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

Beginning with this edition of the newsletter, in addition to addressing regional and global information on COVID-19 vaccines, details related to safety, regulation and other aspects of interest of new vaccines that may potentially be introduced in the Region will be incorporated.

XLVI Report

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OPS Organización Panamericana de la Salud
Organización Mundial de la Salud Oficina Regional para las Américas
In partnership with Canada

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Canada

COVID-19 vaccines

As of 5 January, a total of 105 016 456 doses of COVID-19 vaccines were administered, including 5 694 993 doses of monovalent XBB.1.5 and 9 948 907 bivalent doses. There were 58 712 reports containing AEFIs, of which 11 702 were considered serious; 1 044 were following bivalent vaccines, of which 251 were considered serious (0.003% of bivalent doses administered).

Most adverse event reports were from females (72.4%). The reporting rate for females was 75.9 per 100 000 doses, compared to 31.5 per 100 000 doses in males. However, in the youngest age groups (<18 years), reporting rates were similar in males and females, or slightly higher in males, possibly due to differences in health care-seeking behavior and biological differences.

Number and rate of major adverse event of special interest (AESI) reports by vaccine through 5 January 2024 in the general population.

AESI	Vaccines					
	Pfizer-BioNTech		Modern Spikevax		Covishield and AstraZeneca	
	N*	Rate**	N*	Rate**	N*	Rate**
Guillain Barré Syndrome	5	0.01	5	0.02	12	0.43
Thrombocytopenia	111	0.18	39	0.15	51	1.81
Myocarditis/pericarditis	725	1.19	465	1.82	18	0.64
Thrombocytopenia syndrome (TTS)	24	0.04	8	0.03	56	1.99
Bell's palsy/facial paralysis	146	0.24	45	0.18	14	0.50
Anaphylaxis	557	0.92	177	0.69	25	0.89

*N: number of reports
**Rate: per 100 000 doses administered

Note: Janssen and Novavax vaccines were not included due to the small number of reported cases.

Source: Public Health Agency of Canada. Canadian COVID-19 vaccination safety report. Ottawa: Public Health Agency of Canada; January 19, 2024. https://health-infobase.canada.ca/covid-19/vaccine-safety/. Data reproduced by PAHO/WHO.

Chile

COVID-19 vaccines

In January 2024, the Chilean Institute of Public Health (ISP), through its National Center for Pharmacovigilance, published the second statistical report on AEFIs/ESAVIs associated with the administration of bivalent COVID-19 vaccines in Chile, in persons over 12 years of age".

Number of doses of bivalent COVID-19 vaccines administered; number and reporting rate of serious AEFIs; and total AEFIs, by vaccine, from 11 October 2022 to 6 May 2023 (n= 317).						
Bivalent vaccine	**Omicron variant lineage**	**Total doses administered**	**Number and reporting rate of serious AEFIs**		**Number and reporting rate, with total AEFIs**	
			N*	Rate**	N*	Rate**
Pfizer-BioNTech™	**Original/Omicron BA.1**	917 922	6	0.7	160	17.4
	Original/Omicron BA.4 and BA.5	1 042 424	1	0.1	69	6.6
Moderna™.	**Original/Omicron BA.1**	772 359	3	0.4	75	9.7
	Original/Omicron BA.4 and BA.5	338 131	0	0	13	3.8
Total		**3 070 836**	**10**	**0.3**	**317**	**10.3**

* N= number of reports with AEFIs

** Rate= reporting rate per 100 000 doses administered

During this reporting period, there was one report related to the Pfizer-BioNTech/Omicron BA.1 COVID-19 vaccine in a 26-year-old woman at 22 weeks gestational age. The report was classified as non-serious, as it consisted of pruritus, urticaria, and allergy appearing one day after vaccine administration.

Source: Public Health Institute of Chile. Ministry of Health. Second statistical report on "ESAVI associated with the administration of bivalent COVID-19 vaccines in Chile, in people older than 12 years old". Period: October 11, 2022 to May 06, 2023. Available at: https://www.ispch.cl/wp-content/uploads/2024/02/2-do-informe-vacunas-bivalentes-VF-08.02.2023-VVG.pdf. Data reproduced by PAHO/WHO

Peru

COVID-19 vaccines

Through 31 December 2023, a total of 91 805 958 doses of COVID-19 vaccines were administered, including 3 020 955 bivalent doses. There were 64 311 reports with AEFIs (0.06% of COVID-19 doses administered), of which 304 (0.6%) reports were considered serious.

The majority of the reports were for women 63.9% (41 061); 55.1% (35 418) were for adults between 30 to 59 years of age; 3.3% (2127) were for adolescents between 12 to 17 years of age; 4.8% (3111) were for immunized children between 5 to 11 years of age; and 1.3% (855) were for children under 5 years of age.

Source: Ministry of Health. General Directorate of Medicines, Supplies and Drugs. Pharmacovigilance report. Adverse events presumably attributed to vaccination or immunization (ESAVI) reported to COVID-

19 vaccine. Period 09 February 2021 to 31 December 2023. Available at: https://repositorio-digemid.minsa.gob.pe/items/63dfa41b-3ec8-4e88-b7c4-ec17c0428e69.Data reproduced by PAHO/WHO.

Brazil

Dengue vaccine

As of 4 March 2024, a total of 365 610 doses of (attenuated) tetravalent dengue vaccine from Takeda Laboratory were administered. There were 464 reports with AEFIs, of which 33 (7.1%) reports were considered serious.

Among reported AEFIs, regardless of their seriousness, 70 hypersensitivity reactions were observed with a reporting rate of 19.15 per 100 000 doses administered, including 16 cases of anaphylaxis with three cases of anaphylactic shock. Most cases of anaphylaxis presented clinical manifestations involving, in addition to the skin and mucous membranes, the respiratory (n=9), circulatory (n=4), and gastrointestinal (n=4) systems. None of the cases resulted in death.

Source: Ministério da Saúde, Secretaria de Vigilância em Saúde e Ambiente, Departamento do Programa Nacional de Imunizações, Coordenação-Geral de Farmacovigilância. TECHNICAL NOTE No. 7/2024-CGFAM/DPNI/SVSA/MS; March 7, 2024. Available at: https://www.gov.br/saude/pt-br/centrais-de-conteudo/publicacoes/notas-tecnicas/2024/nota-tecnica-no-7-2024-cgfam-dpni-svsa-ms/.

