Manual for Surveillance of Events Supposedly Attributable to Vaccination or Immunization in the Region of the Americas
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# Acronyms and abbreviations

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACIP</td>
<td>Advisory Committee on Immunization Practices</td>
</tr>
<tr>
<td>BCG</td>
<td>bacille Calmette-Guérin</td>
</tr>
<tr>
<td>CDC</td>
<td>U.S. Centers for Disease Control and Prevention</td>
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<tr>
<td>CMR</td>
<td>child mortality rate</td>
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<tr>
<td>COVID-19</td>
<td>disease caused by SARS-CoV-2 coronavirus, identified in 2019</td>
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<tr>
<td>DTaP</td>
<td>acellular DTP vaccine</td>
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<tr>
<td>DTP</td>
<td>diphtheria-tetanus-pertussis vaccine</td>
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<tr>
<td>DTP/Td</td>
<td>diphtheria, tetanus, pertussis combination vaccine with diphtheria toxoid</td>
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<tr>
<td>ESAVI</td>
<td>events supposedly attributable to vaccination or immunization</td>
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<tr>
<td>ETAV</td>
<td>events temporally associated with vaccination</td>
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<tr>
<td>GACVS</td>
<td>Global Advisory Committee on Vaccine Safety</td>
</tr>
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<td>GAIA</td>
<td>Global Alignment of Immunization Safety Assessment in Pregnancy</td>
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<tr>
<td>H1N1</td>
<td>influenza A virus subtype H1N1</td>
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<td>HIV</td>
<td>human immunodeficiency virus</td>
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<tr>
<td>HPV</td>
<td>human papillomavirus</td>
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<tr>
<td>ICD-10</td>
<td>International Classification of Diseases (Tenth Revision)</td>
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<tr>
<td>IgG</td>
<td>immunoglobulin G</td>
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<tr>
<td>IgM</td>
<td>immunoglobulin M</td>
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<tr>
<td>IIV</td>
<td>inactivated influenza vaccine</td>
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<tr>
<td>IPV</td>
<td>inactivated poliovirus vaccine (injectable)</td>
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<tr>
<td>MMR</td>
<td>measles, mumps, and rubella vaccine</td>
</tr>
<tr>
<td>NIP</td>
<td>National Immunization Program</td>
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<tr>
<td>NMRCDD</td>
<td>U.S. Naval Medical Research Center Detachment</td>
</tr>
<tr>
<td>NRA</td>
<td>National Regulatory Authority</td>
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<tr>
<td>OPV</td>
<td>oral polio vaccine</td>
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<tr>
<td>PAHO</td>
<td>Pan American Health Organization</td>
</tr>
<tr>
<td>PCV</td>
<td>pneumococcal conjugate vaccine</td>
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<tr>
<td>PVV</td>
<td>pentavalent vaccine (diphtheria, whooping cough, tetanus, poliomyelitis, and Haemophilus influenzae type b)</td>
</tr>
<tr>
<td>RT-PCR</td>
<td>reverse transcription polymerase chain reaction</td>
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<td>WHO</td>
<td>World Health Organization</td>
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The Spanish term *evento supuestamente atribuible a la vacunación o inmunización* (ESAVI) ["event supposedly attributable to vaccination or immunization"] was coined in the Region of the Americas at a meeting of the PAHO Technical Advisory Group on Vaccine-Preventable Diseases on November 22-23, 2002, in Washington, D.C. (United States of America). Since then, all Spanish-speaking and some English-speaking countries in the Region have used it in technical publications and national information systems.

Two components are considered essential to understanding the concept of ESAVI, namely:

1. By stating that an event is *supposedly attributable to...*, the emphasis is on the uncertainty regarding the causal relationship between the adverse event and the vaccine. A causal relationship cannot be immediately established at the time of notification; it is necessary to carry out a systematic review of the evidence at the individual and population levels, based on a structured methodology.
2. Differentiating between *vaccination* and *immunization* establishes that the former corresponds to the application or administration of the vaccine, while the latter is the process of generating an immune system response through interaction with an antigen or with components of the vaccine. When an adverse event occurs, it is necessary to determine the causal effect of each component.

During the expert meetings during which the contents of this manual were reviewed, it was decided that the term ESAVI would be used, in light of the considerations stated above and given the disruptions to countries’ surveillance activities and information systems that could be caused by the use of a different term.

Although the terms *adverse events following immunization* (AEFI), *manifestation postvaccinale indésirable* (MAPI), and *eventos adversos pós-vacinação* (EAPV) are prevalent in the English-speaking, French-speaking, and Portuguese-speaking countries of the Region, respectively, it was decided that ESAVI should be used in translations into the four official languages of the Pan American Health Organization in order to employ an equivalent technical concept and in view of the other reasons explained here.
Introduction to safe vaccination in the Region of the Americas

The Global Vaccine Action Plan 2011-2020, approved by the World Health Assembly in 2012, serves as a guide for the worldwide implementation of actions to improve public health through vaccination. It describes the lessons learned and expectations regarding this topic. Among the recommendations resulting from the global evaluation plan, emphasis was placed on the need for new strategies or plans to be based on the use of evidence generated by local information systems and research platforms tailored to the needs of each territory (1).

The Immunization Agenda 2030 incorporates lessons learned from the global plan and, in its implementation, refines the strategic vision in order to correct deficiencies and overcome the barriers identified. The strategic priority set forth in the agenda is the need to develop immunization programs for primary health care and universal health coverage. Meeting this goal requires, among other things, a focus on monitoring vaccine safety and vaccination, so as to ensure a high-quality supply chain and highly effective vaccines linked to a primary care-based service delivery system (2).
A vaccine safety information system is an indispensable tool for decision-making, since such a system is continuously evaluating the risks generated by the proposed interventions.

The vision of the Immunization Agenda 2030 also emphasizes the need to strengthen the commitment of all health-system stakeholders to immunization and to increasing the demand for related services. In the current context of global connectivity that includes all regions of the world, and given the speed with which messages spread, instilling public trust in vaccines requires that relevant information on their safety and effectiveness be made available, in order to effectively answer any questions and address any existing doubts. The vaccine safety information system also fulfills this purpose.

Concurrently, access to innovations in immunization—especially for public health emergencies (e.g., the situation caused by the Severe Acute Respiratory Syndrome Coronavirus 2, or SARS-CoV-2)—requires information-generating platforms that can assess the effect of such innovations on public health and on mitigating the cause of the emergency.1 Having inputs, activities, and communication channels that function on an ongoing basis can streamline the implementation of new surveillance processes and aid in developing research that addresses questions arising from immunization programs, regulatory authorities, and the general public.

In accordance with the approach to the safety of vaccines and vaccination, all countries in the Region of the Americas have national systems for monitoring events supposedly attributable to vaccination or immunization (ESAVI), with varying levels of maturity, and relying on a variety of actors. In 17 (48.6%) of the Region's countries, the National Immunization Program (NIP) is responsible for reporting ESAVI data; in nine countries (25.7%), such data are reported in tandem with the national regulatory authority (NRA); and in only three (8.6%) of the countries, the NRA is solely responsible. Six (17.1%) of the Region's countries have designated an institution other than the NRA or NIP for reporting these data (3).

In 2018, out of a total of 97,932 ESAVI, the Region reported 6,460 serious events. The countries that reported the greatest number of ESAVI were the United States (50,739), followed by Brazil (28,314), Cuba (6,682), and Canada (3,541). No ESAVI were reported in the Bahamas, Costa Rica, Saint Kitts and Nevis, Saint Lucia, and Saint Vincent and the Grenadines (Figure 1) (3).

1 Under Article 1 of the International Health Regulations (2005), a "public health emergency of international concern" is defined as "an extraordinary event which is determined, as provided in these Regulations: (i) to constitute a public health risk to other States through the international spread of disease; and (ii) to potentially require a coordinated international response." See World Health Organization. International Health Regulations (2005). Geneva: WHO; 2008.
FIGURE 1. Number of events supposedly attributable to vaccination or immunization (ESAVI) reported by countries in the Region of the Americas


INTRODUCTION
In addition to the varied outlook in the countries of the Region presented in the report, only 18 (51.4%) countries have a national committee with the capacity to analyze and make decisions related to the emergence of ESAVI (3).

This Manual aims to strengthen ESAVI surveillance in the Region. This is essential in supporting vaccine safety and meeting the goals set by global directives. It is primarily aimed at the heads of government institutions, national technical teams responsible for coordinating and providing guidance on ESAVI surveillance, and all operational technical personnel responsible for deploying activities in their respective national territories. It also contains useful operational tools for local personnel. One of its objectives is to present technical standards for the NIP to guide case management and communication concerning risk events.

Establishing regional surveillance standards is the first step in implementing a regional surveillance system to enable ongoing, real-time monitoring of vaccine and vaccination safety, through a multicenter information network. This monitoring system will also serve as a platform for developing the research needed for decision-making for regional and national immunization plans and policies, and will indirectly add to global knowledge on vaccine safety and vaccination procedures.
In the Region of the Americas, vaccines have achieved fairly high levels of acceptance and trust, compared to other areas of the world, and are seen as a highly effective intervention for reducing the frequency and impact of many infectious diseases. The general public, however, has shown more trust in their effectiveness than in their safety (4).

National authorities and the community of stakeholders working in the areas of immunization and pharmacovigilance should now have tools in place to identify and minimize the real risks associated with vaccines. The goal is to generate objective information that makes it possible to draw valid conclusions and to correctly communicate certainties and uncertainties about adverse events or unforeseen reactions.

The safe-vaccination system consists of various components that must interact in an ongoing way, as well as activities carried out simultaneously by different institutions in all countries.

The first component, during development of the safe-vaccination system, is the application of best practices and the use of good manufacturing practices in production processes. In addition, the relevant NRA must independently control production, and there should be a national regulatory system to ensure the regulation, control, and inspection of the products used throughout the country. The role and functions of NRAs are described in several international documents (5). Figure 2 shows the five components that ensure vaccine safety in production and throughout the vaccine life cycle.
Ensuring the quality and safety of vaccines begins in the research and development (R&D) process, and continues during production, authorization, and post-authorization surveillance, until final disposal.

Throughout what is termed the vaccine life cycle, there are various activities designed to verify compliance with the appropriate clinical research, manufacturing, control, and regulatory practices. The regulatory bodies are responsible for such audits; the World Health Organization (WHO) provides international guidelines and recommendations for implementing these practices.

Currently, in addition to auditing by NRAs, most vaccines purchased by immunization programs are prequalified by WHO (6). This process was established in 1987 at the request of the United Nations Children’s Fund (UNICEF) and the Pan American Health Organization (PAHO) to assess the quality, safety, and efficacy of vaccines, in the context of the NIP. The main objective of prequalification is to ensure that vaccines purchased through UNICEF and other United Nations procurement agencies are safe and effective, and are consistent with the conditions for use by the NIPs. WHO’s vaccine prequalification procedure is designed to strengthen regulatory systems and provide for ongoing auditing of vaccine systems.
The prequalification procedure also includes evaluating programmatic aspects of vaccine use, to ensure that NIPs give consideration to their appropriate use, including: concomitant administration with other vaccines, clinical data for the recommended population and compatibility with vaccination schemes, and policy on the use of open multidose vials.\(^2\)

According to the operating procedures of PAHO’s Revolving Fund for Vaccine Procurement, vaccines purchased by the ministries of health in the Region of the Americas through this route meet internationally recommended quality, safety, and efficacy standards for their development, manufacture, and control (7). In addition, they have been evaluated by the regulatory authorities responsible for control of these products and also, in the case of prequalified vaccines, by WHO. Conditions for the international transport of vaccines should also follow the recommendations established by WHO regarding the appropriate refrigeration and monitoring system for each type of vaccine (8).

Ministries of health and NIPs, for their part, are responsible for ensuring that, from arrival in the country to final use, vaccines are stored and distributed under the recommended temperature conditions and in facilities authorized for this purpose by the NRAs. Moreover, in countries with technical capacity and an available control laboratory, an analytical lot release process is carried out in which identity, sterility, and pyrogens tests are conducted, as well as tests of effectiveness, such as potency and thermal stability, and certain physicochemical tests such as volume or pH variation, among others (9). Any deviation in the cold chain of a vaccine could affect the quality, safety, and efficacy of the vaccine, and should be reported by the NIP and the Ministry of Health in a timely manner to the product supplier, PAHO, and the vaccine prequalification section of WHO.

Once a biological product arrives at the institution where it is to be administered, the responsibility for its custody and the maintenance of the cold chain is that of the health professionals overseeing the vaccine, and the administrative authorities of the institution, who will provide the conditions necessary to have a safe product.

The NIP allocates resources to develop training activities for the staff responsible for maintaining the cold chain, selecting the right person for the right vaccine, correct administration of the vaccine through “safe administration,” and ensuring adequate and sufficient inputs to carry out the procedure at the lowest possible risk.\(^3\)

Despite the availability of the measures described above, which ensure control of multiple vaccination-related risks, there may be ESAVI or situations affecting the health of

\(^2\) The list of vaccines prequalified by WHO through this system, and their assessed program characteristics, can be referenced through the World Health Organization. WHO prequalified vaccines. Geneva: WHO [Internet]. Available at: https://extranet.who.int/pqvdata/.

\(^3\) Safe administration is defined as not harming the recipient, not exposing the service provider to any avoidable risk, and not generating any hazardous waste for others. For more information, see Pan American Health Organization. Module III. Safe injection practices. In: Safe vaccination: training modules. Washington, DC: PAHO; 2007.
vaccine recipients that warrant investigation, in order to determine whether there is an association with the vaccine or the vaccination procedure.

**ESAVI surveillance** is designed to provide early detection and analysis of adverse events, in order to develop a rapid and appropriate response to minimize the negative impact on individuals’ health and on immunization programs. The information generated by the ESAVI surveillance system provides tools for all vaccine safety managers to identify as-yet unidentified risks and risks that may arise from the interaction of the biological product with the recipient's immune system, deviations from proper vaccine-use procedures, quality problems in vaccine production, etc., while ruling out factors that are not associated with vaccination (10).

The identification of problems in the vaccination system will suggest measures that can be taken to mitigate risks and improve ongoing quality. In addition, the data generated will be used to evaluate the performance of the program and to obtain data on the post-marketing efficacy and safety of the vaccine.

In the case of vaccines purchased by PAHO's Revolving Fund, PAHO Member States are expected to report any episodes related to alterations in maintenance of the cold chain or ESAVI that occur during the life cycle of the vaccines. In each situation, investigations are conducted, and recommendations are issued regarding the use of lots of the product involved. The PAHO Revolving Fund is a technical cooperation mechanism that, in addition to providing access to quality, safe, and effective products, provides technical cooperation for subsequent monitoring and investigations of products acquired through this route. Some investigations may require more time than others to resolve, particularly in relation to variations in vaccine quality or to ESAVI, since it could be necessary to analyze the quality control measures adopted by selected laboratories for specific lots.

An essential component of the system for both decision-makers and the community is **risk communication**. With the available information from regulatory activities and from surveillance of safety in vaccine use, crises in public trust should be anticipated and managed appropriately, to avoid adversely affecting the acceptability and financing of the entire system. Risk communication should be based on valid and reliable scientific information, generated by the assessment of circumstances by impartial sources. Efforts to respond to a communication crisis should be planned in advance, bringing together the analysis of official information gathered during the activities involved in each of the vaccine safety components.

Due to its essential nature, risk communication should be budgeted, in order for this component to be professionally developed by experienced staff, allotting sufficient time for the purpose (17).
The main basic concepts related to vaccines, vaccination, and immunization are described below. To understand how vaccines work, and the basis of recommendations for their use, it is helpful to bear in mind the functions of the immune system.

2.1 Immunity
Immunity is the body’s ability to combat or eliminate any harmful material, substance, or microorganism that breaches the biological barriers between the body and the outside world, with the additional ability to recognize and tolerate all components of the organism itself (12). The immune system response occurs by activating cells that specialize in protecting the body from any foreign material or substance, circulating through all tissues and systems. These cells use proteins called antibodies to mark foreign elements and allow them to be removed by defense cell lines.

Newborn humans already have defense tools (innate immunity) that allow them to defend themselves against pathogenic microorganisms, while also having the ability to train their immune system to increase the effectiveness of their innate response.

There are two mechanisms by which the human body can boost the immune response: active immunization and passive immunization.

2.2 Active immunization
Active immunization involves the stimulation of the immune system through exposure to specific molecules (antigens) that are part of the structure of a microorganism; this induces
a humoral response or the production of antibodies, along with activation of defense cell lines, which recognize the antigen and eliminate it by different mechanisms.

There are two ways to actively trigger an immune response: the first is to come into contact with the microorganism, develop the disease, and survive it; the second is by identifying the specific molecule that the immune system must recognize and then administering it to the person (vaccination).

The quality of the immune response to vaccination is measured by the type and quantity of antibodies generated, and the body’s change or response when exposed to the disease (clinical response); this depends on factors such as the presence or absence of maternal antibodies, nature and dose of antigen, route of administration, and presence of added adjuvants to increase the immunogenicity of the vaccine. Factors in the organism receiving the vaccine (host) that affect the response include age, nutritional status, genetic factors, and co-existing diseases, among others.

2.3 Passive immunization
Passive immunization involves the transfer of antibodies that activate a response to the microorganism or substance from a microorganism or from antibodies that by themselves facilitate the removal of the foreign substance.

A natural mechanism by which passive immunization occurs is the transfer of antibodies, from the mother to the fetus during pregnancy, which usually circulate for up to six months in the infant’s bloodstream.

This natural passive immunity can temporarily interfere with the effectiveness of vaccines made using this technology, and can prevent the growth of isolated and infused attenuated viruses.

The mechanism for artificial passive immunization consists of infusing antibodies isolated from other organisms that specifically target the antigen that is to be eliminated; this response is short (one to six weeks), since the receiving organism degrades the antibodies.

2.4 Herd immunity
Herd immunity is the protection of unvaccinated individuals conferred by the presence in their environment of individuals who have received the vaccines. There are multiple protection mechanisms; in some cases, there is direct protection of unvaccinated individuals by transfer of the antigen from vaccinated individuals (as in the case of the oral rotavirus vaccine) or simply by the absence of susceptible individuals who do not transmit the microorganism to non-susceptible individuals (13).

In theory, it is possible to eliminate a disease before population vaccination levels reach 100% of individuals, as demonstrated by the smallpox case model. The proportion of vaccinated individuals in a given population that prevents transmission of a disease is known as the herd immunity threshold. This threshold depends on factors such as the virulence or transmissibility of the disease, vaccine efficacy and coverage, coverage in the population at risk of contracting the disease, and the ease and frequency of risky contact between members of the population (14).
2.5 Vaccines
Vaccines expose the immune system to molecular components of microorganisms or external substances that need to be eliminated, first triggering a recognition and memory response, followed by cell response and destruction.

The goal of vaccination is the production of long-lasting memory lymphocytes that respond quickly and in an organized way to external stimuli.

The first contact with the vaccine triggers a humoral response in which antibodies are produced, signaling the antigen to be eliminated, and allowing it to be recognized by the effector cells. In addition to eliminating the antigen, effector cells stimulate lymphocytes (cellular response) that are able to create memory capable of recognizing the same antigen and initiating a more effective response when new contact with that antigen occurs.

In the initial response, immunoglobulin M (IgM) is secreted; it is produced in small amounts and does not adhere well to the antigen. Subsequently, when immune memory is generated, there is secretion of large amounts of immunoglobulin G (IgG), which adheres very effectively to the antigen. In a second exposure to the vaccine, early and massive production of IgG is stimulated. Vaccination seeks to generate sufficient and specific immune cells and antibodies (IgG) against the microorganism or foreign agent, in order to provide long-lasting protection.

2.6 Classification of vaccines
Vaccines are classified in two types, according to their method of development and their main component: attenuated vaccines and inactivated vaccines; the latter, in turn, are divided into whole, polysaccharide, and fractional vaccines. Fractional vaccines include subunit vaccines (with purified antigen) and toxoids (inactivated toxic compounds) (Table 1). Each type of vaccine has particular properties that determine its mechanism of action and the type of response it triggers.

Since the onset of the pandemic caused by the novel coronavirus (SARS-CoV-2), new technologies are being evaluated and, at the time of publication of this manual, some vaccines have already been incorporated into the WHO emergency use listing. Two new platforms are in use: viral vector vaccines, which can be divided into replicating and non-replicating, and nucleic acid vaccines, which can be either deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) vaccines. In addition, for subunit vaccines, vaccines using virus-like particles are being evaluated. Details of these new platforms will not be discussed in this document, although they can be found in a number of reference documents (15).

2.6.1 Attenuated vaccines
Vaccines containing live attenuated microorganisms are used mostly to combat viral diseases. One exception is the bacille Calmette-Guérin (BCG) vaccine, which contains attenuated bacillus.

These vaccines contain strains of the microorganism in question that have been selected through a repetitive culture process and whose ability to produce the disease has been minimized. Vaccines of this type use live microorganisms which, when replicated, ensure a prolonged antigenic stimulus that increases
the immune response without causing the disease.

Memory cell lines have the ability to amplify the response in number and quality. The response to this type of vaccine is very similar to that obtained after a natural infection.

Risks associated with these vaccines involve the possibility that the attenuated microorganism will return to its natural state, causing the disease. The chances of this happening increase if the receptor is immunocompromised, or when strict storage conditions are not observed. In addition, there is a risk that the vaccine will cause a sustained infection (e.g., lymphadenitis from the TB vaccine, which contains BCG), or that programmatic errors may occur during use, such as interruption of the cold chain or alterations in reconstitution.

In general, the first dose of the vaccine generates protection. For example, 82% to 95% of measles vaccine recipients develop a protective immune response at nine months (16). The second dose increases the rate of people who respond to the vaccine; this guarantees that nearly 99% of people will be immune to the disease.

The properties of these vaccines mean that most people who receive them do not need
boosters, with the exception of the oral polio vaccine (OPV), which requires multiple doses to achieve seroconversion. These vaccines (e.g., BCG, measles, double viral measles-rubella, and triple viral measles-mumps-rubella [MMR]) are sensitive to light and to temperature changes, and require handling under the appropriate conditions.

2.6.2 Inactivated vaccines
These vaccines are made by inactivating viruses or bacteria growing in a culture medium and adding a chemical (e.g., formaldehyde) or exposing them to high temperatures. Given their inactivated state, the microorganism administered in the vaccine cannot replicate, and therefore cannot cause disease, even in a person who is immunocompromised.

These vaccines are usually not affected by circulating maternal antibodies in the first few months of a child’s life, and therefore trigger the immune response at a younger age. In addition, they are more stable and more readily tolerate changing environmental conditions.

More than one dose of these vaccines is usually required, as the first dose merely prepares the immune system, while subsequent doses progressively enhance the protective immune response. Generally, the response to these vaccines is primarily humoral, with a smaller cellular component; thus, their potency diminishes over the years, making it necessary to administer periodic reinforcements.
2.6.3 Subunit vaccines

**Protein subunits**

Vaccines based on protein subunits are a subtype of inactivated vaccines that contain only part of the immune-inducing microorganism. There are several mechanisms by which these vaccines are produced, from fractionation of the microorganism after being cultured (e.g., the acellular whooping cough vaccine) to the use of genetic engineering techniques that make it possible to produce only the molecule that generates the immune response (e.g., the recombinant hepatitis B vaccine).

In the case of recombinant vaccines, the antigen is identical to that found in the intact microorganism, but does not contain the rest of the genetic material, and therefore cannot replicate and cause disease.

**Toxoids**

Toxoids are toxins produced by certain bacteria that have been inactivated through chemical and genetically engineered methods (e.g., the tetanus toxoid). To increase the immune response, the inactivated toxin is combined with an adjuvant, such as aluminum salts. Toxoids, however, do not have a high immunogenic capacity, so booster doses are required. These vaccines are stable, last a long time, and have a good safety profile (16, 17).

**Polysaccharide vaccines**

These vaccines contain only polysaccharides from the surface of certain bacteria that stimulate the immune response in humans. Pure polysaccharide vaccines are those developed to act against pneumococcus, meningococcus, Salmonella typhi, and Haemophilus influenzae type b (16). These vaccines often generate weak and short immune responses, particularly in children, and stimulate a T-cell-mediated response, without the involvement of helper T cells that generate long-term memory. Repeated doses of these vaccines may not generate an immune response of the same magnitude as the first dose; this is associated, among other factors, with a stimulus that mainly produces IgM and scant IgG.

**Conjugate vaccines**

Conjugate vaccines combine protein fractions that can recognize T cells, in order to increase immune response through the involvement of helper T cells, and generate greater immune memory. In this case, repeated doses do trigger an increase in humoral immune response.

New vaccine-production techniques are under development that include, for example, medicines produced using gene therapy. In these, vectors are used to introduce genetic material into the recipient's cells, so that they express the antigen on their surface and are presented to the immune cells. Here, no foreign microorganism is introduced, but, rather, the genetic material that is involved in the immune response is introduced directly.

Table 1 shows types of vaccines, and examples of each vaccine (not a comprehensive list).

2.7 Additional vaccine components

2.7.1 Adjuvants

Adjuvants are substances added to vaccines with the aim of increasing the degree and duration of the immune response; this reduces the amount of antigen per dose or the number of doses needed to achieve protection. Some adjuvants slow the release of the antigen at the
injection site to prolong contact between the antigen and the recipient’s immune system. The most frequently used adjuvant is aluminum salts (aluminum and potassium phosphate, and aluminum and potassium sulphate), which stimulate the immune system’s response to protein extracts. Products of natural origin such as squalene, which is a component that is extracted from shark liver oil, are also used. In recent years, oil-in-water emulsions have been used (adjuvant systems AS03 and AS04).

In rare cases, adjuvants can cause local reactions such as subcutaneous nodules, sterile abscesses, granulomatous inflammation, and contact hypersensitivity, particularly if administered subcutaneously. All vaccines with adjuvants should be given intramuscularly.

2.7.2 Antibiotics
Antibiotics are used to prevent bacterial contamination of the product during manufacture. For example, triple-viral MMR vaccine and the inactivated polio vaccine (IPV) each contain less than 25 mg of neomycin per dose. The presence of neomycin or any antibiotic may trigger a hypersensitivity response in some individuals, so it is necessary to be attentive to the signs of such a reaction in the clinical setting.

2.7.3 Preservatives
Preservatives, such as thiomersal and phenol derivatives, are substances that are added to vaccines (such as inactivated vaccines or subunits) to inactivate viruses, to inactivate bacterial toxins, and to prevent bacterial or fungal contamination of multidose vials. Thiomersal contains ethylmercury. It was determined, at the time, that there was no evidence for the theoretical risks attributed to this substance. WHO has developed concepts and recommendations in this regard that are widely known (18).

