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

LI Report

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OPS Organización Panamericana de la Salud
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CONTENTS

OFFICIAL REPORTS ON PHARMACOVIGILANCE PROGRAMS

Argentina

National Immunization Schedule Vaccines and COVID-19 Vaccines

Between January 2021 and November 2023, an active pharmacovigilance study in adults was conducted in the city of Rosario, Argentina, in the context of the national vaccination schedule and the campaign against COVID-19. The descriptive study, carried out in five primary care centers, involved 183 people, 76.5% of whom were women, with an average age of 43 years.

Of the total number of questionnaires completed, 301 reports were sent to the Argentine Integrated Health Information System (Sistema Integrado de Información Sanitaria Argentino, SISA), which resulted in the identification of 536 AEFIs. Of the 301 reports, 96% (289) were for COVID-19 vaccines. The most common AEFIs were pain at the injection site (22.8%), fever (17.7%), and generalized muscle pain (14.5%). Only two cases were classified as serious, associated with cardiac events in persons with a previous history. Both progressed favorably after follow-up.

Source: Majic, S., Intilangelo, A., Fanucci, T., Townsend, V., & Palchik, V. (2024). Descripción de Eventos Supuestamente Atribuibles a la Vacunación e Inmunización identificados a partir de farmacovigilancia activa en personas adultas en la ciudad de Rosario. *Revista Científica ANMAT*, *5*, e71. https://doi.org/10.62035/rca.5.71

Brazil

Dengue Vaccine

From 1 March 2023 to 7 August 2024, 2,911,003 doses of attenuated dengue vaccine were administered in Brazil. Of these, 2,381,483 (81.8%) were first doses and 529 520 (18.2%) were second doses. In the same period, 2748 AEFI notifications were recorded, equivalent to 94.4 notifications per 100 000 doses administered. Of these, 216 (7.9%) were serious (without fatal outcome). One serious ESAVI with a fatal outcome was recorded, which was evaluated and classified with causality C by the Interinstitutional Pharmacovigilance Committee, concluding that the death was related to a pre-existing condition of severe cystic fibrosis.

A total of 533 cases (183.1 per million doses administered) of AEFI were reported with terms suggestive of hypersensitivity reactions and anaphylaxis. Of these, 400 (75%) were classified as immediate hypersensitivity and 133 (25%) as delayed hypersensitivity. Of the cases of immediate hypersensitivity, 79 (19.8%) were anaphylactic reactions (27.1 per million doses administered). No deaths were reported. Of the cases of anaphylaxis following dengue vaccination, 72 cases (91.1%) occurred after the first dose, with a median age of 11 years (Q1: 10, Q3: 13); Only five cases (6.3%) had a history of known allergies and 15 (19%) had comorbidities. The median time between vaccination and symptom onset was 23 minutes (range: 10-40 minutes), and in 27 cases (40.9%) symptoms began within 15 minutes after vaccination.

Source: Departamento do Programa Nacional de Imunizações, Department of Health Surveillance and Environment, Ministry of Health. Informe: Monitoramento da segurança da vacina dengue atenuada, SE 1 de 2023 à SE 32 de 2024, Brasil. Updated 3 October 2024. Available from: https://www.gov.br/saude/pt-br/vacinacao/esavi/monitoramento-dos-eventos/2024/informe-monitoramento-da-seguranca-da-vacina-dengue-atenuada-se-9-2023-a-se-32-2024.pdf/view. Data reproduced by PAHO/WHO.

Mexico

COVID-19 Vaccine

As of 12 October 2024, 135 972 266 doses of COVID-19 vaccine had been administered in Mexico since the start of vaccination. During this period, a total of 40 228 AEFIs were notified, of which 3.19% (1 285) were classified as serious. Most serious and non-serious AEFIs occurred in the female sex, with 57%. Serious AEFIs were more common in people over age 60.

The main signs and symptoms in non-serious AEFIs were headache (65.35%), pain or tenderness at the injection site (45.94%), and myalgia (41.09%). In serious AEFIs, the predominant symptoms were headache (43.1%), asthenia (37.48%), and dyspnea (28.9%).

Source: Epidemiología, Dirección de Vigilancia Epidemiológica de Enfermedades Transmisibles. Reporte ESAVI COVID-19. September 2024. Available from: https://www.gob.mx/cms/uploads/attachment/file/952655/REPORTEESAVIDVEETSEPTIEMBRE2024.pdf. Data reproduced by PAHO/WHO.