Data reproduced by PAHO/WHO.

PAHO recommendation

It is important that ministries of health in countries considering introduction of the (attenuated) tetravalent dengue vaccine from the Takeda laboratory ensure that they have qualified personnel and adequate equipment at vaccination sites to address potential hypersensitivity reactions, and that vaccinated individuals are kept under observation for 30 minutes. Although the mechanism that produces the reported anaphylactic reactions is unknown, as a precautionary measure it is important to investigate the patient's history of hypersensitivity to other vaccines or to a previous dose of the same vaccine.

COVID-19 vaccines

Adverse events after XBB.1.5-containing COVID-19 mRNA vaccines

On 26 February, this study was published with the objective of investigating the association between the COVID-19 vaccine containing the XBB.1.5-containing vaccine administered as a fifth COVID-19 vaccine dose and the risk of 28 adverse events. A study cohort of all individuals in Denmark aged 65 and older who had received four COVID-19 vaccine doses was established by cross-linking nationwide health care and demography registers on an individual level. The study period was 15 September 2022 (i.e., national rollout date of the fourth dose) to 8 January 2024.

The 28 adverse events analyzed were: ischemic cardiac event, any cerebrovascular event, cerebral infarction only, arterial thromboembolism, deep vein thrombosis, pulmonary embolism, myocarditis, pericarditis, cerebral venous thrombosis, thrombocytopenia and coagulation disorders, Guillain-Barre syndrome, Bell's palsy, transverse myelitis, encephalomyelitis or encephalitis, narcolepsy, appendicitis, aseptic arthritis, type 1 diabetes, subacute thyroiditis, heart failure, arrhythmia, acute liver failure, acute renal failure, acute pancreatitis, erythema multiforme, seizure, arterial aneurysm, and uveitis.

Each outcome was studied separately and identified as any first hospital contact where an outcome diagnosis was recorded. The diagnosis date served as the event date.

The risk period was from day 0 to day 28 after a fifth dose of XBB.1.5-containing COVID-19 mRNA vaccine. The reference period consisted of: a) ≥43 days after a fourth dose (up to the day preceding a fifth dose); and b) ≥43 days after a fifth dose (up to the end of the study). Individuals could contribute person-time both during the 28-day risk period and the two reference periods. The period from zero to 42 days after a fourth dose and the period from 29 to 42 days after a fifth dose was considered a buffer and was not included in the risk period or the reference period follow-up. Among the 1 076 531 included individuals, 902 803 received an XBB.1.5-containing vaccine as a fifth dose during follow-up (contributing person-time in both the risk and reference periods), and 172,756 did not receive a fifth dose (contributing person-time only in the reference period).

Using Poisson regression, the risk and reference period outcome rates were compared by incidence rate ratios, adjusted for sex, age, region of residence, considered at high risk of severe COVID-19, health care worker, calendar time, and number of comorbidities. A 95% CI that did not cross 1 was defined as statistically significant.

The results showed that among the 1 076 531 included individuals, 902 803 received an XBB.1.5-containing vaccine as a fifth dose during follow-up. Receipt of the vaccine was not associated with a statistically significant increase in the rate of hospital contacts for any of the 28 adverse events within 28 days after vaccination compared with reference period rates. For example, the incidence rate ratio was 0.96 (95% CI, 0.87-1.07) for an ischemic cardiac event, 0.87 (95% CI, 0.79-0.96) for cerebral infarction, and 0.60 (95% CI, 0.14-2.66) for myocarditis.

The authors concluded that, in this nationwide Danish cohort of more than one million adults over 65 years of age, there is no evidence of increased risk associated with 28 adverse events following administration of an XBB.1.5-containing vaccine.

Source: Andersson NW, Thiesson EM, Hviid A. Adverse Events After XBB.1.5-Containing COVID-19 mRNA Vaccines. JAMA. Published online February 26, 2024. doi:10.1001/jama.2024.1036.

COVID-19 vaccines and adverse events of special interest: A multinational Global Vaccine Data Network (GVDN) cohort study of 99 million vaccinated individuals

On 12 February, a retrospective observational study by The Global COVID Vaccine Safety Project (established in 2021 under the multinational Global Vaccine Data Network™) was published. The aim of the study was to evaluate the risk of adverse events of special interest (AESIs) following COVID-19 vaccination at 10 sites in eight countries: Argentina, Australia (New South Wales and Victoria), Canada (British Columbia and Ontario), Denmark, Finland, France, New Zealand and Scotland.

Using a common protocol, this observational cohort study compared observed and expected rates of 13 selected AESIs across neurologic, hematologic, and cardiac outcomes.

Neurological conditions selected included Guillain-Barré syndrome (GBS), transverse myelitis (TM), facial (Bell's) palsy, acute disseminated encephalomyelitis (ADEM), and convulsions (generalized seizures (GS) and febrile seizures (FS)), as potential safety signals have been identified for some of these conditions. Hematologic conditions included cerebral venous sinus thrombosis (CVST), splanchnic vein thrombosis (SVT) and pulmonary embolism (PE); the unusual site thromboses (CVST and SVT) were selected as markers of potential TTS that could be accurately identified using diagnostic codes. Thrombocytopenia and immune thrombocytopenia (ITP) were also included due to their association with TTS and reports of ITP as an independent safety signal. Myocarditis and pericarditis were included as cardiovascular conditions and the OE ratios were evaluated separately for each condition.

Expected rates were obtained by participating sites using pre-COVID-19 vaccination healthcare data stratified by age and sex.

Observed rates were reported from the same healthcare datasets since the rollout of the COVID-19 vaccination program. AESIs occurring up to 42 days after vaccination with mRNA (BNT162b2 and mRNA-1273) and adenovirus-vector (ChAdOx1) vaccines were included in the primary analysis.

Risks were assessed using observed versus expected (OE) ratios with 95 % confidence intervals. Prioritized potential safety signals were those with lower bound of the 95 % confidence interval (LBCI) greater than 1.5.

Participants included 99 068 901 vaccinated individuals. In total, 183 559 462 doses of BNT162b2, 36 178 442 doses of mRNA-1273, and 23 093 399 doses of ChAdOx1 were administered at participating sites during the study period.