2.7.4 Stabilizers
Stabilizers are used to maintain the physicochemical properties of the vaccine during storage. To ensure the quality of the biological product, some compounds are added to minimize problems with changes in acidity, alkalinity, stability, and temperature. Stabilizers are essential, especially in conditions where it is difficult to keep the cold chain stable.

Bacterial vaccines can be stabilized through hydrolysis mechanisms and aggregation of carbohydrate and protein molecules. Stabilizing agents include magnesium chloride, magnesium sulfate, lactose sorbitol, and gelatin sorbitol.

2.7.5 Contraindications and precautions
A contraindication is an inherent or acquired state in an individual that increases the likelihood of an adverse reaction to a vaccine. In these individuals, the probability of a reaction is very high, and the expected consequences are usually severe (19).

Precautions apply to situations that could (with a lower probability than in the case of contraindications) increase the likelihood or severity of an adverse reaction to a vaccine or that could compromise the vaccine’s ability to generate immunity (19).

For vaccination, contraindications should always be considered to avoid causing adverse events. A common problem in vaccination practice is false contraindications, arising from a lack of knowledge by health personnel about the
management of specific situations related to a recipient’s comorbidities (20).

The presence of an anaphylactic reaction is an absolute contraindication for the administration of subsequent doses of the same vaccine, and is something that should always be determined before vaccinating a person. The presence of acute infections, with or without fever, and being treated with steroids, are relative and temporary contraindications (21).

Precautions and contraindications, both of which are cited in the product inserts, should be differentiated. Contraindications usually involve situations where there is increased risk, due to the medical conditions of the potential recipient identified; this risk should therefore be assessed, along with the benefits of vaccination.

There is no available evidence of harm to the fetus when inactivated vaccines are administered to pregnant women. Attenuated vaccines have some theoretical risks during pregnancy. When the likelihood of acquiring the disease is high, or when the consequences of infection in the pregnant woman, fetus, or both can be severe, the benefits often outweigh the risks of vaccination. The use of live attenuated vaccines (e.g., for yellow fever) may be considered in special situations, with a rigorous assessment of the risk-benefit ratio (22).

In the case of immunocompromised individuals, the degree and type of immunocompromise should be evaluated in order to make a decision regarding vaccination with attenuated vaccines such as MMR. A specialist in the patient’s disease, along with national and international guidelines, should be consulted to assess the risks of administering a vaccine versus the benefits of protecting the person from a disease that may have more serious consequences than the vaccine itself. In these patients, administration of attenuated vaccines may lead to uncontrolled replication of the vaccine virus or bacteria.
An event supposedly attributable to vaccination or immunization (ESAVI) is defined as any untoward medical occurrence which follows immunization, and which does not necessarily have a causal relationship with the vaccination process or the vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom, or disease.

Like any health intervention, vaccines are not entirely harmless, and interaction with the human body can lead to unwanted responses that become evident during the clinical investigation process. It is also possible that manufacturing or other deviations that affect the quality of the vaccine could cause adverse reactions. Risks could also arise during transportation and handling, affecting the recipients of the product and warranting clinical attention and reporting.

However, not all medical situations that occur after a vaccine is administered are due to one of these circumstances or to vaccination, given that other factors in the person’s physiological state or arising from diseases that appear simultaneously with or after vaccination can also be responsible for the event, or can overlap with the signs, symptoms, or findings in the vaccinated individual.

ESAVI are classified in Table 2 based on an assessment of the cause (17).

3.1 Vaccine product-related events
These events involve situations in which the interaction between the recipient and any of the components of a vaccine,
including the device used for administering it, triggers an unwanted response in the recipient organism. Many of these events occur as a result of over-activation of the immune system, which can be so intense that it generates a response against the recipient’s tissues. Some of the combined mechanisms to which these events may be attributed include: mediation by immune complexes, generation of molecular mimicry, and excessive cytokine discharge, or “cytokine storm,” among other autoimmune mechanisms described (23). Other mechanisms of action include viral activity from viral reactivation or the persistence of viral infection in immunocompromised individuals.

While the mechanism by which many of the adverse reactions occur is unknown, their incidence is measured in clinical trials prior to vaccine approval, allowing for the characterization of risk periods, particularly for the most frequent events.

Table 3 describes some of the ESAVI according to the particular vaccine, severity, risk period, and incidence.

It is clear that serious events are very rare and, when the risk-benefit balance is assessed, the likelihood of developing serious illness when contracting the wild virus is much higher than the chance of experiencing serious events from vaccination.

### TABLE 2. Cause-specific categorization of ESAVI

<table>
<thead>
<tr>
<th>TYPE OF ESAVI, BY SPECIFIC CAUSE</th>
<th>DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine product-related event</td>
<td>An ESAVI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product, whether the active ingredient or any other vaccine component (e.g., adjuvants, preservatives, or stabilizers).</td>
</tr>
<tr>
<td>Vaccine quality deviation-related event</td>
<td>An ESAVI caused by deviations from vaccine quality specifications, including in devices used for vaccine administration, manufacturing processes, storage, or the distribution chain.</td>
</tr>
<tr>
<td>Event related to a programmatic error</td>
<td>An ESAVI caused by deviations from vaccine quality specifications, including in devices used for vaccine administration, manufacturing processes, storage, or the distribution chain.</td>
</tr>
<tr>
<td>Stress-related event occurring immediately before, during, or immediately after vaccination</td>
<td>An ESAVI caused by stress about the vaccination process and related sociocultural factors.</td>
</tr>
<tr>
<td>Coincidental event</td>
<td>An ESAVI that is NOT caused by the vaccine, a programmatic error, or immunization stress, but which has a temporal relationship with the vaccine.</td>
</tr>
<tr>
<td>Non-classifiable event</td>
<td>Such events are defined operationally when, given a lack of information, the event cannot be classified in any other category.</td>
</tr>
</tbody>
</table>

### TABLE 3. Characterization of certain events supposedly attributable to vaccination or immunization based on the particular vaccine, severity, risk period, and incidence

<table>
<thead>
<tr>
<th>CLASSIFICATION BY SEVERITY</th>
<th>REACTION</th>
<th>VACCINE</th>
<th>RISK PERIOD</th>
<th>INCIDENCE RATE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-serious</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>Local redness or pain</td>
<td>Hepatitis B</td>
<td>1-2 days</td>
<td>1-6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DTP</td>
<td>1-2 days</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MMR</td>
<td>1-2 days</td>
<td>10.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Influenza</td>
<td>6-12 hours</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BCG</td>
<td>2-4 weeks</td>
<td>Almost all people vaccinated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatitis B</td>
<td>24 hours</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pneumococcus (PCV)</td>
<td>Minutes to a few hours after administration</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MMR</td>
<td>1-10 days</td>
<td>16.7&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DTP/Td</td>
<td>1-2 days</td>
<td>≤50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Irritability</td>
<td>DTP</td>
<td>≤60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exanthema</td>
<td>MMR</td>
<td>6.24&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Serious</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aseptic meningitis</td>
<td></td>
<td>MMR</td>
<td>2-3 weeks</td>
<td>1-10/100,000 vaccinated</td>
</tr>
<tr>
<td>Neurotropic disease&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Yellow fever 17D-204</td>
<td>3-18 days</td>
<td>4-8/1,000,000 vaccinated</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yellow fever 17DD</td>
<td>3-18 days</td>
<td>5.6/1,000,000 vaccinated</td>
</tr>
<tr>
<td>Viscerotropic disease&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Yellow fever 17D-204</td>
<td>3-60 days</td>
<td>3.1-3.9/1,000,000 vaccinated</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yellow fever 17DD</td>
<td>3-60 days</td>
<td>0.19/1,000,000 vaccinated</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td>MMR</td>
<td>8-9 days</td>
<td>1/30,000 vaccinated</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td></td>
<td>Hepatitis B</td>
<td>In the first hour</td>
<td>1-2/1,000,000 vaccinated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MMR</td>
<td>In the first hour</td>
<td>1-2/1,000,000 vaccinated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Influenza</td>
<td>In the first hour</td>
<td>1/500,000 vaccinated</td>
</tr>
<tr>
<td>Febrile seizures</td>
<td></td>
<td>Hepatitis B</td>
<td>1 month</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DPT</td>
<td>3 days</td>
<td>60/100,000 vaccinated</td>
</tr>
<tr>
<td>Vaccine-associated polio</td>
<td></td>
<td>OPV</td>
<td>4-30 days</td>
<td>1.4-3.4/1,000,000 vaccinated</td>
</tr>
</tbody>
</table>


3.2 Events related to deviations in vaccine quality

During the vaccine manufacturing process there may be situations that lead to non-compliance with standards for good manufacturing practices or approved standard operating requirements, specifications, and procedures, with consequent risk to persons who receive the product. The most common example is microbiological contamination of the vials in which the biological product is stored, which can cause local and systemic infections in the recipient. Toxic shock syndrome is a type of systemic reaction caused by a bacterial toxin; the immune response is characterized by fever, rash, characteristic skin reaction, and multiorgan dysfunction (19).

Another cause of such events is inadequate inactivation of a vaccine virus, causing illness as serious as infection from the wild virus (23). The behavior of an inadequately inactivated virus may be similar to that of wild viruses, and can also pose a risk to public health.

While this manual does not include guidance for reporting and managing quality deviations identified by immunization programs or at official national control laboratories, the NIP is expected to report these events in a timely manner to the WHO product supplier, to PAHO, and to the WHO vaccine prequalification program, where appropriate.

Feedback from ministries of health on findings regarding the quality, safety, and efficacy of prequalified vaccines, within the system for verifying the consistency of product manufacturing, is critical in order to ensure that this in accordance with the recommended criteria.

3.3 Events related to errors in vaccine handling or administration (programmatic errors)

This category includes all events arising from deviations that occur after manufacture, once the product is in the distribution process, and may include problems in transportation, storage, and use or administration of the biological product.

This manual does not cover the reporting of programmatic errors that do not cause symptoms, signs, abnormalities in laboratory results, diseases, or health disorders. However, it is recommended that such episodes be recorded in a parallel system designed to collect information on the quality of the immunization program. The information in this system can complement ESAVI surveillance and assist in important NIP and NRA decision-making.

In some of the Region’s models and successful experiences, the recording of programmatic errors has consistently led to an analysis of the situation and the adoption of measures to prevent a recurrence of such errors and of ESAVI.

Table 4 shows some examples of programmatic errors that may lead to an ESAVI.

Since errors that lead to a deviation in the quality of a biological product often affect more than one unit, this type of event can occur in the form of clusters or groups of cases. Information systems that provide traceability of the product from the time it enters the country make it possible to identify and evaluate the origin of the problem that led to the event, and work to prevent its recurrence.
### 3.4 Stress-related events occurring immediately before, during, or immediately after vaccination

Before classifying an ESAVI as a stress-related response caused by vaccination, thorough investigation and careful analysis should be conducted to rule out the possibility that the symptoms were caused by an organic disease.

Like any health intervention, vaccination is part of a particular cultural context, and is influenced by people’s perception of the concepts of health and disease. This makes for wide-ranging psychological responses to the vaccination process, and triggers observable physical responses that simulate real neurological alterations or diseases. Since the symptoms and signs observed often attract a great deal of attention from those around the affected person, this type of event can cause similar reactions in close contacts who also receive the vaccine. Stress-related events have been

<table>
<thead>
<tr>
<th>TABLE 4. Types of programmatic errors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TYPE OF PROGRAMMATIC ERROR</strong></td>
</tr>
<tr>
<td>Vaccine-handling error</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Error in prescribing the vaccine or non-adherence to recommendations for use</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Errors in administration</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

described not only in the vaccination process, but also in other types of interventions (24). Events of this type can occur in clusters, causing concern in the community, with negative long-range repercussions on vaccination programs.

In situations where the presence of pathology or organic disease is ruled out, no mental health disorder is detected, and the person clearly stands to benefit from simulation, the episode should not be considered an ESAVI. A review of such events is presented in Annex A.

### 3.5 Coincidental events

Administration of vaccines may coincide with the onset of a pathological process leading in the short term to illness or to a disease with mild manifestations not detected before. It is also possible that, immediately after vaccination, a new clinical picture unrelated to the vaccine may appear. In all of the situations described, the chronology suggests that the clinical picture is attributable to a reaction to the vaccine.

One of the tools surveillance systems can use in evaluating these events is the baseline rates of the clinical condition in question, in order to evaluate whether the
frequency of the event changes as a result of administration of the vaccine, or whether the observed frequency corresponds to the expected rate for the patient’s age, and is consistent with the characteristics of the affected population (25).

To exemplify the above, Table 5 shows the infant mortality rate in known post-vaccination time ranges.

For example, in Bhutan, two coincidental deaths are expected for every 106 doses administered, corresponding to a rate of 18.9 per 1,000 doses. This figure can be taken as expected coincidental deaths per dose in the country, and can be compared to the number of actual deaths; if a higher rate is observed, there should be an additional factor that needs to be investigated.

Baseline rates are not known for all conditions, making an aggregate analysis difficult. For this reason, a comprehensive investigation and a structured and objective analysis of each case are very important.

**TABLE 5.** Infant mortality rates and their relationship to vaccination in several countries

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>INFANT MORTALITY RATE PER 1,000 LIVE BIRTHS</th>
<th>NUMBER OF BIRTHS PER YEAR</th>
<th>ESTIMATED NUMBER OF DEATHS</th>
<th>ESTIMATED NUMBER OF DTP PENTAVALENT VACCINATIONS³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>IN ONE MONTH</td>
<td>ONE WEEK</td>
</tr>
<tr>
<td>Bhutan</td>
<td>42</td>
<td>15,000</td>
<td>53</td>
<td>12</td>
</tr>
<tr>
<td>Canada</td>
<td>5</td>
<td>388,000</td>
<td>162</td>
<td>37</td>
</tr>
<tr>
<td>China</td>
<td>13</td>
<td>16,364,000</td>
<td>17,728</td>
<td>4091</td>
</tr>
<tr>
<td>Indonesia</td>
<td>25</td>
<td>4,331,000</td>
<td>9023</td>
<td>2082</td>
</tr>
<tr>
<td>Iran</td>
<td>21</td>
<td>1,255,000</td>
<td>2196</td>
<td>507</td>
</tr>
<tr>
<td>Mexico</td>
<td>13</td>
<td>2,195,000</td>
<td>2378</td>
<td>549</td>
</tr>
<tr>
<td>Sudan</td>
<td>57</td>
<td>1,477,000</td>
<td>7016</td>
<td>1619</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>4</td>
<td>761,000</td>
<td>254</td>
<td>59</td>
</tr>
</tbody>
</table>

Note: ³Assumes a three-dose schedule with 90% coverage; pentavalent vaccine or DTP: triple bacterial vaccine (diphtheria-tetanus-pertussis).

3.6 Other criteria for classifying events supposedly attributable to vaccination or immunization

ESAVI are classified as serious and non-serious. Depending on the frequency of occurrence, they can be classified into very common, common or frequent, uncommon or infrequent, rare, and very rare, as described in Table 6.

**TABLE 6. Classification of events supposedly attributable to vaccination or immunization, by frequency of occurrence**

<table>
<thead>
<tr>
<th>CATEGORY OF FREQUENCY</th>
<th>FREQUENCY EXPRESSED AS A RATIO</th>
<th>FREQUENCY EXPRESSED AS A PERCENTAGE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>≥1/10</td>
<td>≥10</td>
</tr>
<tr>
<td>Common (frequent)</td>
<td>≥1/100 and &lt;1/10</td>
<td>≥1 and &lt;10</td>
</tr>
<tr>
<td>Uncommon (infrequent)</td>
<td>≥1/1000 and &lt;1/1000</td>
<td>≥0.1 and &lt;1</td>
</tr>
<tr>
<td>Rare</td>
<td>≥1/10,000 and &lt;1/1000</td>
<td>≥0.01 and &lt;0.1</td>
</tr>
<tr>
<td>Very rare</td>
<td>&lt;1/10,000</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

4.1 Objectives for surveillance of events supposedly attributable to vaccination or immunization

4.1.1 General objective

The general objective of ESAVI surveillance at the national level consists of early detection, and reporting and analysis of events supposedly attributable to vaccination or immunization, so that a rapid and effective response can be organized to minimize the negative impact on individuals’ health and on the immunization program, as well as to prevent additional or recurring events.

4.1.2 Specific objectives

The specific objectives of ESAVI surveillance depend on the strategic direction that each country defines for its vaccination activities, and the technical capabilities and resources available. The following list of objectives that can be proposed for the system are considered essential to ensure the provision of reliable information to enable decision-making (17):

- Detect and identify health disorders due to: (i) interaction of a vaccine’s active substance with the person receiving the vaccine; (ii)
deviations in the quality of the vaccine due to deviations in production; and (iii) deviations in storage, transportation (cold chain), handling, and use (programmatic errors).

Analyze ESAVI reports to monitor the safety profile of vaccines, identify signals (new undescribed adverse reactions), and evaluate safe-vaccination measures in the immunization program.

Collaborate with all involved in the vaccine-safety chain, including the general population, to generate information and develop recommendations for the immunization program, in order to mitigate risks associated with use of the vaccines and the risks of ESAVI.

Monitor the safety of vaccines administered in vaccination campaigns or in public health emergencies, including the detection of clusters of cases or unusual frequency in the occurrence of ESAVI.

Seek interagency coordination and harmonization of activities between the different actors involved in administering vaccines, from the local to the national level: NIP, NRA, and epidemiology offices or departments.

The objective of ESAVI surveillance systems is to identify the causative factors of these events, develop strategies to reduce or eliminate them, and to prevent harm to the population and the environment.

Trust in and acceptance of vaccines is closely related to the epidemiology and incidence of vaccine safety risk events. It is essential to have reliable evidence and to develop a communication response in support of vaccination programs (Figure 3).

4.2 Types of ESAVI surveillance
Surveillance is defined broadly as the information management process used for public health decision-making (26). Information management is understood as the chain of procedures ranging from data collection to the storage, organization, analysis, and use of information.

The application of a surveillance system varies depending on the methods and mechanisms employed for each phase of the process.

4.2.1 Passive surveillance
This is based on voluntary and spontaneous reports by whoever identifies an adverse event at a health facility, or through reporting by the vaccinated person. A reporting system is in place, which in most cases involves a form in which all relevant event data are recorded. The form may be available in physical, digital, or web-based media. It is recommended that the ESAVI reporting form be consistent with forms for medicinal products and have, at a minimum, key variables, including the 25 variables recommended by WHO. This will avoid a multiplicity of formats and facilitate coordination for reporting at the national level, and between national and international systems.

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4 The forms for reporting and investigation are available at the following link: https://doi.org/10.37774/9789275323861
Cases can be reported through a basic system with manual completion of a paper form and its physical transfer to the various levels required. Digital systems for transfer via the Internet, mobile devices, or magnetic media can also be used. Where access to the Internet is regularly available, a fully digital system could be developed that does not require data transfer between institutions and, instead, allows real-time access to all involved.

An alternative reporting method is using telephone calls, with the data fielded by an operator or by an automatic voice system and recorded in an automatically generated database.
A highly developed national system with sufficient resources could include the general population as the primary reporter. This would require adapting the information-collection tools to fit the conditions of the particular population, and developing a reporting classification system that prioritizes reports that meet the exact definition of ESAVI and that merit investigation.

This type of surveillance makes it possible to identify potential signals and new events not previously identified in clinical trials. In addition, this is very useful for monitoring potential programmatic errors when these become ESAVI. The disadvantages of this type of surveillance are that it is biased, under-reports cases, records frequencies that do not reflect actual behavior, and is not useful for evaluating hypothetical associations between an ESAVI and the vaccine (27).

Stimulated passive surveillance is a subtype of surveillance involving the use of incentives such as regular meetings of primary reporters (doctors, nurses, and staff responsible for patient safety, among others), and “zero reporting” or periodic mandatory reporting even if no cases are detected.

Following is an example of a passive surveillance system in Mexico.

Case example of passive surveillance
Since 1991, Mexico has been monitoring vaccine-related adverse events through a surveillance system known as ETAV. In 2014, after two years of intensive work creating the first national manual, and following multiple regional training sessions, this evolved into an ESAVI surveillance system. The system requires the reporting of serious and non-serious ESAVI, which are detected when the affected person or his/her parents visit a health facility due to symptoms or signs of an event. These can also be reported directly by parents or caregivers.

First, a paper form, called ESAVI 1, is completed, containing the basic data provided by the reporter or by the affected person, including the clinical picture. Once the investigation is carried out, the ESAVI 2 form is completed, also on paper.

The report is transferred to various levels for revision and ultimately reported at the national level, to the General Directorate of Epidemiology, which generates an Excel file containing information on individual cases. This is forwarded to the office of the NIP, overseen by the National Center for Child and Adolescent Health (CeNSIA), and from there to the national pharmacovigilance center, under the direction of the regulatory authority—the Federal Commission for Protection Against Health Risks (COFEPRIS) (28).

4.2.2 Active surveillance
Active surveillance consists of the implementation of systematic search strategies for specific events in the community or in health institutions, using a protocol with detailed instructions to answer questions about the actual frequency of an event and its association with the vaccine (29, 30). For example, records of a particular adverse event can be searched and retrospectively evaluated at the time of vaccination to identify unreported cases associated with a vaccine.

These activities require the allocation of additional personnel and resources.
However, this provides a much higher level of sensitivity, and the calculated frequencies of event occurrences are more closely aligned with reality. To save on cost and effort, active surveillance activities can be carried out on a periodic basis, prioritizing specific events, geographic regions, population groups, or vaccines (such as the ones most recently introduced).

There are new real-time signal verification techniques that can be applied to aggregated, multicenter databases to increase the speed of response to vaccine safety events. These techniques provide a tool for defining priorities for investigating publicly known situations, and tend to lessen media and political concerns (29, 31). Analysis of regional data also allows for the identification of rare or very rare adverse events, since a very large population base is required to identify these.

An additional strategy that can be included in the model consists of structured risk monitoring programs or strategies, which in some countries are being developed as risk management programs or clinical data monitoring programs. These programs essentially function as active monitoring mechanisms for adverse events, increasing the likelihood of detecting and evaluating new adverse reactions to vaccines. They also use data obtained from multiple sources and institutions, and link them to data on the use of medications and clinical data, in order to test hypotheses on links between vaccines and adverse events (29, 30).

Another example would be studies that monitor events in cohorts. These are used to monitor adverse events in patients receiving a particular medication or treatment regimen. A defined cohort (group) of patients is prospectively monitored, and all adverse events that occur during treatment and for a specified time after completion of treatment are recorded. Adverse events monitored in cohorts do not necessarily have a causal relationship to treatment, unlike adverse drug reactions, and therefore a causality assessment is required (32).

Sentinel surveillance also has a place in active surveillance strategies, where an active search for cases of a specific ESAVI is conducted to measure its frequency more accurately and implement observational designs that allow comparison between vaccinated and unvaccinated people in sentinel centers. Before introducing a new vaccine, sentinel centers can plan the monitoring of possible associated events or adverse events of special interest, and then observe changes in frequency once the vaccine is administered.5

5 Adverse events of special interest (AESI) are prespecified, medically significant events that can be caused by a vaccine and that should be closely monitored and confirmed through special additional studies. For more information, see Council for International Organizations of Medical Sciences. CIOMS guide to active vaccine safety surveillance [Internet]. Source: World Health Organization; 2017. Available at: https://cioms.ch/publications/product/cioms-guide-to-active-vaccine-safety-surveillance/.
The following are some examples of scenarios in which the development of active surveillance activities for the Region could be considered:

1. Safety of vaccines in pregnant women, i.e., vaccines given during pregnancy, or the introduction of new vaccines designed for pregnant women. Specifically:
   a) Adverse events during pregnancy, by gestational age; and
   b) Consequences of vaccine administration during pregnancy for fetal development and for the newborn.
2. Risks related to excessive doses of the vaccine.
3. Risks of polyvalent vaccines.
4. Measurement of variation in risk when multiple vaccines are administered simultaneously.
5. Adverse events and aspects related to the overall safety of new vaccines.
6. Age groups, dosing (e.g., use of fractional doses for yellow fever vaccine), or indications not included in the manufacturer’s recommendations.
7. Vaccination campaigns.

In these cases, it is recommended that countries with properly functioning passive surveillance systems consider developing active surveillance systems on these topics, where relevant.

4.3 Ad hoc studies on vaccine safety

In cases where an event corresponds to a signal, it may be necessary to design and carry out epidemiological studies that make it possible to test the hypotheses that have been formulated through passive and active surveillance.

Some of the most frequently used designs are case-control studies, cohort studies, and self-controlled case series. Depending on the frequency of the event, multiple hospitals, several countries in a single region, or multiple regions may be required to obtain a sufficient sample of events.

In the case of new vaccines, the manufacturer may be developing post-marketing clinical trials, whose preliminary results are known when serious or high-impact events are suspected.

Given that the rarest adverse events require data from very large populations of exposed individuals, global vaccine safety initiatives (10, 33) provide a framework to ensure collaboration between institutions and countries, allowing for data exchange and joint analyses to characterize and evaluate such events. The process of detecting signals depends mainly on passive surveillance reports, which in aggregate make it possible to identify similar events in numbers sufficient to describe their behavior and perform a statistically significant assessment. The expectation is that in the long term it will be possible to standardize data collected in multiple countries, in order to characterize rare events and accumulate evidence to facilitate decision-making (34, 35).

*Case example of active surveillance and ad hoc studies*

Since 1990, the Centers for Disease Control and Prevention (CDC), together with
with a network of hospitals, has monitored the incidence of vaccine-related adverse events of interest, and has developed specific research projects based on retrospective data analysis, through the Vaccine Safety Datalink (VSD) (29). The network of institutions involved covers a population of nine million, on two sides of the country, with corresponding electronic clinical and administrative records. Hospitals periodically send a set of standardized files with individual data from vaccinated people, or, depending on the research question being addressed, cases of diseases or clinical conditions. Files may include demographic data, whether the patient is part of a health plan, birth data, records of vaccines administered, clinical data from emergency room visits, external medical consultations, or hospitalization, among other factors.

Data are shared and the network detects signals in real time, using a methodology called Rapid Cycle Analysis (RCA). This identifies early safety issues with administered vaccines. In addition, a team of project-involved researchers formulates research questions on vaccine safety, and proposes methodologies for developing retrospective epidemiological studies. An example of this type of project involved monitoring the safety of the flu vaccine during the 2009 epidemic (29).

