



# IMMUNIZATION STRESS-RELATED RESPONSES

## A Synopsis

A synopsis of the manual for program managers and health professionals to prevent, identify and respond to stress-related responses following immunization



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This synopsis is developed on the contents of the "Immunization stress-related responses. A manual for program managers and health professionals to prevent, identify and respond to stress related responses following immunization".

# ACRONYMS AND ABBREVIATIONS

<b>AEFI</b>	Adverse Events Following Immunization
<b>CIOMS</b>	Council for International Organizations of Medical Sciences
<b>CRPS</b>	Complex Regional Pain Syndrome
<b>DNSR</b>	Dissociative Neurological Symptom Reaction
<b>HPV</b>	Human Papillomavirus
<b>ICD</b>	International Classification of Diseases
<b>ISRR</b>	Immunization Stress-Related Response
<b>POTS</b>	Postural Orthostatic Tachycardia Syndrome

# EXECUTIVE SUMMARY

The cause-specific definitions of an “adverse event following immunization” (AEFI) of the Council for International Organizations of Medical Sciences (CIOMS) and WHO include anxiety-related reactions. It is proposed that an alternative term be used: “immunization stress-related response” (ISRR). Many immunization programme managers and health care professionals are not well trained to recognize or manage this type of AEFI, as prevention, management and communication strategies have not been well defined. The objective of this document is to equip programme managers at local, regional and national levels and health care professionals with the technical knowledge to prevent identify, manage and respond to both individual and clusters of ISRR.

This synopsis outlines the framework of the contents in the manual on immunization stress-related responses. This manual was developed by the World Health Organization for program managers and health professionals to prevent, identify and respond to stress-related responses following immunization. Comprehensive information is available in the main document.





# IMMUNIZATION STRESS-RELATED RESPONSES (ISRR)

A quick reference to the ISRR manual for programme managers and health professionals to prevent, identify and respond to stress-related responses before, during and after immunization

## Immunization stress-related response

The response to a stressor encompasses a range of manifestations (symptoms and signs) that may include an acute stress response, which includes a vasovagal reaction (fainting), hyperventilation or a dissociative neurological symptom reaction (DNSR), which includes non-epileptic seizures (formerly known as a “conversion reaction”).

“Immunization stress-related response” (ISRR) is a response to the stress some individuals may feel when receiving an injection and covers the spectrum of manifestations. Formerly, this spectrum was described as an **Adverse Event Following Immunization** (AEFI) arising from anxiety about immunization. The term ISRR was introduced, as the word “anxiety” does not adequately capture all the elements of the presentation of these AEFI. Unlike other AEFI, ISRR may also occur immediately before immunization. In addition, an ISRR may affect an individual or groups of individuals, resulting in a cluster, often referred to as “mass psychogenic illness”.

## The biopsychosocial model of ISRR

A stress response is complex, as it involves a combination of physiological (biological) factors occurring within individuals, which interact with their psychological strengths, vulnerabilities, knowledge and preparedness and in particular social contexts. For example, certain biological factors may facilitate a vasovagal reaction after immunization; these include age (adolescence is period of risk), gender (females are more predisposed than males) and weight (lower body mass index increases risk). Psychological factors include an individual’s temperament (personality), ability to understand and reason, preparedness for immunization and underlying anxiety, which is influenced by previous experience. All these factors may affect the perception of pain symptoms during and after injection of a vaccine.

Social factors associated with the injection, such as community trust in health care, community perceptions, norms and values about immunization, community and family support for immunization and false or misleading news reports (television, print, radio, online) are also important. Social media messages about immunization affect the behaviour of health care workers, family, friends and others such as peers who are being vaccinated (in mass or school campaigns). Thus, stress responses may involve stressors other than the actual immunization.



## ISRRS ARE NOT THE PATIENT'S FAULT

→ Their reactions are responses to their perceived stress of the event.

## Manifestations of ISRR

Most symptoms and signs of an ISRR are transient and resolve spontaneously, whether they manifest just before, during or immediately after immunization. An initial acute stress response (consistent with a "fight or flight" response) may be followed by an overcompensatory parasympathetic reaction, in which the heart rate and blood pressure fall precipitously. Thus, in some individuals, an acute stress response may lead to physiological overcompensation and a vasovagal reaction.

An acute stress response may range from mild feelings of worry and "butterflies" in the stomach to symptoms of sympathetic nervous system stimulation – increased heart rate, palpitations and difficulty in breathing.

The symptoms of vasovagal reactions ("fainting" in lay terms) range from mild dizziness to a brief loss of consciousness (syncope) because of insufficient blood flow to the brain resulting from low blood pressure due to a decreased heart rate, vasodilatation of blood vessels or both. It can be associated with prodromal symptoms such as nausea, sweating or pallor. Rarely, it is associated with a syncopal seizure or can result in injury from falling.