Risk periods contributed 23 168 335 person-years of follow-up. OE ratios with LBCI > 1.5 were observed for Guillain-Barré syndrome (2.49, 95 % CI: 2.15, 2.87) and cerebral venous sinus thrombosis (3.23, 95 % CI: 2.51, 4.09) following the first dose of ChAdOx1 vaccine. Acute disseminated encephalomyelitis showed an OE ratio of 3.78 (95 % CI: 1.52, 7.78) following the first dose of mRNA-1273 vaccine.

The OE ratios for myocarditis and pericarditis following BNT162b2, mRNA-1273, and ChAdOx1 were significantly increased with LBCIs > 1.5..

The authors concluded that this multi-country analysis confirmed pre-established safety signals for myocarditis, pericarditis, Guillain-Barre syndrome, and cerebral venous sinus thrombosis. Other potential safety signals that would require further investigation were identified.

Source: K. Faksova *et al*, COVID-19 vaccines and adverse events of special interest: A multinational Global Vaccine Data Network (GVDN) cohort study of 99 million vaccinated individuals. Vaccine, https://doi.org/10.1016/j.vaccine.2024.01.100

Respiratory syncytial virus (RSV) vaccines

The following is a concise summary of the most important considerations related to epidemiology and available respiratory syncytial virus (RSV) vaccines.

Epidemiology

RSV is a highly contagious virus that causes lung and respiratory tract infections in people of all age groups. RSV circulation is seasonal, usually beginning in autumn and peaking in winter.[1]

High risk populations include older adults, immunocompromised individuals (hematologic malignancies, hematopoietic stem cell transplant recipients, lung transplant recipients) and those with underlying cardiopulmonary conditions. In pregnant women, RSV infections can result in severe disease requiring hospitalization for respiratory support, including supplemental oxygen, intubation, and/or mechanical ventilation.[2]

Worldwide, it is the most frequent cause of pneumonia and bronchiolitis in infants. It is also the leading cause of hospitalization and death in the first six months of life. In the Americas, most RSV-associated hospitalizations occur in children under 5 years of age, particularly in infants under 2 years of age.[1]

According to the U.S. Centers for Disease Control and Prevention, each year in the United States, RSV causes between 60 000 and 120 000 hospitalizations and 6000 to 10 000 deaths in people 65 years of age and older.[3]

Limited data are currently available on RSV disease burden in adults and women of childbearing age. Pregnancy is considered an immunologically attenuated state, and RSV infection in pregnancy has been associated with more severe disease and adverse outcomes. Vertical transmission of RSV infection in pregnant women to their infants is possible and may be associated with adverse perinatal outcomes. Limited epidemiological studies suggest that RSV infection occurs in approximately 2% to 9% of pregnancies. A cross-sectional study of acute respiratory illness (ARI) in pregnancy found that 10% of ARI in pregnant women were due to RSV. [2]

Available vaccines

To date, two RSV vaccines are available. Their characteristics and indications are summarized in the following table.[4,5]

Abrysvo ® (Pfizer)	Arexvy ® (GSK)
Bivalent vaccine **Antigens**: Recombinant prefusion F protein subunits of RSV subtypes A and B (Buenos Aires 60 µg and Ontario 60 µg genotypes). The RSV vaccine contains equal amounts of stabilized prefusion F (preF) antigens of the two major subtypes: RSV A and RSV B. Without adjuvant. One intramuscular (IM) dose.	**Monovalent vaccine** **Antigen:** RSV prefusion F protein (120 µg). Adjuvant: AS01. One IM dose
Indications: Active immunization for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus (RSV) in persons 60 years of age and older. Active immunization of pregnant women between 32 and 36 weeks gestational age for the prevention of LRTD and severe LRTD caused by RSV in infants from birth to 6 months of age.	**Indications:** Active immunization for the prevention of LRTD caused by RSV in persons 60 years of age and older.

Clinical studies

Abrysvo®: study in pregnant women

Study C3671008 was designed to evaluate the efficacy and safety of Abrysvo® (RSVpreF). It is an ongoing, Phase 3, randomized, double-blind, multicenter, placebo-controlled study to investigate the efficacy and safety of RSVpreF in infants born to women vaccinated during pregnancy (pregnant women ≤49 years with uncomplicated singleton pregnancies), as well as the safety of RSVpreF in pregnant women.

This multicenter study is being conducted in Argentina, Australia, Brazil, Canada, Chile, Denmark, Finland, Gambia, Japan, Mexico, Netherlands, New Zealand, Philippines, South Africa, South Korea, Spain, Taiwan, the United States of America, and South Africa.

In this 1:1 randomized study, 3682 participants received RSVpreF and 3675 received placebo (0.5 ml doses containing the same excipients and in the same amounts as in a single dose of RSVpreF).

Vaccine efficacy: Vaccination in pregnant women at 24–36 weeks gestational age demonstrated 81.8% efficacy against severe lower respiratory tract disease within the first 90 days after birth (99.5% CI, 40.6 to 96.3); and 69.4% efficacy at 180 days after birth (97.58% CI, 44.3 to 84.1).

Vaccine efficacy against RSV-associated hospitalization was 67.7% (99.17% CI, 15.9 to 89.5) in the first 90 days after birth, and 56.8% (99.17% CI, 10.1 to 80.7) in the first 180 days after birth. [2,6]

Solicited local and systemic adverse reactions [2]

Most local and systemic adverse reactions reported in pregnant subjects resolved within 2-3 days post-vaccination. Severe local reactions were reported in 0.3% of pregnant women in the RSVpreF group and none in the placebo group, and severe systemic reactions were reported in 2.3% of pregnant women in both groups within seven days post-vaccination.