4.4 Model for ESAVI surveillance in the Region of the Americas

ESAVI surveillance in the Region of the Americas uses a two-tier model, each with defined objectives and activities.

4.4.1 Regional surveillance model

Vaccine safety monitoring not only benefits from surveillance activities at the national level, but should in addition be complemented by integrated multinational surveillance activities. The aims of the regional surveillance are the following:

1. Identifying and monitoring the behavior of rare and very rare adverse events, by assembling multiple databases of individual case reports.
2. Identification of potential new events (signals) not previously identified, by observing patterns in the occurrence of events in different countries.
3. Monitoring of problems with vaccine quality, and early harm prevention through the use of regional alerts that allow the exchange of information between countries.
4. Strengthening ESAVI technical surveillance capacity and gradually improving the quality of information, by exchanging experiences and capacities between countries and sharing these with PAHO.
5. Developing and implementing multicenter ad hoc research projects to evaluate the association between adverse events and vaccines.
6. Applying big data analytics and data science techniques to generate information useful for ongoing vaccine safety assessment, NIP planning and management, and real-time support for decision-making.
This can only be achieved through each country's commitment to the quality of surveillance activities. Quality regional surveillance requires that each of the information sources be of the highest quality; this in turn depends on the activities taking place at the local level. The recommendations in this manual can help optimize these activities.

The regional monitoring model will be implemented gradually, starting with strengthening passive surveillance and creating a regional database of reports of individual cases from this surveillance. In parallel, and as needed, institutional networks will be established to serve as sentinels for active case detection, with a network of research hospitals, using protocols to assess association hypotheses (29).

Successful experiences in the Region have shown the capacity of some countries to implement active surveillance protocols, and the usefulness of multicenter networks for generating evidence that contributes to vaccine safety (36, 37). Experience and initiatives similar to research networks can also be studied in order to assess the effectiveness of influenza vaccines (38, 39).

4.4.2 National surveillance model
Before establishing surveillance, it is necessary to identify risks and prevent ESAVI by implementing all of the measures suggested by the safe vaccination model. The quality of a vaccine and of vaccination should be monitored on an ongoing basis, under the control of the NIP and documented by the regulatory authority.

Pharmacovigilance should also take into account information contained in the risk management plans submitted to the NRA by the manufacturer, along with periodic safety reports updated at the frequency established by national regulations, containing important international information on the incidence of adverse events. These documents provide high-value information for preventing, mitigating, communicating, and managing potential risks. The above elements point to the urgent need to coordinate actions between the NIP and NRA, in order to ensure effective monitoring of vaccine safety.

Preparatory activities include obtaining up-to-date information on diseases and on signs, symptoms, and abnormal laboratory findings identified as potential adverse events. Information should be obtained on incidence and prevalence, groups most affected, and additional determinants (e.g., environmental). Information on vaccination coverage in the affected region and throughout the country needs to be clearly established, as well as the previous frequency of reported adverse events.

There should be an ongoing vaccine safety communication plan that includes a crisis response plan for any event that jeopardizes the program's credibility (40, 41). Implementation, ongoing communication, and monitoring of results and communication risks should be carried out in tandem with all event surveillance activities. Major emphasis should be placed on the preparation of individual communication with the affected person and his/her family. The information provided should be transparent, and they should be informed of the outcome of the investigation and causality assessment.
The people directly involved should be at the center of the response and of the surveillance system. When ESAVI occur, they are identified by the health personnel who attend to the affected person or family members. These events are most often detected in the first few hours after administration of the vaccine. Attention should first be focused on the person's health status, to ensure accurate diagnosis and effective treatment, as well as any necessary rehabilitation measures. The event should be reported to the country's public health surveillance system as soon as possible, ensuring that all relevant and verifiable clinical and epidemiological information is included.

The investigation should be initiated, with the goal of gaining a full understanding of the events that occurred, confirming the clinical diagnosis, and identifying the context and factors related or contributing to the event. Once the investigation is complete, all available evidence is to be examined; based on the proposed causality assessment methodology, the probability of an association between the event and the vaccine will be established. Next, the role of any contributing factors should be established.

If an ESAVI is non-serious and not associated with a case cluster, or if it occurs in the context of a low-risk public health situation, it will be registered in the reporting system but it will not be necessary to extend the investigation process; it simply needs to be verified by sufficient evidence.

Finally, the findings of the event analysis provide tools to identify gaps in vaccine safety or in the system that ensures safe vaccination. This means that corrective measures should be developed and implemented to reduce the likelihood of a recurrence of the event, leading to improvements in immunization program safety and ESAVI surveillance. The surveillance process and corresponding feedback should also be evaluated.

The functioning of the ESAVI surveillance model varies, depending on the availability of resources and tools, the country's technical capabilities, and the administrative structure and legal responsibilities of the institutions. In addition, interagency coordination between surveillance systems in the country is very important (e.g., epidemiological monitoring of immune-preventable diseases and pharmacovigilance).

Local public health authorities are responsible for the extramural activities needed to monitor and collect community information. They also ensure that information and support are coordinated with subnational and national authorities (Figure 4).

At this level, it is necessary to actively involve professionals with experience in pharmacovigilance, in order to help identify vaccine-specific factors and handle information on traceability available through the regulatory authority, and to oversee product analysis, where appropriate. The NIP, the epidemiological surveillance institution (e.g., national health institutes or epidemiology departments at health ministries), and the NRA should have access to case information as early as possible, so that they can conduct coordinated management activities at the subnational and national levels.
FIGURE 4. ESAVI surveillance cycle

- Detection and comprehensive care of the person
- Report to the health system and communication with the patient and his/her relatives
- Investigation
- Causality assessment and classification
- Design of ongoing communication and crisis response plan
- Implementation of the risk communication plan
- Feedback, remediation, and preparation of the response
- Detection and comprehensive care of the person
- Ongoing monitoring of opinion
- Ongoing communication with stakeholders and media plan
- Report to the health system and communication with the patient and his/her relatives
- Implementation of the risk communication plan
- Detection and comprehensive care of the person
- Ongoing monitoring of opinion
- Ongoing communication with stakeholders and media plan
- Report to the health system and communication with the patient and his/her relatives

Subnational and national authorities should assess the quality of reporting, investigation, causality analyses, and conclusions, as well as identifying major population risks, abnormal patterns in the occurrence of events, and other types of signals.

When events that constitute a local and national public health emergency are identified, a joint response should be planned, and the assignment of activities should be consistent with the roles identified in local regulations and based on experience and technical capacity.

Where appropriate, it will be necessary to coordinate the activities of public health surveillance systems, whether these are mandatory reporting systems for diseases of public health concern or surveillance systems involving products for use in humans.

The national committee on safe vaccination, led by the NIP and NRA, should conduct a periodic interagency analysis of the status of vaccine and vaccination safety at the national level.

If PAHO’s technical cooperation is required, the operational procedures defined and published by the Organization should be followed.

As a regional strategy, and with the aim of detecting vaccine safety signals throughout the Americas, it is recommended that countries regularly report ESAVI data as recommended by PAHO, following publication of this manual.

4.5 Principles of ESAVI surveillance

The principles of ESAVI surveillance will guide the actions of everyone involved, and direct them in situations where there is uncertainty or where there are no specific recommendations on how to proceed.

4.5.1 Humanization of surveillance

The priority focus of ESAVI surveillance should be the affected person. The activities conducted must ensure the health of individuals and their families and the safety of the population. Each country, individually, should establish mechanisms to ensure the care of people affected by ESAVI.

4.5.2 A focus on purpose

The purpose of ESAVI reporting system activities is not to identify those responsible for programmatic failures, but rather to identify risks related to vaccines or vaccination practices. ESAVI surveillance system activities should focus on detecting factors that jeopardize the safety of vaccines or of the vaccination process. ESAVI surveillance systems should not adopt a punitive approach.

4.5.3 Quality of information

In order to achieve its objective, the information provided in the reports needs to be timely and of high quality, in terms of completeness and validity.

4.5.4 Confidentiality

Like any surveillance system that collects personally identifiable data and information on the health status of individuals, measures should be taken to ensure the security of the information. Preserving data confidentiality should be a priority from the moment it is collected.
4.5.5 Systemic approach
The emergence of ESAVI, especially those related to programmatic errors, is usually due to deviations or problems that originate from failures in the health care system, involving a high level of complexity, in which various factors interact simultaneously. To achieve vaccine safety, the approach to events should view the safety system as a whole, rather than seeking to identify a single cause.

4.5.6 Interprogrammatic and interagency coordination
The NIP, NRA, national epidemiological surveillance directorates, and offices and institutions designated by the country’s national health authority need to cooperate on ESAVI surveillance in an organized manner. Clear roles and responsibilities should be assigned to each institution, in order to ensure coordination within its jurisdiction, at the subnational and local levels.

4.5.7 Optimal risk communication
For any surveillance system to be successful, it needs to communicate risks to the population in a timely manner, provide feedback to those making the reports, and clarify any questions that may arise and that could jeopardize confidence in vaccinations. All institutions engaged in ESAVI surveillance must have the staff, physical resources, and time to devote to risk communication, and to define on an ongoing basis what, to whom, when, and why information should be communicated. Priority should be given to communicating with those affected by ESAVI, regarding the results of the investigation and analysis of events relevant to their health care.

4.6 Special considerations for surveillance of events supposedly attributable to vaccination or immunization in pregnant women
Worldwide, there is a growing need to generate data on the safety of vaccine use in pregnancy (42), whether of existing vaccines recommended for all pregnant women (e.g., flu, Td, and DTP vaccine) or those in development, such as the respiratory syncytial virus or Group B Streptococcus vaccine, both of which are designed specifically to be administered to pregnant women.

The most effective mechanism that guarantees immunity in the newborn and for several months after birth is the passage of antibodies generated by the immune response to vaccines administered to the pregnant woman (43). This justifies the indication of other vaccines during pregnancy. Safely expanding recommendations for vaccine use during pregnancy requires passive surveillance systems and special active surveillance systems.

The main vaccines for which there is experience in use during pregnancy are the inactivated flu vaccine, tetanus toxoid, DTP, hepatitis A and B vaccines, meningococcal conjugate vaccine, and pneumococcal vaccine (22). There are reports of other vaccines used in clinical trials and in special situations such as epidemics or emergencies (e.g., yellow fever vaccine) (44).

It is recommended that passive surveillance systems in all countries should include variables that make it possible to collect information about the state of pregnancy or the possibility
of pregnancy in the vaccinated person, in addition to recording the outcomes of the pregnancy for both the mother and the fetus or newborn. Efforts need to be made to establish clear criteria, to include them in the definitions of adverse events, and to ensure that they are adapted to the capacities of each health system. For example, paraclinical criteria for gestational age require that an ultrasound be performed during pregnancy at certain ages, among other examinations, subject to the capacity of the country’s health services. Over the past two years, the Brighton Collaboration has included definitions of ESAVI associated with clinical conditions affecting pregnant women, fetuses, and newborns (45, 46).

Active surveillance systems should be considered for detecting adverse events in pregnant women and newborns, including monitoring of vaccine doses in unintended pregnancies (42, 44).

One source of information that may be relevant to such systems is the congenital anomalies surveillance systems that have been implemented in many countries in the Region. Using these systems, together with the information systems of immunization programs, protocols for research and active surveillance can be formulated to evaluate any association between the vaccine and a specific congenital abnormality being studied.

Two special capacities should be developed: (i) the ability to detect and classify ESAVI during known and unintended pregnancies; and (ii) causality assessment of these events during pregnancy and in the newborn. National committees on safe vaccination should acquire skill and experience in assessing congenital abnormalities and pregnancy-related complications (44). As in other pharmacovigilance approaches, studies will be required to confirm a causal association between an event and a vaccine.

Documents generated by the GAIA (Global Alignment of Immunization Safety Assessment in Pregnancy), a project led by WHO, can be consulted for further information on surveillance of the safety of vaccines in pregnant women.

4.6.1 Platform for active ESAVI surveillance in pregnant women
PAHO, in collaboration with the Latin American Center for Perinatology, Women’s Health and Reproductive Health (CLAP), has initiated a project with the aim of establishing a platform in Latin America for the active surveillance of ESAVI for vaccines administered to pregnant women, based on data collected from the Perinatal Information System (PIS).

This free-access database includes individual population-level and clinical information on pregnant women and their newborns cared for in hospitals and maternity wards in several Latin American countries. In addition, for the past several years, it has collected data on vaccines that women have received before,
during, and after pregnancy. Currently, several hospitals and maternity wards in countries such as Brazil, Colombia, the Plurinational State of Bolivia, Guatemala, Honduras, Nicaragua, the Dominican Republic, Paraguay, and Peru use the PIS and contribute data to the multicenter platform.

The project also aims to harmonize maternal and neonatal clinical events detected using the definitions proposed by GAIA. Collecting and analyzing multicenter data can help identify rare ESAVI. Strengthening this platform and the quality of data collected by each country will be especially important for active ESAVI surveillance, when introducing future vaccines for pregnant women, such as the respiratory syncytial virus and Group B Streptococcus vaccines.
The ESAVI surveillance system should be an integral part of a national vaccine safety system that incorporates all of the components described in Chapter 2. All ESAVI surveillance activities should be coordinated with vaccine safety component activities.

5.1 Steps for implementing a system for ESAVI surveillance

1. Review the country’s regulatory framework and identify regulatory provisions that would justify ESAVI surveillance and all vaccination safety activities. If regulatory gaps are detected, formulate an update or regulatory-development plan with clearly defined times and resources allocated for the purpose.

2. Define the roles and responsibilities of actors involved in ESAVI surveillance, particularly in the NIP, NRA, and epidemiology agencies, according to the operational structure of the country. In countries with a national pharmacovigilance center, it is necessary to designate responsibilities. The capacities of each institution and of the information systems used until now should be determined, based on the availability of resources and the country’s regulatory framework.

3. Develop a national manual with clear objectives, identifying strategies, activities, and availability of resources, and adapting the recommendations of the present regional manual to fit the country’s circumstances. The manual should include case definitions, a list of examples of notifiable adverse events, investigative procedures, causality assessment, and reporting forms. A group of vaccine-safety experts should review and evaluate technical consistency and the relevance...
of the protocol to local conditions. Efforts should be made to ensure that the necessary operational procedures are in place.

4. Establish an information systems development plan for vaccine safety, in collaboration with all of the institutions involved, and taking into account the necessary information technologies, as well as human, physical, and economic resources, and how to manage these resources, and establish the flow of reporting, information, analytic procedures, decision-making, and communication.

5. Create terms of reference for a national committee on safe vaccination with responsibility for reviewing cases of ESAVI that have a major impact on the country or on the national immunization program. Ad hoc committees should be established to review such cases, and experts in relevant areas not represented on the national committee should be invited to participate. The national committee may be established as an ACIP subcommittee.

6. In cases where the country does not have the available technical capacity, a PAHO support and technical cooperation committee may be used. At the subnational level, depending on available capacities and resources, committees can be established to review cases that fall under their jurisdictions. Such committees must report the results of their analyses to the national committee.

7. Ensure that the national committee on safe vaccination terms of reference include the specific functions related to vaccine safety activities.

8. Include a communications support and crisis management unit in the surveillance system.

9. Develop a strategy for training staff involved in ESAVI surveillance. The strategy should include the identification and reporting of adverse events, along with research and analysis at all levels. It should also include training in the safe administration of vaccines, as well as efforts to provide medical care to patients experiencing adverse events.

10. Develop an implementation plan that includes national strategies to communicate the availability of the reporting system.

5.2 Role of institutions involved in ESAVI surveillance
The following is a description of the functions of institutions involved in ESAVI surveillance. Each institution and each body have complementary capabilities that can add to the quality of the surveillance process. Interaction should involve not only the exchange of information, but also a coordination of functions at major stages of the process, such as expectations concerning interactions between the NIP and NRA during an investigation, or when performing a causality assessment of a case. Each section should provide recommendations on how such interactions could be coordinated.

5.2.1 World Health Organization
In 2012, WHO launched the Global Vaccine Safety Initiative (GVSI), as a strategy to establish the roadmap defined by the Global Vaccine Action Plan, formulated in 2010. The initiative defines several WHO functions regarding vaccine safety (33):
1. Lead efforts to promote activities that ensure the safety of vaccines worldwide, in order to continue obtaining the benefits of this public health intervention.
2. Link stakeholders and create partnerships, where required, to develop a global vaccine safety agenda.
3. Provide technical support to the regions in each country regarding vaccine safety issues, including ESAVI surveillance techniques and technologies.
4. Act as Secretariat for the Global Advisory Committee on Vaccine Safety (GACVS), and support its various activities.
5. Evaluate and issue technical concepts regarding the causality of adverse events and their association with any vaccine.
7. Develop systems for appropriate interaction between national governments, multilateral authorities, and manufacturers at the international, national, and regional levels.

5.2.2 Pan American Health Organization
1. Develop and sustain a regional ESAVI surveillance system in order to reach the regional targets of the Immunization Action Plan and the objectives set by GVSI, and monitor the safety of vaccines distributed in the Region.
2. Establish an information system with data on reports of individual cases of ESAVI from all countries, to be able to characterize the safety performance of vaccines in the Region and detect relevant signals for decision-making at the regional and national levels.
3. Serve as a regional technical reference on vaccine safety issues for national committees responsible for these activities.

4. Introduce vaccine safety issues in the Region’s technical committees and groups of experts.

5. Promote, on an ongoing basis, integrated work between the NIP, epidemiological surveillance departments, and the NRA for monitoring vaccine safety.

6. Participate in investigating ESAVI that are suspected or classified as events related to deviations in the quality of vaccines acquired by PAHO’s Revolving Fund.

7. Monitor the status of community acceptance of vaccination, propose joint strategies to prevent rejection, and resolve barriers to vaccination.

8. Form a working group for regional ESAVI surveillance.

9. Promote multicenter research, including possible multinational active surveillance networks for certain vaccines (e.g., in cases where new vaccines are introduced in response to public health emergencies, such as that caused by COVID-19), or for special uses (e.g., vaccines for pregnant women), in order to detect rare adverse events.

5.2.3 PAHO Revolving Fund for Vaccine Procurement

1. Incorporate into its activities, information from ESAVI surveillance in the Region to aid decision-making on the purchase and distribution of biological products.

2. Interact with the regional ESAVI surveillance working group and with national vaccine safety authorities to handle product quality claims and provide necessary information on the vaccines it distributes, in order to help classify any ESAVI and take measures to minimize the impact on people in at-risk situations.

3. Procure high-quality vaccines that meet the quality standards set forth in the operating procedures.

5.2.4 National Immunization Program

1. Be familiar with the entire vaccine supply chain and all of its implementation activities, in order to ensure its safety, and propose, together with the NRA, measures for ongoing improvement.

2. Develop, together with the NRA, a plan for the interoperability of information systems related to vaccine safety.

3. Receive early reports of serious events and clusters, in order to support interventions suggested by the national committee on safe vaccination within its purview.

4. In collaboration with the NRA, plan periodic evaluations of the implementation of all ESAVI surveillance activities, in order to correct and improve their performance.

5. Also, together with the NRA, provide guidance on national policies necessary to ensure vaccine safety, particularly the development of regulations on the reporting of adverse events.

6. Provide technical recommendations on practices to ensure safe administration of vaccines.

7. Together with the NRA, conduct periodic descriptive analyses of reported ESAVI, and apply signal detection techniques for early identification of events that pose a risk to public health.

8. Perform quality analyses of relevant data.

9. Convene expert committees necessary to support the causality assessment
of relevant adverse events at the national level.
10. Together with the NRA, effectively communicate—to the community, health workers, scientific societies, and other major stakeholders involved in vaccination, as well as collaborators in the country—the final results of investigations into serious ESAVI.
11. Develop an ongoing communication plan for promoting vaccination, including the use of social media and efforts to prevent and mitigate rumors and conflicts related to vaccine safety. The plan should include crisis communication.
12. Coordinate with the NRA the reporting of ESAVI and vaccine safety signals to PAHO, by the methods set forth above and with the established frequency.
13. In cases of public health emergencies requiring the introduction of a new vaccine, immunization programs and government authorities concerned with vaccine use should jointly establish a plan for monitoring the risk-benefit balance, with continuous assessment of vaccine use, safety, and effectiveness.

5.2.5 National regulatory authorities
At the national level, the regulatory authority should:

1. Authorize the use of vaccines for the Ministry of Health.
2. Define regulatory and operational frameworks, timelines for authorizing vaccines, and post-authorization surveillance of vaccines in the country, involving both the public and private sectors. In addition, it should perform other WHO-recommended functions (see section 5.2.1).
3. Evaluate plans for monitoring product risk submitted by manufacturers during the authorization process and in periodic safety reports. Based on these inputs, coordinate strategies with the Expanded Program on Immunization (EPI) and other relevant entities to manage potential vaccine-related risks.
4. Actively participate in national committees on safe vaccination, and commit to designing and implementing the activities needed to improve the system.
5. In coordination with the NIP, train all health surveillance personnel on the ESAVI reporting system, and on how to provide technical support to anyone wishing to make a report.
6. Provide all vaccine safety data involving ESAVI reports, and lot release data, where necessary.
7. Conduct joint investigations related to market surveillance and control activities, including: deviations in the cold chain at national-level establishments, deviations in product quality, safety, and efficacy, and assessment of reports and causal associations.
8. Support the collection of vaccine samples during ESAVI investigations, and carry out the necessary tests to determine the extent to which the event is attributable to the vaccine, when this is within its purview based on national regulations.
9. Collaborate with the EPI in analyzing national data, the signal detection process, and all defined functions involved in coordinated implementation by the EPI and the NRA.
10. Report ESAVI to the Uppsala Monitoring Centre, which functions as the WHO Collaborating Center.

The following is a description of the functions applicable to a decentralized management model, such as the one described here, to be implemented by the national organization.

5.2.6 Subnational levels
1. Closely monitor health institutions for compliance with ESAVI surveillance activities.
2. Ensure the development of intensified and prioritized ESAVI surveillance activities in vaccination campaigns.
3. Monitor compliance with ESAVI reporting by all institutions and health professionals caring for vaccinated persons. Also check the quality of the reporting.
4. Analyze local ESAVI monitoring data and characterize the safety status of vaccines at their respective geographic levels.
5. Provide additional local data deemed necessary to analyze ESAVI from the respective geographic area, when required by the national authorities.
6. If a tiered information system is used (with reports transferred to several levels before reaching the central authorities), the subnational level must report all events to the national authorities in a timely manner.
7. When independent ESAVI investigation is required, the subnational level should have the capacity to launch an investigation of the event involved. Otherwise, national intervention should be requested to carry out this task.
8. Develop training activities for institutions and health professionals involved in the ESAVI surveillance process.

5.2.7 Health institutions
1. Develop a plan to implement ESAVI surveillance that includes activities to train health staff.
2. Design activities to provide a stimulus for health workers to identify and report ESAVI.
3. Have the necessary tools for reporting ESAVI.
4. Designate specific resources (time and personnel) for the development of ESAVI surveillance activities, including receiving reports, investigation, analysis, and communication of reports at the regional or national level.
5. Provide comprehensive care for people affected by ESAVI. Ensure that complete medical services are provided.
6. Work together with the regional level on implementing the corrective measures suggested by the national authorities, and evaluate the results of such efforts.

5.2.8 National committee on safe vaccination
The purpose of case review by the national committee on safe vaccination is to provide technical assistance in order to make decisions on the final classification of relevant events and suggest corrective measures to be applied.

Cases to be referred to the committee of experts should, for the most part, be:

1. Cases classified as serious, involving any vaccine on which there is uncertainty as to causation.
2. Cases related to new vaccines or occurring in particular populations, such as children, adolescents, and pregnant women.
3. Cases that have the potential to cause a media crisis or that have already triggered one.
4. Case clusters, regardless of their severity.
5. Cases where there is doubt about the need to withdraw a particular lot of vaccine from the market, or to discontinue the use of a vaccine.
6. Cases related to signal detection at any geographic level.

Specific functions of the national committee on safe vaccination

It is recommended that the national committee on safe vaccination take the following measures regarding vaccine safety:

1. Review the structure and implementation of the national vaccine safety system.
2. Verify risk management for the entire NIP and for mass vaccination campaigns.
3. Analyze reported adverse events, including a review of investigation data, causality assessment using the tools included in this manual, identification of contributing factors, and establishing corrective measures at all levels.
4. Discuss, together with the NRA, the decision to withdraw a particular lot of vaccines or to temporarily discontinue administration of the vaccine, where relevant.
5. Periodically review updates to manuals on safe administration of vaccines, and to all national publications on vaccine safety.
6. Establish a communications board, and together recommend strategies and messages, and designate spokespersons for crisis prevention and response.
7. Advocate the policies and standards suggested by the national program, and by the committee itself, for improving and ensuring vaccine safety in the country.
8. Review data on evaluation of the ESAVI surveillance system, provide opinions on the quality of the system, and formulate hypotheses.

Governance aspects of the national committee on safe vaccination

This is a very sensitive issue, and it is therefore necessary to follow the rules clearly defined in the statutes or national standards for the national committee on safe vaccination. This should include selection criteria for participating experts, selection mechanisms, statements of conflict of interest, and the decision-making process.

The national committee on safe vaccination is a technical committee and must be independent. It must maintain political, economic, ideological, and commercial independence. The area of expertise depends on the type of events to be discussed and the needs involved in discussing vaccine safety. Specialists in pediatrics, neurology, general medicine, forensic medicine, pathology, immunology, microbiology, infectology, epidemiology, psychiatry, and toxicology, among others, should be considered.

Before being included in the committee, all experts must complete the conflict of interest statement form. The national committee on safe vaccination is responsible for whether to accept an expert with a conflict of interest as a participant in the national committee on safe vaccination.

Committee sessions may be attended by members of the pharmaceutical industry or
civil society when the committee deems it appropriate and relevant. These participants will have a voice, but will not vote.

The committee’s terms or operating statutes should be in writing and reviewed every year, bearing in mind that the review and assessment of vaccine safety situations should be conducted with the highest level of transparency, impartiality, and objectivity.
ESAVI detection and reporting

This chapter describes concepts, activities, and recommendations for detection and proper reporting of events supposedly attributable to vaccination or immunization. The following highlights the key points for their implementation and for coordinating recommendations among the institutions involved.

### Key Points for Implementing Activities and Recommendations

1. Serious ESAVI should be reported as soon as possible, within at least the first 48 hours after detection.
2. Non-serious ESAVI should be reported within the first seven days of detection.
3. All reporting forms, serious and non-serious, will at a minimum include the key variables suggested for each category.
4. Tools for collecting information should be designed to minimize the possibility of errors in recording data.
5. Given the limited resources for ESAVI surveillance in some settings, it is the country’s decision whether or not to report non-serious ESAVI. However, it should be understood that monitoring these events allows for early identification of problems related to vaccine quality and to programmatic errors.

