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World Health Organization

Comprehensive Family Immunization

*Family and Community Health Area*



# **Surveillance of Events Supposedly Attributable to Vaccination or Immunization (ESAVI) Linked to the Pandemic (H1N1) 2009 Vaccine and Crisis Prevention**

## **Field Guide**

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## Acronyms

ACIP	Advisory Committee on Immunization Practices (United States)
CDC	Centers for Disease Control and Prevention (United States)
CSF	cerebrospinal fluid
DNA	deoxyribonucleic acid
EAACI	European Academy of Allergy and Clinical Immunology
ESAVI	Event Supposedly Attributable to Vaccination or Immunization
FDA	Food and Drug Administration (United States)
GACVS	Global Advisory Committee on Vaccine Safety (WHO)
GBS	Guillain-Barré syndrome
ICD	International Classification of Diseases
NIP	national immunization program
NRA	national regulatory authority
ORS	oculo-respiratory syndrome
PAHO	Pan American Health Organization
SAGE	Strategic Advisory Group of Experts (WHO)
TAG	Technical Advisory Group on Vaccine-preventable Diseases (PAHO)
WHO	World Health Organization





# 1. Introduction

The prevention of infectious disease through immunization is one of the greatest achievements of public health. In spite of this undeniable success story, immunization is not immune from controversy surrounding the occurrence of a severe or fatal clinical event or series of events that, because they are temporally associated with vaccination, cause the public to lose confidence in vaccines and health services. Moreover, as immunopreventable diseases become less visible due to the decrease or disappearance in cases, as a result of effective immunization programs, adverse reactions to vaccines become more evident and the positive risk/benefit ratio that this implies is questioned.

The mitigation phase of the pandemic from pandemic influenza (H1N1) 2009 involved the implementation of prevention and control measures, including vaccination. New technologies and new potentiators (adjuvants) of immunological response have been used for production of the pandemic vaccine to increase its availability, which was quite limited in the initial production phase.

Pandemic vaccination is targeted to the at-risk population (the chronically ill, pregnant women, etc.) and the occurrence of a serious or severe event temporally associated with vaccination or rumors could ignite an unforeseen public health crisis that, if not handled properly, could cause the achievements made from immunization to be lost or questioned.

This *Field Guide for the Surveillance of Events Supposedly Attributable to Vaccination or Immunization (ESAVIs) Linked to the Pandemic Influenza (H1N1) 2009 Vaccine and Crisis Prevention* provides health workers with key technical information necessary for reporting, complete epidemiological investigation, and final case classification, as well as for honest communication with the public through the mass media.

Most of the information contained in this guide comes from technical articles and manuals on vaccination safety previously produced by the Pan American Health Organization (PAHO). Reports from Technical Committees on Immunization and other publications and documents were also consulted, which are listed in the references.



## 2. Epidemiology of Pandemic Influenza (H1N1) 2009

In April 2009, a novel influenza A(H1N1) virus was identified as the cause of respiratory disease in Mexico and North America, which spread rapidly to other countries and resulted in a new influenza pandemic. On 11 June 2009, the World Health Organization (WHO) reported cases in 74 countries and territories in two of its Regions. This global spread led WHO to increase the pandemic risk level and, finally, to announce on that date that a pandemic was underway.

The pandemic influenza (H1N1) 2009 virus differs in its pathogenicity from seasonal influenza in two key aspects. First, the majority of the human population has little or no immunity to the new virus. Second, the virus can infect the lower respiratory tract and cause rapidly progressive pneumonia, especially in children, young people, and adults.<sup>1</sup>

Symptoms of this new infection are similar to seasonal influenza, requiring a specific diagnostic test to differentiate the two.<sup>2</sup> The most commonly reported symptoms have included fever, cough, sore throat, malaise, muscle aches, and headache. Some patients have experienced gastrointestinal symptoms such as nausea, vomiting, and/or diarrhea.<sup>1</sup>

The most significant complications that have been identified are pneumonia caused directly by the virus and bacterial coinfection caused by pneumococcus and staphylococcus, which contribute to the severity and rapid progression of pneumonia from the disease.

**Figure 1. Overview of the Emergency and Spread of the (H1N1) 2009 Pandemic**



Source: Comprehensive Family Immunization Project and Communicable Diseases Project, PAHO.

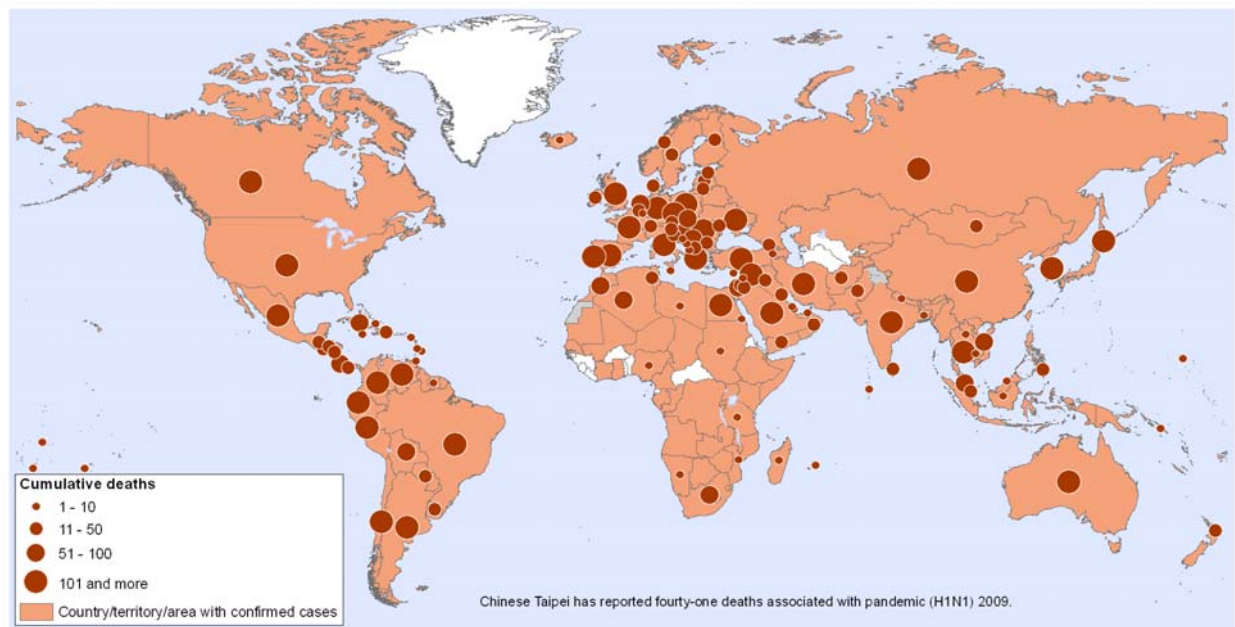
## Current situation

As of 14 March 2010, more than 213 countries and territories worldwide have reported laboratory-confirmed cases of pandemic influenza (H1N1) 2009, including at least 16,813 deaths.<sup>3</sup> The most active areas of pandemic influenza transmission continue to be in Southeast Asia and West Africa.<sup>3</sup>

As of 15 March 2010, the Americas have reported 7,622 deaths among the confirmed cases in 28 countries of the Region.<sup>4</sup> In Central America and the Caribbean, there is active transmission of pandemic influenza (H1N1) 2009, according to available data.<sup>4</sup> There is a mix of trends in acute respiratory disease reported in Central America and the Caribbean: Bahamas, Jamaica, Nicaragua, and Panama reported increasing trends, while Costa Rica and Guatemala reported decreasing trends. Honduras continues to report several outbreaks of respiratory disease in schools in Tegucigalpa and San Pedro Sula. Brazil has reported regional influenza activity, with an increasing trend for acute respiratory disease.<sup>4</sup>

For the past few months, circulation of the pandemic (H1N1) 2009 virus has predominated among type A influenzas isolated in the Americas.<sup>4</sup> Virological surveillance activities are continuing to detect any genetic variation or recombination that could affect viral pathogenicity, and to identify the status of resistance to antivirals.

**Figure 2. Countries and Territories With Pandemic Influenza Laboratory-Confirmed Cases and Number of Deaths as Reported to WHO**



Source: World Health Organization. Map produced on 18 March 2010.

## Risk Groups

The current epidemiology of pandemic influenza (H1N1) 2009 indicates that children and young adults run the greatest risk of disease and death from this novel virus.<sup>1</sup> For example,

as of 12 March 2010, Canada had reported 8,221 hospitalizations, with a median of age of 29 years, while Costa Rica had reported 460 hospitalizations, with a median age of 42 years.<sup>3</sup>

Sixty-four percent of hospitalized cases in the United States and 46% of deaths in Mexico presented underlying conditions of pregnancy or health problems such as asthma, other pulmonary diseases, diabetes, morbid obesity (Body Mass Index >40), autoimmune diseases, immunodeficiency, neurological conditions, and cardiovascular disease.<sup>5,6</sup> However, one-third of patients with severe pandemic influenza admitted to the intensive care unit were previously healthy persons.<sup>1</sup>

A higher risk of severe complications from the pandemic virus has been reported in individuals who are obese (particularly those who are morbidly obese) and among minority and indigenous populations.<sup>1</sup> Furthermore, nearly 6% of confirmed deaths from the pandemic virus in the United States has been in pregnant women,<sup>7</sup> which indicates that pregnant women are another group vulnerable to pandemic infection.

On the basis of the available evidence, the groups at risk for complications or death from pandemic influenza were identified, which are very similar to those for seasonal influenza. These groups are:<sup>1</sup>

- Infants and young children, in particular <2 years;
- Pregnant women;
- Persons of any age with chronic pulmonary disease (e.g., asthma);
- Persons of any age with chronic cardiac disease (e.g., congestive cardiac failure);
- Persons with metabolic disorders (e.g., diabetes);
- Persons with chronic renal disease, chronic hepatitis, certain neurological conditions (neuromuscular, neurocognitive, and seizure disorders), hemoglobinopathies, or immunosuppression, including HIV infection;
- Children receiving chronic aspirin therapy; and
- Persons aged 65 years and older.

## **2.1 Pandemic Influenza (H1N1) 2009 Vaccines**

Given the magnitude and speed of the pandemic, the development of pandemic influenza vaccines was a high priority and a challenge for its production. The specific vaccine to combat the novel pandemic virus is one more tool and not the only one for mitigation of the pandemic. Availability of the vaccine basically depended on the following:

- Reduction of production time, including early preparation of seed viruses and reagents to test vaccine potency.
- Exploration and use of alternative methods of production such as fermentation technology, yield of viruses in tissue culture, and recombinant DNA technology, since current production of seasonal vaccine is based on growth of viruses in fertilized eggs and takes five to six months.

- Use of adjuvants that economize use of the antigen while also maintaining or increasing equivalent effectiveness at low doses of antigen.

Different types of pandemic influenza vaccines are now available worldwide, including inactivated vaccines with or without adjuvants and attenuated vaccines. The presentation of these vaccines ranges from single-dose vaccines in pre-filled syringes or vials to multi-dose vaccine vials ranging in size from 2 to 10 doses, with different quantities of antigen and adjuvant (see Annex 1).

Today there is also a trivalent vaccine, which includes pandemic strain A(H1N1) and seasonal strains A(H3N2) and B. This formulation is similar for the Northern and Southern Hemispheres. Its availability is still limited.

Countries and territories in the Region of the Americas have several mechanisms for acquiring the pandemic influenza (H1N1) 2009 vaccine (Figure 3):

1. Direct purchase of the vaccine through the PAHO Revolving Fund for vaccine procurement (23 countries).
2. Vaccine donations from WHO (10 countries) and Spain (7 countries).
3. Direct purchase from the suppliers (2 countries).
4. Mixed purchases: direct from the suppliers and also from the Revolving Fund (1 country).

It has been estimated that countries and territories in the Region will have access to approximately 140 million doses of pandemic influenza (H1N1) 2009 vaccine.

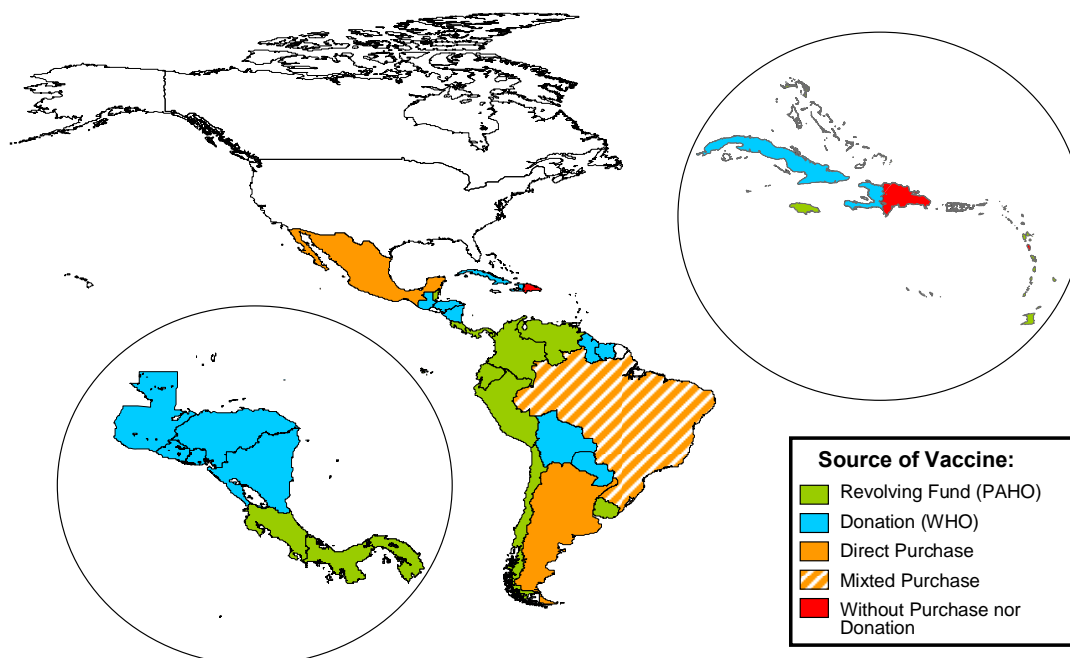
#### 1. Procurement of the vaccine through the Revolving Fund

- To date (March 2010), 23 countries have received 20,457,260 doses of pandemic influenza vaccine.
- Some countries have decreased the number of doses to be purchased, probably due to the cost of the vaccine.
- Dominica and the Dominican Republic have indicated their decision not to purchase the vaccine through the Revolving Fund. Nevertheless, they have been offered the possibility of receiving the vaccine through a donation from Spain.

