COVID-19

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

WASHINGTON, DC
Update: 11 April 2021

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CANADA

- As of 2 April 2021, 5,778,702 doses of vaccines – Pfizer-BioNTech (4,378,832 doses), Moderna (921,335 doses), and Covishield (478,535 doses) – had been administered.
- There were 3,089 individual reports of one or more adverse events (0.052% of doses administered). Of these, 421 were considered serious events (0.007 % of doses administered), with anaphylaxis being the most frequently reported.
- Of the total reports, there were 1,483 non-serious events (0.033% of doses administered) and 327 serious events (0.007% of doses administered) from the Pfizer-BioNTech vaccine. From the Moderna vaccine, 1,149 non-serious events (0.12% of doses administered) and 67 serious events (0.007% of doses administered) were reported, while from the Covishield vaccine, 36 non-serious events (0.007% of doses administered) and 23 serious events (0.004% of doses administered) were reported.
- A total of 9,071 events of adverse events following immunization (AEFI) were reported, with 3,089 reports including one or more such events. The most frequently reported adverse events were injection-site reactions, parestesia, itching, hives, headache, hypoesthesia, and nausea. Only 0.7% of cases of anaphylaxis were reported (60 cases, or 10.2 cases per million doses administered).
- The majority of adverse events reported were in women (84.7% of the total), and in people between the ages of 18 and 49 (49.9% of the total), coinciding with the groups prioritized for vaccination.
- A total of 27 reported adverse events resulted in post-vaccination deaths. Following a medical review, it was determined that 16 of these deaths were not linked to administration of the COVID-19 vaccine. The remaining 11 deaths are still under investigation.

Source: https://health-infobase.canada.ca/covid-19/vaccine-safety/

COSTA RICA

- As of 29 March 2021, the Directorate of Epidemiological Sub-Surveillance, of the Costa Rican Social Security Fund, reported that 384,355 people had been vaccinated against COVID-19 with the Pfizer-BioNTech vaccine.
- From 24 December 2020 to 31 March 2021, 2,761 AEFI were reported.
- On 12-31 March, 522 AEFI were analyzed, of which 66% were in women and 31% were in people ages 30 to 39. All of the AEFI analyzed were classified as non-serious, with 96% of events categorized as mild. Of events reported, 21% were due to headache, 11% to pain at the injection site, 8% to fever, 5% to myalgia, and 4% to fatigue.

- A total of 13 serious cases were reported, seven in the latest period from 12 to 31 March, of which four resulted in death. Three of these were elderly people with a serious personal medical history.
- In this period, no reports of any cases of anaphylactic reaction were received. However, the National Pharmacovigilance Center continues its ongoing search for this type of AEFI.

Source: Reports of adverse events following immunization (AEFI) from the Pfizer-BioNtech COVID-19 vaccine, from 12 to 19 March 2021, 22 to 26 March 2021, and 26 to 31 March 2021. Department of Regulation of Health Products of Interest. National Pharmacovigilance Center; Costa Rican Ministry of Health.

SPAIN

- As of 21 March, 6,125,119 doses of COVID-19 vaccines had been administered, with Comirnaty accounting for 79% of the total, Vaxzevria for 16%, and Moderna for 5%.
- As of that date, 11,182 AEFI had been reported (183 reports per 100,000 doses administered). The majority of these were in women (82% of the total) and in people between the ages of 18 and 65 (93% of the total), coinciding with the largest groups of people vaccinated.
- There were 8,447 reports of AEFI from the Comirnaty vaccine, 901 from the Moderna vaccine, and 1,792 from the Vaxzevria vaccine (formerly known as the Oxford-AstraZeneca vaccine).
- For all three vaccines, the most common adverse events continue to be general complaints such as fever or pain around the injection site, nervous system disorders (mostly headaches and dizziness), and musculoskeletal disorders (primarily myalgia and arthralgia).