### Recommendations on Interagency Coordination

1. The NIP, the NRA, and the epidemiology directorate should adopt the same definition of reportable events, and coordinate the methods for handling all events. The work required for reporting should be minimized.
2. It is recommended that a single national form be adopted for reporting ESAVI (a template may be downloaded from [https://doi.org/10.37774/9789275123867](https://doi.org/10.37774/9789275123867)).
3. According to the reporting mechanism, there should be coordination in the secure transfer of ESAVI information in the country.
6.1 Events supposedly attributable to vaccination or immunization
This refers to any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom, or disease.7

6.1.1 Serious ESAVI
A serious ESAVI is one that meets any of the following conditions:

1. Causes the death of the vaccinated individual.
2. Poses an imminent danger to the life of the vaccinated individual.
3. Requires hospitalization or prolongs a hospital stay.
4. Is a cause of persistent or significant disability or incapacity.
5. Is suspected of having caused a congenital abnormality or stillbirth.
6. Is suspected of having caused an abortion.

6.1.2 Non-serious ESAVI
A non-serious ESAVI is one that does not endanger the life of the vaccinated person (or embryo, fetus, or newborn if the vaccinated person has been pregnant) that disappears without treatment or with symptomatic treatment, that does not require hospitalization of the affected person, and does not cause a long-term disability or disorder.

6.2 Detection and reporting of events supposedly attributable to vaccination or immunization
In a passive surveillance system, ESAVI can be identified by the vaccinated person or by his/her family, or by health personnel. In general, any change in the health of a vaccinated person within the first 30 days after administration should be suspected of being the result of administration of the vaccine;8 however, the occurrence of an event after 30 days does not exclude the possibility of its being associated with the vaccine. The safety profile of the vaccine and historical data in the region on the ESAVI in question need to be assessed in order to exclude a potential association. ESAVI should be reported if, after analyzing the clinical status of the vaccinated person, there is still a suspicion that there may be a relation between the vaccine and the clinical findings.

6.3 Reporting of events supposedly attributable to vaccination or immunization
It is mandatory that serious ESAVI be reported to the surveillance system. Reports must at a minimum include the key variables indicated on the reporting fact sheet.9 In the case of serious ESAVI, the report is to include a complete description based on a full investigation.

Monitoring of non-serious ESAVI is intended to note their frequency and distribution patterns for comparison with expected

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7 During pregnancy, the pregnant woman or the fetus may be affected.
8 To be clear, the risk period varies depending on the adverse event and the vaccine in question. For the actual risk period, refer to the WHO vaccine reaction rates information sheets, available at: https://www.who.int/teams/regulation-prequalification/regulation-and-safety/pharmacovigilance/health-professionals-info/reaction-rates-information-sheets.
9 Available at: https://doi.org/10.37774/9789275123867.
frequencies and patterns. Deviations in the incidence of these ESAVI may be related to systematic programmatic errors or problems in vaccine quality.

The reporting of non-serious ESAVI will depend on a country's available capacity and resources. It is recommended that non-serious ESAVI be reported only if the affected person or his/her family find it necessary to consult health services. Applying active search strategies for these cases is not recommended, except in specific situations where unanticipated clusters of cases are suspected or in the context of specific investigations of a new type of event or a serious unexplained event.

Initial reports may not contain complete information, so systems must be adapted to allow for access to the same record on multiple occasions. The clinical description of the case should be in the words of the person making the report. The diagnosis and classification of the event must be very precise; thus, to the extent possible, standardized case definitions with some level of validation should be used. For the above, clinical case definitions can be used according to the most reasonable body of knowledge or validated definitions, such as, for example, the Brighton Collaboration definitions (47).

The national committee on safe vaccination may suggest that surveillance activities for specific events be conducted if it considers this necessary.

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6.4 Reporting times
Reporting the information obtained in the course of event detection may take some time; therefore, a 48-hour window may be suggested in the national guides. If all verifiable case information is available, the report must be made immediately.

If it poses a high risk to public health, the report should be immediate. For reporting of a non-serious event, a seven-day period following identification of the event is allowable.

6.5 Reporting mechanisms
Reports should be made on a form that collects information for, at a minimum, the variables considered to be necessary to properly analyze the information (48).

While other variables can be included, the increased complexity in filling out the form, and the time required for the person to collect the information, should be evaluated, in addition to the relevance and usefulness of the data collected. Since the form suggests the collection of personally identifiable and other sensitive data, such information should be handled in compliance with local laws.

Use of the criteria established by the national authority will facilitate the exchange of information between institutions and the aggregation of data from different territories. Where national data criteria provisions are available, those recommended by national or international authorities should be used.

Each country can use the reporting system that is most convenient based on its needs and available capacities. A paper reporting form can be filled out by hand, while a digital form (stand-alone or web-based) can be used for completing the form on a computer. The digital format has the advantage of minimizing errors in recording information, ensuring the completeness of the form, and guaranteeing the simultaneous generation of case databases for analysis. Its disadvantage is that it requires a computer and regular Internet access.

The stand-alone digital form (i.e., not web-based) can be used when there is no regular Internet access at the reporting site. It is a form that can be filled out and sent by email, or printed once completed. When stored in digital format, it can be configured for automatic database generation in .csv or .xls (Excel spreadsheet) format.

To the extent possible, a digital form, with transfer of information in non-physical media, should always adopt the necessary security measures.

If a web-based form is used, it is possible to have a centralized reporting system with access for all institutions involved, thus minimizing the complexity of information transfer. In systems where the information flow requires multiple data transfers between multiple institutions, there is a high risk of information loss or corruption, and the possibility of offline information leaks. If a single reporting system is available, under the corresponding legal and administrative agreements, all involved authorities need to have real-time access.

10 For more information on the description of key variables, see the Johns Hopkins Bloomberg School of Public Health Institute for Vaccine Safety website: https://www.vaccinesafety.edu/components-Allergens.htm.
6.6 Case examples of ESAVI detection and classification

The following are two examples of ESAVI detection and classification in Peru and Chile, each with distinctive characteristics that led teams to classify them as serious ESAVI.

6.6.1 Case of yellow fever in Peru

In September and October 2007, following an earthquake and mass vaccination campaign in Peru’s Ica department, the following case was detected, and was classified and studied as an ESAVI:

A day after receiving the yellow fever vaccine, a 23-year-old woman reported general discomfort, fever, headache, arthralgia, and myalgia. Two days later, she experienced nausea, vomiting, and diarrhea. With no sign of improvement, she consulted a health center and a decision was made to hospitalize her.

Laboratory tests revealed only a slight increase in transaminase levels (alanine aminotransferase and aspartate aminotransferase). She then had an episode of psychomotor agitation, hypotension, metabolic acidosis, and acute kidney failure. The patient progressed to multiorgan failure and died nine days later.

During this period, four similar cases were identified with progression to multiorgan failure and death.

The reported case began as a non-serious ESAVI, which then became serious, with the patient requiring hospitalization. It became clear that there was a temporal and geographic cluster of serious cases of a disease that causes multiorgan failure (49).

6.6.2 A case of abscess in Chile

A 7-month-old boy was seen at the clinic with a mass in the left axillary region that had begun one month earlier and progressively increased in size. The child was afebrile and without pain, and in good general health. Drainage of the lesion was performed, with evidence of abundant caseum. A sample of the material was taken and sent for cultivation and bacilloscopy. The results indicated the presence of mycobacteria. The vaccination schedule was reviewed and was found to be complete.

In this case, a late local ESAVI was described, probably related to the BCG vaccine. It was classified as serious, since hospitalization was required to drain the lesion.

Reporting should be immediate once the possible relationship with administration of a vaccine is established.
This chapter describes concepts, activities, and recommendations for the correct investigation of ESAVI. The following highlights the key points for implementing an investigation and for coordinating recommendations among the institutions involved.

### KEY POINTS FOR IMPLEMENTING ACTIVITIES AND RECOMMENDATIONS

1. A thorough and extensive investigation should be carried out for serious ESAVI.
2. It is not necessary to investigate non-serious ESAVI, except in certain high-risk situations.
3. In fully investigating ESAVI, the following actions should be taken:
   a. Define the problem.
   b. Develop the plan for data collection and a structured organization for conducting the investigation.
   c. Consolidate clinical data, laboratory results, and information relating to the vaccine, the device used to administer it, and the diluent, where appropriate, including the storage conditions for these products.
   d. Establish a timeline and identify facts related to the ESAVI.
   e. Identify factors related to the provision of the vaccination service.
   f. Identify group-related factors and those contributing to the ESAVI.
   g. Prepare the ESAVI investigation report and complete the corresponding investigation form.
   h. Submit the investigation report to the relevant authorities to determine causality.
   i. Plan a communication strategy based on the findings, as well as post-research activities, such as withdrawing a particular lot from the market and suspending a vaccination campaign.

### RECOMMENDATIONS ON INTERAGENCY COORDINATION

1. Each country should have standard operating procedures for detecting and responding to an ESAVI. Such procedures should establish the functions and responsibilities of each of the actors involved, in particular the NIP and NRA.
2. Planning of the investigation should involve the NIP and NRA if it is within their purview, under the direction of the epidemiology section. Tasks and resources to deploy in the investigation should be assigned to each participating unit.
ESAVI investigation consists of gathering accurate and comprehensive information about the serious adverse event and events of interest, including the surrounding circumstances, in order to identify the causes and take appropriate action.

Only serious ESAVI are to be investigated.

Non-serious ESAVI should be investigated only in the following special cases:

1. When case clusters (groups of two or more cases), either in time or in space, are identified.
2. When the frequency of the event is higher than expected.
3. When it is a new event, or one not previously described, or is a known event but with new or unexpected clinical or epidemiological characteristics (in terms of population group, geographic area, etc.).
4. When there are findings indicating that the event was caused by a programmatic error or a deviation in the quality of the vaccine, its diluent (if applicable), or the device used for administering the vaccine.

7.1 Objectives of investigating ESAVI
Suggested research objectives are as follows (50):

1. Document information about the vaccine administered, its diluent (if applicable), and the device used for vaccination, as well as the amount of time between administration and manifestation of the event.
2. Confirm whether the diagnosis has been reported; if not, establish the corresponding diagnosis.
3. Document the conclusion of the investigation of the reported adverse event.
4. Identify possible causes of the ESAVI.
5. Determine whether the event is isolated or belongs to a group of similar events. If similar events were detected, identify where the vaccine(s) was/were administered, what type of vaccine was involved, and whether, in such cases, the same lots of vaccine were involved nationally or internationally.
6. Evaluate the operational and technical aspects of the vaccination program or campaign to prevent immunization-related (programmatic) errors.
7. Determine whether there are reports of similar events in individuals who have not received the vaccine in question.

7.2 Scope of ESAVI investigation
The scope of the investigation to be conducted depends on the type of ESAVI, and can be of two types, as described below.

7.2.1 Concise investigation
This type of research consists of collecting basic event information, including personally identifiable data on the affected person and on the vaccine. There do not need to be multiple sources of information, and sometimes a person’s medical history or verbal statement may suffice. In general, these events are considered to have a low impact on public health.

The conditions that must be met for the investigation of a serious ESAVI (or non-
serious ESAVI of special interest) are as follows:

1. There is no ambiguity in the clinical diagnosis of the case.
2. Alternative explanations for the case have been ruled out.

For example, febrile seizures after administration of the measles virus antigen vaccine are classified as serious ESAVI, and the person is usually hospitalized. Once coincidental causes have been excluded, it is sufficient to proceed with an abbreviated investigation and complete the investigation form (in addition to the reporting form), without filling in additional details such as community investigation, cold chain verification, and the conditions of the health care establishment where the vaccination was performed.

7.2.2 Complete investigation
In this case, it is necessary to collect complete, accurate, and detailed information on the circumstances surrounding administration of the vaccine, thus requiring more time and greater resources.

In this type of investigation, a protocol for work on the case should be established; in order to determine the causality of the event, the participation of a multidisciplinary team of experts is needed.

In this type of investigation, the relevant investigation form must be completed. The investigating group should, among other activities, visit the vaccination site; interview the staff who administered the vaccine, the child’s caregivers, the vaccinated person or persons, and the doctor in charge; observe the vaccination procedures; verify the storage conditions of the vaccine, diluent, and device used for administering the vaccine; and expand the investigation to the community level. A file should be prepared that brings together all elements of the investigation for review by the vaccine safety committee, which in turn will form a causality assessment committee.

During the information collection and analysis process, the investigation must be conducted in an objective and impartial manner. Staff involved throughout the process should be free of conflict of interest, and the quality of the evidence collected should always be evaluated to ensure that the analysis of cases is complete and impartial. At the end of this section is an example of a comprehensive investigation (see 7.6.4 Case of yellow fever in Peru).

7.3 Procedure for investigating an event supposedly attributable to vaccination or immunization
One of the best models for investigating adverse events includes the steps described below (50,51).

7.3.1 Defining the problem
When an adverse event is reported, it may be that some aspects of the affected person's clinical picture, but not all details, are reported, or that certain less relevant clinical circumstances or conditions are reported while others go unreported. Moreover, the problem originally identified may turn out not to be the problem when viewed in context. An example of this is the case where a stress-related reaction is reported after vaccination and, in monitoring the event, a progression to a neurological
picture consistent with encephalitis is detected. In that case, the initial symptoms were the prodromes of a more serious disorder.

Another example is the reporting of an abscess in the area of the injection that does not trigger an investigation until the case is recognized as part of a five-case cluster, with a geographic and temporal relation to the vaccination.

Following are some questions to answer in identifying the problem (51):

Who: The number of people affected, sex, age, ethnicity, whether there are pre-existing health conditions, whether or not the people were immunized, whether there were detectable differences between those immunized and those who were not immunized, and whether there are pregnant women among the affected individuals.

Where: Whether the event occurred at home or in the hospital, and, in the latter case, whether it was in the ICU or in an operating room.

How the event occurred: Whether it was spontaneous, acute, chronic, occurred during a regular checkup, or was incidental.

When: Whether the event occurred immediately after, several days after, or several months after vaccination, or after beginning to take a new medication.

At this stage, it is useful to establish how the frequency of the event compares to the expected rate. A full safety profile of the vaccine can also be reviewed to assess whether similar events have been described or reported (17).

Based on the information collected, an evaluation is made as to whether the case meets standard case definition criteria for any known adverse event for any vaccine. A review of the Brighton Collaboration case definitions is recommended (47).

### 7.3.2 Planning data collection and investigation structure

1. The collection of event-related information includes, first, reviewing the medical records and laboratory data of the person or persons affected by the adverse event, along with vaccination records containing information on the type of vaccine administered. The second source of information is direct contact or an interview with the vaccinated person and the health professionals or staff involved.

2. Other alternative sources that can provide evidence in the investigation include samples and results of environmental analyses, administrative records, and official records.

3. It is always necessary to review previous records from surveillance systems to identify temporal and spatial patterns of adverse events and assess whether the event is part of a cluster or is associated with, and explained by, a known outbreak.

4. At this stage, the research team must be established: the field team and clinical and non-clinical specialists must be correctly selected, and it must be decided what level of participation local authorities and the institution's staff will have.
5. The schedule of activities and the resources to be invested in the investigation need to be established.
6. The investigating team can be limited to the local level, with the institution that identified the event proceeding to investigate. Local professionals may also provide support and observe the investigation, or, depending on the degree of independence required and the availability of resources and capacities, national-level personnel may participate.
7. When local or national heads of health institutions participate, it is important to include the participation of those responsible for the immunization, pharmacovigilance, and epidemiological surveillance program.
8. As noted in the investigation flowchart, the findings and analysis may identify gaps.
Details of the information to be collected during a comprehensive ESAVI investigation

Information about the affected or vaccinated person

The goal is to characterize the subject or subjects affected. Complete clinical history data should include:

1. Date and time (if necessary) of the most important ESAVI-related events.
2. Demographic information: age, gender, and place of residence.
3. Recent clinical summary (symptoms and signs, when they appeared, their duration, clinical examination, indicated supplementary examinations, treatment, and developments). Laboratory tests and imaging should be performed at certified institutions. Depending on the type of vaccine suspected to have caused the ESAVI, samples should be taken for viral isolation in order to determine viral load and identify the viral genome, based on the criteria for a given virus.
4. Type of event, date of onset, duration, and treatment of the clinical event. Differentiating and recording the following time references is recommended:
   - **Start date:** This is the date after vaccination when the first sign, symptom, or abnormal laboratory finding of an ESAVI appeared.
   - **Date of diagnosis:** This is the date after vaccination when the event met the case definition.
   - **End of the episode:** The date when the event no longer met the case definition.
5. Pathological or medical history, including perinatal history: depending on the type of ESAVI detected, emphasis should be placed on the pathology before identifying

7.3.3 Collecting clinical data and information on the biological product or vaccine

Based on the sources of information described above, all clinical data related to the event should be recorded, the chronological order of the appearance of signs and symptoms established, the history of vaccination and of other diseases or interventions determined, any reactions or events associated with other immunizations identified, family history recorded, and treatment and changes in the clinical picture described.

The vaccine data to be recorded include the type of vaccine, manufacturer’s name, exact lot number, expiration date, conditions of the diluent, if any, and storage and transportation conditions (cold chain).

With regard to the vaccination process, the date and time of administration and its relation to the onset of symptoms, along with the reconstitution procedure, should be identified; and the origin and storage of vaccine inputs, conditions of inputs for vaccination, vaccination staff, and vaccination technique verified (52).

Following is a list of the information to be collected in the course of the investigation; this information may or may not apply, depending on the cause of the ESAVI.
the ESAVI. For example, if ESAVI symptoms are mainly neurological, the emphasis should be on collecting data on any history of neurological diseases. For children, this should include gestational history, gestational age at birth, birth weight, etc.

6. Surgical history: for example, thymectomy or surgeries that can cause immune problems.

7. Pharmacological history: investigation into the use of chemical, biological, homeopathic, and natural medications. For medications that have an immune effect, inquiry about their use in the last six months should be made.

8. Family history.

9. Vaccination history: type of vaccine used and date of last dose, and nature of any previous reaction. It is important to check for allergies to eggs or any of the vaccine components. In children a complete history of vaccinations should be investigated as well as the history of vaccination in the previous six months, for adults.

10. Toxicological history or exposure to toxic elements.

11. Gynecological history, especially in women of reproductive age and in pregnant women. In women of reproductive age, it is necessary to determine whether the woman was pregnant at the time the vaccine was administered and check the status of the pregnancy.

12. Housing and socioeconomic conditions, availability of shelter, type of bed, and sleeping habits (in the case of sudden death in infants).

13. There should be a description of final health status, whether the event persisted (whether it still meets the case definition after the follow-up period), and the presence of any sequelae.

14. In the event of death, recommendations regarding the investigation of cases of ESAVI associated with deaths should be followed.

Information on vaccines and on vaccination
Information is to be provided on vaccines, diluents, and syringes used and their handling:

1. Lot number.

2. International Nonproprietary Name (INN), trade name, concentration, dose, presentation, manufacturer, and distributor.

3. Identification of the date and place of any quality deviation identified.

4. Vaccine administration device and its characteristics, which may include syringe quality, novel microneedle patch systems with microneedles, needle-free injection systems, etc. If a problem with the device is suspected, the National Technovigilance System should be notified, pursuant to national guidelines.

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11 For more information on potential allergens included in vaccines, see Johns Hopkins University's Institute for Vaccine Safety website: https://www.vaccinesafety.edu/components-Allergens.htm.

12 Throughout this guidance, the term “pregnant women” includes gender-diverse people who can get pregnant. While a majority of persons who are or can get pregnant are cisgender women who were born and identify as female, transgender men and other gender-diverse people may have the reproductive capacity to get pregnant. Therefore, this guidance is inclusive of their experiences.
5. Manufacture and expiration dates of both the vaccine and the diluent.\(^{13}\)
6. Manufacturing laboratory.
7. Provenance of the vaccine, diluent, syringe, and administration device, date of receipt of the vaccine, from the national to the local level, including information on transportation and storage conditions.
8. Macroscopic aspects of the vaccine, diluent, and administration device.
9. Macroscopic appearance of the vaccine after reconstitution (in case of freeze-dried vaccines).
10. Vaccine(s) administered, date and time of administration, details of the anatomical site of vaccine administration, and route of administration. Details of problems observed during administration of the vaccine, and review of recent difficulties with the supply of syringes or devices for vaccination, or with vaccine quality.
11. For the extramural administration of vaccines, accurate information should be included regarding the place (physical space) where the vaccine was administered.

Take a detailed inventory of the items listed below. This is important for detecting deviations in the cold chain and errors in the vaccination technique:

- Program refrigeration equipment (temperature control records, report of the latest equipment maintenance and on exclusive use of the equipment, etc.).
  - Work table.
  - Vaccination room and preparation area for administering the vaccine.
  - Storage conditions of the devices used for administering the vaccine.
  - List of medicines received and delivered to the health service (review the report on the movement of medicines).

The NRA will have the vaccine registration file available and will review the quality control aspects of the vaccine manufacturing process, such as:

12. Compliance with Good Manufacturing Practices (GMP), monitoring of manufacturing facilities. Also includes the results of quality control of the raw materials, of the manufacturing process and on the final product.

On the vaccine’s active substance or antigen:

- Review of the manufacture of other products at the same site, and of the monitoring of precautions against contamination.
- Monitoring of raw materials including: materials of animal origin (e.g., eggs, serums, and proteins), cell substrates (cell propagation), adjuvants, and antibiotics.
- Microbial analysis and sterility testing.

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\(^{13}\) A finding during the ESAVI investigation of an expired vaccine or diluent having been administered, or that the cold chain was not properly maintained, are not by themselves reason to regard them as the cause of the ESAVI and therefore conclude the investigation. From a scientific-biological point of view, an expired vaccine will not necessarily cause an ESAVI; rather, it is much more likely that it will cause reduced biological activity. While clinical evidence is scarce, a specific report of this programmatic error has been identified. For more information, see Pan American Health Organization. Safe vaccination: how to cope with events supposedly attributed to vaccination or immunization. Washington, DC: PAHO; 2002.
• Compliance with specifications for release of raw materials.

Regarding the **finished product**:  
Monitoring of good manufacturing and production practices.

• Compliance with specifications for release of the finished product.
• Review of the certificate of analysis.
• Evaluation of the packaging and closure system.
• Review of the protocol for production of the vaccine involved.

**Review of operational aspects of the immunization program**

This review will provide information on handling and administration of the vaccine. Safety practices should be verified for the person receiving the vaccine, the person administering it, and the environment.

1. **Vaccine storage**: the conditions for vaccine storage throughout the supply chain (distribution center, hospital, pharmacy, and point of administration, etc.) and in the institution itself must be verified. A summary of temperatures in degrees Celsius (°C) and relative humidity levels (%) should be reported.
2. **Levels of stock along the product supply chain**: traceability of vaccine distribution should be performed, and check whether similar events have been reported for the same lot.
3. **Handling and transport of the vaccine**: a review should be made of reports of any incidents during transport and delivery of the vaccine, from the distribution center to the location where the vaccination is administered, as well as verifying cold chain records and, if necessary, those of the chain of custody.
4. **Use of diluents, reconstitution of vaccines, and forms of administration**: a description of the materials and solutions used, the ambient temperature at the time the product is reconstituted, any changes observed (e.g., color, general appearance, and presence of particles, etc.), and other anomalies occurring should be provided.
5. **Proper dosing**.
6. **Availability of needles and syringes, and appropriate practices**.
7. **Circumstances in which vaccinations are administered**, how they are administered, and monitoring of appropriate techniques of administration (aseptic non-touching technique).
8. **Name and professional or academic profile of the person who performed the vaccination**.
9. **Order in which the vial’s doses were administered**.
10. **Photographs should be taken showing any abnormalities in the physical appearance or characteristics of the product**.

**Epidemiological data**

Information on the population affected or potentially affected by ESAVI is to be collected:

1. Identify and track people vaccinated with the same vial or lot. Establish whether some of these people have the same symptoms.
2. Report other diseases in the area and detect outbreaks or environmental risk factors.
3. Determine whether the reported event is an isolated event or if there were other similar cases, and establish the geographic location and relation between cases.

4. Identify the unvaccinated population to determine whether a similar episode occurred in that population.

5. Identify the population vaccinated with a different lot of vaccine (from the same or a different manufacturer) that exhibits similar symptoms, to determine whether a similar episode occurred in that population.

In the case of events not previously reported or not characterized, it may be useful to evaluate the vaccine dossier at the regulatory authority, or analytic data on lot releases, in order to determine whether there are data or characteristics related to production quality that may be related to ESAVI.

7.3.4 Establishing the chronological order of reported and related events

During the investigation and collection of the data, the times at which the events occurred should be identified, and each finding should be placed on the timeline. Developing a timeline will help relate clinical events to other situations, and help in forming hypotheses.

It is recommended that a graphic representation of the timeline be prepared, showing the events that occurred.

7.3.5 Identifying factors related to vaccination services

A specific period of time should be spent evaluating the organization of the vaccination services involved. If there is a mass vaccination campaign in progress, the plan to use services in the area should be reviewed. Opportunities for improvement and possible factors related to the occurrence of the event should be identified, even if it is unlikely that the event was due to a programmatic error.

7.3.6 Grouping of related and contributing factors

Once all individualized information is obtained, a process of analyzing and grouping related or potentially related factors should be performed. Related factors can be grouped under a single name. The idea is to connect all of the clinical tables, events, and situations identified, and to try to establish a connection between them that can help in formulating recommendations.

7.3.7 Completing the ESAVI investigation report

Record all evidence collected during the investigation in the reporting form included in this manual, or in a form developed by the institutions responsible for surveillance.

Summarize the conclusions that were drawn and organize the information to be submitted to the national committee on safe vaccination.

7.4 Laboratory analysis of vaccine samples

The decision on when to take samples of biological products for laboratory analysis should take into account the data collected and the usefulness of the results of such analysis. There should be clarity regarding the specific type of test to be performed, its intended purpose, and how the results could be interpreted. Such tests should not be performed on a systematic basis.

The country’s official control laboratory (if there is one) may not have the infrastructure,
methodologies, and procedures required to conduct quality trials of vaccine lots used by the NIP, in accordance with international recommendations. The recommendation that there be independent testing of vaccine lots involving ESAVI reports should occur only in the following cases:

1. When the investigation indicates that a given lot may be associated with similar events.
2. After verifying that there are no records showing deviations in the vaccine storage conditions.
3. After verifying that, in the case of freeze-dried vaccines, the reconstitution process was carried out in accordance with current recommendations, including use of the suggested diluent.
4. If after reviewing all information regarding production and control processes, there is a suspected deviation in the manufacturing procedures that could affect specifications for vaccine quality.
5. Once it is verified that there is no suspected use of falsified or substandard products.