#### 2. WHO vaccine donations

WHO has selected 10 countries in the Region to receive 6,974,000 vaccine doses. As of 17 March 2010, countries have received 1,234,000 doses. On 3 March, Nicaragua received the first shipment of vaccine donated by WHO, containing 110,000 vaccine doses. Cuba received 1,124,000 vaccine doses, while Honduras has received 140,000 doses of the 700,000 it requested. El Salvador is scheduled to receive the vaccine on 21 March, and Guatemala and Guyana on 25 March.

**Figure 3. Influenza (H1N1) Vaccine Access in Latin America and the Caribbean**



Source: Comprehensive Family Immunization, PAHO.

## 2.2 Groups to be Vaccinated for Pandemic Influenza (H1N1) 2009

The WHO Strategic Advisory Group of Experts (SAGE) on Immunization has emphasized that the target population groups to be vaccinated will be based on the objectives defined at the national level. The national decision to achieve one or more of these objectives will depend on the epidemiological situation, resources, and access to vaccines, as well as the capacity to conduct vaccination campaigns for the target groups and implement mitigation measures other than vaccination.

The PAHO Technical Advisory Group (TAG) on Vaccine-preventable Diseases supports the current recommendations of the WHO SAGE regarding the use of the pandemic influenza vaccine. However, it recognizes that these recommendations may be revised according to current information and availability of pandemic vaccine in the countries of the Region.

In this regard, TAG declared that the national objectives for pandemic influenza vaccination should be to reduce morbidity and mortality and maintain health services operational. Therefore, TAG recommended that the priority groups for vaccination should be health workers, pregnant women, and patients with chronic conditions aged >6 months (heart disease, diabetes, respiratory disease, immunodeficiency, morbid obesity). According to the epidemiological situation, the resources available, and the national immunization program (NIP) capacity, TAG recommends that countries and territories grant priority to the

following risk groups: children aged 6 months-4 years, healthy children aged 5-18 years, and healthy adults aged 19-49 years.<sup>8</sup>

**Table 1. Population to Vaccinate According to SAGE and TAG Recommendations.**

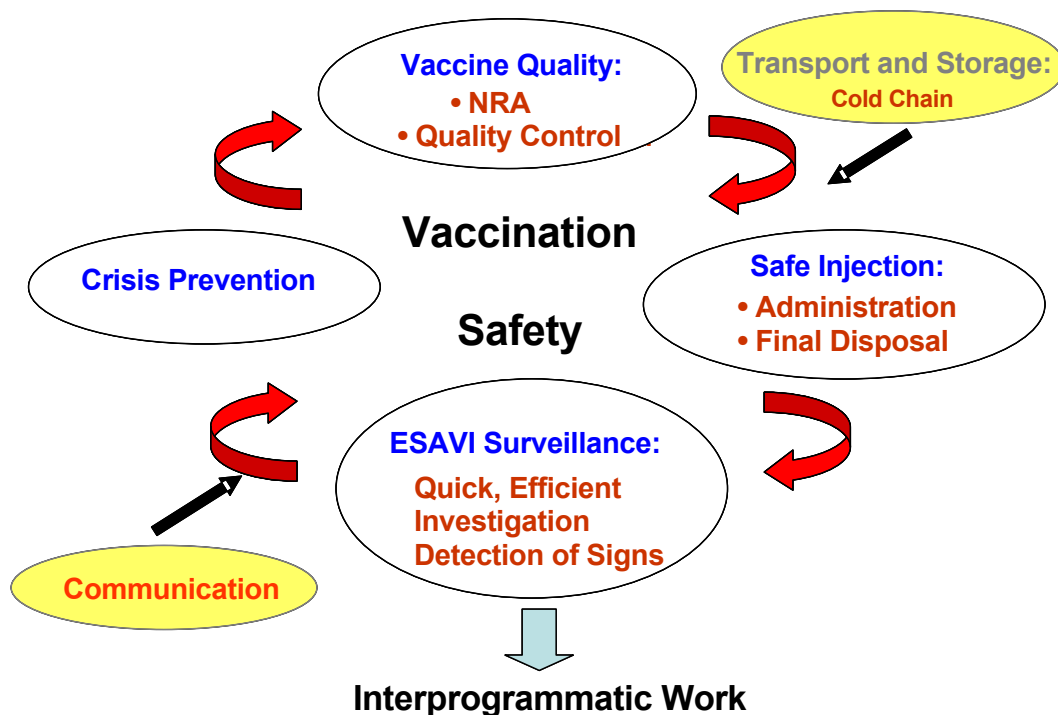
<b>SAGE (WHO) 7 July 2009<sup>9</sup></b>	<b>TAG (PAHO) 24 August 2009<sup>8</sup></b>
Health care workers	Health workers
Pregnant women	Pregnant women
Population >6 months with underlying chronic conditions	Population >6 months with underlying chronic conditions
Healthy young adults (>15 years and <49 years)	Healthy population as follows: <ul style="list-style-type: none"> <li>• 6 months to 4 years</li> <li>• &gt;5 years and &lt;18 years</li> <li>• between 19-49 years</li> </ul>
Healthy adults (>49 years and <65 years)	
Adults >65 years	



### 3. Vaccination Safety

Immunization programs have the responsibility to respond to public concerns about vaccines, providing their workers with the most up-to-date information on vaccination safety and safe injection practices. Vaccination safety is a priority component of immunization programs and encompasses guaranteeing the use of quality vaccines, transport and storage of vaccines at proper temperatures, safe injection practices, ESAVI surveillance, and strengthening the partnership with the mass media to provide the public with clear messages.

Figure 4. Vaccination Safety Components



#### Vaccine quality:

Vaccine quality, especially of this new pandemic influenza virus (H1N1) vaccine, is guaranteed and backed by WHO prequalification of laboratory suppliers, and the quality control conducted by the national regulatory authorities (NRAs) in each country for the registry and release of vaccine lots for their mass use.

#### Safe injection Practices:

Safe injection is based on three important, interrelated elements whose observance ensures an effective and efficient health benefit. These are as follows:

- Safety of the persons receiving the injection (persons vaccinated).
- Safety of the health worker (the vaccinator).
- Safety of the community and the environment (waste disposal).

Ensuring safe injection necessarily includes the following:

- Behavior change among patients and health workers to decrease injection overuse and implement safe injection practices.
- The availability of sufficient injection equipment and supplies for sharps and waste disposal.
- Appropriate, safe sharps waste disposal.

### **ESAVI surveillance:**

ESAVI surveillance is one of the processes included in the surveillance conducted by countries through their NIP or Epidemiology Office, which contributes significantly to post-marketing (phase 4) surveillance of the vaccine. This surveillance includes an operational definition that triggers case-finding and reporting; clinical, epidemiological, and laboratory investigation of the case; and concludes with the final classification of the event. Surveillance is addressed in detail in Chapter 5.

### **Crisis prevention:**

Low vaccine availability; a potentially greater public demand; and its mass administration over a short time to population groups with risk factors, such as co-morbidity with chronic diseases or pregnant women, or healthy persons such as health workers, can generate the report of an ESAVI. This foundation is sufficient to produce a crisis with serious consequences, from the loss of confidence in the vaccines and the credibility of the health services. Being prepared is a way to avoid or minimize these risks and their consequences. To this end, countries are recommended to ensure the following prior to commencement of vaccination:

- A crisis prevention and control plan by management level.
- A crisis committee by management level.
- A partnership with scientific institutions, the media, churches, and leaders of social organizations.
- An ESAVI surveillance system.

## **3.1 Safety of the Influenza (H1N1) 2009 Vaccine and Expected Events**

Although the pandemic (H1N1) 2009 vaccine is new and some of these vaccines were prepared in cell cultures or contain adjuvants that distinguish them from seasonal vaccine, expected adverse reactions could be similar to seasonal influenza vaccine.

The results of studies published to date indicate that the pandemic influenza (H1N1) 2009 vaccines are as safe as the seasonal influenza vaccines. However, clinical trials are not able to identify possible rare events that can become evident when the vaccine is administered to millions of people. In this regard, both PAHO and WHO recommend that all countries administering the pandemic vaccine intensify their surveillance of adverse events to prevent any incident that could harm the credibility of vaccination activities.

As of 11 March 2010, nearly 300 million doses of pandemic vaccine had been administered in the world.<sup>10</sup> Based on reports from countries that have already introduced the vaccine, the safety profile of the pandemic influenza (H1N1) 2009 vaccine seems to be the same as that of seasonal influenza vaccines of the same type.<sup>10</sup> That is, there have been no reports of unexpected events or ones that have questioned the safety of the vaccine. There have been two deaths reported (in Canada and the Netherlands), which were related to programmatic errors.\* In the Canadian case, anaphylaxis was not treated appropriately and on time, which triggered the death; in the Netherlands case, insulin was injected instead of the pandemic vaccine.<sup>10</sup>

Most reported adverse events have been mild. Vaccines containing an adjuvant cause local reactions at the vaccination site more frequently than vaccines without adjuvant. For available vaccines, to date, adverse events after vaccination have been reported with a frequency of 10-100 cases/100,000 doses of pandemic vaccine distributed. Serious events have been reported with a frequency of 0.5-2/100,000 doses distributed. Rates are very dependent on the reporting systems. Anaphylaxis has been reported with a rate of 0.1-1 case/100,000 doses of vaccine administered. An increase in fever incidence has been observed in young children after the second dose of adjuvanted vaccine.<sup>10</sup>

#### **Anticipated events from the introduction of pandemic vaccine**

- Local reactions: fever, pain at injection site, fatigue, malaise
- Nervous system disorders: headache, dizziness, paresthesia, somnolence, lethargy, migraine, seizures
- Musculoskeletal disorders: myalgia, arthralgia, pain in the limbs, muscle weakness
- Gastrointestinal system disorders: nausea, diarrhea, vomiting, abdominal pain
- Immune system disorders: anaphylaxis, hypersensitivity
- Rash, urticaria, and erythema

#### **Considerations on pandemic vaccine safety**

- The safety of this new vaccine has not been tested for some of the potential risk groups targeted for pandemic vaccination.
- However, to date and according to available information, the vaccine is safe and no event has occurred to question its safety.
- Information is available on the safety of inactivated non-adjuvanted vaccine; however, data are limited for other types of vaccine.
- Because of the urgency in making pandemic influenza (H1N1) 2009 vaccine available, the size of clinical trials can limit identification of rare or serious adverse effects.
- There is little experience with the use of adjuvants in influenza vaccines; therefore, surveillance of this vaccine when distributed on a large scale is particularly important.

\* Programmatic errors are those caused by people, in this case, the vaccinator. In general, they can be prevented through the training of personnel, supervision, and the availability of appropriate supplies for injection safety.

- International collaboration on surveillance of vaccine safety and risk communication is essential.
- Surveillance of events associated with pandemic vaccine, in all age groups and in the health services network, should be ensured. Furthermore, surveillance of programmatic errors should be ensured.

As of 17 March 2010, 13 countries of the Region had initiated pandemic vaccination in risk groups: Argentina, Bahamas, Barbados, Belize, Bermuda, Brazil, Costa Rica, Mexico, Montserrat, Panama, Peru, Suriname, and Trinidad and Tobago. Those countries have administered approximately 13 million doses.

Regarding ESAVIs, 227 events have been reported, of which eight have been classified as serious events: Bahamas (2), Mexico (6). To date, none of these events has been associated with the pandemic influenza vaccine.

The technical documents and updates on vaccination in the countries are on the Web page of the Comprehensive Family Immunization Project: [http://new.paho.org/hq/index.php?option=com\\_content&task=view&id=2461&Itemid=569&lang=es](http://new.paho.org/hq/index.php?option=com_content&task=view&id=2461&Itemid=569&lang=es).

## 4. Safety of Pandemic Vaccination in Pregnant Woman

Pregnant women are especially vulnerable to influenza infection, according to morbidity and mortality data from previous pandemics and influenza seasons. There is concern that influenza during pregnancy carries a significantly higher risk of morbidity, hospitalization, and even death, comparable to that in persons aged 65 years and over. The risk of maternal influenza to the fetus is the same throughout pregnancy. A possible association of fetal malformations with congenital influenza infection has not been proven.<sup>10</sup> Furthermore, an increased risk in severity has been observed, resulting in miscarriage and death, especially in the second and third trimesters of pregnancy and in the first two weeks postpartum.<sup>7</sup>

In pregnant women with pneumonia from pandemic influenza, an increase in the rates of miscarriage and premature delivery has been reported; the risk of complications is also high due to the physiological changes of pregnancy, including cardiovascular, respiratory, and immunological changes.<sup>11</sup>

In this regard, the Global Advisory Committee on Vaccine Safety (GACVS) recommended that the risk-benefit of influenza vaccination at all stages of pregnancy be considered, given the high risk to the mother (and thus to the fetus) of the disease itself, and (as far as is known) the small potential risk to mother and fetus of the inactivated influenza vaccines. Such advice would not apply in situations where the risk of influenza is low or to live attenuated vaccines, which in any event would not be indicated in pregnancy. Likewise, it would not apply to pregnant women with known contraindications to influenza vaccines.<sup>10</sup>

The Centers for Disease Control and Prevention (CDC) and the Advisory Committee on Immunization Practices (ACIP) of the United States recommend routine vaccination for every woman who is pregnant or could become pregnant during flu season.<sup>12</sup>

The absence of harmful effects from inactivated influenza vaccine on maternal health during pregnancy has also been shown in several studies, summarized in Tables 3 and 4.<sup>13</sup>

Furthermore, given that seasonal influenza vaccine is not recommended in infants aged <6 months, and that transmission of protective antibodies from the vaccinated pregnant woman is possible, it is considered that vaccination of the pregnant woman could also provide some protection to the newborn. In this regard, passive transfer of antibodies from the mother to the newborn has been shown, where it was 29% effective in preventing influenza in infants aged <6 months.<sup>14</sup>

Finally, it is recommended that inactivated vaccine be administered during any trimester of pregnancy. No study has demonstrated an increased risk of maternal or fetal complications associated with inactivated influenza vaccination. In addition, no scientific evidence exists that thimerosal-containing vaccines are a cause of adverse events among children born to women who received vaccination during pregnancy.<sup>13</sup>

Reporting or notification of an ESAVI in a vaccinated pregnant woman during any trimester of pregnancy should be handled as part of regular surveillance. Routine follow-up of vaccinated pregnant women and their newborns is not recommended.