Paraguay

COVID-19 Vaccine

As of 1 October 2024, 10 157 899 doses of COVID-19 vaccines had been administered in Paraguay, with a total of 2781 notifications of AEFIs, representing 0.028% of the total doses administered. Of these, 476 events were classified as serious, equivalent to 0.005% of the total number of doses administered.

The highest reported rate of ESAVI was associated with the vaccine Covaxin (80.29/100 000 doses administered), followed by AstraZeneca (58.11/100 000 doses administered), and CoronaVac (50.83/100 000 doses administered). Of the total number of AEFIs notified, 70.7% (1967) occurred in women, with most in the age group 25-49.

The most commonly reported clinical manifestations included fever, headache, injection site pain, myalgia, and fatigue.

Ministry of Public Health and Social Welfare, Programa Nacional de Enfermedades Inmunoprevenibles y Programa Ampliado de Inmunizaciones. Boletín informativo de vigilancia de ESAVI relacionada a la vacunación contra COVID-19. 01 October 2024. Available from: https://pai.mspbs.gov.py/esavi-2024/. Data reproduced by PAHO/WHO.

COVID-19 Vaccines

The risk of pregnancy-related adverse outcomes after COVID-19 vaccination: propensity score-matched analysis with influenza vaccination

On 25 November, a propensity score-matched cohort study was released that used the National Health Insurance Service insurance claims database, combined with COVID-19 and influenza vaccination registration data from the Korea Disease Control and Prevention Agency. Pregnant women were included from 18 October 2021 to 3 March 2022. Groups were matched based on age, comorbidities, insurance type, region, hospital type, gestational age at vaccination, and primiparity.

Two comparisons were made. 1) The group that received the COVID-19 vaccines versus the group that received the influenza vaccine. 2) The group that received both vaccines (COVID-19 and influenza) versus the group that received the influenza vaccine. Both groups were matched in a 1:3 ratio. Logistic regression analysis was used to calculate odds ratios (ORs) with 95% confidence intervals (CIs) between the two groups.

The study included 67 522 pregnant women. Of these, 610 received only the COVID-19 vaccine, 49,952 received only the influenza vaccine, and 2,405 received both.

In the COVID-19 vaccination-only group, the risk of large for gestational age was higher than in the influenza vaccination-only group (OR = 2.29, 95% CI = 1.16–4.52, *P* = 0.018). In the group that received both vaccinations (COVID-19 and influenza), the risk of premature birth was higher (OR = 1.37, 95% CI = 1.12–1.66, *P* = 0.002) than that in the influenza vaccination-only group but lower than the domestic baseline incidence rates. No significant differences were observed in other maternal and neonatal outcomes.

The results suggest that mRNA-based COVID-19 vaccination in pregnant women is safe without a remarkable increase in adverse maternal and neonatal outcomes. Given the high morbidity and mortality rates of COVID-19 in pregnant women, it is reasonable to recommend COVID-19 vaccination to protect this population. However, further extensive and long-term studies are needed to confirm these findings and to more accurately evaluate possible side effects, in order to ensure an adequate balance between the potential benefits and risks associated with this immunization strategy.

Source: Yu Jung Choi et al. The risk of pregnancy-related adverse outcomes after COVID-19 vaccination: Propensity score-matched analysis with influenza vaccination
Vaccine Volume 44, 12 January 2025, 126506

Participant-Reported Neurological Events Following Immunization in the Canadian National Vaccine Safety Network-COVID-19 Vaccine (CANVAS-COVID) Study

On 2 December, this prospective cohort study was released, carried out by the Canadian National Vaccine Safety Network (CANVAS). It was conducted as an active participant-based surveillance for AEFIs during the COVID-19 vaccine campaign. The design included online surveys completed by participants to evaluate the association between COVID-19 vaccination and neurological adverse events.

The studied population included 15 273 controls not exposed to the vaccine, 758 619 dose 1 recipients, 406 884 dose 2 recipients, and 126 586 dose 3 recipients. The evaluation period was seven days after COVID-19 vaccination or seven days prior to the survey (unvaccinated controls). Additional follow-up was done seven months later.