The type of test to be carried out, where to take the product sample, the number of samples required, and the reference laboratory recommended to do the analysis should be determined by the relevant regulatory authority, PAHO (if the product was purchased through the Revolving Fund), or WHO (in the case of prequalified vaccines). To this end, PAHO recommends the use of WHO-contracted laboratories, cited at the beginning of this manual. There are public records of WHO-led research on this and other related types of investigation of prequalified vaccines (53).

In addition, where a quality test is required, local health authorities (NIP, Ministry of Health, NRA) should have the infrastructure and logistical arrangements to:

1. Ensure the appropriate transport conditions for the type of vaccine and its diluent, and assume responsibility for shipment to the recommended laboratory.
2. Collect and identify the required samples and, where applicable, quarantine the remaining containers. This type of activity is generally carried out in coordination with the NRA in the country.

Any alteration to the above-mentioned aspects could influence the control results of the vaccine lot to be analyzed. As noted at the beginning of this manual, when an ESAVI investigation includes conducting quality control analysis of a vaccine lot, it could take longer to complete the investigation. This is due to the length of time it takes to test some samples. For example, a test of the potency of a vaccine combined with more than one antigen may require the use of animal substrates with certain weight characteristics, involving an analysis that could take more than three months for each antigen in some cases. The use of quality control laboratories should be the last resort in ESAVI investigations, once other aspects that may have caused the identified or reported event have been excluded.

Table 7 lists some laboratory tests that could be performed, depending on the hypotheses that the investigation is attempting to verify.

When sending a vaccine sample, it is necessary to send the vial containing the extracted biological product that was administered to
the patient, along with the vaccine sample and a vial of unreconstituted vaccine from the same lot (which should be kept at 4° C or at the temperature stated on the manufacturer’s insert); if the vaccine has been reconstituted, the sample should be kept at -70° C. Regarding the vial from which the biological product administered to the patient was extracted, the minimum volume to be sent is 1 mL. However, if this amount is not available, it is recommended that the vial still be sent, with whatever volume it contains.

### 7.5 Investigation of clusters

When investigating events affecting several individuals who are related in time and geographic location, or who are connected with a particular vaccination center or group of vaccination centers, an individual investigation for each case should be conducted, in order to consolidate complete and timely information about the clinic, the event, and the vaccine.

Information about the vaccination center, the geographic location of the person’s home, and

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**TABLE 7. Tests to conduct when investigating an event supposedly attributable to vaccination or immunization, depending on the hypotheses that the investigation is attempting to verify**

<table>
<thead>
<tr>
<th>HYPOTHESIS</th>
<th>TYPE OF SAMPLE</th>
<th>LABORATORY TEST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problems with transportation or</td>
<td>Vial of the vaccine(s) and diluent(s) from the lot(s) involved</td>
<td>Visual inspection, presence of foreign material, turbulence, discoloration, and</td>
</tr>
<tr>
<td>storage</td>
<td>The vials being sent must be from the same refrigerator used at the vaccine</td>
<td>flocculation</td>
</tr>
<tr>
<td></td>
<td>vials administered, and from the same lot from places other than where the</td>
<td>Name of the virus present in the vaccine</td>
</tr>
<tr>
<td></td>
<td>person was vaccinated</td>
<td></td>
</tr>
<tr>
<td>Error in reconstitution (includes</td>
<td>Vial of the vaccine(s) and diluent(s) from the lot(s) involved</td>
<td>Visual inspection</td>
</tr>
<tr>
<td>contamination of the diluent or</td>
<td></td>
<td>Chemical composition to evaluate any abnormal component, or microbiological</td>
</tr>
<tr>
<td>use of a substance other than the</td>
<td></td>
<td>culture to detect contamination</td>
</tr>
<tr>
<td>diluent, e.g., a medication)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-sterile injection</td>
<td>Needle, syringe, vaccine vial, and diluent involved</td>
<td>Sterility</td>
</tr>
<tr>
<td>Problems with the vaccine</td>
<td>Vial of the vaccine(s) and diluent(s) from the lot(s) involved</td>
<td>Visual inspection, identity, name of virus, pH</td>
</tr>
<tr>
<td></td>
<td>The vials should be from the same refrigerator at the place where the</td>
<td>Chemical composition, levels of preservatives or adjuvants</td>
</tr>
<tr>
<td></td>
<td>vaccination was administered, and from the same lot from places other than</td>
<td>Biological tests for contaminants or toxins</td>
</tr>
<tr>
<td></td>
<td>where the person was vaccinated</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>The same tests used for the release of lots can be repeated, since there could</td>
</tr>
<tr>
<td></td>
<td></td>
<td>be errors in the tests</td>
</tr>
<tr>
<td>Problems with the device for</td>
<td>Vaccine vial and administration device</td>
<td>Review of compliance with quality conditions</td>
</tr>
<tr>
<td>administering the vaccine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

the timelines of each case should be complete and accurate.

For clusters, patterns that help identify the cause of the disease need to be identified. Events that present as clusters can result from programmatic errors or deviations in vaccine quality. In these cases, it is common to have more than one affected person with the same pattern of symptoms or signs.

Similar cases occurring in a defined geographic area or in a group of related institutions should be identified through an epidemiological field investigation, using a standard case definition. Other common variables that could explain the initially observed relationship should be characterized, along with environmental factors, toxic exposures, and risk behaviors and customs.

In the case of new vaccines, a cluster may involve new adverse events not previously identified in clinical trials.

Once a cluster has been identified, all necessary measures should be taken to mitigate its impact and prevent dissemination or an increase in the number of cases.

Another type of event that can present as a cluster consists of stress-related reactions, which can develop into mass events and can negatively affect the image of the immunization program. Vaccines for which there have been reports of such events include tetanus toxoid, hepatitis B, tetanus-diphtheria, cholera, and influenza vaccines (23). In investigating these cases, the first step is to correctly identify and classify the person’s clinical picture. Frequently, the symptoms and signs indicate a neurological syndrome that is accompanied by apparent or real alterations in consciousness and symptoms of dysautonomia, including, but not limited to, vomiting, nausea, tachycardia, pallor, and abnormal body movements. A clear differentiation should be made between syncope, an anaphylactic reaction, and symptoms of a panic or anxiety attack (see Annex A for more details) (23).

A decision can be made to conduct only an abbreviated investigation into the occurrence of a cluster of non-serious ESAVI under the following circumstances:

- When there is no ambiguity as to the clinical diagnosis of the case.
- When alternative explanations for the case have been ruled out.
- When the cases do not exhibit any unusual clinical or epidemiological pattern.
- When the cases are not connected with the same lot of vaccine.
- When there is no evidence to suspect programmatic errors or deviations in vaccine quality.

Figure 6 shows the steps for analyzing clusters, and presents relevant questions and an analysis of answers, in order to correctly classify a cluster.

7.6 Investigation of deaths classified as or suspected to have been caused by an event supposedly attributable to vaccination or immunization

Each country should establish a protocol for dealing with cases of deaths following the administration of a vaccine, where an ESAVI is suspected to be the cause of death.
Such a protocol should consider establishing coordination between national forensic-medicine and epidemiological-surveillance authorities.

It is very important to consider the emotional effect on the family of the affected person and on the health personnel involved in his/her care. If necessary, psychological support should be provided to these two groups.

An autopsy should be performed, based on regular protocols, taking into account the investigation and other specific factors.

To be clear, the death itself should not be classified as an ESAVI; rather, it is the cause of death that should be classified as an ESAVI. This requires a complete review of clinical data on the case, from before administration of the vaccine to the time medical care, if any, was provided, up to the time of death.

If the death occurred at the home of the vaccinated individual, the forensic procedure established by the relevant local authorities should be followed. In most cases, an autopsy is needed to determine the cause of death, as there can be sudden deaths with no prior history that clearly suggest a cause unrelated to the vaccine.

In some countries, autopsies related to events of interest to public health are performed.
by the institution responsible for forensic cases, or by forensic-science institutes (54). Each country should review its regulatory framework and include in the national manual the administrative procedures for conducting autopsies in such cases.

In all cases, the verbal autopsy protocol, which allows for collecting a complete history of the event, beginning from before administration of the vaccine, is recommended. The staff in charge of the autopsy should be trained to provide complete and reliable information (55).

7.6.1 ESAVI potentially associated with deaths of undetermined cause
ESAVI potentially associated with deaths of undetermined cause may include the following (55):

1. **Anaphylaxis:** A very rare ESAVI, which varies in incidence depending on the vaccine in question; some studies have reported an overall incidence in children of 0.65 cases per million doses (56). The mortality rate is around 10%. Signs and symptoms are variable, and can range from neurological symptoms to cardiovascular symptoms. It is important to collect data on related symptoms that occurred prior to the death, so as to identify some of the characteristic signs (see Annex A). Since this reaction is highly dependent on the idiosyncratic response of the individual, it does not occur in clusters.

2. **Viscerotropic disease:** This is a specific reaction to the yellow fever vaccine that occurs mainly in patients with debilitating chronic diseases, and is characterized by progressive multiple organ dysfunction syndrome that can lead to death. When this occurs, it is usually four days after administration of the vaccine. To confirm such a case, the virus must be isolated and identified as corresponding to the particular vaccine strain.

3. **Vaccine infections in immunocompromised patients:** In these patients, vaccines with live attenuated microorganisms can trigger serious disease with the same characteristics as the wild-virus infection. Even with proper selection protocols for who to vaccinate, it is always possible that someone may have previously-unidentified immunodeficiencies that could account for such a serious reaction. In such cases, the clinical and pathological pattern will be consistent with the disease caused by the wild virus.

4. **Intussusception or intestinal invagination:** This is a known disorder in children, and is associated with gastrointestinal symptoms that, if it goes unnoticed or without proper treatment, can lead to death from necrosis, intestinal perforation, and sepsis. It is associated exclusively with the rotavirus vaccine.

5. **Problems with vaccine quality:** Any biological or chemical contamination in a vial could cause death if the pollutant has the ability to cause serious damage to the human body (e.g., severe sepsis or fulminant intoxication. Such contamination can occur at any point, from the vaccine manufacturing process to its handling during administration.

In all cases, when in doubt, a full investigation of the circumstances and conditions in which the event occurred should be carried out.
7.6.2 Recommendations for sampling during autopsy

Since health personnel may have access to the body, a full external examination should be performed if this is the case, in order to identify signs of disease. If possible, X-rays of the deceased should be taken.

In the event that the country has the ability to take tissue samples for further analysis, the relevant authorities, PAHO (if the product was purchased through the Revolving Fund), or WHO (in the case of prequalified vaccines) should determine the types of samples to be obtained, and what type of analysis should be carried out to identify the cause of the ESAVI.

For this purpose, it is recommended that WHO-contracted laboratories, cited at the beginning of this manual, be used.

If necessary, and if it is possible to take samples for further analysis, the following protocol, described in Table 8, should be followed.

### TABLE 8. Samples to be obtained during autopsy of a case of a suspected event supposedly attributable to vaccination or immunization

<table>
<thead>
<tr>
<th>TYPE OF SAMPLE</th>
<th>AMOUNT</th>
<th>PRESERVATION</th>
<th>DIAGNOSTIC TESTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver, brain with meninges, kidney, spleen, pancreas, heart, lungs, adrenal glands, skin, and thymus</td>
<td>4 samples from 3 to 4 cm³ of each organ</td>
<td>Tissue frozen at -80º C</td>
<td>Viral culture, Detection of DNA or RNA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tissue fixed in 10% formaldehyde</td>
<td>Detection of DNA or RNA within 24 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tissue fixed in paraffin</td>
<td>Histopathology, Immunohistochemistry</td>
</tr>
<tr>
<td>Liver, brain, and gastric content (failing that, gastric tissue sample)</td>
<td>80-100 g of tissue</td>
<td>No preservative</td>
<td>Toxicology tests</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Store in a wide-mouth bottle</td>
<td>Preserve at 4º C</td>
</tr>
<tr>
<td>Blood</td>
<td>One sample of 2 mL of blood</td>
<td>Freeze a blood sample and a serum sample at -80º C</td>
<td>Viral culture, DNA or RNA detection, and viral load</td>
</tr>
<tr>
<td></td>
<td>Two samples of 5 mL of serum</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>One sample of serum frozen at 4º C</td>
<td>Toxicology tests</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>Two nodes near the vaccination site</td>
<td>Frozen at -80º C or in formaldehyde at 4º C</td>
<td>Detection of viral DNA or RNA</td>
</tr>
</tbody>
</table>

DNA: Deoxyribonucleic acid; RNA: Ribonucleic acid

Source: Adapted from World Health Organization. Surveillance of adverse events following immunization against yellow fever: field guide for staff at central, intermediate, and peripheral levels. Geneva: WHO; 2010. Available at: https://apps.who.int/iris/bitstream/handle/10665/70216/WHO_HSE_GAR_ERI_2010.1_eng.pdf?sequence=1&isAllowed=y.
Two sets of tissue samples should be obtained: one is sent to the national laboratory where the samples are processed, and another, if necessary, is sent to an international reference laboratory.

In each case, the sample will be representative of the suspect area being investigated. Everything should be shipped together in a wide-mouth bottle, with a sufficient amount of formaldehyde to cover all items.

All samples are to have labels with the name of the deceased person and the autopsy protocol number, accompanied by the requested examination and investigation documents, the autopsy conclusions in which the cause of death is determined based on the International Classification of Diseases (10th Revision), and, if possible, the causative agents. In addition, the epicrisis of the medical history should be included.

The reference laboratory will send the results to the Ministry of Health's immunization program or to the institution designated by the country, pursuant to the regulations, to be incorporated in the ESAVI investigation. These results will then be shared with the relevant authorities, as well as with WHO and PAHO, where appropriate.

7.6.3 Case of yellow fever in Peru (continued from paragraph 6.6.1)
In addition to the case described in paragraph 6.6.1, four other cases were reported in the same period. At that point, the situation became a five-case cluster with similar clinical pictures, involving four deaths. All of the deceased had a history of receiving the yellow fever vaccine.

The research team for this case included Peru's Ministry of Health, the U.S. Naval Medical Research Center Detachment (NMRC), in Lima, and the Centers for Disease Control and Prevention (CDC), in Atlanta.

During the investigation, medical records were first reviewed, with the aim of characterizing cases correctly and thereby establishing the etiology of the disease and the cause of death. The investigation of each case was conducted by the professionals who had provided treatment up until the person's death or, in cases where the person survived, until the symptoms resolved. Serological tests were performed for human immunodeficiency viruses, hepatitis B, Mayaro, Oropuche, Venezuelan equine encephalitis, and leptospirosis. Tests for immunoglobulin G (IgG), for yellow fever, were positive in all cases.

Autopsies were performed on all deceased patients. Hepatic necrosis was observed in all cases, and three cases had evidence of acute tubular necrosis. In each case at least one other organ was found to be affected; for example, evidence of pulmonary edema, disseminated endometriosis, white-pulp depletion, or congestion of the spleen, among other findings, was observed.

Samples were taken for the identification of yellow fever virus in the liver, kidney, lung, brain, and spleen.

The virological analysis was conducted at the three participating institutions. An IgM and IgG enzyme-linked immunosorbent assay (ELISA) and a plaque reduction neutralization assay (PRNT) were performed. The virus was cultured and a reverse transcription polymerase chain
reaction (RT-PCR) test was performed on serum and tissue. The virus was also detected in tissues by immunohistochemistry.

A genomic sequencing analysis of viral material was performed on all samples and compared to that of the vaccine virus. In all cases, it was confirmed that the virus was that of the vaccine virus.

Two lots of the vaccine involved were identified, both of which were manufactured by the same laboratory in Brazil. A team of WHO, PAHO, and CDC staff visited the manufacturing plant to review compliance with good manufacturing practices and to examine production records, quality control systems, and quality test results. Sequential potency tests were performed with samples located at the manufacturing site and those in Ica (Peru), using a WHO-approved infectivity test.

An epidemiological investigation was also conducted, which included the identification of additional cases, for which a standard case definition was established and applied to medical records of persons hospitalized in the last month, visits to emergency rooms, and death records. Definitions of suspicious cases were used, and were later expanded to review cases highlighted by the investigation’s panel of experts. National notifications were reviewed to assess suspected cases in addition to those in Ica. At the national level, five additional serious cases of ESAVI were detected during the two months of searching, although it was not confirmed that the people had received vaccinations from the same lot of vaccine, and one case had no connection with the vaccine. None of the cases beyond those in Ica met the definition of viscerotropic disease. No additional suspected cases of viscerotropic disease were found. There also were no outbreaks of additional diseases that could explain the deaths, either before or after the vaccine campaign (49).
This chapter describes concepts, activities, and recommendations for the proper investigation of ESAVI. The following highlights the key points for implementing an investigation and for coordinating recommendations among the institutions involved.

### KEY POINTS FOR IMPLEMENTATION

- In order to minimize the frequency of errors in ESAVI surveillance data, variables should be standardized (including labels and codes), so that they can be analyzed using the procedures recommended in this chapter.

- In order to meet the Region’s vaccine safety monitoring goal, passive ESAVI surveillance data need to be transmitted to PAHO, where periodic descriptive and signal detection analyses will be performed, after which the finding will be reported to the countries.

### RECOMMENDATIONS ON INTERAGENCY COORDINATION

- ESAVI surveillance databases for all institutions must have the same structure and meet defined criteria.

- As part of joint activities, meetings should be organized to review and evaluate periodic analyses, and to assess the safety status of vaccines in the country.
The case described illustrates the extent of a complete investigation of an ESAVI, and activities involved.

The analysis of aggregate data from ESAVI reports and investigations is intended to characterize the population affected by ESAVI and the actual events, in order to identify patterns of occurrence that raise suspicion of new associations between the vaccine and adverse events (signals), problems with biological product quality, or systematic errors in the handling of vaccines or in vaccination (programmatic errors), as well as to evaluate the performance of ESAVI surveillance system activities.

At the local level, the first element in data analysis is a well-structured database with quality information on the characteristics of the population affected by ESAVI, including the complete characteristics of the event with a description of the clinical picture, complementary studies, and a causality assessment, as well as the characteristics of the vaccine administered and a description of the measures taken. Vaccine safety monitoring requires high-quality data, and the application of well-defined standards.

A signal is defined as any information from multiple sources that suggests a new potential causal association, or a novel aspect of a known association between an intervention and an event or related group of events, either adverse or beneficial, that is judged to have sufficient probability of being true to warrant verification actions (57).

The signal management process is fed by the information provided by various reports, and after an analysis of the safety performance of the vaccine in question.

The application of information criteria will enable data sharing between national and international actors, and can expand the capacity of a global vaccine safety system and strengthen signal detection and interpretation (35).

Among the types of information to be standardized in ESAVI surveillance are those described in Table 9.

The expected result is the generation of high-quality reports with information that can be transferred and used with other sources of health information, or with surveillance information sources for other geographic regions or different periods.

**8.1 Analyzing data on surveillance of events supposedly attributable to vaccination or immunization**

Databases constructed using information from the ESAVI surveillance system should be analyzed periodically to assess the aggregate behavior of events. Following is a description of the proposed analytical sequence for all levels.

**8.1.1 Data cleansing and quality assessment**

The first step is to verify that the data are ready to be analyzed in a spreadsheet or using statistical software. The frequency of missing data, inconsistencies among variables, and potential errors in the recording of variables should be evaluated. If repeated and systematic errors are identified, the source of the errors should be reviewed and corrected, and an
assessments made of whether the errors have skewed the results of the analysis.

To minimize the time involved in conducting the review, data validation grids can be used and programmed into statistical packages or data validation rules within the spreadsheet software.

### 8.1.2 Descriptive analysis

Two elements should be characterized: the persons affected and the vaccine used.

Regarding affected individuals, summary measures (means, medians, standard deviations, and percentages, etc.) of variables such as age, gender, sex, location, event frequencies, and characteristics of the person who made the report should be described. In relation to the vaccine, the frequency of adverse events and their relationship to the type of vaccine, dose, vaccine strain, route of administration, and lot, where relevant, should be described.

The period between vaccination and the onset of symptoms, and between the vaccination and the report, should be calculated.

The frequency of cases by geographic location, and the temporal relationship between cases, in an event and time frequency curve, should be characterized. Statistical analyses of real-time or retrospective clusters can be performed (58, 59).

### TABLE 9: Principles and models for surveillance of events supposedly attributable to vaccination or immunization

<table>
<thead>
<tr>
<th>ESAVI SURVEILLANCE PHASE</th>
<th>TYPE OF CRITERION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data collection</td>
<td>Include variables recommended by this manual that are essential to ESAVI reporting. Use an information collection tool whose presentation has been validated, adapted to the language and structure of the local environment.</td>
</tr>
<tr>
<td>Investigation and analysis</td>
<td>Use diagnostic classification criteria (such as Brighton criteria, when available). Use a standardized causality assessment methodology (such as the methodology proposed by WHO). Use a support tool for causality assessment (such as GVSI tools).</td>
</tr>
<tr>
<td>Constructing databases</td>
<td>Use a tool for automatically creating a database, and use a pre-made form rather than constructing it manually. Use an international coding criterion for adverse events and for the other variables included (e.g., MedDRA, ICD-10, and variable-coding criteria or national guidelines provided by national statistical offices).</td>
</tr>
<tr>
<td>Analysis of data</td>
<td>Apply a standard protocol for analyzing vaccine pharmacovigilance data and for signal detection.</td>
</tr>
</tbody>
</table>

If a structured database is not yet available at this stage, it is recommended that a list of cases, including the basic variables of analysis, be drawn up to identify clusters or events of particular interest that should be investigated in greater depth.

8.1.3 Analysis of rates
During the analysis, the incidence rate of ESAVI should be calculated. The most reliable figure available should be used as the denominator for calculating the rate; this will depend on integrating data from the vaccine information system, which in many countries functions as a nominal public system.

Rates should be calculated by type of adverse event, type of vaccine, type of viral strain, the laboratory involved, groups by age and sex, and geographic sites. In addition, rate trends over time should be analyzed.

The following can be used as denominators for calculating ESAVI rates:

1. Number of doses administered: This is the most reliable, but often the information is not available.
2. Number of doses distributed: Sometimes this is the only figure available; its disadvantage is that it can underestimate the rate.
3. Number of doses calculated based on coverage: The absolute number of people vaccinated is estimated from the number of inhabitants in the region and the vaccination-coverage percentage calculated by the NIP. This is highly variable and unpredictable, given the variability of the methods for calculating coverage.
4. Number of individuals targeted: This represents the total target population in planning a program or campaign, and constitutes a very rough estimate. However, a more exact value can be obtained in vaccination campaigns.

To interpret observed ESAVI rates and behaviors over time, it is helpful to obtain two additional measures:

1. **Baseline incidence rate or background rate:** This is the incidence of the clinical picture in the unvaccinated population, i.e., without the effect of the vaccine. This rate is not always easy to obtain for all known events.

2. **Expected or known ESAVI rate:** This is the rate observed in clinical trials or observational studies in the intervention group, i.e., the known frequency of occurrence of the event associated with the vaccine. A high observed rate, higher than the expected rate, may be due primarily to two situations: an excess of cases generated by causes to be investigated (e.g., vaccine quality problems or programmatic errors), or an increase in baseline incidence of the underlying disorder, for example, aseptic meningitis from an outbreak of a virus in the general population. In the latter case, the analytic data should be supplemented with data from the epidemiological surveillance system for other diseases or health conditions.

In the case of new events (signals) or vaccines whose safety profiles are not fully known (e.g., in the case of public health emergencies such
as COVID-19), it is useful to monitor baseline incidence rates and compare them with the rates observed in vaccinated people, in order to determine whether what is being observed may correspond to a coincidental event or is actually due to the vaccine (25) (Figure 7).

In order to interpret the results of comparing the calculated indicators, it is necessary to consider the source of the data in relation to the following variables:

1. **Vaccine type:** There may be variations in the manufacture of the vaccine with the same antigen. Antigen production techniques may vary and in some way change the reactogenicity or the components added to the vaccine; the adjuvants can also explain changes in the frequency of adverse events.

2. **Age:** Differences in the ages at which the schemes are applied may also relate to the incidence of new adverse events or to an increase in the incidence of already known events.

3. **Vaccine dosage:** The number of doses may also be related to a change in the frequency of adverse events. One example is the DTaP vaccine, which may be associated with an increase in the frequency of local reactions when administered as a booster, compared with what is observed when first administered.
4. **Case definition**: The definition of the adverse event may have been different in clinical trials, and therefore the frequency of adverse events may vary depending on the sensitivity or specificity of that definition. Use of the Brighton criteria reduces the variability of the results due to this factor.

5. **Period**: Time periods may have been different; the adverse event may have been measured at a different time after administration of the vaccine. The frequency of certain events in the immediate post-vaccination period is not the same as one month after administration of the vaccine.

6. **Surveillance methods**: Post-marketing pharmacovigilance data are generally less indicative of the actual frequency of an adverse event if the system of capturing information is based on passive reporting. However, if active reporting is involved, the method of detection can bring the figures much closer to real life. Data from clinical trials are often the most reliable, because of how rigorously the data are collected.

7. **Baseline conditions**: The occurrence of particular epidemiological events can increase the frequency of coinciding diseases, as well as errors or problems in interpretation. For example, an outbreak of meningitis in a region can increase the concurrence of this event with vaccination, and therefore change the numerical association.

8.1.4 Calculation of surveillance quality indicators

The same data from adverse event reports can be used to build indicators for monitoring the quality of surveillance activities.

Some of the potential indicators that can be calculated are described in Table 10.

It is recommended that, at each level of surveillance, the indicators for which information is available be calculated. From the start of the surveillance, and for the implementation of the ESAVI surveillance system, the need to quantify these indicators should be anticipated.

8.2 Detecting vaccine safety signals

The detection of vaccine safety signals can be performed for different sources of information, including databases of linked information from various sources, such as clinical history and administrative and vaccination records.

The first step in data management to make it possible to apply signal-detection methods is to standardize the source of information. For example, in order to correctly detect a signal using disproportionality analysis for reports of events associated with a vaccine, such as aseptic meningitis, all cases diagnosed with aseptic meningitis must have the same term and code in the database; in fact, rather than a clinical diagnosis, they should be coded in some other way.