**Table 2. Summary of Data on Safety Outcomes of Prospective Studies of Inactivated Influenza Vaccination During Pregnancy<sup>13</sup>**

Study	Design	Study Group	Control Group	Follow-up Period	Maternal Outcome	Infant Outcome
Zaman et al., 2008	Prospective, randomized, double-blind, controlled trial	172 pregnant women in third trimester	168 pregnant women who received 23-valent pneumococcal polysaccharide vaccine	Mothers: follow-up 7 days post-vaccination; infants follow-up at 24 weeks	No serious adverse events or differences in pregnancy outcome	No differences in gestational age, proportion of delivery by caesarean, birth weight, or APGAR* score.
Yeager et al., 2004	Prospective cohort	319 pregnant women immunized in second and third trimesters	No	Next prenatal visit	No preterm labor or other serious events	Not assessed
Englund et al., 1993	Randomized, controlled trial	13 pregnant women in third trimester	13 pregnant women who received tetanus toxoid vaccine	Not specified	No significant adverse reactions, including fever, moderate or severe pain, or need to visit a physician noted in either group	Similar gestational ages in both groups; no health concerns in infants examined between age 1-3 months
Deinard and Ogburn, 1981	Prospective cohort	189 pregnant women (13 prior to conception; 41, 58, and 77 in first, second, and third trimesters, respectively)	517 non-vaccinated pregnant women	48 hours after immunization; pregnancy outcome to age 8 weeks	No differences in maternal health, pregnancy outcome, or postpartum course	No significant differences in adverse pregnancy outcomes (congenital anomalies, neonatal mortality)
Murray et al., 1979	Prospective, matched cohort	59 vaccinated pregnant women (5, 22, and 32 in first, second, and third trimesters, respectively)	27 non-pregnant vaccinated women	Not specified	No significant side effects after immunization in any woman	Not assessed
Heinonen et al., 1973 and 1977	Prospective cohort	2,291 pregnant immunized women; 650 in first trimester	No	Up to age 7 years		No suggestive associations for congenital malformations, malignancies, or neurocognitive disabilities

\* APGAR: This is a scoring system used to provide a quick assessment of the newborn that is done at the first and fifth minutes following birth. The score at minute 1 determines how well the baby tolerated the birth process, while the score at minute 5 assesses how well the newborn is adapting to the new environment. This is a screening test to determine if a newborn needs medical care to stabilize its respiratory or cardiac functions.

**Table 3. Summary of Data on Safety Outcomes of Retrospective Studies of Inactivated Influenza Vaccination During Pregnancy<sup>13</sup>**

<b>Study</b>	<b>Design</b>	<b>Study Group</b>	<b>Control Group</b>	<b>Follow-up Period</b>	<b>Maternal Outcome</b>	<b>Infant Outcome</b>
France et al., 2006	Retrospective, matched cohort	3,160 infants born to vaccinated mothers	37,969 infants born to non-vaccinated mothers	End of influenza season	Not assessed	No differences with regard to birth weight, gestational age, or length of hospitalization following delivery
Muñoz et al., 2005	Retrospective, matched cohort	225 pregnant women in second and third trimesters	826 non-vaccinated, pregnant women	42 days after immunization at aged 6 months for newborns	No serious adverse events or differences in pregnancy outcomes	No differences in pregnancy outcome (caesarean delivery and premature delivery) and infant medical conditions
Black et al., 2004	Retrospective cohort	3,719 vaccinated pregnant women	45,866 women	Until delivery	No difference in caesarean delivery	No difference in caesarean section or preterm delivery
Sumaya and Gibbs, 1979	Retrospective, matched cohort	56 women in second and third trimesters	40 non-vaccinated, pregnant women	24 hours after immunization	No significant immediate reactions or differences in pregnancy course	No increased in fetal complications associated with the vaccine
Hulka, 1964	Retrospective and prospective cohort	225 vaccinated pregnant women (19 in first trimester)	44 non-pregnant women vaccinated against influenza; 104 pregnant and 25 non-pregnant women vaccinated with placebo	Up to 3 days after vaccination and at delivery	Local pain at injection site and some systemic symptoms greater in women vaccinated with influenza vaccine	No association with fetal anomalies or miscarriage



## **5. Surveillance of ESAVIs Linked to the Influenza (H1N1) 2009 Vaccine**

An adequate, efficient ESAVI surveillance system should guarantee rapid, timely reporting, as well as complete and exhaustive investigation of three components—clinical, epidemiological, and laboratory—to guarantee final case classification. Since this is a new vaccine, it is essential to have a sensitive surveillance system that enables safety monitoring of the new influenza (H1N1) vaccine and rapid and honest response to all the public's concerns about the vaccine.

### **5.1 Surveillance Objectives**

The objectives of surveillance of ESAVIs linked to the new influenza (H1N1) vaccine are as follows:

- Detecting signs of known or new A(H1N1) vaccine events as well as a greater than expected increase in frequency of events.
- Immediate reporting of severe, serious, and fatal events temporarily associated with vaccine administration.
- Timely, exhaustive, and complete investigation of notified events.
- Obtaining a clear, rapid, and transparent response to the event under investigation for parents, family, community, and the media in order to prevent a loss in confidence in the vaccines and in the credibility of health services.

### **5.2 Detection and Reporting**

ESAVI detection and reporting should be systematic; these are the basis of a surveillance system and rely on health workers. Every health worker should know not only the clinical symptoms, but also what actions to take for a patient with an ESAVI. The health worker has, consequently, three main responsibilities: detecting ESAVI cases, reporting them to the health authorities, and investigating them.

Reporting is a mechanism that helps to keep the monitoring system active and the health worker constantly attentive to case-finding. ESAVIs should be communicated within the first 24 hours of their appearance, from the local to the central level, following the procedures set out by the countries' ministries of health.

Those in charge of the surveillance program should visit the sites regularly and frequently to establish the notification system and supervise it. Training and ongoing supervision are important, since staff turnover may be frequent in many areas. Specific information should be provided on what should be notified and how.

### **5.3 What to Monitor**

Based on reports from countries that have introduced pandemic influenza (H1N1) 2009 vaccine, surveillance of adverse events should be able to identify any sign, such as an increase over the expected or historical frequency of events, clusters of events, severe or fatal events, and rumors.

As already mentioned, to date there has not been any unusual or severe event reported that questions the safety of the pandemic influenza (H1N1) 2009 vaccine, based on the clinical trials carried out and reports from countries that have been vaccinating. However, monitoring and surveillance of vaccination actions should continue, particularly in risk groups.

Special efforts, nevertheless, should be made for the surveillance of anaphylaxis and Guillain-Barré syndrome, potential adverse events that have been associated with vaccination for influenza (H1N1) 2009. Both medical conditions are detailed in this guide to adequately aid in case diagnosis and final classification. To this end, the criteria and levels of diagnostic certainty prepared for the Brighton Collaboration have been used.

#### **5.3.1 Anaphylaxis**

Anaphylaxis is an acute hypersensitivity reaction with multi-organ-system involvement that can present as a severe life-threatening reaction.<sup>15</sup> It may occur following exposure to allergens from a variety of sources: food, aeroallergens, insect venom, drugs, or vaccines.

Anaphylaxis attributed to immunization is a rare, but serious event. Estimates are in the range of 1-10 per 1 million doses, depending on the vaccine studied. Accurate estimates are hampered by limited data and lack of standard case definitions.<sup>15</sup>

Most publications on anaphylaxis attributed to immunization are cases reports or series that do not use case definitions. Few publications dealing with larger case numbers have used strict, but quite different case definitions.

The pandemic vaccine contains a limited amount of egg protein, which can induce an immediate hypersensitivity reaction in persons who are allergic to eggs. People who have experiencing symptoms such as urticaria or swelling of the lips or mouth or who have experienced acute respiratory difficulties after eating eggs, should consult with a physician to determine if in the future they should be given the influenza vaccine or any other vaccine prepared in fertilized eggs.

#### **Definition of event**

Anaphylaxis is defined as a clinical syndrome characterized by sudden onset and rapid progression of signs and symptoms and involving multiple ( $\geq 2$ ) organ systems, as symptoms progress.<sup>15</sup> The Brighton Collaboration case definition refers to the European Academy of Allergy and Clinical Immunology (EAACI's) and the American Academy of Pediatrics' use of the term.<sup>15</sup>

In this definition, severity is implied by the presence of cardiovascular and/or respiratory involvement in the presence of multi-system findings. Within the definition context, however, the three diagnostic levels must not be misunderstood as reflecting different grades of clinical severity. They instead reflect diagnostic certainty.

**Major and minor criteria used in the case definition of anaphylaxis**

For case definition, the presence of major and minor criteria should be established as detailed in the following tables.

**Table 4. Major criteria used in the case definition of anaphylaxis<sup>15</sup>**

Dermatologic or mucosal	<ul style="list-style-type: none"> <li>• Generalized urticaria (hives) or generalized erythema</li> <li>• Angioedema, localized or generalized</li> <li>• Generalized pruritus with skin rash</li> </ul>
Cardiovascular	<ul style="list-style-type: none"> <li>• Measured hypotension</li> <li>• Clinical diagnosis of uncompensated shock, indicated by the combination of at least 3 of the following: <ul style="list-style-type: none"> <li>○ Tachycardia</li> <li>○ Capillary refill time of &gt;3 seconds</li> <li>○ Reduced central pulse volume</li> <li>○ Decreased level of consciousness or loss of consciousness</li> </ul> </li> </ul>
Respiratory	<ul style="list-style-type: none"> <li>• Bilateral wheeze (bronchospasm)</li> <li>• Stridor</li> <li>• Upper airway swelling (lip, tongue, throat, uvula, or larynx)</li> <li>• Respiratory distress—2 or more of the following: <ul style="list-style-type: none"> <li>○ Tachypnea</li> <li>○ Chest wall retractions (chest indrawing): sternocleidomastoid, intercostals, etc.</li> <li>○ Respiratory arrest</li> <li>○ Cyanosis and grunting</li> </ul> </li> </ul>

**Table 5. Minor criteria used in the case definition of anaphylaxis<sup>15</sup>**

Dermatologic or mucosal	<ul style="list-style-type: none"> <li>• Generalized pruritus without skin rash</li> <li>• Generalized prickle sensation</li> <li>• Localized injection site urticaria</li> <li>• Red and irritated eyes (with pruritus)</li> </ul>
Cardiovascular	<ul style="list-style-type: none"> <li>• Reduced peripheral circulation as indicated by the combination of at least 2 of the following: <ul style="list-style-type: none"> <li>○ Tachycardia</li> <li>○ Capillary refill time of &gt;3 seconds without hypotension</li> <li>○ Decreased level of consciousness</li> </ul> </li> </ul>
Respiratory	<ul style="list-style-type: none"> <li>• Persistent dry cough</li> <li>• Hoarse voice</li> <li>• Difficult breathing without wheeze or stridor</li> <li>• Sensation of throat closure</li> <li>• Sneezing, rhinorrhea</li> </ul>
Gastrointestinal	<ul style="list-style-type: none"> <li>• Diarrhea</li> <li>• Abdominal pain</li> <li>• Nausea</li> <li>• Vomiting</li> </ul>
Laboratory	<ul style="list-style-type: none"> <li>• Mast cell tryptase elevation &gt; upper normal limit</li> </ul>

## Levels of diagnostic certainty

There are three levels of diagnostic certainty. Major and minor criteria must be met in determining each level of certainty, as follows:<sup>15</sup>

### Level 1

- $\geq 1$  major dermatological criterion and
- $\geq 1$  major cardiovascular criterion and/or  $\geq 1$  major respiratory criterion

### Level 2

- $\geq 1$  major cardiovascular criterion and  $\geq 1$  major respiratory criterion or
- $\geq 1$  major cardiovascular or respiratory criterion and
- $\geq 1$  minor criterion involving  $\geq 1$  different system (*other than* cardiovascular or respiratory systems) or
- ( $\geq 1$  major dermatologic criterion) and ( $\geq 1$  minor cardiovascular criterion and/or minor respiratory criterion)

### Level 3

- $\geq 1$  minor cardiovascular or respiratory criterion and
- $\geq 1$  minor criterion from each of  $\geq 2$  different systems/categories

The definitions of anaphylaxis and the levels of certainty will enable uniformity in reporting anaphylaxis cases; this does not signify any relationship of causality or severity.

## 5.3.2 Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) is a relatively rare (1-2 cases per 100,000 people annually) acute peripheral neuropathy<sup>16</sup> that most frequently occurs without an identified causal event. It can, however, follow some infectious illnesses, of which the most common is caused by *Campylobacter jejuni* (1 case of GBS per 3,000 infectious episodes),<sup>17,18</sup> probably as a result of an autoimmune response.

GBS has also been observed in a temporal association with vaccination; this association has been considered as causal in cases following swine influenza vaccine in 1976 (attributable risk: 9.5 per million doses administered).<sup>19</sup> Among those who were vaccinated, the rate of GBS that exceeded the background rate was slightly less than 10 cases per million vaccinated. The risk of GBS associated with subsequent influenza vaccines (prepared from different virus strains) is less clear. It is difficult to detect a small increase in risk for a rare disease such as GBS.