Solicited events reported within seven days post-vaccination (%):

Local events (%):	**RSVpreF vaccine group**	**Placebo group**
Pain at injection site	40.6	10.1
Redness	7.2	0.2
Swelling	6.2	0.2

Systemic events (%):

Systemic events (%)	**Vaccine group (RSVpreF)**	**Placebo group**
Fever: > 38 degrees C	2.6	2.9
Fatigue	46.1	43.8
Headache	31.0	27.6
Muscle pain	26.5	17.1
Nausea	20.0	19.2
Joint pain	11.6	10.5
Diarrhea	11.2	11.5
Vomiting	7.8	7.0

Unsolicited adverse events (%):

Reported unsolicited adverse events	**RSVpreF group**	**Placebo group**
Reported within 1 month post-vaccination by pregnant women	13.0	13.0
Reported most frequently within 1 month of follow-up	Disorders in pregnancy, puerperium, and perinatal period 7.0	Disorders in pregnancy, puerperium, and perinatal period 6.0

Serious adverse events

Serious adverse events (SAEs) were reported by 16.2% of individuals in the RSVpreF group and 15.2% in the placebo group during the study period. SAEs occurring within one month post-vaccination were reported by 4.2% of the RSVpreF group and 3.7% of the placebo group.

Most SAEs in the pregnant participants were pregnancy-related complications occurring more than one month after vaccination.

The following table includes all SAEs from vaccination to six months postpartum (up to approximately 10 months, depending on the gestational age at the time of vaccination).[8]

Serious adverse events temporally related to pregnancy, occurring any time after vaccination	RSVpreF N=3.662 n (%)	95% CI	Placebo N=3.675 n (%)	95% CI
All maternal serious adverse reactions	598 (16.2)	(1.5; 1.7)	558 (1.2)	(1.4; 1.6)
Preeclampsia	68 (1.8)	(1.4; 2.3)	53 (1.4)	(1.1; 1.9)
Gestational hypertension	41 (1.1)	(0.8; 1.5)	38 (1.0)	(0.7; 1.4)
Premature rupture of membranes	15 (0.4)	(0.2; 0.7)	16 (0.4)	(0.2; 0.7)
Premature sac rupture	15 (0.4)	(0.2; 0.7)	10 (0.3)	(0.1; 0.5)
Hypertension	13 (0.4)	(0.2; 0.6)	6 (0.2)	(0.1; 0.4)
Maternal death	1 (<0.1)	(<0.1; <0.1)	0 (0.0)	(0.0; 0.0)
Fetal death	10 (0.3)	(0.1; 0.5)	8 (0.2)	(0.1; 0.4)

Note: Numbers in parentheses represent the proportion of people affected by each adverse event and the 95% confidence interval for that proportion.

Eclampsia: Occurred in five participants (three in the RSVpreF group and two in the placebo group); HELLP syndrome occurred in five participants (two in the RSVpreF group and three in the placebo group).

Maternal death: There was one maternal death in the RSVpreF group due to postpartum hemorrhage and hypovolemic shock. The FDA agreed with the investigator's assessment that this death was unrelated to vaccine administration.

Fetal death: A total of 18 intrauterine deaths were reported for the baseline pregnancy: 10 in the RSVpreF group (0.3%) and eight in the placebo group (0.2%). None of the intrauterine losses were assessed by the investigator as related to vaccination; the FDA agreed that the fetal deaths reported in this study were unlikely to have been related to the investigational product, based on review of available case narratives and the evident lack of temporal relation of vaccination to the fetal loss events. Up to the data cutoff date, a total of 17 infant deaths were reported: 5 (0.1%) in the RSVpreF group and 12 (0.3%) in the placebo group. None of the infant deaths evaluated by the investigator were related to maternal vaccination. With the exception of one of the infant deaths in the vaccine group, the FDA agreed with the investigator's conclusions; for one death that resulted from prematurity-related complications, the FDA was not able to exclude the possibility that the extreme prematurity and subsequent death were related to receipt of the

investigational product. One infant in the placebo group died from severe respiratory tract infection due to LRTD-RSV.

Adverse reactions in infants

Adverse events in infants from birth to 1 month of age were observed in 37.1% of participants in the RSVpreF group compared to 34.5% in the placebo group.

Low birth weight (LBW) was reported in 5.1% [95% CI: 4.4%, 5.8%] and 4.4% [95% CI: 3.7%, 5.0%] of infant participants in the RSVpreF and placebo groups, respectively. Neonatal jaundice occurred in 7.2% and 6.7% of infant participants in the RSVpreF and placebo groups, respectively. LBW and jaundice occurred more frequently in vaccinated individuals but these differences were not statistically significant.

Premature delivery was reported as an adverse event of special interest (AESI) for maternal participants throughout the study in 5.6% (207/3682) versus 4.8% (175/3675) in the RSVpreF and placebo groups, respectively. The rate of premature deliveries in the general population is typically higher than 6% (CDC, 2022a; WHO, 2022), which is higher than the overall rate of premature deliveries observed in the clinical trial population. The numerical difference represents a potential safety signal. The available data were insufficient to establish or exclude a causal relationship between premature delivery and vaccination. Since premature deliveries occurred more than 30 days after vaccination, and to minimize the potential risk, vaccination is indicated between 32 and 36 weeks of gestational age.[2,7]

ABRYSVO® : study in individuals aged 60 years and older.[2,9]

Study C3671013 is an ongoing, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of Abrysvo® (RSVpreF) in individuals 60 years of age and older. This study is being conducted in the United States, Argentina, Japan, the Netherlands, Canada, South Africa, and Finland. The demographic characteristics of participants who received RSVpreF and those who received placebo were generally similar with respect to age, gender, race, and ethnicity.

Vaccine efficacy: Vaccine efficacy against RSV-associated LRTD with at least two signs or symptoms was 66.7% (CI 96.66%, 28.8 to 85.8). Efficacy against RSV-associated LRTD with at least three signs or symptoms was 85.7% (CI 96.66%, 32.0 to 98.7). Vaccine efficacy against RSV-associated acute respiratory illness was 62.1% (CI 95%, 37.1 to 77.9).[10]

Safety: The safety of Abrysvo® was evaluated in the study, in which 17 215 participants received RSVpreF and 17 069 received placebo (0.5 ml doses, containing the same excipients and in the same amounts as in a single dose of Abrysvo®).

A total of 34 284 participants were included in the safety population, of which 26 395 (77.0%) completed at least six months of post-vaccination safety follow-up (13 273 RSVpreF recipients and 13 122 placebo recipients) by the data cutoff date of 14 July 2022.

Solicited local adverse reactions

Within seven days post-vaccination, the proportion of participants reporting a local reaction was higher in the RSVpreF group (12.2%) than in the placebo group (6.6%).

