Guidance for Implementing the Regional COVID-19 Vaccine AEFI/AESI Surveillance System

Introduction

On 11 March 2020, the World Health Organization (WHO) declared that, based on its assessment, the outbreak of COVID-19—the disease caused by the 2019 coronavirus—could be characterized as a pandemic. Following this declaration, research was launched to develop COVID-19 vaccines on different production platforms. According to WHO, as of 16 February 2021, there were 250 experimental vaccines, 69 of them in different phases of clinical trials, with 16 in phase III. The other 181 were in preclinical trials (*1*). The first phase III trials began in July 2020 and vaccines from different pharmaceutical laboratories are now being administered around the world.

As of 16 February 2021, more than 181 million doses had been administered in 78 countries, 30.5 million of these doses in the United States (*2*). As of December 2020, several countries in the Region of the Americas—including Argentina, Brazil, Bermuda, Canada, Chile, Costa Rica, Ecuador, Mexico, Panama, Peru, and the United States—had begun administering vaccinations on different dates. (*2*). Other countries in the Region started vaccinating health workers and other risk groups in February 2021. It is therefore necessary to continue strengthening the surveillance of adverse events following immunization (AEFI) with these vaccines.

In July 2020, the Pan American Health Organization (PAHO) published the first regional guidance for countries to promote inclusion of the necessary components in national plans for the introduction of COVID-19 vaccines (*3*). One of these components is safe vaccination, for which it issued the following recommendations:

1) Convene the national committee on safe vaccination with participation from scientific societies, national regulatory authorities, and the immunization program (AEFI classification subcommittee).
2) Strengthen or implement surveillance of AEFIs and adverse events of special interest (AESI).
3) Prepare surveillance of potential AESIs to establish incidence rates, prior to introduction of the COVID-19 vaccine.
4) Define requirements to strengthen intensified passive surveillance and active surveillance (sentinel hospital network).
5) Participate in the regional AEFI surveillance system with case reporting from local to national and regional levels.
6) Prepare a risk communication and crisis plan.

In addition to the aspects mentioned above and in keeping with this guidance, national plans for the introduction of COVID-19 vaccines should include existing regulatory mechanisms that guarantee timely access to the vaccines. They should consider aspects related to their use authorization, importation (in the case of products manufactured other than locally), and lot release, as well as pharmacovigilance.

Access to information on the quality and production characteristics of the vaccines and their safety and efficacy profile are part of the post-introduction surveillance system, as is a mechanism for tracing lots used at the national level. Therefore, national plans for the introduction of COVID-19 vaccines should describe the existing regulatory avenues for securing appropriate authorization (*4*) and include subsequent monitoring of the quality, safety, and efficacy of the vaccines to be administered (*5*).

Furthermore, the special meeting of PAHO's Technical Advisory Group (TAG) on Vaccine-preventable Diseases, held on 16 November 2020, issued the following recommendations (*6*):

1) Strengthen national AEFI surveillance capacity in relation to COVID-19 vaccines and other vaccines and support the creation of a regional AEFI surveillance system.
2) Prepare special studies to monitor cohorts of vaccinated people to determine the safety of COVID-19 vaccines and the duration of the protection they confer and create a regional committee on COVID-19 vaccine safety.
3) Emphasize the critical role of communication, including the use of social media and the identification and enlistment of national influencers and personalities, as well as regional champions and ambassadors, in the promotion of COVID-19 immunization once vaccines are available.

At the global level, in November 2020, WHO published guidance for developing national plans for the introduction COVID-19 vaccines containing a section on AEFI surveillance that alludes to the recommendations of the Global Advisory Committee on Vaccine Safety (GACVS) (*7*).

Moreover, on 7 January 2021, WHO published *COVID-19 vaccines: safety surveillance manual*[1] (*8*), based on the recommendations of the GACVS. PAHO will use this manual as a reference for the **surveillance of AEFIs and adverse events of special interest (AESIs)** related to COVID-19 vaccines and for the standardization of concepts across the Region, since it includes modules on different aspects of surveillance.

In addition, PAHO will soon publish a manual for AEFI surveillance in the Region of the Americas[2]**,** whose content has been validated and adapted from the *Global manual on surveillance of adverse effects following immunization,* published by WHO in 2016 (*9*).