A recent study in Latin America and the Caribbean found an average incidence of GBS of 0.82 per 100,000 children aged  $<15$  (range, 0.72-0.90 cases per 100,000 children), with significant differences between Northern and Southern Hemisphere countries (1.08 vs. 0.57 cases per 100,000 children). The study analyzed 10,486 acute flaccid paralysis cases diagnosed as GBS from 2000 through 2008.<sup>20</sup> In four influenza seasons studied between 1977

and 1991, the relative risk of post- influenza vaccination GBS was not statistically significant. However, a small excess risk of GBS was reported in persons aged 18 to 64 years vaccinated during the 1990–1991 vaccination season in the United States.<sup>21,22,23</sup>

A later study found an elevated overall risk for GBS of 1.7 (CI 95%, 1.0-2.8) in the six weeks following influenza vaccination during the 1992–1993 and 1993–1994 seasons.<sup>24</sup> This risk represented an excess of one to two cases per million persons vaccinated. However, if the risk-benefit ratio of vaccination is considered, the risk of contracting severe influenza is higher than the risk of temporal association between the vaccine and post-vaccination GBS.<sup>24</sup>

### **Collaborative International Study on Surveillance of Guillain-Barré Syndrome**

Guillain-Barré syndrome is a rare and infrequent illness and as a result the number of cases occurring within a period of time will be small. Any design that is used to measure the association between the vaccine and GBS will require sample sizes that probably cannot be contributed by one country or region. In this regard, PAHO and other institutions, such as the United States government’s Food and Drug Administration (FDA), have implemented a collaborative international study for surveillance of post pandemic-influenza vaccination GBS in all WHO regions. The principal objective of this study is to investigate the association between immunization with pandemic influenza (H1N1) 2009 vaccines and GBS.

Adequate implementation of this study by the countries of the Americas will contribute to strengthening their surveillance systems, because it will require active surveillance that enables finding all cases of GBS, as well as conducting risk assessments on the development of a specific medical condition (in this case GBS) following vaccination. Furthermore, the study is designed to develop local capabilities for risk analysis and assessment that will then enable the production of useful scientific information on vaccine safety.

PAHO and the institutions participating in the study developed a protocol for the international monitoring of GBS (Annex 2). This field guide summarizes the steps for countries to follow for GBS monitoring. Note that monitoring of GBS should be part of the country’s ESAVI surveillance; that is, this monitoring should not be seen as an individual research study or as separate from regular surveillance.

Due to the nature of the study, the data collected on GBS will be analyzed regionally and/or globally; this means that countries are not required to do the analysis for this specific study. However, all the data collected on GBS in the context of pandemic vaccination will belong to the country.

#### **Step 1: Identification of sentinel hospitals. Criteria for selection of sentinel hospitals**

In participating in this collaborative study, countries should select sentinel hospitals that meet the following criteria:

1. Referral hospitals that have an outpatient or inpatient service that treats neurological cases and whose catchment area corresponds to a population vaccinated against influenza (H1N1) 2009.
2. In the area of the selected hospital, a significant proportion of the population under study should have been vaccinated with any type of pandemic influenza (H1N1) 2009 vaccine.
3. Hospitals that have the capacity to obtain and process cerebrospinal fluid (CSF) samples.
4. Hospitals that have easy access to patient records (hospitalization, clinical history, and vaccination records); these records may be electronic or non-electronic. What is important is that the registries be accessible to the group responsible for hospital surveillance.
5. Hospitals that have an active epidemiological surveillance system that permits reporting and timely GBS case-finding and the resources for investigating them.
6. Hospitals should make an institutional commitment to participate in active GBS monitoring, for which they should designate a person to be responsible for monitoring surveillance (reviewing case registries, collecting data on vaccines, laboratory results for lumbar puncture, and entering data in the database).
7. Hospitals should have a team responsible for surveillance, which should be available and prepared to show evidence that all cases identified during the study period have been diagnosed correctly.

## **Step 2: Methodology for GBS case-finding**

1. Determine the hospital's area of responsibility or geographic catchment area.
2. Determine the vaccination period for the selected hospital's area of responsibility or geographic catchment area.
3. Determine a study period that includes the vaccination period plus 60 additional days, in accordance with the protocol.
4. Find all cases of GBS (vaccinated and unvaccinated) that occur during the period of study and that come from the selected hospital's area of responsibility or geographic catchment area.
5. The person responsible for surveillance in the hospital should obtain the clinical history of the case and obtain the information necessary for determining the level of diagnostic certainty for GBS, using the Brighton Collaboration criteria.
6. A data collection form will be used for each GBS case (Annex 3).
7. Each hospital will send consolidated information on all the cases to the national level in a table using the format in Annex 4.
8. Countries will send this information to the PAHO/WHO office, which in turn will forward it to the Regional Office for the corresponding analysis.

## Case definitions for Guillain-Barré syndrome<sup>25</sup>

### 1. Clinical criteria

- Acute onset of relatively symmetrical bilateral muscular weakness/flaccid paralysis of the limbs, with or without involvement of respiratory or cranial nerve-innervated muscles.

#### And

- Decreased or absent deep tendon reflexes in weak limbs.

#### And

- Monophasic illness pattern, reaching nadir of weakness between 12 hours and 28 days, followed by clinical plateau and subsequent improvement, or death.

### 2. Electrophysiologic criteria

- Electrophysiologic findings consistent with GBS

### 3. Cerebrospinal fluid (CSF) criteria

- Cytoalbuminologic dissociation (i.e., elevation of CSF protein level above laboratory normal value and CSF total white cell count <50 cells/mm<sup>3</sup>).

## Levels of diagnostic certainty

The case definitions have 3 levels of diagnostic certainty:<sup>25</sup>

- Level 1: requires clinical, electrophysiological, and cerebrospinal fluid data.
- Level 2: requires clinical data and/or electrophysiological **or** cerebrospinal fluid data.
- Level 3: requires clinical data.

All levels of diagnostic certainty require the absence of an identified alternative diagnosis for muscular weakness.

### 5.3.3 Other clinical entities reported

Rare reactions with a temporal association to seasonal influenza vaccine have been reported, which means that their reporting during vaccination against pandemic influenza (H1N1) 2009 should be fully investigated.

#### *Asthma*

It has been reported that attenuated influenza vaccine exacerbates bronchial hyper-reactivity in children under 5. This has not been verified, although some studies have suggested that there may be a small risk.<sup>26</sup>



### *Oculo-respiratory syndrome*

Oculo-respiratory syndrome (ORS) was first described in Canada, during the 2000-2001 seasonal influenza season. Symptoms of ORS appear within 24 hours of administration of the inactivated vaccine.

The initial definition of ORS consists of one or more of the following symptoms that appear from 2 to 24 hours after vaccination: bilateral red eyes, facial edema, respiratory symptoms (cough, wheezing, tightness of the chest, difficulty breathing, sore throat, difficulty swallowing). There may be associated systemic symptoms, including high fever. Symptoms vary from mild to severe, resolving fully within 48 hours.<sup>27</sup>

The cause of ORS has not been established; however, studies suggest that this is not an IgE-mediated reaction.<sup>28</sup> During 2000-2001, 96% of reported cases were related to inactivated seasonal influenza vaccine produced by one of the two manufacturers of vaccines for Canada (*Fluviral S/F®*, *Shire Biologics, Quebec, Canada*).<sup>29</sup> Following changes in the process for preparation of the vaccine associated with ORS, the incidence of ORS dropped considerably in Canada. To date, a causal relation has not been shown.

## **5.4 Investigation and Response**

### **5.4.1 Stages of the investigation**

#### **Initial evaluation**

The first step is to confirm the information. As soon as any ESAVI is recognized, the health worker will inform the parents or family members that immunization is safe, give them confidence, and explain to them that there can be simultaneous events that are not necessarily due to the vaccine. If the case is in one of the aforementioned diagnostic categories, the report will be made and all steps of the investigation will be carried out with expert guidance from the central level.

#### **Investigation**

The principal investigation foci are: the service, the vaccine, the user, the health worker, parents, the field work, and the legal area. This presumes that observation, interviews, record review, inspection of services, autopsy, and home visits have to be carried out.

Until the investigation is completed, it is impossible to determine the causes of the event. They may be related to operational aspects of the program (program error) or to the vaccine, or bear no relation to it (coincidental), or be of unknown cause.

These concepts are explained below.

- **The service.** The investigator will look for program operation errors at any stage in service delivery by the health facility.
- **Inventory.** The first step in the investigation is to make a detailed count and thorough observation in the health facility of everything that is related to the program with regard to service delivery and logistics. A workplace inventory includes:

- program refrigerator;
  - work table;
  - vaccination room;
  - place where syringes and diluents are stored;
  - list of drugs that are received and delivered to the health services (to review the flow of drugs);
  - biosafety measures.
- **The vaccine.** Obtain the following data on the vaccine and syringe used:
    - name of the vaccine (description on the label);
    - batch number;
    - dates of manufacture and expiration;
    - manufacturing laboratory;
    - origin of the vaccine and syringe, date of shipment, and transport data;
    - physical appearance of the vaccine and syringe;
    - outcome of vaccine quality control testing;
    - review of the production protocol of the implicated vaccine;
    - reassessment of quality control for the implicated vaccine lots will depend on the situation; e.g. expected ESAVIs or unexpected ESAVI rates.
  - **Program logistics.** Review the following aspects of the program:
    - vaccine storage;
    - vaccine transport and handling;
    - movement records, inventory controls, and others.
  - **The health worker.** Evaluate staff performance with regard to vaccine administration and skills for giving guidance to parents. Observe the following:
    - use of diluents, reconstitution of vaccines, and forms of administration;
    - correct dosage;
    - availability of needles and syringes, and correct practices;
    - circumstances and the way vaccination is administered;
    - health care practices in the facility;
    - personnel performance of vaccination technique;
    - order of administration of the dose from the vial;
    - cold chain;
    - work and organizational environment during vaccination.
  - **The user.** The basic information to be collected, usually through interviews with parents or family members, is:
    - demographic data;
    - age, sex, place of residence, and information on how to find it;
    - family history;
    - recent clinical summary (signs and symptoms, duration, clinical examination, auxiliary diagnostic tests, treatment, course, pay particular attention to neurological examination);
    - type of event, date of appearance, duration, and clinical treatment;

- medical background and clinical history of the patient (at birth, previous reactions to vaccines, allergies to certain pharmaceutical preparations, preexisting neurological disorders, sleep apnea, drugs currently taken, etc.);
  - vaccination history (type of vaccine utilized, date of last dose, and type of previous reaction, if any).
- **The field worker.** Data will be obtained from interviews, home visits to the people affected, and follow-up of people who received vaccines from the same lot or vial. Field work includes:
    - Describing socioeconomic conditions, including type of housing, source of heat used, where the person sleeps (if it is a child, who s/he sleeps with), the number of people per room, access to drinking water, and sanitation.
    - In the event of death, describe how the body was found (position, temperature); type of secretion from the mouth or nostrils, if any).
    - Submit a full autopsy report, toxicological screening, and anatomical pathology.
    - Follow-up on other children vaccinated with the same lot or vial.
    - Determine whether the reported event is an isolated incident or if there were other cases. Obtain data on:
      - population vaccinated with the same lot of vaccine in the same period and with the same symptoms;
      - unvaccinated population, to determine if a similar incident occurred in that group;
      - population vaccinated with a different vaccine lot (from the same manufacturer or another one) that has similar symptoms, to determine if a similar event occurred in the population vaccinated with another lot.
  - **Autopsy.** In the cases of deaths reported as ESAVIs it is recommended that the autopsy be performed within the first 72 hours, following the procedure below:
    - If the person dies at home with no evident cause, at the health facility the physician will carry out a verbal “autopsy” with the mother or guardians, following the steps of a clinical history, and will conduct an anatomical pathology examination searching for signs of disease, such as jaundice (yellow staining of skin and sclerae), petechiae, hemorrhage, cyanosis, or pallor.
    - If possible, x-ray the body.
    - The following actions will be coordinated with the autopsy department of each jurisdiction:
      - Perform the autopsy as soon as possible to avoid tissue lysis, which can hinder diagnosis (as happens with adrenal glands). The autopsy procedure will provide the medical expert with all the information on the patient.
      - Sampling for:
 

Toxicological screening: 80 to 100 g of liver, 80 to 100 g of brain, and the stomach contents. If there are no gastric contents, a section of stomach should be sent. All the samples will be sent together in a wide-mouthed bottle with no additives (without formalin or other additional substance). For preservation, use only ice packs.

Anatomical pathology examination: A sample of 3 to 4 cm will be taken of each organ for the anatomical pathology examination; e.g. a fragment of the brain with meninges, a fragment of each of the five lobes of the lung, fragments from both kidneys and suprarenals, as well as from any other organ in which lesions are suspected. In each case, the sample will be representative of the suspicious area. The specimens are to be sent together in a wide-mouthed bottle, with sufficient formalin to cover all the pieces.

- Both sets of samples should be shipped to the reference laboratory for thanatological and auxiliary examinations. All the samples should be labeled with the name and autopsy form number, and be accompanied by the documents requesting the examination and investigation. The conclusions of the study should list the cause of death, using the ICD-10, and if possible, the causative agents. The summary of the clinical history will also be enclosed.
- The reference laboratory for thanatological and auxiliary examinations will send the results to the immunization program, to epidemiology, and to the laboratory.
- **Neurological examination for anticipated ESAVIs.** The neurological examination begins with bearing in mind the patient's overall condition, whatever his/her age. It is not the same to examine a well-nourished patient or a malnourished one, an alert patient or a patient in coma, a patient with chronic disease or an acute patient. However general guidelines do exist and in the end each one makes his own scheme with which he feels comfortable but which should be consistent.

#### **5.4.2 Investigation findings: final classification of ESAVIs**

After the investigation, the information should be analyzed to determine the cause, confirm the diagnosis, or suggest other possible interpretations. ESAVIs are classified into three categories:

##### **1. The event is definitively not related to the vaccination**

These are events that occur following vaccination but that are not caused by vaccines: it is a risky association; that is, there is a temporal relationship but not a cause-and-effect one (these are independent events).

Some clinical cases simply coincide with the vaccination; that is, the event could have occurred even if the person had not received the vaccine. The best way of sustaining the argument that the event is simply coincidental is to demonstrate that the same event or others also occurred in a population group that was not immunized. However, the clinical and laboratory evidence in the case explain the individual's response.

Even though an ESAVI has not been linked to the vaccination, it may require appropriate monitoring by a physician. In that case, a mechanism for referral to the necessary health services will be coordinated.

## 2. The event is related to the vaccination

### a. Event related to operational problems in the program (program error)

This is an event caused in the cycle of vaccine use by a mistake in its storage, preparation and handling, or administration. Events caused by “program operation error,” that is, an operational error of the program, can be prevented by the vaccinator. This error is more frequently human than caused by the vaccine or the technology.