Source: https://www.aemps.gob.es/informa/boletines-aemps/boletin-fv/2021-boletin-fv/4o-informe-de-farmacovigilancia-sobre-vacunas-covid-19/

UNITED STATES

- Nearly 167 million doses of vaccines were administered between 14 December 2020 and 5 April 2021.
- Of those vaccinated, the Vaccine Adverse Event Reporting System (VAERS) received 2,794 reports of death (0.0017% of the total number vaccinated), though tests failed to show a connection between these deaths and the vaccinations.
- Anaphylaxis following the COVID-19 vaccine remains very rare, with approximately two to five cases per million people vaccinated in the United States. When this occurs, it is approximately 30 minutes after the vaccination. Effective and immediate treatment is possible in such cases.

Source: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/mrna.html

MEXICO

- As of 13 April 2021, 12,252,769 doses of Pfizer-BioNTech, Oxford-AstraZeneca, Sinovac, Sputnik V, and CanSino vaccines had been administered.
- As of that date, 15,019 AEFI were reported (0.12% of doses administered), of which 13,290 were from the Pfizer-BioNTech vaccine, 849 from the Oxford-AstraZeneca vaccine, 577 from Sinovac, 221 from Sputnik V, and 75 from the CanSino vaccine.
- There were 171 reports of serious events, 1.1% of total events reported. Of these serious events, 92 occurred with the Pfizer-BioNTech vaccine, 33 with the Oxford-AstraZeneca vaccine, 32 with Sinovac, 7 with Sputnik V, and 7 with the CanSino vaccine. Of these events, 98 occurred in women and 79 in men; 55 cases remain hospitalized.

Source: https://www.gob.mx/salud/acciones-y-programas/versiones-estenograficas-conferencia-de-prensa

The number of reported cases of venous thromboembolism associated with the Oxford-AstraZeneca vaccine in Denmark is lower than the expected number of cases in the population

An electronic population study of Denmark's hospital patient registry (Danish National Patient Registry, or DNPR) of 4.9 million adults estimated the number of thromboembolic events and the incidence of such events in the Danish population between 2010 and November 2018. Considering the calculated incidence, the number of expected events per month for a population of the same size as the vaccinated population was estimated. For people between the ages of 18 and 99, an estimated 736 events per month would be expected, while for people between ages 18 and 64, the expected number of events was estimated at 398 per month. The number of reported cases of venous thromboembolism in the vaccinated population appears to be lower than the number of cases that would be expected in the general population. However, such estimates have their limitations, and the risk of thromboembolic events associated with this vaccine should continue to be monitored.

Source: Ostergaard SD, Schmidt M, Horváth-Puhó E, Thomsen RW, Sørensen HT. Thromboembolism and the Oxford-AstraZeneca COVID-19 vaccine: side-effect or coincidence? Lancet. March 2021. doi: 10.1016/S0140-6736(21)00762-5.

Intranasal COVID-19 vaccine

The experimental DelNS1-2019-nCoV-RBD-OPT1 COVID-19 vaccine, based on a replicating viral vector (influenza virus), developed by the University of Hong Kong, Xiamen University, and Beijing Wantai Biological Pharmacy, is currently under a phase II clinical trial.

This intranasally administered vaccine has the potential advantage of preventing COVID-19 infection by stimulating mucosal response in the vaccinated population. The development is supported by the Coalition for Epidemic Preparedness Innovations (CEPI), which is collaborating on vaccine research and development for the COVAX Mechanism. More information about this study can be found at: http://www.chictr.org.cn/enIndex.aspx.

Source: CEPI and University of Hong Kong expand partnership to develop intranasal COVID-19 vaccine candidate. CEPI NEWS. 18 March 2021

Use of the Janssen (Johnson & Johnson) vaccine has been paused in the United States

Following the administration of more than 6.8 million doses of the Janssen vaccine, the U.S. Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) decided to implement a pause in the use of this vaccine, in light of the onset of six cerebral venous sinus thrombosis events. These events are being investigated, and more information will be provided in the next report updates.

Source: U.S. Food & Drug Administration. Joint CDC and FDA Statement on Johnson & Johnson COVID-19 Vaccine, available at: https://www.fda.gov/news-events/press-announcements/joint-cdc-and-fda-statement-johnson-johnson-covid-19-vaccine.