The most frequently reported local reaction in both groups was pain at the injection site, reported by 10.6% of participants in the RSVpreF group and 6.0% in the placebo group. Serious solicited local adverse

reactions (grade 3) were rare, reported by eight (0.2%) and two (<0.1%) participants in the RSVpreF and placebo groups, respectively.

Solicited systemic adverse reactions [2]

The incidences of systemic adverse reactions (ARs) within seven days post-vaccination were similar between the RSVpreF (27.5%) and placebo (25.7%) groups. Fatigue was the most frequently reported systemic AR (RSVpreF 15.5%; placebo 14.4%), followed by headache (RSVpreF 12.8%; placebo 11.7%) and muscle pain (RSVpreF 10.1%; placebo 8.4%). Fever was reported in 1.4% of participants in each group. Fever with maximum temperature between 38.9 and 40.0°C was reported by one (<0.1%) and two (<0.1%) participants in the RSVpreF and placebo groups, respectively. Fever >40.0°C within seven days post-vaccination was only reported by one placebo participant (measured 40.1°C, on day of vaccination only). Overall, severe (Grade 3 or above) systemic Ars were reported in 0.7% of RSVpreF recipients and 0.6% of placebo recipients.

Subgroup analysis

Gender: Solicited local and systemic ARs were reported more frequently among female RSVpreF recipients (15.9% and 32.7%, respectively) compared to male RSVpreF recipients (8.8% and 22.7%, respectively). In the placebo group, systemic ARs were also reported at a higher rate among female participants as compared to males, but local ARs were reported by a similar proportion of female and male placebo recipients.

Age: Among RSVpreF recipients, the proportions of participants reporting solicited ARs were inversely related to increasing age, with a higher rate of solicited local and systemic reactions reported in the 60-69 years of age group (14.0% and 30.2%, respectively) as compared to the 70-79 (10.4% and 24.1%, respectively) and ≥80 (3.6% and 19.1%, respectively) years of age groups.

Unsolicited adverse events [2]

The proportions of participants who reported unsolicited AEs within one month after vaccination were similar across groups (8.9% RSVpreF and 8.5% placebo). Adverse events that were assessed as related to study intervention by the investigator were reported in 1.3% of RSVpreF recipients and 0.9% of placebo recipients. These AEs primarily represented reactogenicity events and were mostly reported within seven days post-vaccination.

Guillain Barré Syndrome (GBS)[2]

Based on an FDA review of available data, two GBS events were identified in the RSVpreF group and none in the placebo group.

Cardiac arrhythmias[2]

Within one month after vaccination, a numerical imbalance in cardiac arrhythmia events was observed, with 21 events reported by 17 participants (0.1%) in the RSVpreF group and eight events reported by seven participants (<0.1%) in the placebo group.

This imbalance was mainly driven by atrial fibrillation (10 events in 10 participants [<0.1%] in the RSVpreF group compared to four events in four participants [<0.1%] in the placebo group), of which four in the RSVpreF group and three in the placebo group were serious adverse events. Event onset ranged from 18

to 30 days after vaccination. Among participants reporting atrial fibrillation, a medical history of atrial fibrillation was 25 reported by six (60%) RSVpreF recipients and two (50%) placebo recipients. The investigators considered that none of the atrial fibrillation events were related to the study intervention. Currently available information on atrial fibrillation is insufficient to determine a causal relationship to the vaccine**.**

No other notable imbalances observed in other queries, including immune-mediated/autoimmune disorders, were considered clinically relevant by the FDA.

Deaths[2]

Through the data cutoff, there were 52 (0.3%) deaths among RSVpreF recipients and 49 (0.3%) deaths among placebo recipients. In general, the causes of death among study participants were representative of the most common causes of death in the older adult population.

The most frequently reported causes of death were cardiac disorders for participants in both the RSVpreF (20 participants, 0.1%) and placebo (19 participants, 0.1%) groups.

By preferred term, these were most frequently described as cardiorespiratory arrest in the RSVpreF group (n = 6) and acute myocardial infarction in the placebo group (n = 5). None of the deaths were assessed as related to study intervention by the study investigators. Based on independent review of event narratives, FDA agreed with the investigators' assessments of causality.

Serious adverse events (SAEs)[2]

SAEs were reported in 2.3% of participants in both the RSVpreF (n = 396) and placebo (n = 387) groups.

There were three SAEs in the RSVpreF group that were assessed as related by the investigator, and none in the placebo group:

- a hypersensitivity event, not classified as anaphylaxis, beginning 8 hours after vaccination.
- a case of Guillain-Barré syndrome (GBS) with onset 7 days after vaccination.
- a case of Miller Fisher syndrome (considered a variant of GBS) with onset 8 days after vaccination.

Given the temporal association and biological plausibility, the FDA concurred with the investigators' assessments that these events were possibly related to the study vaccine.

Across all studies, the safety data collected at the RSVpreF clinical sites demonstrated an acceptable safety profile.

Possible safety signals[2]

- Identified significant risk of preterm delivery
- Significant potential risk of Guillain-Barré syndrome (GBS)
- Allergic reactions
- Supraventricular arrhythmias
- Hypertensive disorders of pregnancy, including preeclampsia.

AREXVY®: study in individuals aged 60 years and over[11-14]

The safety and efficacy of a single dose of Arexvy® (RSVPreF3 OA) are based on FDA analysis of data from an ongoing, placebo-controlled, randomized clinical study (AReSVi-006 ClinicalTrials.gov, number NCT04886596) conducted in the United States and internationally in persons 60 years of age and older. Participants will remain in the study for three RSV seasons to assess the duration of efficacy and the safety and efficacy of repeated vaccination. Data from a single dose of RSVPreF3 OA from the first RSV season of the study were available for FDA analysis. In this study, approximately 12 500 participants had received RSVPreF3 OA and 12 500 had received placebo.[9]

Efficacy and safety:

The vaccine significantly reduced the risk of developing RSV-associated LRTD (-82.6%) and severe RSV-associated LRTD (-94.1%). Among the subset of participants who received RSVPreF3 OA, the most frequently reported side effects were injection site pain, fatigue, muscle pain, headache, and stiffness or pain in the joints. [7-10]

RSVPreF3 OA was observed to have higher reactogenicity compared with placebo; the rates of grade 3 reactions after vaccination with RSVPreF3 OA were low (≤1.7%). The frequency of reported SAEs up to six months after vaccination was 4.0% and 4.5% in the vaccine and placebo groups, respectively. [3]

In both study groups, many of the SAEs were events common to the older adult population and/or associated with underlying medical conditions (e.g., respiratory infections and cardiac disorders).