Hyperventilation syndrome (rapid breathing) may be part of an acute stress response and include features of a DNSR. The presenting features are dyspnoea (shortness of breath), chest pain, paraesthesia (tingling sensation) in the fingers, light-headedness, dizziness and headache. In some individuals, this may be a recurrent symptom and not necessarily associated with recent provocative stress. Syncope and non-epileptic seizures characterized by pseudo-absence spells may occur. Episodes may often recur, and the diagnosis may be missed and ascribed to cardiac or other life-threatening disorders.

Importantly, ISRR can sometimes manifest with dissociative neurological symptoms such as weakness or paralysis, abnormal movements or limb posturing, gait irregularities, speech difficulties or non-epileptic seizures with no apparent neurological basis. The symptoms and signs may be delayed, especially when such symptoms occur in clusters involving many vaccine recipients. DNSRs appear to be more common in females; they are not typically diagnosed in infants. In children, DNSRs typically manifest with a single symptom. DNSRs are considered to be the result of numerous factors that interact at different levels, which can be understood within the biopsychosocial framework

One form of DNSR presents as non-epileptic seizures, which are less common in early childhood (the youngest patient reported was 5 years old) and appear to become more common in adolescence. This is typically a diagnosis of "exclusion". Non-epileptic seizures are also often referred to as pseudo-seizures or psychogenic seizures. They are events that resemble an epileptic seizure but without the characteristic neural discharges (detected on an electroencephalogram) associated with epilepsy. Non-epileptic seizures are considered involuntary, and affected individuals may or may not report feeling fearful or anxious.



## What is not an ISRR?

A variety of delayed and ongoing AEFI have been reported after immunization for which the symptoms and signs are unexplained after appropriate medical investigations, and a causal association with immunization has currently not been established after review of the evidence. These events include complex regional pain syndrome, postural orthostatic tachycardia syndrome and chronic fatigue syndrome. In some countries, these conditions have been reported as AEFIs and have caused significant concern to the public and health authorities.

## Prevention of ISRR

A trained, competent, compassionate vaccinator with good communication skills; who uses a friendly, confident, relaxed approach and a trusting relationship is likely to minimize the occurrence of ISRR. Before immunization, individuals with predisposing risk factors should be identified, such as adolescent age group (10–19 years), history of vasovagal syncope, previous negative experience of immunization, an expressed fear of injections or needles and pre-existing conditions such as an anxiety disorder or a developmental disorder such as autism spectrum disorder.

General preventive interventions include talking to parents or caregivers, about how to help the person to be vaccinated and avoid modeling fear of needles. Other interventions to reduce pain include an age- and developmentally-appropriate, evidence-based approach to the vaccination environment, the health care provider, physical position and psychological strategies such as distraction. If possible, all vaccines should be administered in a calm, private, planned ambient environment, even during administration to a large group, such as in a school. Syncope can be avoided by measures such as vaccinating the individual while he or she is seated or in the supine position and encouraging muscle tension.

Communication should be directed towards both the vaccine recipient and any accompanying parent or caregiver. Before mass vaccination, especially of adolescents, targeted messages and awareness sessions might help to alleviate some concerns.

## Diagnosis of ISRR

An acute stress response can include a variety of cardiovascular (tachycardia, palpitations), respiratory (shortness of breath, hyperventilation) and neurological or sensory (dry mouth, hot or cold sensation, tingling or numbness of limbs and sweating) manifestations. Some individuals may have a parasympathetic nervous system response with bradycardia (slow heart rate) and blood vessel dilatation, both of which can result in hypotension (low blood pressure).

**Table 1.1 Differentiation of anaphylaxis from an acute stress response of general and vasovagal reaction with syncope**

	ANAPHYLAXIS	ACUTE STRESS RESPONSE	
		GENERAL	VASOVAGAL REACTION WITH SYNCOPE
Onset	Usually 5 min after immunization but may be delayed up to 60 min	Sudden, occurs before, during or shortly after (< 5 min) immunization	Sudden, occurs before, during or shortly after (< 5 min) immunization. May present after 5 min if the individual stands suddenly.
<b>System</b>			
Skin	Generalized urticaria (hives) or generalized erythema, angioedema, localized or generalized, generalized pruritus with or without skin rash, generalized prickle sensation, localized injection site urticaria, red and itchy eyes	Pale, sweaty, cold, clammy	Pale, sweaty, cold, clammy
Respiratory	Persistent cough, noisy breathing and airway constriction: wheeze, stridor. If very severe, respiratory arrest.	Hyperventilation (rapid, deep breathing)	Normal to deep breaths
Cardiovascular	↑ heart rate, ↓ blood pressure, circulatory arrest	↑ heart rate, normal or ↑ systolic blood pressure	↓ heart rate with or without transient ↓ in blood pressure
Gastrointestinal	Nausea, vomiting, abdominal cramps	Nausea	Nausea, vomiting
Neurological and other symptoms	Uneasiness, restlessness, agitation, loss of consciousness, little response when supine or lying flat	Fearfulness, light-headedness, dizziness, numbness, weakness, tingling around the lips, spasms in hands, feet	Transient loss of consciousness, good response once supine or lying flat, with or without tonic-clonic seizure