Usually, it can be prevented through training for personnel, supervision, and an adequate supply of equipment for safe injection. A program operation error may lead to a cluster of events, especially if a vaccinator does not follow what s/he was taught during training. Improper practices can give rise to abscesses or other blood-borne infections. The most serious result is toxic shock caused by improper handling of the vaccine vial after reconstitution. Several people vaccinated from the same vial could die shortly after injection. Table 6 lists the most frequent program operation errors.

**Table 6. Possible operational program errors and their consequences**

Operational program error	Anticipated event
<p><b>Non-sterile injection:</b></p> <ul style="list-style-type: none"> <li>• Recycling of a syringe or disposable needle</li> <li>• Inadequate sterilization of a syringe or needle</li> <li>• Use of contaminated vaccine or diluent</li> <li>• Use of lyophilized vaccines longer than indicated time of use</li> </ul>	<ul style="list-style-type: none"> <li>• Infection, such as a localized abscess at the injection site, sepsis, toxic shock syndrome, or death</li> <li>• Blood-borne infection, such as hepatitis or human immunodeficiency virus (HIV)</li> </ul>
<p><b>Reconstitution error:</b></p> <ul style="list-style-type: none"> <li>• Reconstitution with the incorrect diluent</li> <li>• Replacement of the vaccine or diluent with a drug</li> </ul>	<ul style="list-style-type: none"> <li>• Local abscess from improper agitation</li> <li>• Adverse event associated with the drug administered; e.g. insulin</li> <li>• Death</li> <li>• Ineffective vaccine</li> </ul>
<p><b>Injection in the wrong place:</b></p> <ul style="list-style-type: none"> <li>• BCG vaccine administered subcutaneously</li> <li>• DPT/DT/TT administered too superficially</li> <li>• Injection in the buttock</li> </ul>	<ul style="list-style-type: none"> <li>• Reaction or local abscess</li> <li>• Probable injury to the sciatic nerve in infants</li> </ul>
<p><b>Improper transport or storage of vaccines</b></p>	<ul style="list-style-type: none"> <li>• Ineffective vaccine</li> <li>• Local reaction due to frozen vaccine</li> </ul>
<p><b>Ignoring of contraindications</b></p>	<ul style="list-style-type: none"> <li>• Preventable serious reaction</li> </ul>

In summary, program operation errors are due to one or more of the following situations:

- Improper dosage

- Incorrect administration
- Improper use of disposable needles and syringes
- Failure to check packaging that guarantees the sterility of needles and syringes
- Improper handling of needles and syringes
- Reconstitution of vaccines with the wrong diluent
- Wrong amount of diluent
- Improper preparation of vaccine
- Substitution of vaccines or diluents with drugs or other substances
- Contamination of the vaccine or the diluent
- Improper storage of vaccines and syringes
- Vaccines and syringes used after their expiration date
- Incorrect recording of movements or administration

### **What should be checked?**

If several cases occur, observe the following:

- Whether the same health worker administered the vaccines.
- Whether the unimmunized population in the same age group and geographical area presents the same symptoms.
- Whether the other people immunized with the same lot of vaccine in the same geographical area present the same symptoms.
- Whether the other people immunized with the same lot of vaccine in the same facilities on the same day do not present the same symptoms.

#### **b. Vaccine-related event**

This type of event involves an effect that might occur in the patient. The most common reactions are usually mild and expected, while serious reactions are very rare.

If an ESAVI is classified as a vaccination-related or unknown reaction, it should be investigated further to classify it according to the usually accepted criteria for causality. The vaccine was administered properly but, due to its properties or components, it caused the adverse event or precipitated it.

**Intrinsic reactions:** response of the body associated with the biological as such.

**Extrinsic reactions:** regarding a vaccination-related reaction, it is necessary to take into account that other components of the formulation could cause the observed events (extrinsic events) and that often reactions vary in intensity and form; they are mistakenly associated with the biological vaccine product, but are reactions of the body to the adjuvants in the formulation, e.g.:

- resuspension agents: such as water or saline solution;
- preservatives: such as thiomersal;
- stabilizers: sorbitol and hydrolyzed gelatin;
- adjuvants: aluminum salts;

- residue from culture media;
- antibiotics: neomycin, streptomycin

**Factors related to the host:** event caused by genetic susceptibility, anxiety, or pain from the injection, not the vaccine.

**Unacceptable quality:** Divergence from vaccine-licensing parameters, such as an increase in the concentration of the virus. Each case must be investigated, since depending on the case classification related to the vaccine, different situations can occur:

- a) The event happened within the margin of the expected frequency:
  - if the event is mild, explain to parents how they should proceed for treatment;
  - if the event is serious, notify the working group responsible for ESAVI monitoring to initiate an investigation.
  
- b) The event was unexpected or occurred with an unexpected frequency; in this case the following measures will be adopted immediately:
  - report to the working group responsible for ESAVI investigation;
  - temporarily suspend the use of the product (suspected type or lot of vaccine or syringe);
  - coordinate with the NRA on reevaluating the quality of vaccine and communicate with the manufacturer if necessary;
  - arrange the return of the vaccine if appropriate;
  - report to PAHO, to disseminate the information internationally, if necessary.

Reporting and investigation of ESAVIs will depend on the organizational structure in each country; however, it is necessary to guarantee that all stages of the process are carried out up to case classification.

### 3. When the investigation is inconclusive

When it is not possible to determine causality, in addition to reporting the investigation findings to the interested parties, it should be explained to them why a conclusion could not be reached and how much progress has been made.

#### 5.4.3 Measures

The measures that are adopted will be based on the conclusions of the investigation, which will have one of the following results:

- a) The event definitively is not related to the vaccination.
- b) The event is related to the vaccination:
  - due to operational problems of the program (plan training or take other necessary measures);
  - due to problems with the vaccine.

- c) The investigation is inconclusive (confirm the frequency of uncompleted investigations by geographical region; indicate the need for training or other necessary measures).

When the investigation is finished, the conclusions will be reported to the interested parties. To this end, communication should be clear and information will be disseminated to parents, the community, region, central area, health authorities, professional associations, or the entire country, including the mass media when appropriate. When investigating ESAVIs, it is important to have the ongoing support of the NRAs in the countries.

During safe vaccination activities, it is necessary to have regulatory instruments that back the decisions of the working group through technical tools to analyze the information obtained by the epidemiological component, to learn the entire safety profile of the vaccines.

Safe vaccination activities can be part of the epidemiological surveillance system of the country; it is not necessary to have a specific system for vaccines. The criteria for reporting and investigation should be jointly established with the immunization and epidemiological surveillance program.

#### **5.4.4 Integrated Safe Vaccination Information System**

PAHO's interprogrammatic work on vaccination safety in the Americas includes having high-quality vaccines working in coordination with the NRA, promoting safe injection practices, ESAVI surveillance that includes rapid response and effective investigation, and crisis prevention and management.

Moreover, all vaccines acquired through United Nations system agencies (PAHO and UNICEF Revolving Fund) for the NIP meet various requirements to be prequalified by WHO, and for the release of lots they work jointly with the NRAs in vaccine-producing and vaccine-receiving countries. An integrated computerized vaccination safety system should be developed to guarantee a standardized method for reporting, collection, timely analysis, and feedback of data related to ESAVIs, in addition to improving comparability of data, and the quality and management of vaccines and syringes.

The principal objectives of the safe vaccination information system for the Americas are the following:

1. Ensure a standardized ESAVI surveillance method, in particular, for monitoring serious events.
2. Identify potential signs on the safety of new vaccines in a timely fashion.
3. Improve post-registry safety data on prequalified vaccines.
4. Have information on the safety of vaccines to support vaccination policies and recommendations.
5. Maintain the credibility of the NIPs in the Region.

The computerized system is a Web-based application, which will permit its use by the local level in every country, hospitals, health centers and posts, as well as private health services



who report ESAVI cases at the intermediate level (state, region, department, or province) following then to the central level of the Ministry of Health in every country. In this regard, any health worker (who assumes the role of notifier) can report an ESAVI, whether from the public or private sector, for which it will only be necessary for the person to register in the system.

The immunization focal points in the PAHO countries will also review ESAVI information in coordination with the Ministry of Health. At the regional level, PAHO will analyze the information on ESAVIs, provide feedback to countries, and provide the necessary data to the WHO global database.

The information system is based on a Web application that will take advantage of PAHO's existing technological resources. The system will have three data modules: ESAVI surveillance, quality control, and management of biologicals and devices.

The online system can be accessed at the following address: [www.paho.org/ESAVI/demo](http://www.paho.org/ESAVI/demo). Note that as of March 2010, the system is not still finalized and we are currently implementing some suggestions that will make it much friendlier and more flexible. Any suggestions about the system may be sent to the following E-mail: [revillaf@paho.org](mailto:revillaf@paho.org)

### Roles of the online system user:

- **Notifier:** The notifier, after registering and entering contact information in the system (or reentering his/her user profile if already registered), can complete the form with the ESAVI information. Subsequently, new data can be added to the original report, but never deleted. Reporting can occur at the local level (hospital, health center or post, private physician's office) or at the national level (Ministry of Health) in a country.

Figure 5. ESAVI Reporting Screen

The screenshot displays the 'Notificación de Nuevo ESAVI' form. It is divided into two main sections: 'Datos del Notificador' and 'Datos del ESAVI'. The 'Datos del Notificador' section includes fields for Username (investigador), Key (79a4ab4af9f82358353d668a46f6f9aa), Name (José), Surname (García), Email (josegarcia@correo.com), Phone (1235555), Fax, and Address (Hospital XYZ, Avenida Principal 888, Rosario, Argentina). The 'Datos del ESAVI' section includes Description, Vaccines coincident with the ESAVI, Vaccination Date, Patient Vaccinated (checkbox), Patient Name, Date of Birth, Patient Tutor, Patient Address, Patient Phone, and Case Country (Argentina). At the bottom of the form are 'Guardar' and 'Cancelar' buttons. The footer of the page reads '© 2010 Organización Panamericana de la Salud. Todos los Derechos Reservados.'

- **Investigator:** The investigator, previously registered in the system, initiates the investigation of the reported ESAVI. Initial classification of the event is the first step in the investigation (initial classification: serious event, potential program error, rumors, and if the occurrence is in a group of people).

After the initial classification of the notified event, the investigator records the details of their investigation, which is complemented with documentation related to the event. Details can be recorded on input forms while complementary or supporting documentation in an electronic format can be annexed to the Web application.

The investigator should conclude the investigation, choosing among the following options:

- The event is definitively not related to the vaccination.
- The event is related to the vaccination through operational or program error, or the vaccine itself.
- The investigation is not conclusive.

**Figure 6. ESAVI Investigation Screen**

- **National monitor:** The national monitor, previously registered in the system, “closes” the ESAVIs (no more investigation). The monitor also notes his/her own final conclusions in the case of an ESAVI where there is more than one investigator and there are differences in the conclusions of the investigation.

- **Information system administrator (national):** This person is responsible for immediate support to users and for backing up system data. The administrator can update the data of the notifier, investigator, and national monitor.



## 6. Crisis Management and Prevention

### What is a crisis?

A crisis is a situation in which a real or potential loss of confidence in the vaccines and/or vaccination service occurs, usually precipitated by a report of real or supposed adverse events.

### Why does a crisis arise?

The great demand for a new vaccine and its mass administration can produce crises and affect the credibility of the NIP. For this reason, it is important to be prepared with a plan to address possible crises, maintain good media relations, and ensure adequate dissemination of the immunization policies for this new vaccine.

### How to prevent a crisis?

1. Highest-level political commitment.
2. Participation of scientific and professional societies, establishing agreed upon technical guidelines and disseminating information at all levels.
3. Partnerships with the mass media before, during, and at the end of the vaccination campaign.
4. Consensus-building and involvement of opinion leaders, churches of all religious creeds, unions, and governmental and nongovernmental organizations.
5. Training for all public and private sector staff.
6. Availability of up-to-date information for different audiences: political, professional, and general public.
7. Access and timely response to doubts using various means: pamphlets, free telephone lines, Web pages, E-mail, etc.
8. Formation of immediate response groups to detect potential crisis situations and provide an immediate, integrated response.

## 6.1 Crisis Management Plan

### 6.1.1 Objective

Undo public mistrust and ensure maintenance of vaccination activities as quickly as possible, for the purpose of ensuring continuity in activities, protecting the NIP's corporate image and reputation.

### 6.1.2 Components

**1. Form the response team (crisis committee):** Create a special crisis group, which must not lack the institution's communicator for any reason. This group will be responsible for defining legal, technical, and communications issues. Make it clear which person or persons will be responsible for making decisions.

A crisis committee should be organized as follows:

a. Technical Committee

- In charge of the immediate investigation of reported cases.
- Made up of an epidemiologist, safe vaccination coordinator, communicator, person in charge from the NIP.
- Conducts the initial case investigation.

b. Advisory Committee

- Provides technical scientific guidance, which shall provide the foundation for the communication strategy developed to address the crisis.
- Made up of representatives of professional associations: pediatrician, neurologist, immunologist, legal adviser, forensic physician, among others.

**2. Gather and disseminate relevant information:** If some time has passed since health workers received training, their vaccination and communication knowledge and skills should be refreshed. Relevant information can come from prior experiences in the Ministries of Health, national/international literature, or materials produced by international technical agencies (e.g. PAHO, CDC, etc.).

**3. Coordinate efforts (identify focal point and determine functions):** Look into the possibility of obtaining support from political authorities, scientists who can generate opinion, and celebrities who are willing to step into the fray in support of immunization.

**4. Damage control:** Victim support should be organized and announced (e.g. help with expenses, set up a telephone hotline, etc.) without taking blame or accepting liability. The following should be taken into account:

- Parents and the affected person
  - psychological and emotional support
  - support from the health system (accompaniment)
  - referral outside the system
  - logistical support
- Health workers and their perceptions
  - keep them informed
  - retrain them
  - offer emotional/legal support
- The community and its perception

**5. Implement the epidemiological investigation (rapid response team):** A technical investigation should start and the press should be kept informed of its progress:

- Affected patient (clinical history)
- Vaccine in question
- Vaccination process
- Setting (health services and community)

- Laboratory testing
- Anatomical pathology studies
- Final case classification

**6. Prepare the crisis communication plan:** Quickly establish a press office or press contact, determining and announcing the person or persons who will be in charge of informing the press (spokesperson/s). A preliminary statement or press release will be made within the first hours. Contact the press with which there is already an established relationship. In the case of an important event, a daily press conference will be held and the media will be served in all possible ways.