In another study in which approximately 2500 participants aged 60 years or older received RSVPreF3 OA concomitantly with an FDA-approved influenza vaccine, two participants developed acute disseminated encephalomyelitis (ADEM), 7 and 22 days, respectively, after receiving RSVPreF3 OA and influenza vaccine. One of the participants who developed ADEM died. The study investigator considered this to be possibly related to Fluarix® Tetravalent vaccination and the FDA considered it to be possibly related to Fluarix® Quadrivalent vaccination or RSVPreF3 OA vaccination. In another study, one participant developed Guillain-Barré syndrome (GBS) nine days after receiving RSVPreF3 OA; the study investigator and the FDA considered the SAE (Guillain-Barré syndrome) to be related to vaccination.

A numerical imbalance in atrial fibrillation was observed. Among all study participants, atrial fibrillation was reported within 30 days of vaccination in 10 participants who received RSVPreF3 OA and four participants who received placebo.

Vaccines and Related Biological Products Advisory Committee (VRBPAC): Committee members emphasized the need for postmarketing surveillance to further evaluate SAEs, potential immune-mediated disease, and atrial fibrillation. In addition, the committee highlighted incomplete information on the safety and efficacy of repeated vaccination and its use in immunocompromised populations, concomitant use with relevant vaccines, and the potential for immune-mediated diseases such as GBS and ADEM. Post-marketing safety studies have been solicited to evaluate GBS, ADEM, and other immune-

mediated demyelinating conditions associated with RSVPreF3 OA. In addition, the sponsor has been advised to include cardiac disorders in the pharmacovigilance plan as a potential major risk.[15]

Possible safety signals:

- SGB
- ADEM and other demyelinating diseases
- Supraventricular arrhythmias (atrial fibrillation)

Gaps in safety information

Information is missing on its use in immunocompromised pregnant women and immunocompromised older adults.[2]

Recommendations for pregnant women in the Region

Recommendations of the PAHO Technical Advisory Group on Immunization (TAG)[1]

At this time, RSVPreF maternal vaccine for the prevention of RSV-associated disease in infants (Abrysvo, produced by Pfizer) is the only vaccine on the market approved by the FDA and EMA for use in pregnant women.

In clinical trials, the maternal vaccine has been shown to be effective in preventing severe RSV-associated disease in infants from birth to 6 months of age. In addition, the vaccine demonstrated a favorable safety profile for both mother and infant. In the clinical trial, an excess of preterm births was observed in the vaccinated group versus placebo, although the differences were not statistically significant.

There are still many information gaps related to the efficacy, impact, and cost-effectiveness of this vaccine.

If any country or territory in Latin America and the Caribbean chooses to introduce the maternal RSVPreF vaccine, PAHO recommends its use at 32-36 weeks gestational age to prevent RSV disease in infants and minimize the risk of preterm delivery. Introduction of the maternal RSVpreF vaccine should be accompanied by:

- Identification of the optimal timing for vaccine administration according to country-specific seasonal patterns in RSV.
- Robust studies of vaccine effectiveness and impact.
- Well-designed studies of safety, cost-effectiveness, economic burden, and affordability.
- Studies of behavioral and social factors to facilitate vaccine adoption.
- Integration with other programs, services, and outreach operations related to prenatal immunization (e.g., influenza).
- Careful balancing of the resources needed to introduce this vaccine and the requirements/objectives of existing vaccination programs (e.g., maintaining measles elimination).
- Documentation of the programmatic challenges of introducing new vaccines, especially in the context of reinvigorating national immunization programs with limited financial resources.

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COVID-19 VACCINE

National Health Surveillance Agency (ANVISA) of Brazil

On 8 January 2024, ANVISA authorized the registration of the recombinant COVID-19 vaccine manufactured by the Serum Institute of India. This monovalent vaccine, containing recombinant spike (S) antigen with saponin-based adjuvant, was approved for persons 12 years of age and older.

The primary vaccination schedule is two doses of 0.5 ml each at 21-day intervals; and a booster dose for persons over 18 years of age six months after primary immunization.

For more information, see: https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2024/anvisa-aprova-mais-uma-vacina-contra-a-covid-19

DENGUE VACCINE

National Health Surveillance Agency of Brazil (ANVISA)

On 6 February 2024, ANVISA reported that it will adopt a continuous submission procedure to evaluate the technical dossier for the Butantan-DV vaccine developed by the Butantan Institute. The vaccine is composed of four attenuated dengue virus serotypes (DENV-1, DENV-2, DENV-3, and DENV-4).

The continuous submission procedure was implemented by ANVISA during the COVID-19 pandemic, allowing the laboratory to submit data and documents in stages as research and development progress. ANVISA also supported the Butantan Institute by organizing technical meetings on the submission requirements.

On 2 March 2023, ANVISA authorized the registration of the Qdenga dengue vaccine (Takeda Pharma Ltd.), composed of four attenuated serotypes of the dengue virus for the pediatric population 4 years of age and older, adolescents, and adults over 60 years old.

For more information, see: https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2024/anvisa-adotara-o-procedimento-de-submissao-continua-para-a-vacina-da-dengue-do-butantan and https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2023/anvisa-aprova-nova-vacina-para-a-dengue.

Authorizations from other RNAs

National Drug, Food, and Medical Technology Administration (ANMAT)

On 26 April 2023, ANMAT authorized the use of the Qdenga (TAK-003) dengue vaccine from the Takeda laboratory for people over 4 years of age, whether or not they have previously had the disease.

For more information, see: https://www.argentina.gob.ar/noticias/la-anmat-aprobo-el-uso-de-la-vacuna-del-laboratorio-takeda-contra-el-dengue

European Medicines Agency (EMA)

On 16 December 2022, the European Medicines Agency (EMA) licensed the Qdenga dengue vaccine for children aged 4 years and older, adolescents, and adults.

