.int/es/news/item/18-04-2024-who-prequalifies-new-oral-simplified-vaccine-for-cholera

https://extranet.who.int/prequal/vaccines/prequalified-vaccines

https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(24)00059-7/fulltext?rss=yes

COVID-19 Vaccines

WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) and WHO Global Advisory Committee on Vaccine Safety (GACVS)

A summary of the joint meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) and WHO Global Advisory Committee on Vaccine Safety (GACVS) held on 13-15 November 2023, at WHO headquarters in Geneva, Switzerland, was published in *WHO Pharmaceuticals Newsletter*, No. 2, 2024.

At this meeting, an update on the Cohort Event Monitoring (CEM) project was presented. This approach focused on implementation in pandemic response, especially in relation to COVID-19 therapies such as molnupiravir and nirmatrelvir-ritonavir. It was reported that two of the four countries that expressed interest (Bangladesh, Egypt, Jordan, and the Philippines), are currently collecting data, although it was noted that number of patients recruited is limited due to the drop in usage of these therapies. The plan to conduct a survey for lessons learned was shared. The objective is to understand the challenges and successes, identify gaps in infrastructure, processes and capacity needed to perform active surveillance, and use findings to develop recommendations for preparedness.

The Ghana FDA also shared their experience of conducting active surveillance which was used during the COVID-19 pandemic to compliment existing spontaneous reporting systems. Key lessons learned for success included collaboration with the expanded program of immunization (EPI), involvement of regional level at planning stages, involvement of National Service staff as the study team members, and making participants feel cared for through the follow up process leading to more willingness to share information.

In another session, an update was given on safety issues due to administration errors of medicines and vaccines. The WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre (UMC) provided an overview of reports of medication errors in VigiBase (the WHO global database). Using "medication error" as the search term (October 2023), there were more than 1.5 million cases of medication errors reported in VigiBase, with 78% medicines and 22% vaccines. The Committees recognized that the opportunity should be taken to conduct further analysis of reports in VigiBase.

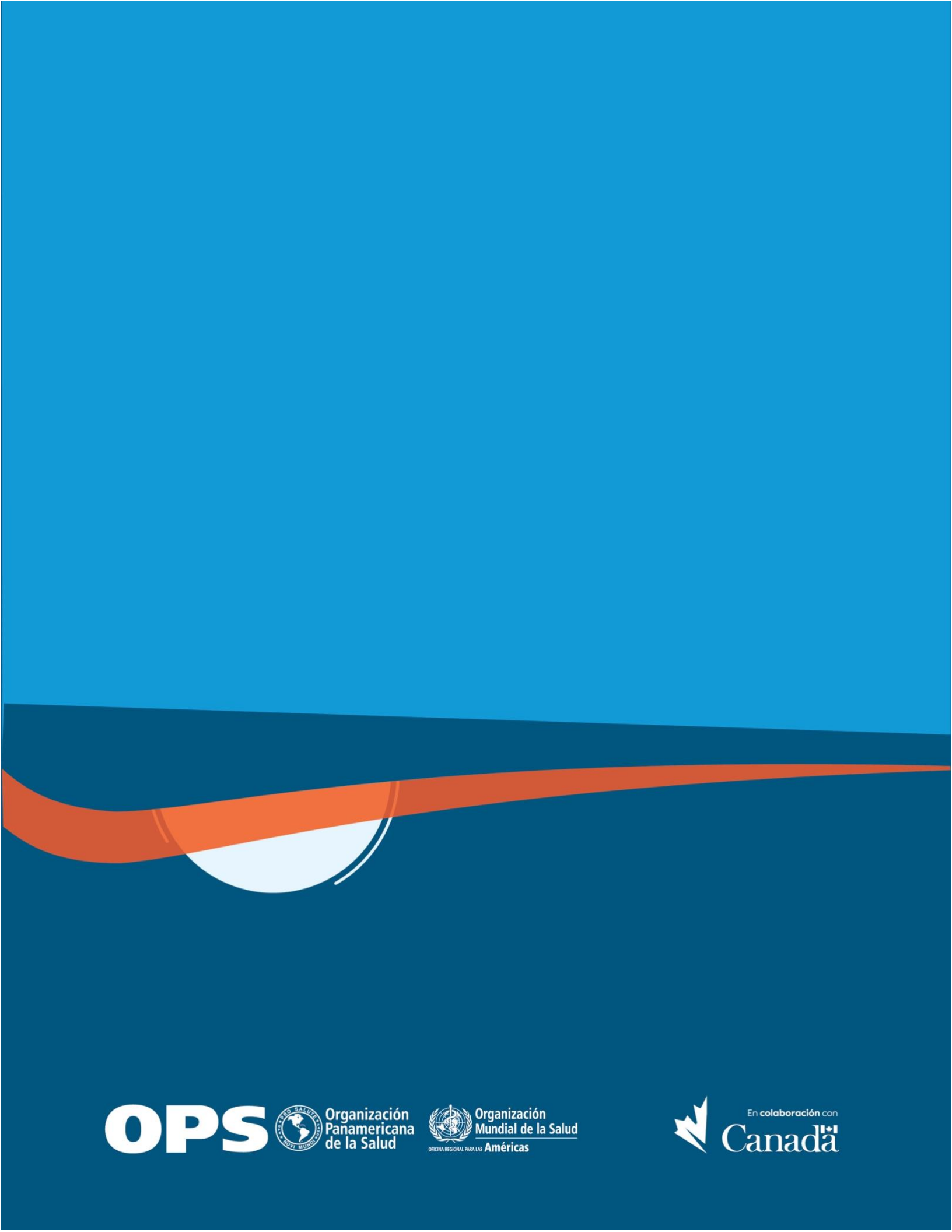
The next ACSoMP meeting is planned to be a virtual meeting in May 2024, with a joint ACSoMP/GACVS in-person/hybrid meeting in November 2024.

Additional information available from: https://www.who.int/publications/i/item/9789240092426

EMA Announces Withdrawal of Marketing Authorization for the Vaccine Vaxzevria

On May 7, The EMA announced the withdrawal of the marketing authorization for AstraZeneca's COVID-19 (ChAdOx1-S [recombinant]) vaccine Vaxzevria, at the request of the marketing authorization holder.

Additional information available from: https://www.ema.europa.eu/en/medicines/human/EPAR/vaxzevria-previously-covid-19-vaccine-astrazeneca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