If sudden loss of consciousness occurs more than 5–10 min after immunization, in addition to vasovagal syncope, anaphylaxis should be considered as a possible diagnosis. As anaphylaxis may be life-threatening, it requires immediate management with intramuscular adrenaline. Thus, it is important to exclude anaphylaxis and then to define manifestation of the ISRR. This will guide proper and immediate case management, which is critical to preventing further concern and possible development of a cluster. Clusters of cases of anaphylaxis have not been reported. Therefore, a cluster of individuals presenting with these symptoms and signs, including collapse, is likely to be an ISRR and not anaphylaxis.

Clues that a patient has a DNSR include the disappearance of symptoms or signs when the patient is distracted, signs or symptoms that are not consistent with known neurological disorders, and no response to pharmacological interventions. Symptoms and signs may be intermittent and vary by presentation. For example, there may be inconsistent neurological findings, such as unusual gait or posture. Limb power and sensation may be normal when the patient is lying down, but he or she may be unable to stand or walk. If a DNSR presents as a seizure, non-epileptic seizures must be differentiated from seizures due to other causes, such as epilepsy, meningitis and encephalopathy.



## Management of ISRR

An ISRR must be differentiated from anaphylaxis and other diagnoses. If a vasovagal reaction occurs, the individual should remain in the supine position. Once an ISRR has been identified, the vaccine provider should clearly ascertain and exclude a vaccine product-related reaction and an immunization error-related reaction. The nature of the symptoms, the fact that they are expected and not harmful and will resolve spontaneously without the need for medication should be explained. Medication and hospitalization should be avoided if possible, as they may aggravate the situation and cause additional cases.

Management of a DNSR, including a non-epileptic seizure, requires a multidisciplinary approach, with medical and psychological assessments to reduce the functional disability. As a first measure, reassure the affected person and others, assist the person to lie down in a calm, well-ventilated place, and, importantly, keep calm and confident; encourage a return to "normal activity". In general, referral to a health practitioner or a health centre with expertise will be required. Treatment must be tailored to the constellation of symptoms and may include physiotherapy, cognitive behavioural therapy and/or pharmacological interventions.

## Clusters of ISRR

In social situations, such as schools and other places where people congregate, one person's syncope may trigger syncope in others, in what is often referred to as "mass psychogenic illness" or "mass hysteria" in the literature; however, patients may find the term demeaning, which may worsen the problem. This pattern can be exacerbated when children or adolescents waiting to be vaccinated observe others who are experiencing stress responses after immunization.

Clusters of events after immunization have occurred in the past in both rural and urban settings and in high-, middle- and low-income countries throughout the world, and the size of the clusters has varied widely, from 7 affected individuals in one school to over 800 in several schools. Individuals in the clusters described similar symptoms of dizziness, headache and syncope, with rapid onset after vaccination. Abdominal symptoms were also reported. Vaccination programmes have been negatively affected (and in some instances suspended), particularly when these events were reported in traditional and/or social media. Investigations showed that the clusters were not due to the vaccine product or immunization error. Both males and females were affected, and most published clusters involved adolescents. Various vaccines were implicated, although some of the clusters involved a new vaccine or a change in the routine vaccination programme, including a novel vaccine, a new age group or a new setting for vaccination.

In some instances, clinical management of cases within clusters has involved invasive testing or treatment that led to even greater harm, as the link with stress was not recognized. Small clusters occurring in one group setting (typically a school) have spread quickly to a larger number, often escalated by media reports.

As previously mentioned, it is extremely rare and almost impossible for anaphylaxis to occur in clusters. A wrong diagnosis of anaphylaxis has resulted in mismanagement of ISRR clusters, resulting in hospitalization and inappropriate treatment, further worsening the patients' condition.

## ISRR during mass immunization campaigns

During mass immunization, health care workers should anticipate and take measures to avoid or minimize ISRR by assessing the local setting for vaccine administration, including the waiting area, during the planning phase.