Elevated neutralizing antibody titers and SARS-CoV-2 variants

There is growing concern that emerging variants of SARS-CoV-2 may evade neutralizing antibodies induced by prior infection or vaccination, through mutations in the spike protein, including the receptor-binding domain (RBD). A group of researchers from the Department of Microbiology at Mount Sinai Hospital School of Medicine, in New York City, USA, note in the article "SARS-CoV-2 spike E484K mutation reduces antibody neutralization," that the substitution of asparagine (N) by tyrosine (Y) at position 501 (N501Y), present in the variants belonging to the B.1.1.7, B.1.351, and P.1 lineages, does not appear to affect the in vitro neutralization of convalescent or post-vaccination human serum. Other substitutions, however, such as the E484K present in the B.1.351 and P.1 lineages, could evade neutralizing antibodies.

This group of researchers has conducted several neutralization trials using convalescent serum with different levels of SARS-CoV-2 antibody titers, and serum from individuals who received two doses of the Pfizer-BioNTech BNT162b2 COVID-19 vaccine. Their results suggest that a single mutation (E484K) present in the PANGO (Phylogenetic Assignment of Named Global Outbreak) B.1.351 and B.1.1.28.1 lineages, alias SARS-CoV-2 P.1, could affect the neutralizing activity of convalescent and post-vaccination polyclonal serum (infected with previous strains of SARS-CoV-2). However, they point out that serum containing high neutralizing antibody titers would still be able to neutralize the E484K rSARS-CoV-2 mutation.

It is not yet clear which neutralizing antibody titer correlates with total protection, or the extent to which other immune mechanisms, such as cell cytotoxicity dependent on non-neutralizing antibodies, or T-cell-mediated immunity, contribute to protection. However, the results from this research group highlight the importance of vaccines inducing high neutralizing antibody titers, in order to maximize protection against SARS-CoV-2 variants. They also cite the need for the global vaccination effort to achieve the target of full vaccination in as many people as possible.

Source: Sonia Jangra et al. SARS-CoV-2 spike E484K mutation reduces antibody neutralization. The Lancet. 7 April 2021.

Duration of the efficacy of the Pfizer-BioNTech mRNA vaccine

According to information from Pfizer-BioNTech, the results of monitoring the efficacy of the COVID-19 vaccine trial, at the six-month point, show that the vaccine remains highly effective. The manufacturers indicated that six months after the second dose, or possibly longer, the vaccine remains effective in more than 91% of vaccinated individuals. Of the 927 symptomatic cases of COVID-19 confirmed in the study, 850 cases of COVID-19 occurred in the placebo group, while there were 77 cases in the vaccinated group, representing 91.3% efficacy (95% CI, 89.0%-93.2%). In

addition, the results suggest that the vaccine is effective against variant B.1.351 of the virus, the dominant strain in South Africa, which was thought to have evolved to evade vaccine protection. This information must be evaluated and confirmed by the regulatory authorities.

Source: Pfizer and BioNTech confirm high efficacy and no serious safety concerns for up to six months following second dose in updated topline analysis of landmark COVID-19 vaccine study. 1 April 2021.

FDA updates emergency use authorization for Moderna COVID-19 vaccine with respect to the number of available doses per vial

The U.S. Food and Drug Administration (FDA) announced a review of the number of available doses per vial of the Moderna COVID-19 vaccine. For 10-dose vials, the maximum number of doses authorized to be extracted from a vial is 11, with a range of 10 to 11 doses, depending on the type of syringes and needles used to extract each dose. In addition, the FDA authorized the use of an additional multidose vial, containing a maximum of 15 doses, with a range between 13 and 15 potentially extractable doses.

It should be noted that Moderna's COVID-19 vaccine contains no preservatives. Any remaining product, from several vials, that does not constitute a full dose should not be combined to create a full dose. For more information, see the updated Moderna COVID-19 vaccine fact sheet, available at: https://www.fda.gov/media/144637/download.

ANVISA requests modification of Oxford-AstraZeneca-Fiocruz vaccine package insert

On Wednesday, 4 April 2021, ANVISA reported that it had requested modification of the insert for the Oxford-AstraZeneca-Fiocruz vaccine, to include in the warnings and precautions section the possibility of very rare cases of blood clots associated with thrombocytopenia. In addition, ANVISA noted that the recommendation is to continue its use, as the benefits, to date, outweigh the risks of using the vaccine.