A *neurological event* was defined as a participant-reported health event that prevented daily activities and/or required medical attention and where the participant reported that the most "severe" symptom associated with the health event (with severity defined and determined by the participant) was any one of the following neurological symptoms: anesthesia/paresthesia (numbness or tingling, pins and needles, decreased sensation or burning sensation anywhere in the body), loss of taste and/or smell, loss of vision, sudden onset facial weakness or paralysis, seizure, or other neurological symptoms captured as one survey item and defined as: weakness or paralysis of the arms or legs, confusion, change in personality/behavior or difficulty with urination or defecation

The results showed that rates of neurological events ranged from 15.9 (95% CI 13.6–18.4) per 10 000 dose 1 ChAdOx1 recipients to 8.4 (6.5–10.8) and 7.9 (5.7–11.0) per 10 000 dose 3 mRNA-1273 and BNT162b2 recipients, respectively, versus 9.2 (5.2–15.8) per 10 000 controls.

Multivariable regression adjusted for age, sex, previous SARS-CoV-2 infection, and baseline health status showed an increased risk of neurological event among ChAdOx1 dose 1 recipients versus controls (adjusted OR 2.3, 95% CI 1.2–4.3), but not among mRNA vaccine recipients after any dose.

Additionally, risk of anesthesia/paresthesia was increased following ChAdOx1 dose 1 (aOR 4.7, 1.7–13.1), and consistently but not statistically significantly higher following any dose of either mRNA vaccine. Risk of loss of smell/taste was decreased among recipients of any dose of either mRNA vaccine versus controls.

The results suggest that neurological events following COVID-19 vaccination are rare and are not increased after COVID-19 mRNA vaccination compared to background rates. The finding of an increase in anesthesia and paresthesia after ChAdOx1 dose 1 vaccination and homologous mRNA-1273 primary vaccination warrants further study. These results reinforce the safety of COVID-19 vaccination and demonstrate that participant-based AEFI surveillance can detect safety signals consistent with other surveillance systems

Source: Karina A. Top et al. Participant-reported neurological events following immunization in the Canadian National Vaccine Safety Network-COVID-19 vaccine (CANVAS-COVID) study. Vaccine 42 (2024) 126445.

Herpes Zoster Vaccine and Influenza Vaccine

Safety of Simultaneous Vaccination With Adjuvanted Zoster Vaccine and Adjuvanted Influenza Vaccine: A Randomized Clinical Trial

On 24 October, a randomized blinded clinical trial was released, designed to evaluate the safety and reactogenicity after simultaneous administration of recombinant adjuvanted zoster vaccine (RZV) and quadrivalent adjuvanted inactivated influenza vaccine (aIIV4), compared to simultaneous doses of RZV with quadrivalent high-dose inactivated influenza vaccine (HD-IIV4).

The study population consisted of 267 community-dwelling older adults over 65 years of age, stratified by age (65-69 years and ≥70 years), during the 2021-2022 and 2022-2023 influenza seasons. The study was carried out at two centers in the US and analysis was performed on an intention-to-treat basis.

The primary objective was to compare the safety of both vaccine combinations, using as primary outcome the proportions of participants with one or more severe solicited reactions during the first eight days after administration. A 10% noninferiority margin was established to evaluate the differences between groups. Serious adverse events and adverse events of clinical interest were also evaluated during the 43 days of the study period.

The median age of the participants was 71.0 years (range, 65-92 years); 51.3% were men. Of the total, 130 received simultaneous RZV and aIIV4, and 137 received simultaneous RZV and HD-IIV4. The proportion of patients reporting one or more severe reactions was 11.5% in the RZV and aIIV4 group and 12.5% in the RZV and HD-IIV4 group, with an absolute difference of −1.0% (95% CI, −8.9% to 7.1%) which was noninferior. There were no significant differences in the number of serious adverse events or adverse events of clinical interest between the groups.

The results suggest that simultaneous doses of RZV and aIIV4 and simultaneous doses of RZV and HD-IIV4 have similar safety profiles. From a safety standpoint, this study supports the simultaneous administration of RZV and aIIV4 among older adults.

Source: Kenneth E. Schmader *et al.* Safety of Simultaneous Vaccination with Adjuvanted Zoster Vaccine and Adjuvanted Influenza Vaccine A Randomized Clinical Trial. JAMA Network Open. 2024;7(10):e2440817. doi:10.1001/jamanetworkopen.2024.40817

DECISIONS OF REGIONAL AND INTERNATIONAL REGULATORY AUTHORITIES

COVID-19 Vaccine

The European Medicines Agency Committee for Medicinal Products for Human Use Recommends an Update to Nuvaxovid and Bimervax Vaccines

On 18 October, the European Medicines Agency (EMA) announced that the Committee for Medicinal Products for Human Use (CHMP) gave a positive opinion to update the composition of Nuvaxovid, a vaccine to target the SARS-CoV-2 JN.1 variant following the recommendations issued by EMA's Emergency Task Force to update COVID-19 vaccines for the 2024/2025 vaccination campaign.