[1] As of this writing, PAHO is preparing the Spanish and Portuguese versions of this publication.
[2] The final version of the Spanish manual will be available in May 2021. The manual will also soon be published in English, Portuguese, and French.

The forthcoming *manual for the surveillance of adverse events following immunization in the Region of the Americas will cover all the basics for conducting AEFI surveillance for any vaccine not described in *COVID-19 vaccines: safety surveillance manual***. Thus, it will be necessary to use both manuals to strengthen national AEFI surveillance capacity for all vaccines (including COVID-19 vaccines). The manuals will also be used to update the reporting and investigation forms with the basic variables that should be included in each country's national AEFI surveillance system.**

* The final version of the manual in Spanish will be available in May 2021 (it will also soon be published in English, Portuguese, and French).
** As of this writing, PAHO is preparing the Spanish and Portuguese versions of this WHO publication.

Again, a spirit of solidarity and collaboration in the Region will be essential for publishing real-time information, with robust technical support from PAHO, to detect risks that can be avoided with action based on standard cross-country comparable criteria.

Finally, it should be kept in mind that this guidance will be updated as new information and recommendations from the **WHO Strategic Advisory Group of Experts on Immunization (SAGE) and the GACVS** become available. These groups are responsible for continuous oversight of matters related to the introduction of COVID-19 vaccines, including planning, efficacy, and safety. The initial SAGE recommendations are already available for the first vaccine authorized for emergency use, the Pfizer–BioNTech mRNA COVID-19 vaccine, BNT162b2 (*10*), and for the Moderna mRNA-1273 vaccine (*11*).

Purpose and objectives of the Regional AEFI/AESI Surveillance System

Purpose

Develop a sensitive, timely, standardized, reliable, and integrated regional AEFI surveillance system with the participation of all actors involved in safe vaccination to maintain trust in vaccination and acceptance of immunization in the Americas.

General objective

Contribute to the early detection and correct classification of serious AEFIs and risk markers to generate a rapid and appropriate national and regional response.

It is important to mention that while this system will start off with the introduction of the new COVID-19 vaccines, the ultimate objective is to cover AEFI surveillance for all vaccines.

Specific objectives

1) Obtain and review information on the different types of AEFIs: *a*) events related to the vaccine, *b*) events caused by a vaccine quality defect, *c*) events caused by an immunization-related program error, *d*) events related to anxiety about immunization, and, *e*) events coinciding with vaccination, in order to issue alerts and take corrective action.
2) Design and implement COVID-19 vaccine safety surveillance through intensified passive surveillance, active sentinel surveillance, and epidemiological studies.
3) Coordinate action with the PAHO Revolving Fund in the case of AEFIs related to potential defects in the quality of COVID-19 vaccines or temperature excursions involving COVID-19 vaccines procured through this mechanism.
4) Provide countries with systematic feedback on the data compiled at the regional level.

The Regional COVID-19 Vaccine AEFI/AESI Surveillance System

With regard to the surveillance of events associated with COVID-19 vaccines, the Regional AEFI/AESI Surveillance System will strengthen national capacity to guarantee appropriate, high-quality surveillance in each country through the detection, reporting, investigation, causality assessment, and final classification of such events. Some of the most significant benefits and comparative advantages of this regional system for the countries are:

- There will be sufficient evidence for data analysis at the regional level, since the low frequency of AEFIs in a single country may not be enough to arrive at conclusions about a particular event;
- Member States will be able to receive timely, evidence-based feedback and thus base decisions on regional data to establish best practices and interventions and thereby minimize the risks of an adverse event following immunization;
- PAHO will be able to formulate recommendations to prevent unnecessary risks to the health of the population and maintain trust in vaccination;
- The system will help minimize the social and economic impact of the pandemic by increasing vaccination acceptance and maintaining transparency in early alerts about certain events that can and should be prevented with appropriate and expeditious data analysis at the regional level.