The following should be taken into account in preparing the communications plan:

- Identify the problem
- Identify the target audience
- Develop communication skills
- Identify the spokesperson
- Press release/press conference
- Identify friends in the mass media (to forge alliances)
- Work with professional associations
- Provide the outcomes of the investigation

**7. Prepare the plan for legal aspects:** This depends on the laws and their application in each country as well as on the availability of resources.

**8. Evaluate the plan:** Evaluate what happened and how the situation could be addressed better the next time. For this, it is helpful to develop a plan to evaluate the events (How were they faced?) for which indicators are useful. This plan would help to identify the lessons learned and make the appropriate corrections.

**9. Develop algorithms:**

- Develop an algorithm for each plan; clearly establish the flows, referrals, and responsibilities.
- Ensure that it is available to all staff.
- Ensure that everyone knows how to read it and that the audience understands it.

**6.1.3 Implementation**

Implementation is the phase in which all the planned activities are put into action. Before the implementation of a plan, those in charge of doing so should assess their strengths and weaknesses (internal forces), and their opportunities and threats (external forces). Strengths and opportunities are positive forces that should be taken advantage of in efficiently implementing the plan. Weaknesses and threats are obstacles that can halt the implementation of the plan and need to be overcome.

Supervision is important during the plan's implementation phase to ensure that it is done correctly. This is a continuous process that should be defined before implementation begins.

Supervision activities should appear in the work plan, and all stakeholders should participate in them. If the activities do not progress well, the necessary provisions should be adopted for recognizing the problem in time, in order to correct it.



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# Annexes



## Annex 1. Current Characteristics of Pandemic (H1N1) 2009 Influenza Vaccines

Producer	Type of vaccine		Adjuvant		Preservative		Presentation		Age groups	Dose	Number of doses	Form of administration	Interval between doses
	Inactivated	Live attenuated	YES	NO	YES	NO	Multi-dose vial	Prefilled syringe					
A	X					X		0.25 mL	6 a 35 m	0.25 mL	2	IM	≥ 3 wks
	X					X		0.5 mL	≥ 36 m	0.5 mL	1 o 2*	IM	≥ 3 wks
	X				X		5 mL		≥ 6 m	0.5 mL	1 o 2*	IM	≥ 3 wks
	X		X		X		1.5 mL + 4.5 mL adjuvant ***		≥ 3 yr	0.5 mL	1 o 2**	IM	?
B	X				X		5 mL		≥ 4 yr	0.5 mL	1 o 2	IM	≥ 3 wks
	X				X			0.5 mL	≥ 4 a	0.5 mL	1 o 2	IM	≥ 3 wks
	X		X		X		10 doses, cellular		??	0.5 mL	2	IM	?
	X			X	X		10 doses, eggs		≥ 4 yr	0.5 mL	1 o 2*	IM	4 wks
	X			X		X		0.5 mL	≥ 4 yr	0.5 mL	1 o 2*	IM	4 wks
C	X					X		0.5 mL	≥ 18 yr	0.5 mL	1	IM	
	X				X		5 mL		≥ 18 yr	0.5 mL	1	IM	
D	X		X		X		10 doses 2.5 mL + 2.5 mL adjuvant		≥ 18 yr	0.5 mL	2	IM	≥ 2 wks
E	X			X		X		0.25 mL	6 a 35 m	0.25 mL	2	IM	≥ 3 wks
	X			X		X		0.5 mL	3 a 8 yr	0.5 mL	2	IM	≥ 3 wks
	X			X		X		0.5 mL	≥ 9 yr	0.5 mL	1	IM	
	X		X		X		10 doses 1.25 mL + 1.25 Adjuvant		??	0.25 mL	2?	IM	?
F	X		X		?	?	2 doses 1 mL		3 a 60 yr	0.5 mL	1	IM	
	X		X			X	1 doses 0.5 mL		3 a 60 yr	0.5 mL	1	IM	
	X		X			X		0.5 mL	3 a 60 yr	0.5 mL	1	IM	
G	X		X		?	?	1 doses 0.5 mL		6 a 35 m	0.25 mL	2	IM	4 wks
	X		X		?	?	5 doses 2.5 mL		3 a 9 yr	0.5 mL	2	IM	4 wks
	X		X		?	?	5 doses 2.5 mL		≥ 10 yr	0.5 mL	1	IM	
H		X		X		X		Spray 1 doses 0.2 mL	2 a 49 yr ****	0.2 mL	1	Intra nasal	

\* One dose for population > 9 yrs

\*\* One or two doses depending on the results of clinical trials

\*\*\* Use within 24 hours of reconstitution

\*\*\*\* Healthy individuals



## Annex 2. Protocol of the International Collaborative Study for the Monitoring of Guillain-Barré Syndrome

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### Abbreviations

DS	Discharge Summary
H&P	Admission History and Physical
NC	Neurologist Consult notes
R	Right
L	Left
UTD	Unable to Determine

### Synonyms for GBS

Guillain-Barré Syndrome  
Acute Inflammatory Demyelinating Polyneuropathy (AIDP)  
Acute motor sensory axonal neuropathy (AMSAN)  
Acute motor demyelinating neuropathy (AMDN)  
Acute motor axonal neuropathy (AMAN)  
Miller Fisher Syndrome (MFS)  
Fisher Syndrome

### Synonyms for CIDP

Chronic Inflammatory Demyelinating Polyneuropathy

**Preferred Data Sources** are listed in order of priority. This priority is used for searching. It is also used for determining what information to use when there is conflicting information. However, this depends on there being adequate information from that source; if not, consider other sources.

**Acknowledgment:** Some excerpts or adaptations from the GBS Medquest tool used in the McBean project are included in these instructions.

After each question, proceed to the next question UNLESS instructions state otherwise.

-----  
Abstractor Initials: \_\_\_\_\_

Date Abstracted: \_\_\_\_/\_\_\_\_/\_\_\_\_  
                          mm      dd      yyyy

Electronic Index date: \_\_\_\_/\_\_\_\_/\_\_\_\_  
                          mm      dd      yyyy

Unique Subject ID# \_\_\_\_\_  
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### Patient Demographics

Age: \_\_\_\_\_ years

Gender: Female \_\_\_\_\_ Male \_\_\_\_\_

---

**1/a. Is there a FINAL diagnosis of GBS in the chart?**

\_\_\_\_ Yes, diagnosis of GBS has been established (there are no competing/alternative diagnosis), continue to questions 1/b and 1/c.

\_\_\_\_ Yes, diagnosis of GBS is listed, but there are still competing diagnosis (GBS not definitely established), continue to questions 1/b and 1/c, then **STOP ABSTRACTION and refer to neurologist**

\_\_\_\_ No, GBS is not listed at all in the final diagnosis, complete question 1/b then **STOP ABSTRACTION and refer to neurologist for review.**

**Comment:**

Use the **LAST** chart documentation to determine final diagnosis. The last documentation may be the discharge summary or the last/latest available inpatient/outpatient medical record.

**Preferred Data Sources:**

DS, NC, progress note, other

**1/b. FINAL diagnosis (check all that apply):**

- \_\_\_\_ Guillain-Barré syndrome
- \_\_\_\_ Acute Inflammatory Demyelinating Polyneuropathy (AIDP)
- \_\_\_\_ Acute Motor Sensory Axonal Neuropathy (AMSAN)
- \_\_\_\_ Acute Motor Demyelinating Neuropathy (AMDN)
- \_\_\_\_ Acute Motor Axonal Neuropathy (AMAN)
- \_\_\_\_ Miller Fisher Syndrome (MFS)
- \_\_\_\_ Fisher syndrome
- \_\_\_\_ Other, specify \_\_\_\_\_

**IF Other, STOP ABSTRACTION and refer to neurologist.**

**1/c. Competing Diagnoses**

- \_\_\_\_ None
- \_\_\_\_ Yes, specify \_\_\_\_\_
- \_\_\_\_ Yes, specify \_\_\_\_\_

**IF Yes, STOP ABSTRACTION and refer to neurologist.**

**Comment:**

Use final documentation to determine if another plausible diagnosis besides GBS is still being considered or has not been ruled out by time of hospital discharge. If so, specify up to 2 competing diagnoses. Pay particular attention to presence of the following diagnoses:

1. Spinal cord myelitis, compression or infarct, cauda equina compression
2. Carcinomatous meningitis, brainstem or Bickerstaff encephalitis, acute disseminated encephalomyelitis, intracranial or cerebellar tumor
3. Tick paralysis, snake bite
4. ALS (Lou-Gehrig's Disease)
5. Chronic inflammatory demyelinating polyneuropathy (CIDP)
6. Metabolic derangements such as hypermagnesemia or hyphosphatemia
7. Heavy metal toxicity such as arsenic, gold, or thallium



8. Drug induced neuropathy such as vincristine, platinum compounds, Nitrofurantoin, paclitaxel, cisplatin, suramin, Tacrolimus (FK506), Cyclosporine
9. Porphyria
10. Critical illness neuropathy or myopathy
11. Vasculitis
12. Diphtheria
13. Neuromuscular junction disease such as myasthenia gravis, organophosphate poisoning, or botulism
14. Hypokalemic or hyperkalemic myopathy
15. Dermatomyositis , polymyositis
16. Wernicke Encephalopathy

Diagnoses considered early in admission and subsequently ruled out should **NOT** be entered here. Diagnoses considered in the initial differential can be ruled out in a variety of ways, including medical history, physical examination, and/or diagnostic tests.

**1/d. Is there a clear statement from a neurologist that GBS is the final diagnosis?**

\_\_\_\_\_ Yes    \_\_\_\_\_ No

**Preferred Data Sources:**  
DS, NC, progress note, other

**2. History of GBS?**

\_\_\_\_\_ Yes, patient has a history of GBS in the past, but no evidence of acute relapse (i.e., GBS occurred in the remote past and this is not a new episode or relapse of GBS). List dates of prior GBS episode(s) as specifically as possible and then **STOP ABSTRACTION, form is complete.**

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

\_\_\_\_\_ Yes, patient has a past medical history of GBS, but chart suggests that this may be a relapse or a new episode. **STOP ABSTRACTION and refer to neurologist for review.**

\_\_\_\_\_ No, patient has no recorded past medical history of GBS. Continue abstraction

**Preferred Data Sources:**  
NC, DS, H& P, progress note, other

**3. Did the patient have extremity weakness? Describe weakness at maximal severity (make sure you use the same date/time examination for the R and L sides).**

UPPER extremities \_\_\_\_ Yes, Bilat \_\_\_\_ Yes, Unilat \_\_\_\_ No, \_\_\_\_ UTD

LOWER extremities \_\_\_\_ Yes, Bilat \_\_\_\_ Yes, Unilat \_\_\_\_ No, \_\_\_\_ UTD

**If No, unilateral, or UTD, STOP ABSTRACTION and refer to neurologist.**

**Comment:**

Same day/exam for both sides. Muscle strength 4 or less (out of 5).

Grading of Muscle Strength (Oxford Scale)*	
Grade 0	No movement
Grade 1	A flicker or trace of movement without joint motion
Grade 2	Partially moves body part with gravity eliminated
Grade 3	Completely moves body part against gravity
Grade 4	Completely moves body part against gravity and some resistance
Grade 5	Normal

\*DeGowin & DeGowin's Bedside Diagnostic Examination. New York: McGraw-Hill, Inc. 1993, p.790.

Physician notations of weakness/paresis, without quantification, are acceptable.

If weakness of muscles is bilateral, mark 'Yes, bilateral'.

If weakness of muscles is unilateral, or at least unilateral but unable to determine if bilateral, then mark 'Yes, Unilat'.

If muscle strength is normal then indicate 'No'.

If unable to determine if there is any weakness of muscles, mark, 'UTD'.

Exclusions:

Spastic paralysis

**Preferred Data Sources:**

NC, DS, H&P, physician progress notes, physical therapy notes.

**4. Did the patient at maximal weakness have relative symmetry of muscle weakness? (make sure you use the same date/time examination for the R and L sides).**

UPPER extremities \_\_\_\_\_ Yes, Symmetric \_\_\_\_\_ No \_\_\_\_\_ UTD  
 LOWER extremities \_\_\_\_\_ Yes, Symmetric \_\_\_\_\_ No \_\_\_\_\_ UTD

**If Asymmetric or UTD, STOP ABSTRACTION and refer to neurologist.**

**Comment:**

Same day/exam for both sides.

Answer symmetry questions for each muscle group (upper extremities, lower extremities) for which bilateral weakness was indicated in item 3.

'Symmetric' can be based on physician description, or muscle strength score, as follows.

**Mark 'Symmetric' if described by a physician as symmetric. Mark 'Symmetric' if R and L side had the same muscle strength score, or differed by only 1. Muscle scores must be 4 or less on both sides (out of 5).**

Compare the same muscle groups on both sides. This can either be specific or quite general.

Example 1: R biceps and L biceps were both 3/5.

Example 2: R arm and L arm strength were 3/5 throughout.

Ignore + and – signs after a muscle strength score.

Use the same date/time examination for the R and L side.

Mark 'No' only if a physician clearly describes the weakness as asymmetric and/or there is a pattern of asymmetry in muscles scores.

Otherwise, mark 'UTD'.

**Preferred Data Sources:**

NC, DS, H&P, physician progress notes, physical therapy notes

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**5/a. At maximal severity, did the patient have hypo/areflexia? (make sure you use the same date/time examination for the R and L sides).**

Right UPPER extremity \_\_\_\_\_ Yes \_\_\_\_\_ No \_\_\_\_\_ UTD  
Left UPPER extremity \_\_\_\_\_ Yes \_\_\_\_\_ No \_\_\_\_\_ UTD

Right LOWER extremity \_\_\_\_\_ Yes \_\_\_\_\_ No \_\_\_\_\_ UTD  
Left LOWER extremity \_\_\_\_\_ Yes \_\_\_\_\_ No \_\_\_\_\_ UTD

**If No or UTD, STOP ABSTRACTION and refer to neurologist.**

**5/b. Are reflexes relatively symmetric? (make sure you use the same date/time examination for the R and L sides).**

UPPER extremities \_\_\_\_\_ Yes \_\_\_\_\_ No \_\_\_\_\_ UTD  
LOWER extremities \_\_\_\_\_ Yes \_\_\_\_\_ No \_\_\_\_\_ UTD

**If UTD, refer to neurologist.**

**Comment:**

Same day/exam for both sides.