The CHMP also gave a positive opinion to update Bimervax, a vaccine targeting the Omicron XBB.1.16 subvariant. This approval indicates the ability to update the vaccine composition in view of further updates.

Additional information available from: https://www.ema.europa.eu/en/news/meeting-highlights-committee-medicinal-products-human-use-chmp-14-17-october-2024

Brazil's National Health Surveillance Agency Approves Update of Comirnaty and Spikevax Vaccines

On 22 November, Brazil's National Health Surveillance Agency (ANVISA) approved the update of the Comirnaty vaccine from Pfizer do Brazil Ltda. and the Spikevax vaccine from Adium S.A., using the JN.1 strain recommended by the WHO for the 2024/2025 season.

In September of this year, ANVISA prioritized the analysis of data and evidence submitted by companies, as these vaccines are intended for the National Immunization Program of the Ministry of Health, in accordance with Resolution RDC 204/2017.

The indication for these vaccines remains the same as authorized in their respective registrations: for use in individuals from 6 months of age. The dosage schedule varies according to the product to be administered, its nature, and previous vaccination.

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

COVID-19 Treatment

The Federal Commission for Protection against Health Risks authorized the registration of the medication Nirmatrelvir/Ritonavir for the treatment of COVID-19 in adults

The Federal Commission for Protection against Health Risks (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 (CMN) 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 ANVISA, the FDA, and Health Canada.

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

Respiratory Syncytial Virus (RSV) Vaccines

The Federal Commission for Protection against Health Risks Authorized the Respiratory Syncytial Virus (RSV) Vaccines for Pregnant Women and Older Adults

On 17 December, the Federal Commission for Protection against Health Risks (COFEPRIS) announced that it had granted the registration to the respiratory syncytial virus (RSV) vaccine Abrysvo for administration to pregnant women and people 60 years of age and older.

Additional information available from: https://www.gob.mx/cofepris/articulos/cofepris-autoriza-vacunas-contra-virus-sincicial-respiratorio-vsr-para-aplicar-a-mujeres-embarazadas-y-adultos-mayores-386366?idiom=es

Mpox Medications

The International Coalition of Drug Regulatory Authorities Released a Report on the Development, Clinical Trials, and Availability of Vaccines and Therapies for Mpox

On 2 October, International Coalition of Medicines Regulatory Authorities (ICMRA) released a report highlighting their considerations on the development, clinical trials and availability of vaccines and therapeutics for mpox. The report presents the outcomes of a workshop held virtually that brought together representatives from international medicines regulatory authorities and experts from WHO to explore how they can support access to mpox medicines in the most affected countries during the ongoing outbreak.

During the workshop, the WHO, US Food and Drug Administration (FDA), Japan Pharmaceuticals and Medical Devices Agency (PMDA), UK Medicines and Healthcare products Regulatory Agency (MHRA) and EMA offered an overview of the global epidemiological status of mpox and the WHO strategic response plan, a summary of the overall features, regulatory status, and evidence available for different mpox vaccines and therapeutics.

International regulators stressed the need for large clinical trials to generate the evidence to enable faster development and rapid approval of mpox medicines. They also agreed that using a more coordinated approach would be the most effective strategy to tackle current and future public health emergencies.

Additional information available from: https://www.ema.europa.eu/en/news/fostering-regulatory-collaboration-improve-access-mpox-medicineshttps://www.icmra.info/drupal/news/mpox_news_announcement_25oct2024/mpox_ws_report_2oct2024

Dengue Treatment

ANVISA Authorized Phase 2a Clinical Trial of Dengue Medication EYU688

On 21 October, ANVISA announced that it had authorized the initiation of a Phase 2a randomized, double-blind, placebo-controlled clinical trial aimed at evaluating the pharmacokinetics, safety, and efficacy of the medication EYU688 in patients infected with any of the dengue serotypes.

The clinical development of the medication EYU688 is sponsored in Brazil by the pharmaceutical company Novartis Biosciences and plans to include 38 patients who will be recruited at clinical research centers located in Brasilia, Sorocaba, São José de Rio Preto, Manaus, and Rio de Janeiro. In addition to Brazil, this clinical trial is being conducted in Singapore, India, Malaysia, and Vietnam.