In its statement, ANVISA clarifies that more than four million doses of the Oxford-AstraZeneca-Fiocruz vaccine have been administered in Brazil, with a total of 47 suspected cases of thromboembolic adverse events, with only one thrombocytopenia-associated event. In addition, it reported that no causal link between these 47 suspected cases of thromboembolic events and the use of the vaccine could be established.

In addition, ANVISA emphasizes that most of the side effects that occur with the use of the Oxford-AstraZeneca-Fiocruz vaccine are mild and transient in nature, lasting only a few days. Thus, while the risk of blood clots is very low, people receiving the vaccination should be attentive to possible symptoms, and seek immediate medical attention should they occur. These symptoms include dyspnoea, chest pain, swelling of the leg, and persistent abdominal pain; in addition to neurological symptoms, such as severe and persistent headaches or blurred vision.

Source: Brazil drug watchdog calls for update in Oxford vaccine package insert. 08 April 2021. Available at:

https://agenciabrasil.ebc.com.br/en/saude/noticia/2021-04/brazil-drug-watchdog-calls-update-oxford-vaccine-package-insert

Summary of topics included in the weekly reports

For ease of consultation, following is a list of the topics included in the weekly reports issued to date, and in the official reports of the pharmacovigilance programs.

First report (12 February 2021)

NEW STUDIES AND DEVELOPMENTS

- Scientists develop COVID-19 nasal vaccines
- Use of vaccines in children and adolescents
- Combined vaccines

IMPACT OF NEW SARS-CoV-2 VARIANTS

CONCLUSIONS REGARDING AEFI PRESENTED IN PREVIOUS COMMUNICATIONS

- Cases in Norway
- Sinopharm vaccine trial volunteer in Peru dies of COVID-19-associated pneumonia

PROGRAMMATIC ERRORS, LOGISTICS, AND RELATED ISSUES

- The most common vaccination errors occurring since COVID-19 vaccination began in the United States
- Vaccination of people with COVID-19 infection
- Use of vaccines in older adults
- Authorization of the Pfizer-BioNTech vaccine in 6-dose formulation

Second report (15 February 2021)

NEW STUDIES AND DEVELOPMENTS

- CanSino COVID-19 vaccine shows 65.7% efficacy (2/8)
- IMPACT OF NEW SARS-CoV-2 VARIANTS
- South Africa: SARS-CoV-2 Variants
- Bell's Palsy study (facial paralysis)
- Immune thrombocytopenia
- Impact of one dose of vaccine on people previously infected with COVID-19

PROGRAMMATIC ERRORS, LOGISTICS, AND RELATED ISSUES

- Moderna and 15 doses
- Japan: Importance of low dead space syringes
- Second dose of Moderna and Pfizer vaccines

- Argentina: Update on special situations in the target population to be vaccinated (pregnant and nursing women, individuals who are immunocompromised or who have autoimmune diseases)
- Use of drones for delivering COVID-19 vaccines

Third report (24 February 2021)

NEW STUDIES AND DEVELOPMENTS

- Pfizer-BioNTech begins global clinical studies to evaluate COVID-19 vaccine in pregnant women
- Spread of SARS-CoV-2, and Pfizer/BioNTech vaccine

IMPACT OF NEW SARS-CoV-2 VARIANTS

- Evolution of SARS-CoV-2 virus, impact of circulating variants and new vaccines
- New strategies to reduce SARS-CoV-2 infection and viral transmission
- The Oxford/AstraZeneca vaccine is most effective with a longer interval between doses

PROGRAMMATIC ERRORS, LOGISTICS, AND RELATED ISSUES

- Problems with the difference in dosages between vaccines
- Request to change storage conditions
- Inclusion of pregnant and nursing women in COVID-19 vaccine research

Fourth report (4 March 2021)

NEW STUDIES AND DEVELOPMENTS

- Effectiveness of the Pfizer-BioNTech's Comirnaty COVID-19 mRNA vaccine (with modified nucleosides)
- European project for research on SARS-CoV-2 variants and vaccine development
- Study of effectiveness of a first dose of COVID-19 vaccines in hospital admissions in Scotland
- Mass vaccination in the municipality of Serrana, Riberao Preto, Brazil
- Adaptation of COVID-19 vaccines to SARS-CoV-2 variants: a guide for vaccine producers