Text description or stick figure may be used.

At least one reflex in each upper extremity must be hyporeflexic or areflexic to mark 'Yes'. At least one reflex in each lower extremity must be hyporeflexic or areflexic to mark 'Yes'.

Mark No to symmetry question ONLY IF chart clearly states that reflexes are asymmetric OR reflex grading differs by more than 1 on right and left sides.

Grading of Reflexes*		
Grade 0	0	Absent
Grade 1	+	Diminished but present
Grade 2	++	Normal
Grade 3	+++	Hyperactive
Grade 4	++++	Hyperactive with clonus

\*DeGowin & DeGowin's Bedside Diagnostic Examination. New York: McGraw-Hill, Inc. 1993, p.811.

Synonyms for areflexia:

- Areflexia
- Absent reflexes
- Deep Tendon Reflexes (DTRs) absent
- DTRs 0

0 (stick figure or text)  
Ankle Jerk (AJ) 0  
AJ absent  
Knee Jerk (KJ) 0  
KJ absent

Synonyms for hyporeflexia:

Hyporeflexia  
Reflexes decreased or diminished  
1 (stick figure or text)  
1+  
+/-  
±  
trace  
tr

**Preferred Data Sources:**

NC, DS, H&P, physician progress notes, physical therapy notes

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**Answer questions 6---9 ONLY IF patient does NOT have limb weakness and/or chart indicates patient has Fisher syndrome:**

**6a. Did the patient, at any time over the course of the acute illness, have Cranial nerve III, IV, and/or VI muscle(s) weakness (also referred to as ophthalmoplegia or ophthalmoparesis)?**

\_\_\_\_\_ Yes, Bilateral weakness  
\_\_\_\_\_ Yes, Unilateral weakness  
\_\_\_\_\_ No  
\_\_\_\_\_ UTD

**If No, unilateral, or UTD, STOP ABSTRACTION and refer to neurologist**

**6b). If yes, to above, is ophthalmoplegia considered relatively symmetric?**

\_\_\_\_\_Yes    \_\_\_\_\_No    \_\_\_\_\_UTD

**IF NO or UTD, STOP ABSTRACTION and refer to neurologist**

**Comment:**

Although this question asks for signs at any time during the acute illness, it is especially important to note what was present during nadir (the time of maximal severity), if possible. Same day/exam for both sides.

Look for physician notation of the following: impaired eye movement in any direction, impaired extraocular movement, extraocular muscle deficit, ophthalmoplegia, ophthalmoparesis, or impaired cranial nerve III (oculomotor nerve), IV (trochlear nerve) and /or VI (abducens nerve).

If weakness of muscles innervated by cranial nerves is bilateral, mark 'Bilat'.

If weakness of muscles innervated by cranial nerves is unilateral, or at least unilateral but unable to determine if bilateral, then mark 'Unilat'.

If cranial nerves are normal or "intact", then indicate 'No'.

If unable to determine if there is any weakness of muscles innervated by cranial nerves, mark, 'UTD'.

Answer NO to symmetry question ONLY if chart clearly states that ophthalmoplegia is asymmetric or is present only on one side.

**Preferred Data Sources:**

NC, DS, H&P, physician progress notes, physical therapy notes

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**7/a. Did the patient, at any time during the course of the illness, have ataxia?**

\_\_\_\_\_Yes \_\_\_\_\_No \_\_\_\_\_UTD

**IF No or UTD, STOP ABSTRACTION and refer to neurologist**

**7b) If yes to above, is ataxia considered relatively symmetric?**

\_\_\_\_\_Yes \_\_\_\_\_No \_\_\_\_\_UTD

**IF No or UTD, STOP ABSTRACTION and refer to neurologist**

**Comment:**

Although this question asks for signs at any time during the acute illness, it is especially important to note what was present during nadir (the time of maximal severity), if possible. Please mark "Yes" if physician states "ataxia" is present.

Answer NO to symmetry question ONLY if chart clearly states that ataxia is asymmetric or is present only on one side.

**Preferred Data Sources:**

NC, DS, H&P, physician progress notes, physical therapy notes

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**8. Did patient at any time over the course of the acute illness have Corticospinal tract signs?**

\_\_\_\_\_Yes \_\_\_\_\_No \_\_\_\_\_UTD

If yes, specify \_\_\_\_\_

**If Yes or UTD, STOP ABSTRACTION and refer to neurologist**

**Comments:**

Although this question asks for signs at any time during the acute illness, it is especially important to note what was present during nadir (the time of maximal severity), if possible.

Corticospinal tract signs (also called upper motor signs) can be described or manifest as clonus, muscle spasticity or rigidity, extensor plantar reflex (also called Babinski or "upgoing toe"), hyperreflexia (or "brisk" reflexes), and pseudobulbar palsy. If physician states any of the above is present, mark "Yes".

**Preferred Data Sources:**

NC, DS, H&P, physician progress notes, physical therapy notes

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**9/a. At any time over the course of the acute illness, did the patient have any alterations in consciousness?** \_\_\_\_\_Yes    \_\_\_\_\_No    \_\_\_\_\_UTD

**9/b. If yes, is the alteration in consciousness felt to be directly due to the primary neurological illness or other cause (specify suspected cause):**

\_\_\_\_\_ neurological illness

\_\_\_\_\_ Other, specify: \_\_\_\_\_

**Comments:**

**If Yes or UTD, STOP ABSTRACTION and refer to neurologist**

Although this question asks for signs at any time during the acute illness, it is especially important to note what was present during nadir (the time of maximal severity), if possible.

Alterations in consciousness can manifest or be described as depressed level of consciousness, obtundation, loss of consciousness, lethargy, disorientation, confusion, stupor, or coma or semicoma.

Causes of alteration in consciousness NOT directly due to the neurological illness can include secondary or hospital-derived infection, medications or sedatives given while in the hospital, respiratory failure, and others.

**Preferred Data Sources:**

NC, DS, H&P, physician progress notes, physical therapy notes

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**10. ONSET of neurologic symptoms/signs**

Specified ONSET DATE \_\_\_\_\_/\_\_\_\_\_/\_\_\_\_\_  
mm    dd    yyyy

**OR**

Estimated ONSET DATE \_\_\_\_\_/\_\_\_\_\_/\_\_\_\_\_  
mm    dd    yyyy

**OR**

Hospital/clinic arrival date \_\_\_\_\_/\_\_\_\_\_/\_\_\_\_\_  
mm    dd    yyyy

**If UTD, refer to neurologist**

**Comment:**

Onset of neurologic symptoms/signs. This date will be used in the final analysis, so it is important to record this as accurately as possible. Since recorded histories may differ, pay attention to the priority order of sources.

Onset of motor weakness is especially important, but some persons with GBS also have sensory symptoms, and the latter could be noted prior to weakness symptoms. (General symptoms such as “not feeling right” could be considered if other documentation suggests them to be clearly related to the onset of the neurologic episode.)

Where an exact date of onset is not available, but a range is provided, use the midpoint of the range to estimate the date.

Example 1: 1-2 weeks prior to admission should be abstracted as 11 days prior to admission.

Example 2: A few weeks prior to admission should be abstracted as 21 days prior to admission.

Example 3: Several months prior to admission should be abstracted as 120 days prior to admission.

If unable to determine either the documented or estimated onset date, indicate the date of arrival at the hospital or clinic (which could be either the day of or day prior to admission). For persons whose symptoms clearly started prior to the date of arrival, it is preferable to estimate the onset date as best possible (to the extent allowed by the documentation).

Carefully determine the date corresponding to onset using available tools (e.g., computer calculation, calendars, etc).

**Preferred Data Sources:**

NC, DS, H&P, physician emergency department notes

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**11. Nadir**

**11/a. Date of the 28<sup>th</sup> day after disease onset:** \_\_\_\_/\_\_\_\_/\_\_\_\_  
mm dd yyyy

**11/b. Was nadir reached between 12 hours and 28 days after onset?**

\_\_\_\_ Yes \_\_\_\_ No \_\_\_\_ UTD

**If No or UTD, STOP ABSTRACTION and refer to neurologist.**

**11/c. Evidence for nadir.**

If yes to 11 b, specify evidence (select one):

\_\_\_\_ Yes, because patient died on or before the 28<sup>th</sup> day after onset

Date of Death: \_\_\_\_/\_\_\_\_/\_\_\_\_  
mm dd yyyy

\_\_\_\_ Yes, because neurological symptoms did not worsen after 28 days of onset

\_\_\_\_ Yes, because patient was discharged to a lower level of care or home on or before 28 days after onset (and subsequent medical records are unavailable)

If No to 11b, specify evidence:

\_\_\_\_ No, because neurological symptoms continue to worsen after 28 days after onset.

\_\_\_\_ No, because neurological symptoms reached maximum severity in less than 12 hours from onset (i.e. interval of onset to maximal severity is < 12 hours)

If UTD, specify (select one):

\_\_\_\_ UTD because patient was transferred for acute or higher level of care (and subsequent medical records are unavailable)

\_\_\_\_ UTD because this form is being completed <28 days after symptom onset and clinical plateau has not yet been reached; additional records not available. \*

\* Record should be flagged for re-review in a couple of weeks.





Please indicate any POSITIVE viral, bacterial, fungal, or parasitic CSF test. Specify pathogen, test (such as PCR, VDRL, India ink, or culture), and result.

Pathogen \_\_\_\_\_ Test \_\_\_\_\_ Result \_\_\_\_\_

Pathogen \_\_\_\_\_ Test \_\_\_\_\_ Result \_\_\_\_\_

Pathogen \_\_\_\_\_ Test \_\_\_\_\_ Result \_\_\_\_\_

Pathogen \_\_\_\_\_ Test \_\_\_\_\_ Result \_\_\_\_\_

Pathogen \_\_\_\_\_ Test \_\_\_\_\_ Result \_\_\_\_\_

Pathogen \_\_\_\_\_ Test \_\_\_\_\_ Result \_\_\_\_\_

Pathogen \_\_\_\_\_ Test \_\_\_\_\_ Result \_\_\_\_\_

**If there is a positive viral, bacterial, fungal, or parasitic CSF test, STOP ABSTRACTION and refer to neurologist**

**Comment:**

Please indicate lab's reference upper level of normal protein in CSF. Indicate the highest CSF WBC and protein recorded (does not need to have been from the same CSF exam)

Make sure units are correct for CSF protein and cells (mg/dl, cells/mm<sup>3</sup>). If not, cross out and indicate units from laboratory report.

A report of WBCs in the CSF is assumed to be total WBCs (unless otherwise specified).

If total WBC is reported as a range, enter the range.

If RBC count is reported as a range, enter the range. If reported as "too numerous to count", or similar, enter 'TNTC'. RBC count should be from the same tube as WBC count.

If spinal tap is bloody (high RBCs), write all information for an additional tube (or different date of collection) in additional notes section and/or additional spinal tap results. Also, indicate the tube numbers (and date of collection) for each tube entered on form. For example, tubes #1 and #4 from the same collection date might be entered on the form.

**Preferred Data Sources:**

Laboratory reports.

Only use other sources (DS, NC, physician progress notes) if laboratory report missing.

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**13. Electrodiagnostics (EMG/NCV test)**

**Enter ALL dates and results of electrodiagnostic studies.**

\_\_\_\_\_ Normal      \_\_\_\_\_ Abnormal

Date completed \_\_\_\_/\_\_\_\_/\_\_\_\_\_  
                          mm    dd    yyyy

If abnormal, indicate results: \_\_\_\_\_

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\_\_\_\_\_ Normal      \_\_\_\_\_ Abnormal

Date completed \_\_\_\_/\_\_\_\_/\_\_\_\_  
                         mm    dd    yyyy

If abnormal, indicate results: \_\_\_\_\_

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\_\_\_\_\_ Normal      \_\_\_\_\_ Abnormal

Date completed \_\_\_\_/\_\_\_\_/\_\_\_\_  
                         mm    dd    yyyy

If abnormal, indicate results: \_\_\_\_\_

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\_\_\_\_\_ Normal      \_\_\_\_\_ Abnormal

Date completed \_\_\_\_/\_\_\_\_/\_\_\_\_  
                         mm    dd    yyyy

If abnormal, indicate results: \_\_\_\_\_

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**Comments:**

If more than four studies were performed, photocopy this page and record all electrodiagnostic results and dates.

**Preferred Data Sources:**

Electrodiagnostic test report, NC  
Use DS only if other sources missing.

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**14/a. Spinal Cord MRI**    \_\_\_\_\_ Normal    \_\_\_\_\_ Abnormal    \_\_\_\_\_ Not Done

Date completed \_\_\_\_\_/\_\_\_\_\_/\_\_\_\_\_  
                          mm    dd    yyyy

If abnormal, indicate results: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

**14/b. Brain MRI**    \_\_\_\_\_ Normal    \_\_\_\_\_ Abnormal    \_\_\_\_\_ Not Done

Date completed \_\_\_\_\_/\_\_\_\_\_/\_\_\_\_\_  
                          mm    dd    yyyy

If abnormal, indicate results: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

**Comments:**

If brain and/or spinal cord MRI is abnormal, STOP ABSTRACTION and refer to neurologist.

Use the interpretation/summary of the MRI study for results

If more than one study was performed, enter the one that has the most definitive diagnostic interpretation. If unclear which is the most definitive study, add all other MRI studies, dates of exam, and results.

**Preferred Data Sources:**

MRI/radiologist test report, NC  
Use DS only if other sources missing

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**15. Other neurodiagnostic studies**

Yes, specify \_\_\_\_\_  
\_\_\_\_\_ Normal      \_\_\_\_\_ Abnormal

Date completed \_\_\_\_/\_\_\_\_/\_\_\_\_\_  
                         mm    dd    yyyy

If abnormal, indicate results: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Yes, specify \_\_\_\_\_  
\_\_\_\_\_ Normal      \_\_\_\_\_ Abnormal

Date completed \_\_\_\_/\_\_\_\_/\_\_\_\_\_  
                         mm    dd    yyyy

If abnormal, indicate results: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Yes, specify \_\_\_\_\_  
Normal      \_\_\_\_\_ Abnormal

Date completed \_\_\_\_/\_\_\_\_/\_\_\_\_\_  
                         mm    dd    yyyy

If abnormal, indicate results: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Yes, specify \_\_\_\_\_  
Normal      \_\_\_\_\_ Abnormal

Date completed \_\_\_\_/\_\_\_\_/\_\_\_\_\_  
                         mm    dd    yyyy

If abnormal, indicate results: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

**Comments:**

Other neurodiagnostic tests include evoked potentials, myelogram, CT of brain or spine (record CT ONLY if abnormal), etc.