The details of this clinical protocol (inclusion and exclusion criteria, design, and objectives) are available on the *ClinicalTrials.gov* platform under the code NCT06006559.

Additional information available from: https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2024/autorizado-ensaio-clinico-de-medicamento-oral-contra-dengue

Mpox Vaccine

WHO adds LC16 KMB Vaccine to the Emergency Use Listing

On 19 November, the WHO announced that the first mpox vaccine was added to the Emergency Use Listing (EUL), indicated in people over 1 year of age. The main features of this vaccine are summarized below.

Vaccine	Commercial Name	Manufacturer	NRA of Reference	Pharmaceutical Form	Presentation/ Storage/ Shelf Life
Mpox vaccine, obtained by culturing *live attenuated vaccinia virus (strain LC16m8) in primary rabbit kidney cells* (PRK cells).	LC16 KMB (LC16m8 vaccine)	KM Biologics Co., Ltd, Japan	Pharmaceutical and Medical Devices Agency (PMDA), Japan	Freeze-dried powder	Multidose vial 2° - 8°C 24 months without reconstitution

There is another mpox vaccine, Imvanex® (also known as JYNNEOS in the US and IMVAMUNE in Canada), created by Bavarian Nordic A/S, which was prequalified by the WHO in September 2024.

Additional information available from: https://extranet.who.int/prequal/vaccines/mpox
https://extranet.who.int/prequal/sites/default/files/document_files/mpox-lc16m8_tag-report-19-11-2024-final.pdf
https://extranet.who.int/prequal/vaccines/p/imvanexr

New Vaccines

WHO Lists Top 17 Pathogens for Which New Vaccines are Urgently Needed

On 5 November, in a new study published in *eBioMedicine*, the WHO listed 17 pathogens that regularly cause diseases in communities as top priorities for new vaccine development. It is the first global effort to systematically prioritize endemic pathogens based on criteria that included regional disease burden, antimicrobial resistance risk, and socioeconomic impact.
The global priority list of endemic pathogens for vaccine R&D supports the Immunization Agenda 2030's goal of ensuring that everyone, in all regions, can benefit from vaccines that protect them from serious diseases. The WHO priority endemic pathogens are:

- **Pathogens where vaccine research is needed**
  - Group A streptococcus
  - Hepatitis C virus
  - HIV-1
  - *Klebsiella pneumoniae*

- **Pathogens where vaccines need to be further developed**
  - Cytomegalovirus
  - Influenza virus (broadly protective vaccine)
  - *Leishmania* species
  - Non-typhoidal *Salmonella*
  - *Norovirus*
  - *Plasmodium falciparum*
  - *Shigella* species
  - *Staphylococcus aureus*

- **Pathogens where vaccines are approaching regulatory approval, policy recommendation or introduction**
  - Dengue virus
  - Group B streptococcus
  - Extra-intestinal pathogenic E. coli
  - *Mycobacterium tuberculosis*
  - Respiratory syncytial virus

Additional information available from: https://www.who.int/news/item/05-11-2024-who-study-lists-top-endemic-pathogens-for-which-new-vaccines-are-urgently-needed
https://www.who.int/news/item/10-10-2024-better-use-of-vaccines-could-reduce-antibiotic-use-by-2.5-billion-doses-annually--says-who

Vaccine Safety

Chile's Institute of Public Health Implements Automated System for Regional Vaccine Safety Surveillance

On 28 October, Chile's Public Health Institute (Instituto de Salud Pública, ISP) announced that it had successfully implemented the automated system for regional vaccine safety surveillance, based on the HL7 FHIR standard, to send reports on AEFIs from the ISP to PAHO's regional database.

This implementation allows the ISP to efficiently and securely send PAHO information on adverse events following immunization, facilitating a faster and more coordinated regional response.

To ensure the consistency and completeness of vaccination-related information, one of the key points was the promotion of vaccine data sharing between the National Immunization Program and the ISP. The Department of Health Statistics and Information and the Department of Information and Communication Technologies of the Ministry of Health also participated.

Additional information available from: https://www.ispch.cl/noticia/instituto-de-salud-publica-de-chile-lider-en-la-implementacion-de-sistema-automatizado-para-la-vigilancia-regional-en-seguridad-de-vacunas/

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