Necessary steps for implementing the Regional AEFI/AESI Surveillance System

The actions that countries should take to implement the Regional COVID-19 Vaccine AEFI/AESI Surveillance System as part of their national plan are:

1. **Nationwide dissemination of the reference documents for COVID-19 vaccine AEFI/AESI surveillance**

   To widely disseminate the reference documents to health services in the public and private sector, PAHO will publish the WHO ***COVID-19 vaccines: safety surveillance manual*** (*8*), which is based on GACVS recommendations. As mentioned above, PAHO will use this manual as a specific reference for the surveillance of **AEFIs and AESIs** associated with COVID-19 vaccines. It is also recommended to follow the recommendations of the ***manual for the surveillance of adverse events following immunization in the Region of the Americas*****.** This publication will cover all the basics necessary for conducting AEFI surveillance for any vaccine **not described in WHO's *COVID-19 vaccines: safety surveillance manual***. Thus, it will be necessary to use both manuals.

   PAHO will also schedule seminars to present the reference documents for implementing the Regional COVID-19 Vaccine AEFI/AESI Surveillance System. These seminars (details to be announced on the PAHO website) will cover the system's objectives and purposes, reporting and investigation tools, active surveillance protocols, mass communication strategy, etc.

2. **Coordination of activities among national immunization programs, the Revolving Fund for Access to Vaccines, national regulatory authorities, and other actors involved in AEFI surveillance at the country level**

   To be more effective, AEFI surveillance requires joint efforts and shared responsibilities, especially between national immunization programs (NIPs) and national regulatory authorities (NRAs). This means establishing agreements, procedures, and roles in the detection, reporting, causality assessment, classification, communication, and eventual decision-making derived from AEFI assessment. Furthermore, regional and global reporting implies coordination, which is currently marked by gaps in a significant proportion of the Region's countries. Bridging these gaps will require NIPs and NRAs to work together to rapidly identify breakdowns in communication flows and roles, and to adopt simple but effective procedures to facilitate coordination and data flow. At the global level, documents and agreements on good practices are moving in this direction, and even NRA assessment systems include a requirement for such coordination.

3. **Strengthening AEFI surveillance through the actions proposed in national plans for the introduction of COVID-19 vaccines**

   The Regional AEFI/AESI Surveillance System is based on the combined efforts of all countries to develop national surveillance systems capable of detecting, reporting, investigating, assessing, and classifying AEFIs that occur following the introduction of COVID-19 vaccines. **National plans for the introduction of COVID-19 vaccines** should therefore include a specific AEFI surveillance component indicating the activities that can be deployed prior to the introduction of COVID-19 vaccines.

   These plans should describe planned actions for the detection, investigation, causality assessment, and final classification of AEFIs by a national (or subnational) AEFI review committee. The plans should also describe the treatment measures for serious AEFIs that will be guaranteed at each level of the country's health system. They should also specify the human and financial resources required to follow the global and regional guidance found in *COVID-19 vaccines: safety surveillance manual* and the forthcoming PAHO manual for AEFI surveillance in the Region of the Americas, in order to strengthen both passive and active surveillance of AEFIs related to these vaccines.

4. **Creation or reactivation of national committees on vaccine safety (and subnational committees, when appropriate)**

   A multidisciplinary group of experts should create or reactivate the national committee on safe vaccination (or subnational committees, if appropriate) in each country to properly review causality and arrive at the final classification of each case. Committee members should have the knowledge and experience necessary for correctly reviewing and classifying AEFIs investigated because they are considered serious or those that are

not considered serious but are of special interest. The committee may consist of representatives of immunization and epidemiological surveillance programs and the national regulatory authority, as well as the PAHO focal point for this issue, with PAHO serving as the secretariat.

This committee is expected to fully classify at least 90% of AEFIs in a timely manner. It must therefore have complete, reliable, and timely information to enable it to arrive at a correct classification.

However, regardless of any delays in the investigation, assessment, and final classification, it is necessary for the Comprehensive Family Immunization Unit to receive reports on individual cases of serious AEFIs and clusters of non-serious events of special interest. In the meantime, countries will go through the entire process, culminating in the final classification of the AEFIs, and report the fully reviewed and classified events to the Comprehensive Family Immunization Unit.