Specify type of study.

Use the interpretation/summary of the study for results

**Preferred Data Sources:**

Test report, NC

Use DS only if other sources missing.

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**16 Other Diagnosis at Discharge or as of last available record.**

Please list up to 9 other diagnosis (primary, secondary, tertiary., etc) in the SAME ORDER as listed in the discharge summary in ADDITION to GBS.

Primary diagnosis \_\_\_\_\_

Secondary diagnosis \_\_\_\_\_

Tertiary diagnosis \_\_\_\_\_

Other Diagnoses:

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

**Comment:**

This is NOT a competing diagnosis to GBS, but diagnosis in ADDITION to GBS

For example, if individual's primary diagnosis is GBS, but secondary diagnosis is viral infection, please state viral infection as secondary diagnosis.

**Preferred Data Sources:**

Only list diagnosis listed in DS

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**17. Refer to neurologist?** \_\_\_\_\_

(Describe questions)



## Annex 3. GBS Data Collection Form

Abstractor Initials: \_\_\_\_\_ Date Abstracted: \_\_\_\_/\_\_\_\_/\_\_\_\_  
mm    dd    yyyy

Electronic Index date: \_\_\_\_/\_\_\_\_/\_\_\_\_  
mm    dd    yyyy

Subject ID#: \_\_\_\_\_

Subject Age: \_\_\_\_\_ years                      Gender:    Female \_\_\_\_\_    Male \_\_\_\_\_

1	Is there a FINAL diagnosis of GBS in the chart?	<p>1/a. Is there a FINAL diagnosis of GBS in the chart?</p> <p>____ Yes, diagnosis of GBS has been established (there are no competing/alternative diagnosis), continue to questions 1b and 1c.</p> <p>____ Yes, diagnosis of GBS is listed, but there are still competing diagnosis (GBS not definitely established), continue to questions 1b and 1c., then <b>STOP ABSTRACTION and refer to neurologist</b></p> <p>____ No, GBS is not listed at all in the final diagnosis, complete question 1 b then <b>STOP ABSTRACTION and refer to neurologist for review.</b></p> <p>1/b. FINAL diagnosis (check all that apply):</p> <p>____ Guillain-Barré syndrome</p> <p>____ Acute Inflammatory Demyelinating Polyneuropathy (AIDP)</p> <p>____ Acute Motor Sensory Axonal Neuropathy (AMSAN)</p> <p>____ Acute Motor Demyelinating Neuropathy (AMDN)</p> <p>____ Acute Motor Axonal Neuropathy(AMAN)</p> <p>____ Miller Fisher Syndrome (MFS)</p> <p>____ Fisher syndrome</p> <p>____ <b>Other, specify</b> _____</p> <p><b>IF Other, STOP ABSTRACTION and refer to neurologist.</b></p> <p>1/c. Competing Diagnoses</p> <p>____ None</p> <p>____ Yes, specify _____</p> <p>____ Yes, specify _____</p> <p><b>If Yes, STOP ABSTRACTION and refer to neurologist</b></p> <p>1/d. Is there a clear statement from a treating neurologist that GBS is the final diagnosis?</p> <p>____ Yes    ____ NO</p>
2	History of GBS	<p>____ Yes, patient has a history of GBS in the past, but no evidence of acute relapse (i.e., GBS occurred in the remote past and this is not a new episode or relapse of GBS). List dates of prior GBS episode(s) as specifically as possible and then <b>STOP ABSTRACTION, form is complete</b></p> <p style="margin-left: 40px;">_____</p> <p style="margin-left: 40px;">_____</p> <p style="margin-left: 40px;">_____</p> <p>____ Yes, patient has a past medical history of GBS, but chart suggests that this may be a relapse or a new episode. <b>STOP ABSTRACTION and refer to neurologist for review.</b></p> <p>____ No, patient has no recorded past medical history of GBS. Continue abstraction</p>

3	<p>Did the patient have extremity weakness? Describe weakness at maximal severity (make sure you use the same date/time examination for the R and L sides)</p>	<p>UPPER extremities ____ Yes, Bilateral ____ Yes, Unilateral ____ No, ____ UTD</p> <p>LOWER extremities ____ Yes, Bilateral ____ Yes, Unilateral ____ No, ____ UTD</p> <p><b>If No, unilateral, or UTD, STOP ABSTRACTION and refer to neurologist.</b></p>
4	<p>Did the patient, at maximal weakness, have relative symmetry of muscle weakness? (make sure you use the same date/time examination for the R and L sides).</p>	<p>UPPER extremities ____ Yes, Symmetric ____ No, ____ UTD</p> <p>LOWER extremities ____ Yes, Symmetric ____ No, ____ UTD</p> <p><b>If Asymmetric (No) or UTD, STOP ABSTRACTION and refer to neurologist.</b></p>
5	<p>Deep Tendon Reflexes</p>	<p>5/a. At maximal severity, did the patient have hypo/areflexia? (make sure you use the same date/time examination for the R and L sides)</p> <p>Right UPPER extremity ____ Yes ____ No ____ UTD</p> <p>Left UPPER extremity ____ Yes ____ No ____ UTD</p> <p>Right LOWER extremity ____ Yes ____ No ____ UTD</p> <p>Left LOWER extremity ____ Yes ____ No ____ UTD</p> <p><b>If No or UTD, STOP ABSTRACTION and refer to neurologist.</b></p> <p>5/b. Are reflexes relatively symmetric? (make sure you use the same date/time examination for the R and L sides)</p> <p>UPPER extremities ____ Yes ____ No ____ UTD</p> <p>LOWER extremities ____ Yes ____ No ____ UTD</p> <p><b>If UTD, refer to neurologist.</b></p>
6, 7, 8, 9	<p>Answer questions 6----9 ONLY IF patient does NOT have limb weakness and/or chart indicates patient has Fisher syndrome:</p>	<p>6/a. Did the patient, at any time over the course of the acute illness, have Cranial nerve III (oculomotor nerve), IV (trochlear nerve) , and/or VI (abducens nerve) muscle(s) weakness/(also referred to as ophthalmoplegia or ophthalmoparesis)?</p> <p>____ Yes, Bilateral weakness</p> <p>____ Yes, Unilateral weakness</p> <p>____ No</p> <p>____ UTD</p> <p><b>If No, unilateral, or UTD, STOP ABSTRACTION and refer to neurologist</b></p> <p>6/b. If yes, to above, is ophthalmoplegia considered relatively symmetric?</p> <p>____ Yes ____ No ____ UTD</p> <p><b>IF NO or UTD, STOP ABSTRACTION and refer to neurologist</b></p> <p>-----</p>



		<p>7/a. Did the patient, at any time during the course of the illness, have ataxia?  <input type="checkbox"/> Yes   <input type="checkbox"/> No   <input type="checkbox"/> UTD</p> <p>7/b. If yes to above, is ataxia considered relatively symmetric?  <input type="checkbox"/> Yes   <input type="checkbox"/> No   <input type="checkbox"/> UTD</p> <p><b>IF No or UTD, STOP ABSTRACTION and refer to neurologist</b></p> <p>-----</p> <p>8. Did patient at any time over the course of the acute illness have Corticospinal tract signs?  <input type="checkbox"/> Yes   <input type="checkbox"/> No   <input type="checkbox"/> UTD</p> <p>If yes, specify _____</p> <p><b>IF Yes or UTD, STOP ABSTRACTION and refer to neurologist</b></p> <p>-----</p> <p>9/a. At any time over the course of the acute illness, did the patient have any alterations in consciousness? <input type="checkbox"/> Yes   <input type="checkbox"/> No   <input type="checkbox"/> UTD</p> <p>9/b. If yes, is the alteration in consciousness felt to be directly due to the primary neurological illness or other cause (specify suspected cause): <input type="checkbox"/> neurological illness   <input type="checkbox"/> Other  Specify: _____</p> <p><b>IF Yes or UTD, STOP ABSTRACTION and refer to neurologist</b></p>
10	Onset of neurological symptoms/signs	<p>Specified ONSET DATE <input type="text"/> / <input type="text"/> / <input type="text"/>  mm / dd / yyyy</p> <p><b>OR</b></p> <p>Estimated ONSET DATE <input type="text"/> / <input type="text"/> / <input type="text"/>  mm / dd / yyyy</p> <p><b>OR</b></p> <p>Hospital/clinic/ER arrival date <input type="text"/> / <input type="text"/> / <input type="text"/>  mm / dd / yyyy</p> <p><b>IF UTD, refer to neurologist</b></p>
11	Nadir (maximal severity of weakness if GBS or ataxia/ophthalmoplegia if Fisher Syndrome)	<p>11/a. Date of the 28<sup>th</sup> day after disease onset: <input type="text"/> / <input type="text"/> / <input type="text"/>  mm   dd   yyyy</p> <p>11/b. Was nadir reached between 12 hours and 28 days after onset?  <input type="checkbox"/> Yes   <input type="checkbox"/> No   <input type="checkbox"/> UTD</p> <p><b>IF No or UTD, STOP ABSTRACTION and refer to neurologist.</b></p> <p>11/c. Evidence for nadir.</p> <p>If yes to 11/b., specify evidence (select one):  <input type="checkbox"/> Yes, because patient died on or before the 28th day after onset  Date of Death: <input type="text"/> / <input type="text"/> / <input type="text"/>  mm   dd   yyyy</p> <p><input type="checkbox"/> Yes, because neurological symptoms did not worsen after 28 days of onset .</p> <p><input type="checkbox"/> Yes, because patient was discharged to a lower level of care or home on or before 28 days after onset (and subsequent medical records are unavailable).</p> <p>If No to 11/b, specify evidence:  <input type="checkbox"/> No, because neurological symptoms continue to worsen after 28 days after onset.</p>





14	MRI	<p>14/a. Spinal Cord MRI    <input type="checkbox"/> Normal    <input type="checkbox"/> Abnormal    <input type="checkbox"/> Not Done</p> <p>Date Completed: <input type="text"/> / <input type="text"/> / <input type="text"/>                                   mm    dd    yyyy</p> <p>If abnormal, results: _____  _____  _____  _____  _____  _____  _____  _____  _____  _____</p> <p><input type="checkbox"/> Normal    <input type="checkbox"/> Abnormal    <input type="checkbox"/> Not Done</p> <p>Date Completed: <input type="text"/> / <input type="text"/> / <input type="text"/>                                   mm    dd    yyyy</p> <p>If abnormal, results: _____  _____  _____  _____  _____  _____  _____  _____  _____  _____</p> <p><input type="checkbox"/> Normal    <input type="checkbox"/> Abnormal    <input type="checkbox"/> Not Done</p> <p>Date Completed: <input type="text"/> / <input type="text"/> / <input type="text"/>                                   mm    dd    yyyy</p> <p>If abnormal, results: _____  _____  _____  _____  _____  _____  _____  _____  _____  _____</p> <p>14/b. Brain MRI    <input type="checkbox"/> Normal    <input type="checkbox"/> Abnormal    <input type="checkbox"/> Not Done</p> <p>Date Completed: <input type="text"/> / <input type="text"/> / <input type="text"/>                                   mm    dd    yyyy</p>
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		<p>If abnormal, results: _____          _____          _____          _____          _____          _____          _____          _____          _____          _____          _____</p> <p>_____ Normal    _____ Abnormal    _____ Not Done</p> <p>Date Completed: _____ / _____ / _____                                           mm    dd    yyyy</p> <p>If abnormal, results: _____          _____          _____          _____          _____          _____          _____          _____          _____          _____          _____</p> <p>_____ Normal    _____ Abnormal    _____ Not Done</p> <p>Date Completed: _____ / _____ / _____                                           mm    dd    yyyy</p> <p>If abnormal, results: _____          _____          _____          _____          _____          _____          _____          _____          _____          _____          _____</p> <p><b>If any brain and/or spinal cord MRI is abnormal, STOP ABSTRACTION and refer to neurologist.</b></p>
15	Other neurodiagnostic studies	<p>Yes, specify _____</p> <p>_____ Normal    _____ Abnormal    Date Completed: _____ / _____ / _____             mm    dd    yyyy</p> <p>If abnormal, results: _____</p>











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**Instructions:**

- Column 1 Case number: Each country will be assigned a letter. For example, A for USA and the US cases will be A0001, A0002, etc.
- Column 2 Country.
- Column 3 Center (if applicable): Please provide complete information on where the case was identified.
- Column 4 Hospital (if applicable): Please provide complete information on where the case was identified.
- Column 5 Age: Age in years and months. For example, a 60-year old (who will turn to 61 in 1 month) will be 60 years and 11 months; an 11-month old will be 0 years and 11 months.
- Column 6 Gender (Male/Female/Unknown): Transgender will be categorized as is.
- Column 7 GBS Onset Date (YYYY-MM-DD).
- Column 8 GBS Diagnosis Date (YYYY-MM-DD).
- Column 9 Final Diagnosis / Brighton Level (1, 2, 3, or 4a).
- Column 10 First GBS diagnosis ever (Yes/No/Unknown): New case in the lifetime.
- Column 11 Other conditions of importance occurring 30 days prior to GBS (Yes/No/Unknown; If yes, please specify).
- Column 12 H1N1 vaccination (Yes/No/Unknown).
- Column 13 (If Yes) H1N1 vaccination date (YYYY-MM-DD). If >1 dose administered, please record additional doses in separate lines.
- Column 14 (If Yes) H1N1 vaccine product name. If >1 dose administered, please record additional doses in separate lines.
- Column 15 Seasonal flu vaccination (Yes/No/Unknown).
- Column 16 (If Yes) seasonal flu vaccination date (YYYY-MM-DD). If >1 dose administered, please record additional doses in separate lines.
- Column 17 (If Yes) seasonal flu vaccine product name. If >1 dose administered, please record additional doses in separate lines.