Emergency kits and information, education and communication messages should be readily available, and job aids or posters showing differentiation of anaphylaxis from an acute stress response (including vasovagal syncope) should be available to health workers. Planning should include primary responders (with addresses, phone numbers and transport plans) to an event and to clusters of events and ensure that they are aware that they might be called in the event of an ISRR. Mitigation of environmental factors known to contribute to clusters, such as an overheated, crowded waiting area, prolonged standing, lack of privacy and access to e-communication tools (e.g. for text messaging, social media), should be considered.

If vaccination requires an injection, vaccine recipients should be offered privacy and care taken to recognize the local culture and sensitivity with regard to dress and gender. Individuals with risk factors for ISRR should be vaccinated separately. General pain management techniques should be used. If a cluster of cases has occurred, it should be de-escalated by separating affected individuals from each other and from healthy vaccine recipients.

The presence of local community leaders and local health workers who are familiar to the vaccine recipients can calm and comfort the vaccine recipients and thereby support the immunization team. After vaccination, the vaccine recipients should be advised to wait for 30–60 min in a waiting area that is well lit and provides basic distractions and a relaxing ambience.

## ISRR as a component of AEFI surveillance

In general, individual acute stress responses need not be notified or reported as part of AEFI surveillance, with the exception of a vasovagal reaction with syncope, especially if an injury results. DNSRs, including non-epileptic seizures that develop later, may be reported if the patient seeks the intervention of a health care provider and attributes the symptoms to immunization.

The standard national AEFI reporting form should be used to document the signs and symptoms observed and the basic clinical features. Clusters of such events should be reported immediately to higher authorities by the fastest means possible (e.g. telephone). Depending on the seriousness of the event or the presence of a cluster, the responsible authorities should initiate a detailed investigation. During the investigation, it is important to ask relevant stakeholders probing questions and collect evidence on the biopsychosocial aspects to determine whether the event is a stress response to immunization.

The causality of all ISRR should be assessed with the WHO classification of causality for AEFI. The first step is to determine whether the reported symptoms and signs fulfil the definition of an acute stress response, vasovagal reaction or DNSR. If so, causality assessment should be continued. The next step is to formulate the question. Unlike other adverse events, the symptoms of an acute stress response may precede administration of a vaccine. After exclusion of coincidental events, such cases may be classified as “consistent with a causal association to immunization” in the category of ISRR.



## Communication of ISRR

Countries must have a strong communication plan to anticipate, prepare for and respond effectively to ISRR. After an assessment of the background information, communications to help prevent ISRR may be broadly divided into “primary” and “secondary” strategies.

Primary prevention strategies are conducted at population level, at an early stage, when risk factors are present. The strategies include emphasizing the importance and safety of vaccines and immunization, continuously collecting and analysing data on the situation and preparing and testing key messages and tools. At the same time, health care providers should be trained in communication and interpersonal skills and the importance of staying calm during an event. They should be given refresher courses on AEFI and ISRR and be advised to plan immunization sessions in such a way as to avoid long waiting times for immunization and to avoid observation of immunization by others. In addition, they should use pain management strategies and techniques for relaxing vaccine recipients by talking to them and increasing their confidence before vaccination. They should also be trained in the process and timelines for reporting events and following them up.

Secondary prevention strategies are conducted at local level and involve detecting and responding to ISRR. In addition to the components of primary prevention strategies, secondary strategies include activating the communications team and deciding if, when and what to communicate, according to the crisis communications plan. Information should be provided continuously to stakeholders, especially the media when necessary, and they should also monitor public sentiment through both media coverage and social media and counteract any rumours. Health care providers should share lessons from experience with previous ISRR and review the structure of the immunization environment to identify any immediate adjustments that might be required, such as more privacy and shorter waiting times.

In individual cases, the main goal of communication is rapid management and local de-escalation of the situation to avoid increasing the number of affected individuals. Health care providers and other staff should be ready to take all the necessary steps to isolate the person concerned (“index case”) tactfully to prevent the transmission of fear and anxiety to others and to reduce stress. It is important to remember that ISRR are not the patient’s “fault”, nor are they “crazy”. Their reactions are responses to their perceived stress of the event. Patients with stress-related AEFI must be managed by professionals who are qualified and experienced in diagnosis and managing such reactions. Cultural sensitivity must be taken into consideration during case management.

Monitoring and evaluation are complementary to the communications plan, which should therefore include a system for monitoring the process, outputs and outcomes and for evaluating the results. Documentation of lessons learnt, good practices and innovations in communication of ISRR and other AEFI will benefit immunization programmes. It is important to continue to maintain relationships built with stakeholders and the media long after events have taken place to ensure that these groups continue to be strong programme partners and contribute to sustaining trust in vaccines and in the health authorities who deliver them.



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