PAHO will convene a regional committee on COVID-19 vaccine safety that will review all serious AEFIs in the Region and support national committees in the causality assessment and final classification of AEFIs whose review was requested by both the countries and PAHO. Thus, an alert about possible AEFIs related to the vaccine or vaccination will be maintained and reported by PAHO to the respective regional authorities.

5. AEFI reporting to the Regional AEFI/AESI Surveillance System.

Since October 2020, PAHO has been working on the development of an AEFI reporting system that includes digital solutions and standard operating procedures to facilitate information exchange among the actors involved in the Regional AEFI/AESI Surveillance System. The Comprehensive Family Immunization Unit will be responsible for receiving the information and share it with the Medicines and Health Technologies Unit, the PAHO Revolving Fund for Access to Vaccines, and the regional committee on COVID-19 vaccine safety. This mechanism is expected to be ready in the second half of 2021.

The design of this reporting system will depend on the maturity of the national surveillance systems. This has been assessed through a regional survey that has identified the strengths and weaknesses of each country. The results of this survey will be published shortly. With this system, data transfer is depicted in a flow chart indicating the flow of data from the local to the national level, and ultimately, to the regional and global level, once the full surveillance cycle for each case—detection, reporting, investigation, causality assessment, and final classification—has been completed in each country.

Initially, while an expeditious regional mechanism for the automatic transfer of country data is being finalized, the first phase will involve setting up a virtual mechanism so that authorized individuals in the ministries of health can send weekly data on a case-by-case basis (classifying events as serious and non-serious AEFIs) using Microsoft Excel or

another electronic format chosen by agreement between the country and the Comprehensive Family Immunization Unit at PAHO headquarters. This information consists chiefly of the basic variables identified by WHO in the AEFI reporting form. Personal data, such as names and addresses, are excluded to protect patient confidentiality. For this reason—and to provide other specific technical information—the necessary coordination will be established between the national AEFI surveillance team and the PAHO regional advisory team on immunization.

Countries lacking AEFI databases are urged to create them using some of the supporting tools presented in the technical recommendations and AEFI surveillance manuals. An Access file with the reporting form will be provided to digitize the information at the national level and, subsequently, a copy will be sent to the regional level. As of 1 March 2021, each country will transfer the data directly from the ministry of health database to PAHO, with PAHO technical support. This is a regional mechanism recommended by the TAG that countries can freely use (see TAG recommendations on page 2 of this document).

6. **Reporting serious AEFIs using the reporting and investigation forms adapted by PAHO: implementation or adoption.**

The *COVID-19: safety surveillance manual* (*8*) and the forthcoming *manual for the surveillance of adverse events following immunization in the Region of the Americas* contain a list of basic variables that will be monitored at the global level and are included in the **reporting forms**[3]. These variables are considered essential for answering important safety questions, and their inclusion in the AEFI reporting form and national databases is recommended.

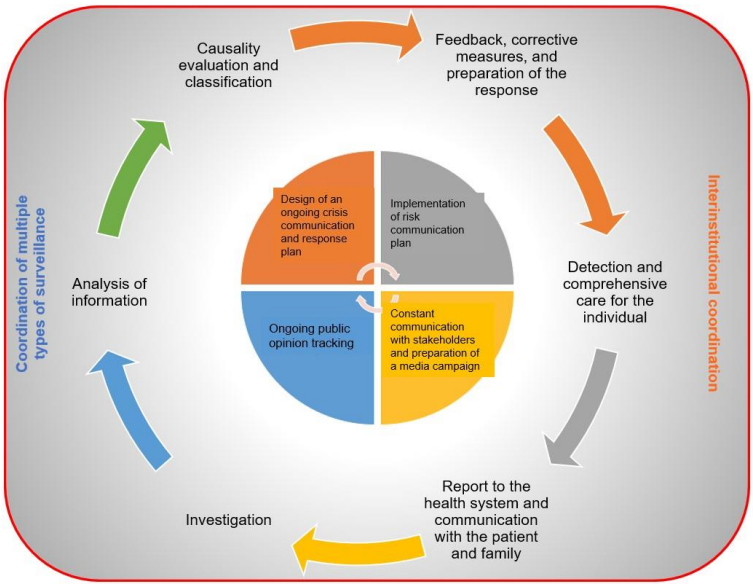
At the local level, training should be provided on how to complete the **reporting form,** and this information should follow the information flow established by the country. Each time a person experiences a serious AEFI or a set of non-serious AEFIs that are considered of special interest and require surveillance according to *COVID-19 vaccines: safety surveillance manual*, this form should be sent to the subnational level, and from there to the national level.