CLARIFICATIONS/CONCLUSIONS REGARDING AEFI PRESENTED IN PREVIOUS COMMUNICATIONS

- BRAZIL

PROGRAMMATIC ERRORS, LOGISTICS, AND RELATED ISSUES

- Vaccines included in the WHO Emergency Use Listing (EUL)
- Accidental overdose with COVID-19 vaccine
- Janssen vaccine receives Emergency Use Authorization from FDA
- Clarifications on indications for use and recommendations for administration of COVID-19 vaccines

Fifth report (11 March 2021)

NEW STUDIES AND DEVELOPMENTS

- AstraZeneca in Canada
- Safety of COVID-19 vaccines: reports of late local reactions
- Vaccination of people previously infected with SARS-CoV-2 virus
- SARS-CoV-2 genomic sequencing to improve surveillance
- COVID-19 vaccines authorized in the Region of the Americas, in the country of origin and other authorities

PROGRAMMATIC ERRORS, LOGISTICS, AND RELATED ISSUES

- Pregnancy and COVID-19 vaccines
- Use of COVID-19 vaccine in the Region of the Americas
- Summary of the characteristics and conditions of use of vaccines used in the Region

Sixth report (19 March 2021)

VACCINE REGISTRATION AND AUTHORIZATION

- Emergency Use Listing (EUL/WHO): Janssen COVID-19 vaccine
- Pfizer-BioNTech and AstraZeneca Vaccines

NEW STUDIES AND DEVELOPMENTS

- The Finlay Institute (Cuba) is making progress in development of its SARS-CoV-2 vaccines
- Phase III clinical trial with Soberana 02 vaccine candidate
- Cellular immune response to COVID-19 and mRNA vaccines

CLARIFICATIONS/CONCLUSIONS REGARDING AEFI PRESENTED IN PREVIOUS COMMUNICATIONS

- Update on the AstraZeneca COVID-19 vaccine and thrombosis

PROGRAMMATIC ERRORS, LOGISTICS, AND RELATED ISSUES

- Critical recommendations for administering vaccines
- Emerging information from a pre-published (non-peer-reviewed) study: Distribution of reconstituted mRNA vaccines
- Destruction of used vials to prevent falsification

Seventh report (22 March 2021)

NEW STUDIES AND DEVELOPMENTS

- Development of new vaccines

- Vaccination and patients with prolonged symptomatology
- Influenza-like illness after administration of COVID-19 vaccines

PROGRAMMATIC ERRORS, LOGISTICS, AND RELATED ISSUES

- Recommendations for countries using AstraZeneca vaccines or adenovirus vaccines in general
- Use of the COVID-19 vaccine in the Region of the Americas as of 17 March 2021

Eighth report (31 March 2021)

UPDATE

- Possible explanation of rare prothrombotic events with the AstraZeneca vaccine in Europe
- GACVS statement on rare thrombotic events with AstraZeneca vaccine in Europe

NEW STUDIES AND DEVELOPMENTS

- ANVISA and Butantan discuss anti-SARS-CoV-2 equine serum tests
- Development of new vaccines
- Variants and impact on COVID-19 vaccination

LOGISTICS AND RELATED ISSUES

- "GAVI COVID-19 Vaccines Advance Market Commitment" Initiative (COVAX AMC)
- Recommendations for recently vaccinated people
- Traceability and information on COVID-19 vaccines
- Alert on Falsified COVID-19 vaccine identified in Mexico

Ninth report (8 April 2021)

SAFETY OF AUTHORIZED VACCINES: EUROPEAN MEDICINES AGENCY (EMA)

UPDATE

- COVID-19 vaccination and children.
- Pfizer-BioNTech announces positive results for its study on COVID-19 vaccine in adolescents.

LOGISTICS AND RELATED ISSUES

- Evaluation of the effectiveness of the COVID-19 vaccine
- Protection against possible falsification of COVID-19 vaccines.
- Use of the COVID-19 vaccine in the Region of the Americas as of 17 March 2021

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