One of the most commonly used standards for regulatory purposes is the Medical Dictionary for Regulatory Activities (MedDRA), which is licensed free to regulatory and non-profit authorities. The standard is organized into a series of conceptual hierarchies, grouping together adverse events affecting the same organ or system, or associated with a common medical procedure. In pharmacovigilance reporting systems, there is, ideally, a list of terms (names of adverse
events) that appears in the user interface; the reporting system classifies each event in the most appropriate group or level of nomenclature employed. However, even in the most sophisticated systems, personnel are assigned to review reports and clinical data, and to verify the classification of reports (31, 60).

The probability of detecting a rare adverse event increases in proportion to the number of records added to the signal detection process.

Thus, many national and global initiatives strive to increase the store of data by combining multiple sources of information. This is the case with the Uppsala Monitoring Center (UMC), which is responsible for facilitating drug and vaccine safety reports from around the world and for applying statistical data analysis methods for signal detection, and characterizing the safety of products for use in humans. To date, the UMC has not detected any vaccine-related signals.

In the case of ESAVI surveillance, it is essential to obtain information on the vaccination status of the affected person; this requires that the nominal immunization information system be interoperable, or be linked to the ESAVI surveillance system.
8.2.1 Recommendations for signal detection
Following are some recommendations for signal detection (57, 60):

1. Many of the tasks should focus on ensuring that the quality of the reports, in terms of completeness and validity, is very high. If the information in the databases is unreliable, the results of the signal detection process will be incorrect.
2. Resources should be dedicated to training the staff that reviews the reports, in order to ensure that cases are properly classified and coded.
3. Established criteria for classifying adverse events should be used, with staff trained in the use of those criteria.
4. The signal detection process can use terms from the MedDRA nomenclature, or adopt detailed classifications used by ICD-10 or ICD-11. The level of analysis can vary.
5. Adverse event analysis categories for applying statistical signal detection methods can be created based on a knowledge of engineering techniques.
6. The analysis should be performed by a person with experience in quantitative data analysis, ideally a professional statistician.
7. The database should include, at a minimum, the core variables set forth in the chapter on data reporting. Classification codes for adverse events should also be added.
8. The first method in analyzing data should be to generate statistics on disproportionality, due to their ease of application, interpretation, and efficiency.
9. Data analysis protocols and algorithms for signal detection need to be established, as an alternative to disproportionality analysis.
10. Attention should be given to publications that evaluate methods of analysis and signal detection algorithms.
11. Analysis of subgroups has shown clear benefits, and should be applied.
12. Stratified or adjusted analysis is not recommended, as these have not been shown to have additional benefits.

It is recommended that efforts be made to create strategies for the exchange and analysis of information that allows for longitudinal data analysis.
Causality assessment of events supposedly attributable to vaccination or immunization

This chapter describes concepts, activities, and recommendations for the correct causality assessment of ESAVI. The following highlights key points for its implementation and provides recommendations for coordination among the institutions involved.

The purpose of this analysis is to establish the level of certainty with which it can be affirmed that the vaccine or the vaccination process was the origin or cause of the clinical picture and of the symptoms or signs observed in the vaccinated person.

<table>
<thead>
<tr>
<th>KEY POINTS FOR IMPLEMENTATION</th>
<th>RECOMMENDATIONS ON INTERAGENCY COORDINATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Two levels of analysis should be differentiated: individual analysis and population analysis. Each of these should have clear objectives.</td>
<td></td>
</tr>
<tr>
<td>The terms of reference of the national committee on safe vaccination should clarify the role of each of the participating institutions (NIP, NRA, and epidemiology directorate) and the contributions they will be expected to make.</td>
<td></td>
</tr>
<tr>
<td>2. The final decision on the causality of an ESAVI should be left to a committee of experts, and should not consist of the opinion of a single professional.</td>
<td></td>
</tr>
<tr>
<td>All institutions should be trained and be keenly aware of the causality assessment methodology. Joint training to prepare a coordinated response is ideal.</td>
<td></td>
</tr>
<tr>
<td>3. Depending on the available technical capacity at the subnational level, the determination of causality can occur at that level.</td>
<td></td>
</tr>
<tr>
<td>4. It is recommended that the methodology and classification proposed by this manual be used for assessing causality and final classification of ESAVI.</td>
<td></td>
</tr>
</tbody>
</table>
Causality assessment requires the consideration of several criteria, not limited to the observation of a temporal relationship between the administration of the vaccine and the onset of symptoms, or to the observation of a mathematical relationship (association) in the pattern of the frequency of cases over time.

In the manifestation of the event, it is important, in addition to defining the relationship between administration of the vaccine and the clinical picture of the person, to identify other factors that may have contributed to its occurrence. While it is true that the vaccine safety system must guarantee that both the active ingredient and the additional substances that make up the product used for vaccination do not cause harm to the population in which they are used, other factors in the health care process related to vaccination activities, which may contribute to causing such harm, must be evaluated, controlled, or modified. This is the case, for example, when an incorrect injection technique causes infection at the injection site.

Table 11 shows a summary of causality assessment levels, methods, and responsible parties.

**TABLE 11. Levels of causality assessment for an event supposedly attributable to vaccination or immunization**

<table>
<thead>
<tr>
<th>LEVEL OF EVALUATION</th>
<th>QUESTIONS POSED</th>
<th>METHOD OF EVALUATION</th>
<th>WHO IS CONDUCTING THE EVALUATION?</th>
</tr>
</thead>
</table>
| Individual          | Could the vaccine given to the person be the cause of his/her signs or symptoms?  
                      | How were health care and immunization program factors related to the observed signs or symptoms? | Analysis of clinical data and their relationship to the vaccine, based on available evidence and experience | Institutional Committee on Patient Care Quality and Safety  
                      | | | National committee on safe vaccination |
| Population          | Does the “XXX” vaccine increase the risk of the “YYY” event occurring in the community? | Analysis of aggregated ESAVI surveillance data  
                      | Analysis of data from observational epidemiological studies seeking to test the hypothesis of association between the vaccine and the clinical picture in question | Regional or national committee on safe vaccination  
                      | | | Data from other basic-science studies and theoretical publications to meet the Bradford Hill causation criteria |

9.1 Bradford Hill criteria
In the case of new events, or events whose causal association is unknown, individual case analysis generally can only generate hypotheses on causality between the vaccine and the event. However, verifying this relationship (using population analysis) requires a complete analysis, taking into account the totality of epidemiological evidence and laboratory research, following the Bradford Hill criteria as a guide (61):

1. **Strength of association:** Association is a statistical or mathematical measure of the degree of relationship between two or more variables. The strength of association is usually measured in epidemiological studies, and in measuring the frequency of events, and is evaluated by measuring the risks or frequencies of the event. The higher the frequency of events in vaccinated individuals compared to unvaccinated individuals, the greater the association is said to be. This requires gathering evidence from several reliable epidemiological studies that have evaluated the hypothesized association between the vaccine and the event.

2. **Consistency:** The results of multiple studies evaluating the same causal relationship produce the same results.

3. **Specificity:** The particular factor generates only the effect at issue. When it is shown that the event can be produced by several factors, it is more difficult to demonstrate a causal relationship with any of them.

4. **Temporality:** The onset of the condition caused by the event occurred at a time when it is plausible that it was caused by the vaccine.

5. **Biological gradient:** As the exposure increases, the risk or likelihood of the event occurring increases. So far, this pattern has not been shown to be observed in the incidence of adverse events (62); however, it could be considered in the future once new technologies become available.

6. **Biological plausibility:** The mechanism by which the vaccine causes adverse events is consistent with existing knowledge of human biology.

7. **Coherence:** There is coherence between epidemiological data and biological mechanisms, as well as knowledge of the known disease or clinical picture.

8. **Experimental evidence:** There is evidence from randomized controlled clinical trials and other experimental studies demonstrating causation. Adverse events detected in clinical trials can be a source of such evidence, in demonstrating the association between the vaccine and the clinical picture of the individual.

9. **Analogy:** This involves the presence of data on the relationship between other vaccines and similar events or clinical conditions. For example, febrile seizures are common events with administration of the DTP vaccine; by analogy, it is reasonable to believe that, given the immune mechanism, another vaccine could produce fever and seizures in susceptible children (same type of event).

As can be seen, it is not possible to meet all of these criteria in a single case; however, in the case of any event, they serve as a guide in
Two types of evidence are recognized for population analysis, as described in Table 12 (23).

The WHO methodology is used for individual causality assessment, and summarizes two general types of evidence: epidemiological evidence of an association between the vaccine and the adverse event, and evidence of the mechanism by which the vaccine produces the adverse event. It is recommended that these two major bodies of evidence be taken into account when preparing the report to be submitted to the national committee on safe vaccination, which will conduct the analysis (63).

9.2 Responsibility for the causality assessment
Below is a description of those responsible for the causality assessment at each level.

9.2.1 Causality assessment of an individual case
This should be performed by the national committee on safe vaccination, which should be formed and operate according to the recommendations described above.

14 For an example of population causality analysis, the following publication is recommended: Rasmussen SA, Jamieson DJ, Honein MA, Petersen LR. Zika virus and birth defects: reviewing the evidence for causality. NEJM. 2016;374:1981-7. Available at: https://www.nejm.org/doi/full/10.1056/nejmsr1604338.
Once the committee’s report is final, the health staff of the institution where the event occurred may conduct its own analysis to assess whether there is a possibility that a new vaccine may have been related to the event, or whether the event was due to a programmatic error. This will allow corrective and risk management measures to be implemented at that level. It also serves to rule out, at this level, a concurrent event incorrectly associated with the vaccine and, in the future, improve the specificity of the reporting.

9.2.2 Population-level causality assessment
This analysis should be performed by an interdisciplinary committee of experts (at the level with the necessary capabilities) since it requires a complex analysis with robust technical evidence, including epidemiological data, a summary of evidence in the literature, and analysis of data from numerous reports, not limited to the individual case. At the national level, this is done by the committee of vaccine safety experts, and it may be necessary to seek opinions from regional and global committees (e.g., GACVS).

9.3 Procedure for performing individual causality assessment
The WHO Global Vaccine Safety Group has proposed a procedure and several causality assessment tools and methodologies, which are summarized and described below (63).

Step 1. Evaluation of eligibility
The case diagnosis must be confirmed and must meet standardized classification criteria, according to standard clinical practice, national or international clinical practice guidelines, or according to some standardized definition, as discussed in previous chapters. In addition, the vaccine involved and the temporal relationship with the case should be verified in order to ensure that the vaccine was administered before the onset of symptoms or signs of the event, with the exception of stress-related events that may be triggered immediately prior to administration of the vaccine.

In order to perform the causality assessment, the investigation must first be completed and all details of the case made available.

In this step, it is suggested that the question to be evaluated be defined and formulated:

Is the ________ vaccine or the vaccination with ________ the cause of ______________? The causality assessment should be performed for each vaccine administered, and for each sign, symptom, abnormal laboratory finding, syndrome, or disease, as the case may be.

Step 2. Verification checklist
The checklist should be used (see Annex B) to evaluate the analytical elements and to ensure that all of the data collected during the investigation can be used. Questions, grouped into four areas, should be answered:

1. Is there evidence of other causes?
2. Is there a known association with the vaccine or vaccination that is described in the medical literature?
3. Is there evidence against a causal association?
4. Have other factors (e.g., baseline event rate, health history, potential risk factors, medications, and biological plausibility) been considered?
The checklist includes four possible answers: Yes, No, Not known, Not applicable. If yes to any of the questions, comments and supporting evidence should be included.

**Step 3. Causality assessment algorithm**

Once the analytic questions have been answered, the algorithm is applied, making it possible to detect any trend in the evidence for the case. If it is not classifiable after applying the algorithm, it is recommended that all possible measures be taken to collect all of the missing information needed to classify it. The algorithm does not make decisions based on who is performing the analysis, but, rather, serves only as a guide on what direction to pursue; it is up to the committee to make a decision and assess whether or not it agrees with the results of the algorithm.

**Step 4. Classification of the event**

Possible classifications are as follows:

**A. Consistent causal association with the vaccine or with the vaccination process**

This group includes two different types of events: those that are causally related to the vaccine or one of its components, and those that are related to the conditions or setting in which the vaccination took place.

Events that have a causal association with the vaccine or any of its components:

A2. Event related to a deviation in vaccine quality.

Event that has a causal association with the vaccination process:

A3. Event related to a programmatic error.

A4. Event caused by stress that occurred immediately before, during, or immediately after vaccination.

**B. Undetermined**

This group of events includes situations in which, after reviewing the evidence, there is uncertainty regarding causal association, either because the evidence is insufficient or because there is conflicting evidence.

B1. The temporal relationship is consistent, but there is not enough definitive evidence to determine that the vaccine is the cause. It may be an event recently associated with the vaccine. This is a potential signal and consideration should be given to extending the investigation.

B2. Qualifying factors result in conflicting trends of consistency and inconsistency with causal association to immunization.

**C. Inconsistent with causal association to vaccination (coincidental event)**

The event is caused by an underlying or emerging disease, or by a condition caused by exposure to something other than a vaccine.

**D. Non-classifiable**

The information available does not allow for classifying the case in any of the categories. Additional information may be required, and may become available in the future. It is therefore recommended that all case information be stored in a database that allows for periodic reviews to analyze signal detection.

Once each case has been classified, the appropriate interventions for each should be planned.
### 9.4 Case of yellow fever in Peru (continued from section 7.6.3)

The causality assessment of the case of yellow fever in Peru is described below.

The question of causality:

Did the yellow fever vaccine cause multiple organ dysfunction syndrome (viscerotropic disease)?

<table>
<thead>
<tr>
<th>I. Is there strong evidence of other causes?</th>
<th>Yes</th>
<th>No</th>
<th>UK</th>
<th>NA</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. In the case of this person, did the medical history, clinical examination, or laboratory tests confirm another cause?</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td>All complementary studies to determine another etiology were negative</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>II. Is there a known causal association with the vaccine or the vaccination?</th>
<th>Yes</th>
<th>No</th>
<th>UK</th>
<th>NA</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine components</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Is there evidence in the literature (published and peer-reviewed) that this vaccine or vaccines can cause the reported event, even if administered correctly?</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>This event was reported in several evidence reports</td>
</tr>
<tr>
<td>2. Is it biologically plausible that the vaccine may have caused the event?</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>Yes, the vaccine contains live virus and, in very rare cases, can be actively disseminated and replicated, especially in immunocompromised patients</td>
</tr>
<tr>
<td>3. In the case of this person, did a specific test demonstrate that the vaccine or any of its ingredients had a causal role?</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>In autopsies, the vaccine virus was detected in multiple organs</td>
</tr>
<tr>
<td>Vaccine quality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Was there a deviation in the quality of the vaccine administered to this person, or was it of substandard quality or a falsified vaccine?</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td>In evaluating the lots of vaccine, and in visiting the production plant, it was established that there were no problems in the quality of the vaccine</td>
</tr>
<tr>
<td>Programmatic error</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. In the case of this person, was there an error when prescribing or non-adherence to recommendations for the use of the vaccine (e.g., used beyond the expiration date, administered to the incorrect recipient, etc.)?</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>Thyroid neoplasm in the patient was identified in autopsy, and there was a prior diagnosis of an autoimmune disease</td>
</tr>
<tr>
<td>6. In the case of this person, was the vaccine (or any of its ingredients) administered in a non-sterile manner?</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>Based on verification of the administration technique, and given the absence of similar cases related to the same vaccination center</td>
</tr>
<tr>
<td>7. In the case of this person, was the macroscopic appearance of the vaccine (e.g., color, turbidity, or presence of foreign substances) abnormal at the time of administration?</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
<td>No vial sample was available at the time of the investigation</td>
</tr>
</tbody>
</table>
8. When this person was vaccinated, was there an error, by the person who administered the vaccination, in constituting or preparing the vaccine (e.g., use of the wrong product or wrong diluent, improper mixing or improper syringe filling, etc.)? No such errors were evident in the records or when evaluating the technique.

9. In the case of this person, was there an error in the handling of the vaccine (e.g., interruption in the cold chain during transport, or in the storage or administration of the vaccine, etc.)? No such errors were evident in the records or when evaluating the handling of the vaccine.

10. In the case of this person, was the vaccine administered incorrectly (e.g., incorrect dose, incorrect site or route of administration, incorrect needle size, etc.)? No such errors were evident in the records or when evaluating the technique.

Vaccination stress (response triggered by vaccination-related stress)

11. In the case of this person, could the event have been a response triggered by vaccination-related stress (e.g., acute stress response, vasovagal disorder, hyperventilation, or anxiety)? The medical history is not consistent with a stress response.

If the answer is “Yes” to any of the questions in Section II, did the event happen within the expected period of increased risk?

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>UK</th>
<th>NA</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. In the case of this person, did the event occur within a reasonable time after administration of the vaccine?</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>The risk window is three to 60 days post-vaccination</td>
</tr>
</tbody>
</table>

III. Is there strong evidence against a causal association?

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>UK</th>
<th>NA</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is there a published, robust body of evidence (systematic reviews, GACVS reviews, etc.) against a causal association between the vaccine and ESAVI?</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>Strong evidence indicates otherwise</td>
</tr>
</tbody>
</table>

IV. Other qualifying factors for classification

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>UK</th>
<th>NA</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. In the case of this person, did such an event occur previously after receiving a dose of a similar vaccine?</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>Clinical history</td>
</tr>
<tr>
<td>2. In the case of this person, has such an event occurred previously, independent of vaccination?</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Could the event have occurred independent of the vaccination (background rate)?</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>There is no evidence that another health problem could have caused this disease</td>
</tr>
<tr>
<td>4. Did this person have any illnesses, pre-existing condition, or risk factor that may have contributed to the ESAVI?</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>The patient had thyroiditis and thyroid neoplasm. Although the mechanism is unclear, these are problems that could affect the interaction of the immune system with the vaccine virus.</td>
</tr>
<tr>
<td>5. Was the vaccinated person taking any medications prior to vaccination?</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>Yes. She had received radioactive iodine treatment several months before.</td>
</tr>
<tr>
<td>6. Was the vaccinated person exposed to any potential risk factors (other than the vaccine) prior to the event (e.g., allergens, drugs, herbal products, etc.)?</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td>Not all of the patient’s movements were identified; however, risk factors do not appear to be present in the person’s living environment.</td>
</tr>
</tbody>
</table>
According to the analysis presented, the trend of the evidence is as follows:

I. **Is there strong evidence of other causes?**
   - Yes

II. **Is there a causal association with the vaccine/vaccination?**
   - Yes
   - (Time) Did the event occur in the period of greatest risk?
   - Yes
   - II A. Causal association consistent with the vaccine/vaccination
   - No
   - IV A. Causal association consistent with the vaccination
   - IV B. Indeterminate

III. **Is there strong evidence against there being a causal association?**
   - Yes
   - III C. Inconsistent causal association with the vaccine/vaccination

IV. **Review other classification factors**
   - Yes
   - No
   - IV D. Non-classifiable

Final classification:

A. **Causal association consistent with the vaccine or the vaccination**
   
I. **Vaccine product-related event**

ESAVI: Events supposedly attributable to vaccination or immunization; GAVCS: Global Advisory Committee on Vaccine Safety.
The first response to a report of an ESAVI is attention to the clinical picture of the affected person, which will depend on the type of event. Appropriate communication with the person and his/her family or companions should also be maintained, the origin of the clinical picture should be explained, and the balance between the risk and benefit of vaccination should be clearly presented.

In the case of most adverse events associated with the active substance in a vaccine, the mechanism of action involves the immune response being stimulated by contact with the vaccine antigen, or is due to the toxic effect that one or more of the vaccine components may have. The treatment of these ESAVI is modulation of the immune response or symptomatic treatment, if the clinical condition does not spontaneously resolve.

In the case of programmatic errors, the damage is caused by problems in the injection procedure or in the conditions present before the vaccine is administered. Medical treatment is also symptomatic, and is specific to the type of event; for example, antibiotics are used systemically to treat infections at the injection site.

As established in the ESAVI surveillance model, the communication response occurs in parallel with the actions outlined in this chapter. Further details on how to handle that response are provided in the next chapter.
10.1 Decision-making process following report of an adverse event

The decision-making processes for each institution, after the report of an ESAVI, are described below.

10.1.1 Health institutions

The health institution should take steps to assess the risks within its purview, and make the appropriate corrections. It should review compliance with all national guidelines and standards for vaccination centers published by the NIP.

In the case of serious ESAVI, although a preliminary individual causality assessment may be carried out, recommendations for the higher subnational and national levels should be followed. The health institution is the place where the measures suggested by the national committee on safe vaccination or the national vaccination program are to be implemented.

10.1.2 Local level

Once it has received the report and the outcome of the investigation, the local government health authorities undertake an evaluation of the quality of such activities, reviewing whether all of the necessary information has been collected, and, when necessary, providing support for the investigation and classification of the adverse event.

The local level is also responsible for reporting to the subnational or national authorities, in accordance with the country’s administrative structure.

This level is usually responsible for expanding the investigation to the extra-institutional level in cases where this is required, and for involving other institutions, such as subnational pharmacovigilance centers and epidemiological surveillance authorities, in monitoring public health events. The local level also investigates clusters occurring in the community, or within institutions unrelated to the health sector.

In cases of deaths suspected of being related to a vaccine, authorities at this level should verify compliance with autopsy procedures, in accordance with national regulations.

10.1.3 National Immunization Program (NIP)

The NIP should closely observe the results of ESAVI surveillance. The goal is early detection and correction of errors in program operations or problems directly related to the vaccine.

Once the case or case dossier has been reviewed, the national level authorities conduct a quantitative and qualitative analysis of reports through the national committee on safe vaccination, using the tools proposed in this manual.

The committee issues technical recommendations, and the program assesses the applicability of these recommendations.

Programmatic decisions should be made after a deliberative exercise among the members of the national committee on safe vaccination. Potential measures will depend on the causal factors and factors contributing to the event, and should take into account the program components described below.
**Measures related to the vaccine**

Once there has been a review of the vaccine distribution chain, work should be carried out with the NRA to recommend or implement risk mitigation measures, according to the type of event and contributing factors, as follows:

1. Withdraw the involved vaccine from the market.
2. Change the manufacturer at which there has been a deviation in the quality of the affected product.
3. Change the protocols for cold chain preservation and for inputs used for that purpose, or re-train staff.
4. Verify and adjust lot release protocols.
5. Intensify monitoring of vaccination activities and supply logistics.
6. Adjust surveillance activities to improve the collection of information in future cases, and to correct current errors.

At this point, the program should establish a crisis plan based on the impact of the event.

It is also necessary to ensure the supply of a new vaccine, so as not to affect vaccination coverage. Guidance should be provided on what measures to take during a contingency situation.

**Staffing**

Thought should be given to the technical capacity and sufficiency of the health personnel in charge of vaccination. In the context of a vaccination campaign, the participation of additional health personnel is needed; thus, the campaign plan should include the time and resources required to train new staff. In addition, direct observation measures are needed during the start of the campaign, in order to identify and correct any errors in implementing the secure management protocols reviewed during training.

Staff should be informed, at an early stage, of the results of adverse event investigations, and of corrections to procedures or implementation of new measures. If necessary, recommendations on human resource management aspects necessary for vaccination need to be presented.

**Health institutions**

Local actions for health institutions should occur on two fronts, the first being managing risks of a recurrence of the reported event, the second being medical care for those affected by the event and the complications arising from it.

For managing risks of a recurrence of the event, case analysis tools need to have been applied, local contributing factors identified, and external factors that could affect the development of the event cited.

Using this analysis, the risk of a recurrence and the impact of the event can be assessed, and preliminary intervention measures within the institution’s purview can be proposed.

The decision to suspend vaccination or the use of a vaccine lot should always be made based on a national recommendation issued by the immunization program or NRA.

For preventing programmatic errors and caring for people affected by them, the guidelines and technical documents published by the NIP directorate should be followed.
10.1.4 National Regulatory Authority

NRA participation includes providing information relating to historical data on vaccine safety, details of the manufacturing process, and compliance with best practices by the vaccine manufacturer in the country. Also, if required the regulatory authority could guide vaccine sampling to be sent overseas for more complex analysis unavailable in the country. Such analysis should be completely independent of those involved in the event, including the vaccine's manufacturer.

If it becomes necessary to withdraw a lot or a vaccine from the market, the NRA will be responsible for coordinating actions throughout the entire supply chain.

International alerts regarding a vaccine that is circulating in the country should be identified through the networks of the regulatory authorities; and once a national analysis has been completed, a national alert should be published, with notice given to the relevant authorities so that an international alert can be posted.

In parallel with the immunization program, the NRA will use its experience in signal detection to conduct periodic analyses, the results of which will be shared with the ESAVI surveillance committee.

10.2 Actions following classification of an adverse event

The actions to be taken, according to the type of adverse event, are listed below.

A. Causal association consistent with the vaccine or the vaccination process

A1. Vaccine product-related event

If it is a known and previously described event, the patient should be given clinical care, and the necessary follow-up should be conducted. If it is an event not previously described, the national committee on safe vaccination should issue recommendations and adopt the appropriate measures.

In this case, a joint evaluation with the regulatory authority and the manufacturer is to be undertaken and, if necessary, the lot should be quarantined or withdrawn from distribution, and a purchase of vaccine from another manufacturer made.

A2. Event related to a deviation in the quality of the vaccine

If after the analysis it is determined that the deviation in quality has affected one or more lots, the protocol for withdrawing the defective lot or lots from the market is to be followed. This decision should be made in conjunction with the national committee on safe vaccination, the NRA, and the sponsor or manufacturer of the vaccine in the country.

The NRA should prepare the alert and inform PAHO, in order to ensure that it reaches the entire Region.

A3. Event related to a programmatic error

Complete vaccination program procedures need to be reviewed in order to identify systematic errors or problems. Although basic training activities should be conducted, the analysis needs to be completed and the causal factors responsible for the problem identified. For example: in one vaccination
center, in the course of two consecutive months, two cases of soft tissue infections at the injection site are reported, with the two vaccinations having been administered by two different people. When an investigation is carried out, it is determined that, in addition to problems in staff training on safe administration techniques, there is a problem with high turnover among vaccination center staff. Contracts are very short and working conditions are inadequate, causing contracted workers to leave if they receive a better offer of work. Strategies for solving this problem at the local level should go beyond training, and action should be taken by the human resources office of the institution involved.

A4. Event caused by stress that occurred immediately before, during, or immediately after vaccination

Efforts should be made to ensure that vaccination is conducted in a safe and calm environment. A number of recommendations for preventing and dealing with such events are given in Annex A.

B. Indeterminate

B1. There is a consistent temporal relationship, but definitive evidence of a causal relationship with the vaccine is insufficient (the association with the event or signal could be recent)

A review of the presence of clusters in time and space should be conducted. If none are immediately identified, trends may later be detected and interpreted as a sign of a new causal association or a new aspect of a known association. Signal analysis requires that there be a standardized database that contains information on all reports.