This initial report should trigger instructions to the respective level to conduct an in-depth investigation of the serious AEFI or non-serious AESI, using **the investigation form**. The form (containing sufficient information) will be sent to the national or subnational committee on safe vaccination for a causality assessment and final classification of each serious AEFI or non-serious AESI.

[3] The reporting and investigation forms are available at the same link as these recommendations: https://iris.paho.org/handle/10665.2/53340.

Ideally, the database will contain these basic variables to achieve standardization in all countries, permitting an in-depth assessment of all AEFIs. In addition, the regional data standard for AEFI surveillance will facilitate information exchange with other WHO actors to support regional and global surveillance activities.

The country can also report AEFIs that occurred during clinical trials. This information can be found in post-authorization safety studies.



7. **Strengthening AEFI investigation and causality assessment through subregional training workshops for self-teaching on AEFI surveillance and proper use of new tools by national committees on safe vaccination**.

   To strengthen national capacity, training workshops on AEFI surveillance and proper use of the new tools for investigation and causality assessment will be offered by subregion––Mexico and Central America, Latin Caribbean, English-speaking Caribbean, Andean countries, and Southern Cone countries—with the object of improving AEFI surveillance in the Region.

   The main recipients of this training will include the members of the committee on safe vaccination and representatives of the national immunization program and the national regulatory authority. This will promote interaction among national immunization programs, national regulatory authorities, and national epidemiological surveillance units, as appropriate. These subregional meetings convened by PAHO will also be used to review and discuss the regional situation and transmit recommendations on safety aspects of COVID-19 vaccines.

8. **Training at the subnational and local level for good AEFI case reporting and investigation.**

PAHO will offer an online training course with contents from the forthcoming *manual for the surveillance of adverse events following immunization in the Region of the Americas.* Available to the countries in several languages, it will provide regional standards for AEFI surveillance and promote good case reporting and investigation. In addition, PAHO will soon provide other platforms for document sharing and tools for subnational and local capacity building, including a microsite on vaccine and vaccination safety, webinars, and infographics. It will also take advantage of other tools offered by WHO in several languages that could be useful in strengthening national capacity in the different components of national plans for the introduction of COVID-19 vaccines (*12*).

9. **Establishment of active surveillance in countries and hospitals that meet PAHO inclusion criteria for AEFI/AESI surveillance in vaccinated groups.**

   For active surveillance of the safety of COVID-19 vaccines, PAHO formed an expert working group on immunization and pharmacovigilance. After a thorough review of successful experiences with sentinel surveillance in the Region of the Americas, the experts identified the essential inclusion criteria for selecting hospitals that meet the requirements that guarantee successful outcomes. Application of the active surveillance protocol for the sentinel hospital network will be begin in March 2021 in selected countries and hospitals of the Region that agree to participate, with PAHO support.

   Furthermore, in March 2021, PAHO will launch several observational event surveillance studies in cohorts of vaccinated health workers, older persons, and inadvertently vaccinated pregnant women, using a WHO standard protocol adapted by PAHO. The protocol will be applied in selected countries capable of conducting this type of study.

10. **Development and implementation of mass AEFI crisis communication strategies and other materials targeting health workers.**

    To support communication strategies, PAHO has published two documents aimed at strengthening the capacity of national authorities and health workers: *Communicating about Vaccine Safety: Guidelines to help health workers communicate with parents, caregivers, and patients* and *Communication in Crises Related to Vaccine Safety: Technical Guidance.* (*13, 14*).

    PAHO will program webinars to promote the dissemination of these documents and assist in the deployment of mass communication strategies to tackle crises triggered by AEFIs.

Finally, it should be noted that national documentation on lessons learned and best practices will be used to systematize regional experiences and create a historical memory for future generations of public health workers, as occurred in the wake of the H1N1 influenza pandemic (*15*).

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