For more information, see: https://www.ema.europa.eu/en/medicines/human/EPAR/qdenga

PAHO /WHO recommendations

WHO Strategic Advisory Group of Experts on Immunization (SAGE)

In September 2023, SAGE evaluated the results of studies of the Takeda TAK-003 vaccine, including its efficacy and safety, and issued the following recommendations:

- Countries should consider introducing the vaccine in settings with high disease burden and high transmission intensity.
- The vaccine should be introduced in children aged 6 to 16 years. Within this age range, the vaccine should be introduced 1–2 years before the peak age-specific incidence of dengue-related hospitalization.
- Introduction should be accompanied by a well-designed communication strategy involving the community.
- Post-authorization studies should be conducted to determine the benefit-risk profile in seronegative individuals.

For more information, see: https://www.who.int/publications/i/item/WER-9847-599-620

PAHO Technical Advisory Group (TAG) on Vaccine-preventable Diseases

On 11 January 2024, highlights of the 11th Ad Hoc Meeting of the PAHO Technical Advisory Group (TAG) on Vaccin-preventable diseases were released. The following is a summary of session 1:

- PAHO accepts the TAG's endorsement of the SAGE's recommendation on the introduction of the TAK-003 vaccine for children aged 6-16 years of age who live in settings with high dengue disease burden and high transmission intensity, provided that careful steps are taken to ensure evaluation and follow up of the safety and effectiveness of the vaccine, and that the communities and healthcare providers involved are fully informed of the potential benefits and risks and support the use of the vaccine.
- PAHO recommends that any introduction of the TAK-003 vaccine in a country should be considered a pilot and be accompanied by a robust Phase 4 post-marketing study.
- PAHO accepts the TAG's recommendation that Member States should not implement country-wide immunization programs with the TAK-003 vaccine at this time. Also, Member States that do not have a vaccination platform for adolescents should not consider the introduction of the TAK-003 vaccine at this time.

- PAHO accepts the TAG's recommendation that Takeda should undertake a Phase 4 vaccine trial to address information gaps.

For more information, see: https://www.paho.org/en/news/11-1-2024-paho-technical-advisory-group-tag-immunization-provides-regional-recommendations

INFLUENZA VACCINE

World Health Organization (WHO) recommendations for the 2024-2025 flu season in the northern hemisphere

On 23 February 2024, WHO published recommendations on the composition of influenza virus vaccines for use in the 2024-2025 season in the northern hemisphere. It is recommended that trivalent vaccines (3 strains) and quadrivalent vaccines (4 strains) contain the following:

- **Trivalent egg-based vaccines:**
  - an A/Victoria/4897/2022 (H1N1)pdm09-like virus;
  - an A/Thailand/8/2022 (H3N2)-like virus; and
  - a B/Austria/1359417/2021 (B/Victoria lineage)-like virus.
- **Trivalent cell-culture or recombinant-based vaccines:**
  - an A/Wisconsin/67/2022 (H1N1)pdm09-like virus;
  - an A/Massachusetts/18/2022 (H3N2)-like virus; and
  - a B/Austria/1359417/2021 (B/Victoria lineage)-like virus.
- **Quadrivalent vaccines:** WHO recommends the addition of the B/Yamagata lineage to the above recommended composition, according to vaccine type (egg-based, cell-culture, or recombinant):
  - B/Phuket/3073/2013 (B/Yamagata lineage)-like virus.

For more information, see: https://www.who.int/publications/m/item/recommended-composition-of-influenza-virus-vaccines-for-use-in-the-2024-2025-northern-hemisphere-influenza-season

PANDEMIC INFLUENZA VACCINE (H5N1)

European Medicines Agency (EMA)

On 26 January 2024, the EMA Committee for Medicinal Products for Human Use (CHMP) recommended the approval of two vaccines for active immunization against the H5N1 subtype of influenza A virus, also called avian influenza or bird flu.

One of the vaccines recommended by CHMP is a zoonotic influenza vaccine (H5N1) (composed of surface antigen, prepared in cell cultures, inactivated, and with adjuvant) intended for immunization during outbreaks of influenza from animals, including when public health authorities anticipate a possible pandemic. The other is a pandemic influenza vaccine (H5N1) (composed of inactivated and

adjuvanted surface antigen prepared in cell cultures) intended for use only if an influenza pandemic has been officially declared.

CHMP noted that, in the event of a pandemic, once the virus strain causing the pandemic is identified, the manufacturer can include this strain in the authorized pandemic preparedness vaccine and apply for the vaccine to be authorized as a 'final' pandemic vaccine. Because the quality, safety, and efficacy of the vaccine has already been assessed with other potential pandemic strains, authorization of the final pandemic vaccine can be accelerated.

For more information, see: https://www.ema.europa.eu/en/news/meeting-highlights-committee-medicinal-products-human-use-chmp-19-22-february-2024

World Health Organization (WHO)

WHO notes that there are four types of influenza viruses: A, B, C, and D. Influenza A and B viruses circulate in humans and can cause seasonal epidemics, but only type A viruses can cause global pandemics.

Influenza A viruses are established in many animal species and are classified into subtypes according to combinations of proteins present on the surface of the virus. When influenza (flu) viruses affect an animal species, they are named after the respective natural host, e.g., avian flu viruses or swine flu viruses. These animal influenza viruses are distinct from human influenza viruses and are not easily transmitted to humans, nor between humans.

Zoonotic influenza is the disease caused by animal influenza viruses transmitted to humans. The A(H5N1) and A(H9N2) subtypes and the A(H1N1) and A(H3N2) subtypes from poultry can often infect humans.

For more information, see: https://www.who.int/es/news-room/fact-sheets/detail/influenza-(avian-and-other-zoonotic) and https://www.who.int/es/news-room/spotlight/spotlight/zoonotic-influenza#:~:text=Se%20denomina%20gripe%20zoon%C3%B3tica%20a,pueden%20infectar%20a%20las%20personas

RESPIRATORY SYNCYTIAL VIRUS (RSV) VACCINE

Mexican Federal Commission for Protection against Health Risks (COFEPRIS)

On 12 February 2024, the COFEPRIS New Molecules Committee issued a favorable opinion on the quality, safety, and efficacy of the respiratory syncytial virus (RSV) vaccine submitted for health registration by Pfizer, S.A. de C.V.

This vaccine is indicated for pregnant women between 32 and 36 weeks' gestational age for the prevention of disease in infants from birth to 6 months of age, and in persons 60 years of age and older.