B2. Qualifying factors result in conflicting trends of consistency and inconsistency with causal association to the vaccination

Case documentation should be evaluated to ensure that the information required to classify a case in another category is not available. The appearance of other similar cases may make it necessary to reclassify cases that ultimately fall into this category.

If assistance is required, these cases may be submitted for consultation to the national committee on safe vaccination and, if necessary, to the PAHO representative office for technical support.

C. Inconsistent with causal association to vaccination (coincidental event)

As with all other events, the absence of an association between the event and the vaccine should be communicated to individuals who have been vaccinated, to health professionals, and to the community. Evidence against association with the vaccine should also be presented. The recommendations provided in the section on risk communication should be followed to ensure appropriate communication of the situation.
Chapter 11

Communication regarding events supposedly attributable to vaccination or immunization

11.1 Risk communication for teams involved in ESAVI surveillance

Vaccines are given as a preventive strategy throughout the life course, most of them during childhood, so the population has quite high expectations as to their safety. Any situation perceived as a risk can have negative consequences on people’s acceptance and trust. For this reason, optimal communication with the public is essential.

Providing the right message to the target public at the right time can have a positive impact, and can maintain or increase confidence in vaccines, credibility in health authorities and in health personnel generally, and avoid a negative effect on the public’s perception of the NIP, which would have a corresponding negative effect on vaccination coverage. Institutional silence, by contrast, can encourage rumors and diminish credibility and trust in authorities and in vaccination.

In formulating communication on vaccination safety, consideration should be given to an ongoing communication program or strategy to sustain public confidence, rather than being limited to responding during a crisis involving vaccine safety. Recommendations regarding communication on vaccine safety, which should be implemented on an ongoing basis, are as follows (41, 64, 65):

1. Maintain, strengthen, or regain trust.
2. Develop a plan for communication on vaccination safety.
This chapter reviews a number of recommendations on preparing surveillance reports, and obtaining feedback on results as an important communication tool, along with recommendations on risk communication regarding the incidence of ESAVI.

Additional tools for deepening communication on vaccination safety can be found in Annex C of this manual, and in “Crisis communication related to vaccine safety: Technical guidance” (65).

Recommendations for the preparation of ESAVI case surveillance reports and for obtaining feedback on results

For purposes of maintaining a record and historical archive of ESAVI, each investigation report form for the event being studied should be maintained as an official document. For serious events, an extensive report should be prepared providing additional details of each case, with a thorough explanation of the conclusions of the national committee on safe vaccination.

This guide is for use in reporting an individual case, or for reporting other related cases. For multiple related cases, a single report should be prepared, with a complete summary of data for, and identification of, each case.

In short, the report should provide full answers to the following questions:

1. What happened?
2. Who was affected?
3. When did it occur?
4. Where did it occur?
5. How did it occur?
6. Why did it occur?

The suggested content of individual case reports is as follows:

1. Presentation and introduction: This should include identifying data for the institution generating the report, type of report, number of ESAVI, authors, names of the committee members who reviewed the case, and other formalities required by the institution.
2. Summary: This consists of a short summary of the report, to give the public an overview of what the document is about. The following key points can be included:
   - Description of the event and its consequences.
   - Identifying information on the event and on the report.
   - Methodology for conducting the investigation.
   - Findings and results of the investigation.
   - Analysis of individual causality and contributing factors.
   - Lessons learned and recommendations.
   - Follow-up plan.
3. Complete description of the event and its consequences.
4. Background and context of the event: A brief description of the status of ESAVI surveillance at the time the event was reported. Trends in similar events or previous clusters of the same event should be cited, indicating whether the event occurred in the context of a vaccination campaign, and if so, the point in the campaign when it occurred, etc.
5. Presentation of the investigative team: names, affiliations, and details of the conflict-of-interest statements.
6. Investigation methodology: This should include a description of the investigation process and the methods used. It should explain how the information was collected (interviews, retrospective review of clinical records, meetings with health-institution staff, etc.), and describe the findings.

7. Findings of the investigation:
   - Chronology of events: Timeline.
   - Detection and reporting mechanism.
   - Description of the evidence of the complete clinical events, and of the clinical outcome.
   - Description of factors related to the vaccine: type of vaccine, manufacturer, date of licensing or of authorization to market the vaccine, origin, history of adverse events reported in the Region and in the country, etc.
   - Description of the immunization program roll-out and all the vaccination activities.
   - Identification of contributing factors and problems in the provision of vaccination services or in the provision of health services to deal with the events.


It is recommended that an aggregated periodic report be prepared at least every six months, and always prior to special events such as mass vaccination campaigns, or after introduction of a new vaccine.

The objective of the reports is to present the state of vaccine safety in the country, the state of surveillance, and to support decision-making at all levels, for the permanent improvement of the vaccine safety system.

The suggested content of this periodic and aggregated case report is as follows:

- Presentation.
- Summary update of the current state of the immunization program.
- Description of relevant facts that emerged since the last report.
- Presentation of ESAVI surveillance indicators, and thorough characterization of event developments.
- Presentation of special cases: response and recommendations.
- Complete recommendations based on the analysis.
- Presentation of the quality assessment, and of the quality-monitoring system.
- Conclusions.

In addition to the report, the communications team should develop additional strategies to obtain feedback and communication on their work, and on the findings of the ESAVI surveillance system, even if no special or high-risk event is involved.

11.2 Communication strategy for risk events

As noted in the surveillance model, communication activities are intertwined with surveillance activities. Figure 8 describes the three phases of the ongoing strategy for developing a risk communication plan.
This plan assists in developing tools to deal with crisis situations that may arise, including the emergence of an ESAVI. The team and the community will thus be prepared to deal with situations surrounding an ESAVI, and will know how to respond in a coordinated way to different events that could compromise the functioning of the immunization program.

Following is a description of the three phases of the risk communication plan in the event of an ESAVI.

### 11.2.1 Preparatory phase: prevention, preparation of communications, and response to vaccination-related events

The communication process must be ongoing, to maintain confidence in vaccine safety and in vaccination. It is suggested that constant communication with the media be maintained, and that an ongoing strategy be proposed for social networks, providing tools to deal with the public’s perception of risk regarding vaccines and vaccination (65, 66). The benefits of vaccines should also be communicated, in order to maintain a high level of public confidence in them.

As part of this effort, the following activities are suggested:

1. **Know the evidence**
   - Understanding the determinants of vaccination safety communication: It is important to recognize that there is a gap between health personnel and the general population with regard to the perception of risk.
   - Monitoring public perception: Identify concerns, background data, public

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**FIGURE 8. Phases of the communication strategy for a vaccination-related crisis**

<table>
<thead>
<tr>
<th>PHASE I: PREPARATION</th>
<th>PHASE II: IMPLEMENTATION</th>
<th>PHASE III: EVALUATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Know the evidence</td>
<td>Coordinate and engage</td>
<td>Evaluate</td>
</tr>
<tr>
<td>Contact the key actors</td>
<td>Create a response and implement communication strategies</td>
<td>General feedback</td>
</tr>
<tr>
<td>Establish response mechanisms</td>
<td>Share the information</td>
<td>Evaluate the work of the actors</td>
</tr>
<tr>
<td>Inform the public to build resilience</td>
<td>Monitor and continue the response</td>
<td>Evaluate relations with the public</td>
</tr>
<tr>
<td>Monitor and evaluate events</td>
<td>Convene the response group</td>
<td>Share lessons learned</td>
</tr>
<tr>
<td></td>
<td>Share information</td>
<td>Identify best practices</td>
</tr>
<tr>
<td></td>
<td>Identify key groups</td>
<td>Prepare a report with positive and negative elements</td>
</tr>
<tr>
<td></td>
<td>Define the communication goals</td>
<td>Revise the crisis communication plan based on lessons learned</td>
</tr>
<tr>
<td></td>
<td>Adapt the messages</td>
<td>Incorporate a remediation plan to optimize future response</td>
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<tr>
<td></td>
<td>Select the media</td>
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<tr>
<td></td>
<td>Brief the spokesperson</td>
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<tr>
<td></td>
<td>Inform the public</td>
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<tr>
<td></td>
<td>Inform the media</td>
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</tr>
<tr>
<td></td>
<td>Monitor public opinion</td>
<td></td>
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<tr>
<td></td>
<td>Monitor the media</td>
<td></td>
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<tr>
<td></td>
<td>Continue the response</td>
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</tbody>
</table>

opinion, and information on social media. Recommended tools for monitoring include press summaries, opinion polls, scientific research, rumor surveillance, monitoring of social media, and information from health personnel.

2. Work with interested stakeholders
   • Create a stakeholder map: This makes it possible, at this stage, to efficiently plan messages and deploy resources. Importantly, both collaborating stakeholders and those creating obstacles to the process should be identified (66).
   • Build strategic alliances with media actors and civil society groups.

3. Establish the response mechanism: In the event of an emergency or crisis, it is advisable to establish a working group with the stakeholders identified in the previous stage. The following are recommended:
   • In case of a vaccination-related event, be clear about each participant’s functions. An official spokesperson and media support team should be designated. The spokesperson is usually a high-level official (the minister or the person designated to be the official spokesperson) who can make decisions and who inspires trust among the public. All ESAVI program and surveillance personnel should be informed and trained on how to respond.
   • Identify potential situations and scenarios, as well as questions that might be asked at such a time, and identify in advance the source of information that will be relied upon for the answer, and the type of information that will be required.
   • In special situations such as a vaccination campaign, provide information on the potential risks of vaccination in the given situation, and provide messages and information to the media.
   • Allocate a budget item for training, planning, and crisis response for immunization program activities.
   • Staff training: It is advisable to provide ongoing team training on handling crisis communication.
   • It is strongly recommended that a media manual or guide be developed. It is also useful to include a journalist, or communicator with experience in communicating health risks, in national immunization programs.
   • Prepare general and specific messages for each vaccine.

The message
When the plan is developed, key messages, consisting of short, clear phrases that do not use technical language, should be prepared if the audience is the general public. Technical language can be used if the audience consists of experts, health personnel, or scientists, and if their collaboration in disseminating the message is required.

The involvement of key players, including the community, will make it possible to adapt, evaluate, and validate the prepared message and predict the impact it could have.

Depending on the causal-association category of the event, messages can be situation-specific:
1. Causal association consistent with the vaccine or the vaccination process:
   • Vaccines carry minimal risks associated with their active product, the manufacturing process, and vaccine administration (provided, in the latter case, that proper vaccination practices are followed). These risks are much lower than the risk of unvaccinated people acquiring the disease.
   • The process of manufacturing and approving vaccines is very rigorous; this minimizes errors that can cause harm or injury to people. Remaining vigilant is the first step in correcting any errors.
   • Health personnel can make mistakes when administering any vaccine. Monitoring these errors, promoting good vaccination practices, and ongoing training will help prevent future mistakes.

2. Causal association undetermined:
   • The information obtained does not provide a basis for establishing the cause of the observed event; the authorities are nevertheless working to minimize the chance that the vaccine is the problem.

3. Causal association inconsistent with the vaccine or the vaccination:
   • All tests ruled out any role of the vaccine or how the vaccine is being administered.
   • The event was caused by a characteristic of the patient.

**Recommendations for formulating key messages**

Don't overload the public with a lot of information. Establish two or three key messages and some specific facts to highlight.

1. When some action by the public is required, highlight the value of public participation.
2. Point out the human aspect of the situation. Think about how to connect the public with the situation. Emotional messages with personal narratives are preferable.
3. More technical messages can be prepared for trained health personnel.
4. Carefully choose the graphic design of the messages or materials to be used for the response. It is recommended that sufficient resources be invested in the proposed graphics.
5. If the message is being delivered periodically, include a logo or a graphic icon that identifies all messages that are part of the same plan.
6. In short, the message should be: concise, without too much technical language or acronyms, using phrases connoting action; mention what can be done rather than emphasize what cannot be done (positive messaging); and use short, easy-to-remember, specific phrases that can be stated in 15 seconds.
7. Teach the public to build resilience: Raise public awareness of the huge benefits, and minor risks, associated with immunization, and the benefit of immunization against vaccine-preventable diseases.
8. Monitor and evaluate events.

In the course of the work, it is important to monitor and evaluate events that could potentially lead to a crisis (Figure 9), such as ESAVI, publications and discussions on vaccination safety, and changes in vaccination schemes. Based on this evaluation, the appropriate response can be determined.
Events can be classified, depending on their potential impact, into low-, medium-, or high-impact. Each of these categories requires a different response. The appropriate sources of information for providing details of the event need to be selected. The primary source of official information should be ESAVI surveillance teams operating under the Ministry of Health, the Public Health Institute, or the NRA. Having communication personnel participate in the national committee on safe vaccination prior to any actual event occurring can give them the opportunity to be fully prepared when an event does occur; moreover, they can help plan the communication measures and provide guidance to the rest of the surveillance team.

Once the problem has been characterized, its potential impact should be determined, taking into account factors that could affect the level of care that will be needed. Such factors include:

1. Uncertainty regarding the causality of the event.
2. The fact that serious, feared, dramatic, or memorable events can arouse emotions and fears.
3. The fact that the risk of the event is higher if it occurs in children or pregnant women (nature of the population involved).
4. Whether it is part of a vaccination campaign, and whether an appropriate prevention strategy was implemented.
5. Whether the vaccine is relatively new.
6. Whether the event or vaccine is of concern to a specific segment of the public or to a wider audience.
7. Whether it involves a rumor, and if so, how credible is the rumor?

Since the ongoing communication plan includes monitoring events, if a potential crisis is detected, trained personnel are needed to deal with the response.

**Determine whether the event merits a communication effort**

In general, communication about events with little impact should be limited to the affected population, while monitoring any changes in public confidence in the program; most such events are recorded and are reported in periodic reports, which should be publicly available. Medium-impact events should be monitored and the preparatory phase intensified. By contrast, high-impact events require a high-level and immediate response. In that case, matters should proceed to the deployment phase. An assessment of the context may also affect the decision of whether or not to communicate the information to the public; for example, if there is a non-serious event that occurs at a time of political tension for the country, it may be prudent to first confirm its causality, or wait for the right time to communicate.

The communication plan should be disseminated quickly, and the response should be implemented as soon as possible, before events have a chance to progress so quickly that they overcome the ability to respond.

**11.2.2 Implementation phase**

The communication plan needs to be disseminated quickly. The contents of the plan can include the following (40):

1. Background.
2. Goals.
3. Objectives.
4. Audience.
5. Messages.
7. Time frame.
8. Budget.

**Steps in the implementation phase**

1. Coordinate and engage: During this stage, the working group should meet immediately and establish a coordination mechanism, including technical staff in the area of immunization and, ideally, staff to help handle communications. This mechanism makes it easier for all participants to have a single voice, and for publicly communicated messages to be consistent with the communication plan.
2. Formulate the response and implement the strategy: Selection of the target audience begins at this stage; the previously developed messages are then adapted to
each type of audience, and the appropriate media selected.

3. Share information: The spokesperson is designated, and he/she is taught the techniques for dialoging with the media. When there is no spokesperson, a written communication and written statements can be issued, after review and approval by the committee.

4. Questions and scenarios raised by the media and by the community should be anticipated, and appropriate communication strategies devised (65).

5. Whether this involves an interview, a statement, or a press conference, it must be preceded by a preparatory phase. For more information regarding general commonly applicable recommendations for these strategies, refer to “Crisis communication related to vaccine safety: Technical guidance” (65).

6. If no information or insufficient information is available, the following should be considered:

   • Remain confident, and reflect that confidence. If something is not known, say so. Be transparent, and calm the population; for example: “We are studying this situation, and as soon as we have the answer, we will communicate it to you through official channels, which are the following...”
   • Do not say anything that cannot be supported by evidence, or make promises that it may prove impossible to keep.
   • Be completely honest.
   • Be empathetic about the situation. Ensure that all possible steps have been taken to address the situation, and provide timely information.
   • Do not forget to mention and insist on the benefit of vaccination, in relation to deaths and the diseases they can prevent.
   • Provide information on the history of the vaccine and of the immunization program.
   • Identify the time and date when more information will be provided to the public.
   • Show appreciation for people's patience and participation, especially when the public needs to take certain actions.

   If time allows, the quality and projected impact of prepared messages should be evaluated in advance.

   The communications plan and the barriers or contingencies encountered should be monitored in an ongoing manner, and taken into consideration in the strategy's budget.

   Six determinants of public confidence have been identified, as described in Figure 10.

   **The media**

   It must be recognized that the media have their own particular interests and spaces to sell, so the size of the audience generated by your messages will be a priority. The success of an immunization program or vaccination campaign can be just as attractive to the media as its failure. In addition, the way the message is presented can increase a negative public perception.

   The guidance provided by the vaccination program, as well as the confidence on the part
of the media transmitting the message, can be essential. Just as the media can undermine confidence in the program, they can also be important partners in minimizing risks during a crisis situation.

The means used to convey the message will depend on the individual country, and on the subnational level at issue. Thus, it is necessary to identify the most widely used media in the country, and learn how to use that platform to convey the message.

At the beginning of a crisis or high-impact situation, only limited information may be known, but early reporting is important in order to avoid the spread of rumors. The nature of the information being provided should be clearly expressed, as well as when more details will be available. In general, the opinions of experts tend to have more credibility than those of an official institution.

When selecting the type of media to use, consideration should be given to the particular characteristics of each, its attributes, and its costs.

There are various tools and communication channels; to review them in depth, consult the technical guidance manual cited above (65).

### FIGURE 10. Determinants of public confidence in crisis communication

<table>
<thead>
<tr>
<th>Determinant</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td><strong>Capacity</strong></td>
<td>Demonstrate that enough is known to manage the crisis.</td>
</tr>
<tr>
<td><strong>Objectivity</strong></td>
<td>Information and actions for managing the crisis should not be affected by any conflict of interest.</td>
</tr>
<tr>
<td><strong>Transparency</strong></td>
<td>It is essential that communication be transparent, honest, and open. Facts should not be concealed.</td>
</tr>
<tr>
<td><strong>Inclusivity</strong></td>
<td>Consider all relevant options.</td>
</tr>
<tr>
<td><strong>Consistency</strong></td>
<td>All communication strategies should be coordinated and consistent, giving special attention to differences in contexts and cultures.</td>
</tr>
<tr>
<td><strong>Empathy</strong></td>
<td>Dialogue should be two-way, with consideration for concerns about the safety of vaccines and vaccination, and emphasizing individual and societal wellbeing.</td>
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</table>

It is important to work on the proposed graphics; charts should be presented representing the risk-benefit balance of vaccines, clearly indicating the risks of acquiring the wild disease. Infographics can be highly useful.

Participating in media debates about the safety of vaccination can create a false sense that the arguments for and against are equally credible. It is preferable not to participate in such discussions, since this can confuse the public.

Monitoring and evaluation during implementation
Monitoring consists of measuring the activities that take place during the course of the communication strategy, while evaluation is a structured process that usually takes place at the end of the implementation phase, gauging the effectiveness of the strategy, the actual costs, and lessons applicable to future events.

Monitoring should include not only indicators of implementation progress, in terms of time and costs, but should also include monitoring developments in public and media opinions about vaccination, as well as detecting unfounded rumors or messages that require a response.

In formulating the evaluation, what is most important is to clearly define the evaluation criteria, and ensure that they are realistic, credible, and specific.

Managing a media-crisis situation
A crisis situation is one in which there is a real or potential loss of trust in a vaccine or a vaccination program, initiated by ESAVI-related information (66).

As mentioned above, crises should be anticipated, and an initial plan should be developed at an early stage to provide an immediate response. In general, the same activities described for risk communication should be followed here. Specific recommendations for crisis management include the following:

1. Prepare for the worst-case scenario and develop response strategies:
   - Identify preventive actions to mitigate the effect of an event by monitoring the media and using the strategic alliances that have been formed.
   - Initiate mitigation actions; in other words, act early to prevent the situation from escalating.

2. The first actions to initiate are as follows:
   - Keep key messages and statements clear (consistent with the cultural context), for example:
     a) “We have allocated all necessary resources to investigate this unfortunate event, and are doing everything we can to determine the causes as soon as possible.”
     b) “We have implemented a crisis response plan.”
   - Prepare a list of frequently asked questions, and corresponding answers.
   - Develop a list of non-program, non-government experts who can be trusted sources of information.
   - Prepare a list of media contacts and a record of calls and contacts made.
   - Prepare a list of all stakeholders who should be kept informed, including the appropriate channels of information for each.
• Ensure that governing bodies are aware of and support the defined plan.
• Define and assign roles and responsibilities, as well as collaborations.
• Establish channels of communication with the media, and determine the frequency of messages and the mechanisms for delivering them.
• Track news, social networks, and newspapers to identify the status of communication and public perceptions.

A case of communication crisis in Colombia
On 3 June 2014, Colombia’s National Institute of Health was notified of a potential outbreak of unknown cause. It was reported that 15 girls between the ages of 11 and 17 who were being treated at the municipal hospital in Carmen de Bolívar showed similar symptoms, such as tachycardia, dyspnea, and paresthesia in their hands and legs, after administration of the human papillomavirus vaccine. During field research, the number of cases gradually increased, reaching 517 reported cases with similar symptoms in the first six months following the initial report. News spread through social media, television, radio, and newspapers, and the number of cases increased as media attention grew. In investigating the event, comprehensive clinical evaluations of the patients were carried out, and experts in neurology, toxicology, and psychiatry were enlisted to take part. A case-control study was also conducted in the area to assess the possible association with multiple risk factors. National and international consultations were conducted on vaccine safety. In the end, no association between the vaccine and the symptoms was found.

Faced with the massive societal impact, government institutions developed a number of communication interventions, such as supporting local communication response by the Ministry of Health, creating a national response coordination group, building partnerships with scientific societies and with the media, and helping the media report on the situation in the municipality. In addition, there was direct involvement by the Minister of Health and public sector leaders in the area, who addressed the needs and complaints of the community. An ongoing support team in the municipality, coordinated by the Ministry of Health, monitored the situation at the local level and supported the coordinated implementation of central-level strategies proposed by the local authorities.

In addition to communication activities, social welfare strategies directed at the general public, and mental health strategies directed at vulnerable populations were deployed.

News of the event, which spread nationally and internationally, had major effects on vaccination coverage, which declined in the country and in some other Latin American countries.

The WHO Regional Office for Europe has developed a checklist, which is included in Annex C, to assess whether or not a health system is prepared.

11.2.3 Evaluation phase
In this phase, the communication response to the vaccine-related crisis should be evaluated in order to identify lessons learned, assess whether the original goals and objectives were met, and analyze what actions could be put in place to achieve better outcomes in the future.
However, it will not always be easy to assess whether the goal of maintaining or strengthening confidence in vaccination was achieved.

Particular attention should be given to the following:

1. Coordination with the crisis response group and other key actors.
2. Factors related to transparency and communication with the public.
4. Choice and effectiveness of the communication channels used.

Although the vaccine-related crisis may have been effectively managed and concluded, preparation for a potential future crisis should be initiated. This means that all relevant stakeholders must know their roles and continue monitoring public perceptions of vaccines.

**Evaluation**

In this phase, teams should assess the success and effectiveness of the crisis management, in particular whether there has been success in maintaining or regaining public trust. Following are questions that can help guide this phase (Table 13).

**Sharing lessons learned**

Prepare a report with key findings, lessons learned, best practices, and positive and negative elements registered during the crisis management, and share these with the response group and other important key actors.

**Reviewing and strengthening the crisis communication plan**

Ensure that the lessons learned and best practices identified in the evaluation process are incorporated in a crisis communication remediation plan, in order to optimize the response to a future crisis.
TABLE 13. **Questions to guide the evaluation phase**

<table>
<thead>
<tr>
<th>GENERAL FEEDBACK AND EVALUATION</th>
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</thead>
<tbody>
<tr>
<td>1. How successful was the crisis management?</td>
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<tr>
<td>2. Was the overall response to the crisis effective?</td>
</tr>
<tr>
<td>3. Was it instituted in a way that was timely and rapid?</td>
</tr>
<tr>
<td>4. Was the overall communication objective met?</td>
</tr>
<tr>
<td>5. What weaknesses were identified?</td>
</tr>
<tr>
<td>6. In the event of a new vaccine-related crisis, what could be improved, and how?</td>
</tr>
<tr>
<td>7. Was appropriate consideration given to vulnerable populations, and to those with different capacities or disabilities?</td>
</tr>
<tr>
<td>8. Was there a budget for managing the vaccine crisis, including, if necessary, additional human resources? If so, were the available resources sufficient?</td>
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<thead>
<tr>
<th>COMMUNICATIONS WORKING GROUP ON IMMUNIZATION AND MANAGEMENT OF STAKEHOLDERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Was the crisis response group, or other response mechanisms, established in time?</td>
</tr>
<tr>
<td>2. Were all of the key actors involved?</td>
</tr>
<tr>
<td>3. Were the key actors properly informed during all stages of the process?</td>
</tr>
<tr>
<td>4. Were the key actors receptive, and did they fulfill their responsibilities and roles?</td>
</tr>
<tr>
<td>5. Was there any conflict of interest among the key actors involved?</td>
</tr>
<tr>
<td>6. How could the team be better prepared in a future crisis? (e.g., planning specific training sessions).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PUBLIC RELATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Was the public informed in a timely and transparent manner?</td>
</tr>
<tr>
<td>2. Was appropriate consideration given to public concerns and fears?</td>
</tr>
<tr>
<td>3. Were public concerns and fears appropriately monitored during all phases of the process?</td>
</tr>
<tr>
<td>4. Was a two-way communication strategy implemented at every stage of the process?</td>
</tr>
<tr>
<td>5. Did all key actors respond appropriately to the needs of the media?</td>
</tr>
<tr>
<td>6. Was the team able to respond effectively to public concerns?</td>
</tr>
</tbody>
</table>

References


52. Hesse EM, Hibbs BF, Cano M V. Notes from the field: administration of expired injectable influenza vaccines reported to the vaccine adverse event reporting system, United States, July 2018-March 2019. MMWR [Internet]. 2019 [cited 6 October 2020];68(23):529–30. Available at: http://www.cdc.gov/mmwr/volumes/68/wr/mm6823a3.htm?s_cid=mm6823a3_w.


Bibliography

**Global Vaccine Safety Initiative (GVSI)**
Contains all relevant documents and tools for understanding the global approach to vaccine safety and practice at the national level. Available at: https://vaccine-safety-training.org/global-vaccine-safety-Initiative.html.