For more information, see: https://www.gob.mx/cofepris/acciones-y-programas/comite-de-moleculas-nuevas-70667 and https://twitter.com/COFEPRIS/status/1759669181438435669.

Authorizations by other NRAs:

Health Canada

In January 2023, Health Canada licensed the first respiratory syncytial virus vaccine for use in Canada. Abrysvo (Pfizer Inc.) is indicated for pregnant women from 32 to 36 weeks gestational age for the prevention of lower respiratory tract disease (LRTD) and severe LRTD caused by RSV in infants from birth through 6 months of age and for people 60 years of age and older.

In May 2023, Health Canada licensed GlaxoSmithKline Biologicals' Arexvy respiratory syncytial virus vaccine for people aged 60 years and older.

For more information, see: https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/respiratory-syncytial-virus.html https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/respiratory-syncytial-virus.html

U.S. Food and Drug Administration (FDA)

In May 2023, the U.S. Food and Drug Administration (FDA) approved GlaxoSmithKline Biologicals' Arexvy, the first respiratory syncytial virus (RSV) vaccine for use in the United States in individuals 60 years of age and older.

In August 2023, the FDA approved Pfizer Inc.'s Abrysvo, the first RSV vaccine for use in pregnant women between 32 and 36 weeks gestational age, to prevent lower respiratory tract disease (LRTD) and severe LRTD caused by RSV in infants from birth through 6 months of age. It is also indicated for individuals 60 years of age and older.

For more information, see: https://www.fda.gov/news-events/press-announcements/fda-approves-first-respiratory-syncytial-virus-rsv-vaccine and https://www.fda.gov/news-events/press-announcements/fda-approves-first-vaccine-pregnant-individuals-prevent-rsv-infants.

European Medicines Agency (EMA)

In June 2023, GlaxoSmithKline Biologicals' Arexvy was approved by EMA for people aged 60 years and older.

In September 2023, EMA authorized the registration of Pfizer Inc.'s Abrysvo vaccine for people aged 60 years and older, and in pregnant women between 24 and 36 weeks gestational age, to protect infants from birth through 6 months of age.

For more information, see: https://www.ema.europa.eu/en/medicines/human/EPAR/arexvy and https://www.ema.europa.eu/en/medicines/human/EPAR/abrysvo

National Administration of Medicines, Food and Medical Technology (ANMAT) of Argentina.

On 8 September 2023, ANMAT reported that it had authorized Abrysvo (produced by PFIZER S.R.L.), a bivalent vaccine against the recombinant respiratory syncytial virus (RSV), for use in pregnant women between 32 and 36 weeks gestational age.

For more information, see: https://www.argentina.gob.ar/noticias/la-anmat-autorizo-la-inscripcion-de-la-vacuna-contra-el-virus-sincicial-respiratorio

National Health Surveillance Agency of Brazil (ANVISA)

On 4 December 2023, ANVISA authorized the registration of GlaxoSmithKline's Arexvy vaccine, the first vaccine registered in Brazil for use against respiratory syncytial virus (RSV) in adults aged 60 years and older.

In accordance with Resolution 204/2017 of its Board of Directors, ANVISA prioritized the application for registration of this vaccine, as RSV is a disease with great public impact, mainly due to the age group affected, and the high rate of hospitalizations due to RSV infection.

On 28 August 2023, Pfizer submitted the application for registration of the Abrysvo RSV vaccine for use in pregnant women, infants from birth through 6 months of age, and adults over 60 years of age.

For more information, see: https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2023/anvisa-aprova-registro-de-primeira-vacina-para-bronquiolite and https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2023/anvisa-recebe-pedido-de-registro-de-vacina-para-bronquiolite-da-pfizer

4 CLARIFICATIONS/CONCLUSIONS OF EVENTS PRESENTED IN PREVIOUS COMMUNICATIONS

No report to date.

COVID-19 medications

Safety Committee of the European Medicines Agency reminds healthcare professionals of the risk of using nirmatrelvir with ritonavir in combination with certain immunosuppressants

On 9 February, EMA's safety committee (PRAC) reported that they had reviewed all available evidence, including reports of serious adverse reactions, some of which were fatal, resulting from drug-drug interactions between nirmatrelvir/ritonavir and immunosuppressants such as calcineurin inhibitors (tacrolimus and cyclosporine) and mTOR protein inhibitors (everolimus and sirolimus). They noted that, in several of the cases reviewed, blood levels of these immunosuppressants increased rapidly to toxic levels, resulting in life-threatening conditions.

The PRAC agreed on a direct healthcare professional communication (DHPC) to remind them of the risk of serious and potentially life-threatening adverse reactions when nirmatrelvir/ritonavir is used in combination with immunosuppressants such as tacrolimus, cyclosporine, everolimus, and sirolimus, and that this combination should only be used when blood levels can be closely monitored to reduce the risk of drug-drug interactions causing serious reactions.

Nirmatrelvir/ritonavir should also not be administered in combination with medicines for which elimination from the body is highly reliant on CYP3A, including the immunosuppressant called voclosporin.

The communication to be issued by the PRAC should be disseminated to healthcare professionals by the respective marketing authorization holder, in accordance with an established communication plan.

For more information, see:https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-5-8-february-2024
https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-5-8-february-2024

U.S. Food and Drug Administration issues guidance on assessing COVID-19-related symptoms in outpatient adult and adolescent subjects in clinical trials of drugs and biological products for COVID-19 prevention or treatment

On 23 February, the U.S. Food and Drug Administration (FDA) updated its guidance for industry entitled "Assessing COVID-19-related symptoms in outpatient adult and adolescent subjects in clinical trials of drugs and biological products for COVID-19 prevention or treatment," superseding the initial guidance issued on 29 September 2020.

FDA noted that, although the public health emergency has ended, COVID-19 remains a public health problem that requires continued prevention and treatment efforts. This guidance is intended to provide sponsors and investigators with considerations for approaches on how common COVID-19-related symptoms can be measured and analyzed in clinical trials evaluating drugs or biological products for the prevention or treatment of COVID-19 in outpatient adults and adolescents.

For more information, see: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-covid-19-related-symptoms-outpatient-adult-and-adolescent-subjects-clinical-trials-drugs https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-covid-19-related-symptoms-outpatient-adult-and-adolescent-subjects-clinical-trials-drugs