**WHO fact sheets on vaccine reaction rates**
Brief reports with the description of adverse events related to each vaccine and their estimated frequency. Useful document for those administering vaccines, and particularly for those responsible for public health-related analyses. Available at: https://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/.

**Vaccine Information Statements (VIS)**
These are instructions intended for the general public, containing a description of each vaccine and the risks related to its use. Centers for Disease Control and Prevention (CDC). Available at: https://www.cdc.gov/vaccines/hcp/vis/index.html.

**Contraindications for the most widely used vaccines**
CDC material listing contraindications for the most widely used vaccines. Available at: https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html.

**Guidelines for vaccinating pregnant women**
Section of the CDC guide, with important recommendations for vaccination of pregnant women; includes a table of evidence and recommendations on each vaccine. Available at: https://www.cdc.gov/vaccines/pregnancy/hcp-toolkit/guidelines.html.

**Verbal-autopsy protocol and tools for its application**
Manual and tools for developing a verbal autopsy and recording it are presented in detail. A second link to a tool adapted to ESAVI cases is included.

**PAHO yellow fever case studies**
Includes the complete and adapted report for training involving cases reported in the outbreak of viscerotropic disease occurring in Peru and reported in the document. Available at: https://iris.paho.org/bitstream/handle/10665.2/31366/9789275117538-eng.pdf.¹

**Vaccine Safety Net**
WHO initiative that references and certifies websites around the world that contain reliable vaccine-related information and vaccine safety information. Among the criteria for selecting websites is a presentation of the balance between the risk and the benefit of each vaccine. The “Members” section lists all websites evaluated. Available at: https://www.vaccinesafetynet.org/.

---

## Glossary

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Causal association</td>
<td>A cause-and-effect relationship between a causative (risk) factor and an outcome.</td>
</tr>
<tr>
<td>Cluster</td>
<td>Two or more cases of the same event or similar events related in time, place, and/or vaccine administered. ESAVI clusters are usually associated with a particular supplier/provider, health facility, and/or vial or a lot of vaccines.</td>
</tr>
<tr>
<td>Vaccine quality deviation-related event</td>
<td>An event in which the vaccine presents attributes different from those specified by the manufacturer, affecting its quality and possibly presenting a risk to patient safety.</td>
</tr>
<tr>
<td>Programmatic error</td>
<td>Any deviation in recommended standard procedures at any stage in the vaccine cycle, from distribution by the manufacturer to use, including waste disposal. Not all programmatic errors involve an ESAVI. In such cases, surveillance is not conducted.</td>
</tr>
<tr>
<td>Event supposedly attributable to vaccination or immunization (ESAVI)</td>
<td>Any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom, or disease.</td>
</tr>
<tr>
<td>Serious ESAVI</td>
<td>An ESAVI that results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.</td>
</tr>
<tr>
<td>Non-serious ESAVI</td>
<td>An ESAVI that is not “serious” and does not pose a potential risk to permanently affect the health of the recipient.</td>
</tr>
<tr>
<td>Causality assessment</td>
<td>A systematic review of data about ESAVI case(s) in order to determine the likelihood of a causal association between the event and the vaccine(s) received. This assessment must be conducted by a group of experts.</td>
</tr>
<tr>
<td>Coincidental event</td>
<td>An ESAVI that is caused by something other than the vaccine product, immunization error, or immunization stress, but which has a temporal relationship with vaccine administration.</td>
</tr>
<tr>
<td>Vaccination failure</td>
<td>Failure of a vaccine to stimulate the immune system to protect against a disease. It is measured on the basis of clinical endpoints or immunological criteria, where these exist. Primary failure (e.g., lack of seroconversion or seroprotection) needs to be distinguished from secondary failure (waning immunity), where seroconversion diminishes rapidly or is insufficient to protect against the target disease.</td>
</tr>
<tr>
<td>Vaccine pharmacovigilance</td>
<td>The science and activities relating to the detection, assessment, understanding, and communication of ESAVI and other vaccine- or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization.</td>
</tr>
<tr>
<td>Safe injection practices</td>
<td>Practices which ensure that the process of vaccine injection does not create risk for the vaccinated person, other persons, or the environment.</td>
</tr>
<tr>
<td><strong>Stress-related event occurring immediately before, during, or immediately after vaccination</strong></td>
<td>An ESAVI arising from anxiety about the vaccination process and the sociocultural factors surrounding it.</td>
</tr>
<tr>
<td><strong>Event related to a programmatic error</strong></td>
<td>ESAVI caused by inappropriate handling or use of a vaccine, or an incorrect prescription. A programmatic error that does not cause changes in health is not an ESAVI.</td>
</tr>
<tr>
<td><strong>Vaccine product-related reaction</strong></td>
<td>An ESAVI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product, whether the active component or one of the other components of the vaccine (e.g., adjuvant, preservative, or stabilizer).</td>
</tr>
<tr>
<td><strong>Event related to any deviation in vaccine quality</strong></td>
<td>An ESAVI caused by deviations from vaccine quality specifications, including in devices used for vaccine administration, manufacturing processes, storage, or the distribution chain.</td>
</tr>
<tr>
<td><strong>Vaccine safety</strong></td>
<td>The orienting of institutional and human behavior that seeks to minimize the risks generated by vaccines and vaccination, and work toward maintaining their effectiveness.</td>
</tr>
<tr>
<td><strong>Safety signal</strong></td>
<td>Information from one or multiple sources (including observation and experiments) which suggests a new and potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.</td>
</tr>
<tr>
<td><strong>Baseline incidence rate (background rate)</strong></td>
<td>Incidence rate of health conditions or diseases in the unvaccinated population that may have a temporal relationship with vaccination.</td>
</tr>
<tr>
<td><strong>Expected rate</strong></td>
<td>Known incidence rate of a health condition or disease with a confirmed relation to the vaccine. This incidence rate is usually measured in clinical trials.</td>
</tr>
<tr>
<td><strong>Excess rate</strong></td>
<td>Difference between the unanticipated incidence rate of a confirmed vaccine-related health condition or disease and the expected rate of that condition or disease.</td>
</tr>
<tr>
<td><strong>Observed rate</strong></td>
<td>Measured incidence rate of an ESAVI in a population. This consists of the baseline rate in the vaccinated population and the expected rate.</td>
</tr>
<tr>
<td><strong>Substandard-quality vaccine (out-of-specification)</strong></td>
<td>Authorized vaccine that does not meet quality standards, specifications, or both.</td>
</tr>
<tr>
<td><strong>Public health surveillance</strong></td>
<td>Systematic collection, consolidation, evaluation, and purposeful use of data on a health risk to the population.</td>
</tr>
</tbody>
</table>
Annex A. Special situations involving surveillance of events supposedly attributable to vaccination or immunization (ESAVI)

**Surveillance during vaccination campaigns**

Mass vaccination campaigns are opportunities for vaccine safety systems, since multiple doses of a single vaccine are usually given in a short period of time, allowing for a close-up review of vaccine safety behavior. In addition, they can provide an opportunity to assess the performance of ESAVI surveillance systems that have been implemented.¹

Additional risks introduced in vaccination campaigns, such as an increase in the number of programmatic errors, need to be considered. This is often due to an increase in staff with little experience in vaccination or poor training, who may be recruited to work in a campaign to meet its needs. The increase in the number of vaccines used in a short period of time, with a consequent increase in the risk of errors in handling and using the vaccines in new populations, or in populations largely unfamiliar with the experience (such as pregnant women, or elderly people with comorbidities), can also change the pattern of adverse events that occur.²

The dissemination of information on vaccination campaigns in the mass media can raise awareness in the public and among health professionals about the detection of adverse events, especially when injectable vaccines are used, and this can lead to an increase in reports of certain events.³ The likelihood of rumors also increases, since these situations can be seen as opportunities for groups that do not accept vaccines or that have doubts about their safety to politically attack the group promoting the campaign.

It is important that additional measures to monitor vaccine safety be included in the vaccination campaign implementation plan. The definition of ESAVI should be borne in mind, and a distinction should be made between case definitions and the clinical tables most often associated with the vaccine. Reporting mechanisms should also be optimized and, if possible, alternative means of reporting in addition to existing ones should be designed. In addition, the response capacity of surveillance institutions and offices overseeing surveillance should be strengthened, in order to effectively deal with large-scale risk events.

As an alternative means of reporting during a mass vaccination campaign, a community hotline for adverse event reporting could be installed, or a mobile app could be developed for the same purpose.

Following are some recommendations for ESAVI surveillance during vaccination campaigns:

1. Design a simple, flexible, and rapid surveillance intensification strategy.
2. Decide which ESAVI activities to focus on. It is recommended that priority be given to detecting programmatic errors and serious ESAVI.
3. Track all lots of vaccines distributed during the campaign.
4. During the training phase of the vaccination campaign, include activities dedicated to identifying, investigating, and reporting ESAVI.
5. Introduce additional reporting mechanisms such as telephone, fax, and digital applications.
6. Remember and teach that the objective of ESAVI investigation in the context of a campaign is to identify risks of a recurrence of the event, spread of a communicable disease, or the expansion of an event that attracts media attention and that is incorrectly reported by the media, thus jeopardizing the vaccination campaign.
7. Have a mechanism for rapidly transmitting large amounts of information to relevant stakeholders or leaders responsible for coordinating and overseeing the campaign, so that safety alerts can be issued when necessary (e.g., identifying a falsified lot of vaccines or the contamination of vaccine vials).
8. Include strategies for actively detecting high-risk ESAVI in the protocol for monitoring coverage, or in activities involving vaccination campaign monitoring or audits.
9. Prior to the start of the campaign, personnel should be informed and trained about the most frequent ESAVI, their baseline or expected rates, and the incidence or historical rate of the clinical condition in the area where the campaign is to be conducted.
10. Remember to develop a crisis plan that anticipates possible situations that may occur during the vaccination campaign.
11. It is important to streamline the analysis of data that emerges in the course of a campaign. Early detection of geographic or temporal clusters can prevent a public health emergency.
12. In periodic reports, include progress in the campaign, vaccine safety reports that include the measurement of ESAVI indicators, and feedback on campaign procedures, where necessary.
13. Consider creating a committee, which could meet as needed, to review ESAVI and analyze the causality of reported facts; this could, for example, include specialists in neurology, pediatrics, immunology, and pathology. Its members should be official representatives of the most important professional associations.⁴

Response to clusters of cases of vaccine-related stress response or mass psychogenic illness

The vaccination-related stress response, formerly called the anxiety response related to vaccination, is "a response to stress that some individuals may experience when faced with being injected. It includes a spectrum of manifestations ranging from an acute stress response (e.g., vasovagal syncope or presyncope and hyperventilation) or dissociative neurological symptoms that may include non-epileptic seizures or pseudoseizures."\(^5\)

This type of ESAVI has garnered particular attention in several countries in the Region because of the level of attention ESAVI have attracted in the general community and in the media,\(^6\) and because of the negative effect they can have on national vaccination programs when occurring in regional clusters.

Since 2017, the Global Advisory Committee on Vaccine Safety (GACVS) has drawn the interest of the World Health Organization in working on guidelines to standardize an evidence-based approach to these events, enabling national authorities to respond in an organized manner, without affecting vaccine use, or affecting it only minimally. Following are some specific recommendations for caring for cases of ESAVI.

Important aspects in caring for individual cases

The first recommendation is to characterize and correctly classify the event. A stress-related response may occur immediately before, during, or, in most cases, a few minutes after vaccination. There are three syndromes that can be confused and must be differentiated, since one of them could endanger the life of the person affected. The three syndromes are anaphylaxis, syncope, and anxiety. The only one that can be life-threatening is anaphylaxis, because of its effect on cardiorespiratory physiology. Moreover, its treatment is not without risks, so it is essential to correctly identify the observed response. In general, stress response is a diagnosis based on exclusion, and every effort should be made to be certain as to the cause of the symptoms and signs of the vaccinated person.

Anamnesis and physical examination are essential in order to correctly classify the event (Table A1).

---

### TABLE A1. Clinical presentation and management of anaphylaxis, syncope, and stress associated with vaccination

<table>
<thead>
<tr>
<th>CLINICAL CHARACTERISTICS</th>
<th>ANAPHYLAXIS</th>
<th>SYNCOPE</th>
<th>STRESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Early, 5 to 30 minutes after vaccination</td>
<td>Before, during, or shortly after vaccination</td>
<td>Before, during, or shortly after vaccination</td>
</tr>
<tr>
<td>Clinical presentation and behavior</td>
<td>Restlessness, unease, agitation</td>
<td>Fear, dizziness, lightheadedness, weakness, numbness</td>
<td>Fear, dizziness, lightheadedness, weakness, numbness, hyperventilation, and tingling</td>
</tr>
<tr>
<td>Occurs in clusters</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Clinical management</td>
<td>Adrenaline</td>
<td>Rotate the body to one side</td>
<td>Place the patient in a sitting or lying position</td>
</tr>
<tr>
<td></td>
<td>Evaluate the ABCs of cardiopulmonary resuscitation</td>
<td>Perform airway-opening maneuver</td>
<td>If the patient is hyperventilating, indicate the necessary measures and control breathing</td>
</tr>
<tr>
<td></td>
<td>Intravenous fluids</td>
<td>Monitor breathing and pulse</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antihistamines</td>
<td>Assess the presence of injuries</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Corticosteroids</td>
<td>Treat the underlying cause</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hospitalization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SYSTEMIC SYMPTOMS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermal</td>
<td>Welts, swelling of the eyes and face, widespread exanthem</td>
<td>Paleness, sweating, cold, sticky skin</td>
<td>Paleness, sweating, cold, sticky skin</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Loud breathing with airway constriction (stridor and wheezing)</td>
<td>Normal or deep breathing</td>
<td>Fast, shallow breathing</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Increased heart rate, drop in blood pressure, dysrhythmia, cardiac arrest</td>
<td>Decreased heart rate, transient drop in blood pressure</td>
<td>Increased heart rate, normal or high arterial blood pressure</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea, vomiting, abdominal cramps</td>
<td>Nausea and vomiting</td>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td>Neurological</td>
<td>Loss of consciousness, lack of response in supine position</td>
<td>Transient loss of consciousness, good response in supine position, tonic-clonic seizure</td>
<td>Pseudoseizure, tremor, weakness, tingling in the face and limbs</td>
</tr>
</tbody>
</table>

In treating anaphylaxis, national guidelines should be followed; if these are not available, some international emergency management guidelines are recommended. In the case of syncope, anamnesis should be expanded to define the underlying causes, and the relevant specialists should be consulted. Stress reaction includes a spectrum of disorders that must be diagnosed and evaluated by a mental health specialist.

**Dealing with clusters of cases**

A cluster is defined as “two or more cases of the same or similar events related in time, geography (place), and/or vaccine administered.” It should always be borne in mind that the emotional response to a stressful event or situation can spread rapidly.

Case clusters occur most often in closed communities or institutions (e.g., schools, care facilities for people in conditions of vulnerability, military barracks, etc.), in situations with elements that attract media attention, such as the use of a new vaccine, or a vaccine that is new to the country’s or territory’s immunization program, a change in the application of a vaccine already in the program, or interventions that are eye-catching or considered invasive to those affected.

The response is most common in certain age groups, such as adolescents and young adults, and is not present in children. There could also be a connection to wide coverage, in the media or on social media, of first cases or an exaggerated response by others, such as adults or emergency personnel.

When large numbers of people are affected by an exaggerated response, it is called “mass hysteria” or “mass psychogenic illness.” It is always necessary, even in cases where the etiology is psychogenic, to rule out any organic pathological phenomenon that could explain the event. It should be recognized that, mixed in with cases of conversion disorder, there could always be cases involving real syndromes that merit urgent medical attention.

It is important to give proper attention to such events, because they can have serious consequences for program continuity, as has been demonstrated in some reports of these events.

Following are some recommendations for handling these events:

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9. However, patients may find the term demeaning, which may exacerbate the problem.” See: https://www.who.int/publications/i/item/978-92-4-151594-8.
1. People with risk factors for developing a stress-related response to vaccination should be vaccinated at different times, and in private settings.
2. When the event has occurred in several subjects, they should be cared for in places with a separation between them and unaffected individuals.
3. The risk of this situation occurring in the context of mass vaccination campaigns should be evaluated, and the necessary measures taken when planning details of the operation.
4. Consideration should be given to ventilation of the vaccination area, temperature, long lines, lack of privacy, and potential overcrowding, all of which are conditions that facilitate possible vasovagal reactions.
5. Use partnerships with community leaders and opinion leaders to send targeted calming messages to the non-affected population.
6. Have communication and information kits with evidence-based messages about vaccine safety.
7. Following vaccination, the person should be advised to remain in the vaccination area for 30 minutes; this area should be well lit and ventilated, with strategic external distractions.
8. In risk situations, health personnel should be trained, prior to vaccination, to respond to such events. Information should be available on differentiating and caring for anaphylactic responses, syncope, and vaccination-related stress.
9. Once an event has occurred, deploy the campaign's crisis plan for dealing with such events.

It is essential that health professionals have a cordial, friendly, and empathetic attitude in responding to individual patients. Appropriate care should be given, adapted to the cause of the symptoms of the vaccinated person, avoiding an exaggerated response in cases where invasive interventions are not required.
Annex B. Tools for causality assessment of events supposedly attributable to vaccination or immunization

**Step 1. Eligibility and formulation of the causality question**

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>UK</th>
<th>NA</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full name of the vaccinated person</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Name of one or more of vaccines administered</td>
<td></td>
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</tr>
<tr>
<td>What is the valid diagnosis?</td>
<td></td>
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</tr>
<tr>
<td>Does the diagnosis meet a case definition?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Causality question:

Did the ____________ vaccine (or the vaccination with ____________) cause ___________?

Does this case meet the requirements for causality assessment? If the answer is “Yes,” proceed to step 2.

**Step 2. Event checklist**

Check any boxes that apply

<table>
<thead>
<tr>
<th>I. Is there strong evidence of other causes?</th>
<th>Yes</th>
<th>No</th>
<th>UK</th>
<th>NA</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. In the case of this person, did the medical history, clinical examination, or laboratory tests confirm another cause?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>II. Is there a known causal association with the vaccine or the vaccination?</th>
<th>Yes</th>
<th>No</th>
<th>UK</th>
<th>NA</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine components</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Is there evidence in the literature (published and peer-reviewed) that this vaccine or vaccines can cause the reported event even if administered correctly?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Is it biologically plausible that the vaccine may have caused the event?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. For this person, was there any specific evidence demonstrating that the vaccine or its ingredients had a causal role?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccine quality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Is there a deviation in the quality of the vaccine given to this person? Is it of poor quality or falsified?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Programmatic error</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. In the case of this person, was there an error when prescribing or making recommendations on the use of the vaccine (e.g., use beyond the expiration date, verifying the correct recipient, etc.)?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
6. In the case of this person, was the vaccine (or any of its ingredients) administered in a non-sterile manner?  

7. In the case of this person, was the macroscopic appearance of the vaccine (e.g., color, turbidity, or presence of foreign substances, etc.) abnormal at the time of administration?  

8. When this person was vaccinated, was an error committed when the person administering the vaccine constituted or prepared the vaccine (e.g., incorrect use of the product or incorrect diluent, improper mixture or inappropriate filling of the syringe, etc.)?  

9. In the case of this person, was there an error in the handling of the vaccine (e.g., interruption of the cold chain during transport, storage or administration of the vaccine, etc.)?  

10. In the case of this person, was the vaccine administered incorrectly (e.g., incorrect dose, incorrect injection site or route of administration, incorrect needle size, etc.)?  

Vaccination-related stress (response caused by vaccination-related stress)  

11. In the case of this person, could the event have been a response triggered by vaccination-related stress (e.g., acute stress response, vasovagal disorder, hyperventilation, or anxiety)?  

If the answer is "Yes" to any of the questions in Section II, did the event happen within the expected period of greatest risk?  

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>NK</th>
<th>NA</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. In the case of this person, did the event occur within a reasonable amount of time after administration of the vaccine?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

III. Is there strong evidence against a causal association?  

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>NK</th>
<th>NA</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is there a published, robust body of evidence (systematic reviews, reviews by GAVCS, etc.) that argues against there being a causal association between the vaccine and ESAVI?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IV. Other qualifying factors for classification  

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>NK</th>
<th>NA</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. In the case of this person, has such an event occurred in the past after receiving a previous dose of a similar vaccine?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. In the case of this person, has such an event occurred in the past after receiving a previous dose of a similar vaccine?</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>3. In the case of this person, could the event have occurred independent of being vaccinated (baseline rate)?</td>
<td></td>
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</tr>
<tr>
<td>4. Did this person have any illness, pre-existing condition, or risk factor that may have contributed to the ESAVI?</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>5. Was the vaccinated person taking any medications prior to the vaccination?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Was the vaccinated person exposed to any potential risk factors (other than the vaccine) prior to the event (e.g., allergens, drugs, herbal products, etc.)?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NK: Not known; NA: Not applicable; GAVCS: Global Advisory Committee on Vaccine Safety; ESAVI: Events supposedly attributable to vaccination or immunization.
According to the analysis conducted, the trend of evidence is as follows:

**Step 3. Algorithm**

Review all steps, follow the required route (red arrow), and check all possible answers with a 🗩.

I C. Inconsistent causal association with the vaccine/vaccination

II. Is there a causal association with the vaccine/vaccination?

III C. Inconsistent causal association with the vaccine/vaccination

IV. Review other classification factors

II. (Time) Did the event occur in the period of greatest risk?

II A. Causal association consistent with the vaccine/vaccination

III. Is there strong evidence against there being a causal association?

IV A. Causal association consistent with the vaccination

IV B. Indeterminate

IV C. Inconsistent causal association with the vaccine/vaccination

IV D. Non-classifiable

IV. Review other classification factors

I. Is there strong evidence of other causes?

Yes

No
### Step 4. Event classification

#### Sufficient information available

**A. Causal association consistent with the vaccine**

- **A1.** Vaccine product-related event (as published in the literature)
- **A2.** Event related to a deviation in the quality of the biological product or vaccine

**A. Causal association consistent with the vaccination process**

- **A3.** Event related to a programmatic error
- **A4.** Stress-related event that occurred immediately before, during, or immediately after vaccination

#### B. Undetermined

- **B1.** Related in time, but without sufficient and definitive evidence of a causal relation with the vaccine (could be an event recently associated with the vaccine [signal])
- **B2.** Qualifying factors result in conflicting trends of consistency and inconsistency with causal association to immunization

#### C. No causal association consistent with the vaccine or vaccination process

- **C. Coincidental cause**
  
  An underlying or emergent illness or a disorder caused by exposure to something other than the vaccine or the vaccination process

#### Sufficient information NOT available

**Non-classifiable**

Specify the additional information required to classify the case.

In situations in which false events are identified, and a causality analysis has been initiated, these are to be classified in this category.
Annex C. Checklist to assess communication preparedness during a crisis

Table C1 shows the checklist for evaluating communication preparedness during a crisis.

**Table C1. Checklist to assess communication during a crisis**

<table>
<thead>
<tr>
<th>PLANNING FOR COMMUNICATION DURING A CRISIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>A crisis communication plan has been developed</td>
</tr>
<tr>
<td>The crisis communication plan has been shared with all relevant actors, including decision-makers, partners, and influencers</td>
</tr>
<tr>
<td>The plan has been adopted at the top management or administrative level</td>
</tr>
<tr>
<td>The communication plan is flexible, so it can be applied to different types of crises</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COORDINATION AND COLLABORATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>A communications group or similar collaborative mechanism has been established</td>
</tr>
<tr>
<td>In a crisis, there is clear coordination between actors representing different ministries and public institutions, and different areas of technical expertise</td>
</tr>
<tr>
<td>The plan defines mechanisms for rapid approval during a crisis (e.g., for press releases)</td>
</tr>
<tr>
<td>The plan is reviewed once a year</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CRISIS RESPONSE MECHANISMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>In case of a crisis, it is clear who is responsible for having information on the website and ensuring that press releases have been prepared</td>
</tr>
<tr>
<td>There are clear guidelines on the rapid dissemination of information at regional and local levels</td>
</tr>
<tr>
<td>The spokespersons have received training</td>
</tr>
<tr>
<td>Messages and statements have been drawn up</td>
</tr>
<tr>
<td>A list of frequently asked questions about immunization has been prepared</td>
</tr>
<tr>
<td>The rates of events to be expected without administration of the vaccines have been calculated</td>
</tr>
<tr>
<td>THE MEDIA</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>There are ongoing activities aimed at strengthening relations with editors and journalists</td>
</tr>
<tr>
<td>Journalists and editors are trained to expand their knowledge of vaccination</td>
</tr>
<tr>
<td>Mechanisms have been established to ensure that media questions are answered during a crisis</td>
</tr>
<tr>
<td>A list of media contacts is available and is continually updated</td>
</tr>
<tr>
<td>There is a list of external (independent) experts – including spokespersons and relevant experts – who will be effective sources of information for communicating with the media</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DECISION-MAKERS, PARTNERS, AND INFLUENCERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>There are ongoing activities to build relationships with people who have influence on opinions regarding vaccination</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PUBLIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>There are systematic communication activities to ensure public awareness of the risks and benefits of immunization and disease</td>
</tr>
<tr>
<td>Research has been conducted to understand the factors leading to acceptance of and demand for vaccination</td>
</tr>
<tr>
<td>Public opinion on vaccines is monitored in such a way that new problems can be detected and answers provided</td>
</tr>
<tr>
<td>Frontline health workers have received training on vaccine safety and on communication with parents and vaccinated people</td>
</tr>
</tbody>
</table>

One of the essential components of the safe vaccination system is the surveillance of events supposedly attributable to vaccination or immunization (ESAVI). This surveillance is aimed at early detection of any adverse events that may occur following immunization, in order to monitor and classify risks related to a vaccine, the manufacturing process, transportation, storage, administration, and any pre-existing condition in the vaccinated person, and to rule out an association between the event and the vaccine.

This manual has been adapted for the Region of the Americas from the *Global Manual on Surveillance of Adverse Events Following Immunization*, published by the World Health Organization in 2014. It provides a comprehensive technical review of all processes and procedures for applying and implementing high-quality ESAVI surveillance systems. It brings together the expertise of vaccine safety specialists from the Region and from around the world, experts from national immunization programs, national regulatory authorities, and other institutions that have developed relevant knowledge about the surveillance of these events.

It is hoped that this document will serve as a guide to provide national immunization program managers, pharmacovigilance officers of national regulatory authorities, and other institutions responsible for monitoring vaccine safety with tools to facilitate their task, enabling them to apply international standards to issues such as event detection, event investigation, causality assessment, management of ESAVI data, and risk communication.