Immunization stress-related response (ISRR) - A synopsis

A quick reference to the ISRR manual for program managers and health professionals to prevent, identify and respond to stress-related responses following immunization
**Immunization stress-related response**

The response to a stress 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 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 about getting an injection, and encompasses the spectrum of manifestations mentioned previously. Formerly, this spectrum was described as “an AEFI arising from anxiety about the immunization”. ISRR was necessitated since the term “anxiety” does not adequately capture all the elements of how these AEFI may present. In contrast to other AEFI, the symptoms of an ISRR may also occur immediately prior to immunization. In addition, an ISRR may only affect an individual or groups of individuals resulting in a cluster which is often referred to as mass psychogenic illness.

**The biopsychosocial model of ISRR**

A stress response is complex. It involves a combination of physiological (biological) factors occurring within individuals interacting within their own psychological strengths, vulnerabilities and knowledge/preparedness and within a particular social context.

For example, certain biological factors may facilitate a vasovagal reaction following immunization. These include age (adolescence is risk period), gender (females are more predisposed), weight (lower body mass index increases risk), etc. Psychological factors include an individual’s temperament (personality), ability to understand and reason, preparedness for the immunization event, and underlying anxiety which is influenced by previous experience. These all may affect the perception of pain symptoms following the injection of a vaccine.

Social factors around the immunization injection such as community trust in healthcare, community perceptions, norms, and values around immunization, community and family support for immunization and false or misleading news reports (TV, print, radio, online) are also important. Social media messages around immunization have an impact on the behavior of healthcare workers, family or friends and others such as peers being vaccinated (such as may occur in mass or school campaigns). Thus, stress responses can occur with stressors other than the actual immunization.

**Manifestation of ISRR**

Most symptoms and signs of an ISRR are transient and resolve spontaneously manifesting just before, during, or immediately after immunization. It is important to remember that an initial acute stress response (which is consistent with fight or flight response) may be followed by an over compensatory parasympathetic reaction in which heart rate and blood pressure fall precipitously. Thus, an acute stress response in some individuals 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 those of sympathetic nervous system stimulation – increased heart rate, palpitations and difficulty breathing.

Vasovagal reactions (known as fainting in lay-terms) manifest with symptoms 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 can be associated with a syncopal seizure and/or can result in injuries from falling.

Hyperventilation syndrome (rapid and fast breathing) may be part of an acute stress response and include features of a dissociative neurological symptom reaction. The presenting features are dyspnoea (shortness of breath), chest pain, paraesthesia (tingling sensation) in fingers, light-headedness, dizziness, and headache. In some individuals this maybe a recurrent symptom and is not necessarily associated with recent provocative stress. Syncope and non-epileptic seizures characterised by pseudo-absence spells may occur. Adolescent girls are usually affected and episodes are associated with anxiety or be a component of an anxiety disorder. 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, and/or non-epileptic seizures with no apparent neurological basis. The symptoms and signs may be delayed, especially in cases where such symptoms occur in clusters involving many vaccine recipients. Dissociative neurological symptom reactions appear to be more common in females. They are not typically diagnosed in infants. In children, dissociative neurological symptom reactions more typically manifest with a single symptom. Dissociative neurological symptom reactions are thought to be the result of numerous factors interacting at different levels which can be understood within the biopsychosocial context.

One form of a dissociative neurological symptom reaction presents with non-epileptic seizures which are less common in early childhood (youngest age reported is 5 years) and appear to increase in adolescence. This is typically a diagnosis of “exclusion”. Non-epileptic seizures are also often referred to as pseudo-seizures or psychogenic seizures. Non-epileptic seizures are events resembling an epileptic seizure, but without the characteristic neural discharges (detected in EEG) associated with epilepsy. Non-epileptic seizures are seen as involuntary and effected individuals may or may not report feeling fearful or anxious before the event.

**What is NOT an ISRR**

A variety of delayed and ongoing AEFI have been reported post-immunization where the symptoms and signs are unexplained after appropriate medical investigations and the causal association with immunization, after review of the current evidence, has not been established. These include, complex regional pain syndrome (CRPS), postural orthostatic tachycardia syndrome (POTS) and chronic fatigue syndrome (CFS). In some countries these conditions have been reported as AEFI and have been of significant concern to the public and health authorities.

**Prevention of ISRR**

A trained, competent and compassionate immunizer with good communication skills utilizing a friendly, confident and relaxed approach with a trusting relationship is more likely to minimize emergence of an ISRR. Prior to immunization, it is helpful to identify individuals with predisposing risk factors such as adolescent age group (10-19 years), history of vasovagal syncope, previous negative experience with immunization, an expressed fear of injections/needles, and pre-existing conditions such as an anxiety disorder or, a developmental disorder such as autism spectrum disorder.
General preventive interventions, include taking the parent or caregiver present into confidence who have hopefully not instilled fear of needs and fear of health care professionals. Preventative interventions also include using an age- and developmentally-appropriate evidence-based approach focusing on immunization environment, health care provider and family communication, physical position, and psychological strategies like distraction to reduce pain. As far as possible, all immunizations should be administered in a calm, private and planned environment even when administered to a large group such as a school setting. If syncope is anticipated, it can be avoided by using specific additional measures such immunizing the individual seated or in the supine position and using “muscle tension”.

Communication should be directed towards the vaccine recipient but also any accompanying parent or caregiver (as relevant). Prior to mass vaccination, especially for adolescents, targeted messages and awareness sessions might help to alleviate some concerns.

**Diagnosis of ISRR**

An acute stress response could occur with a variety of cardiovascular (tachycardia - an increased heart rate, palpitations - feeling the heart beat), respiratory (shortness of breath, hyperventilation i.e. breathing fast and deep) and neurological/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).

**Differentiating anaphylaxis from an acute stress response - general and vasovagal reaction with syncope**

<table>
<thead>
<tr>
<th></th>
<th>Anaphylaxis</th>
<th>Acute Stress Response</th>
<th>General</th>
<th>Vasovagal reaction with syncope</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>Usually occurs after 5 minutes but maybe delayed up to 60 minutes</td>
<td>Sudden, occurs before, during, or shortly after (&lt; 5 minutes) immunization</td>
<td>Sudden, occurs before, during, or shortly after (&lt; 5 minutes) immunization. May present after 5 minutes if individual changes position – stands suddenly</td>
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<tr>
<td><strong>Systems</strong></td>
<td></td>
<td><strong>Skin</strong></td>
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<td></td>
<td>Generalized urticaria (hives) or generalized erythema, angioedema, localized or generalized, generalized pruritus with or without skin rash, generalized prickle</td>
<td>Pale, sweaty, cold, clammy</td>
<td>Pale, sweaty, cold, clammy</td>
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| **sensation, localized injection site urticaria, red and itchy eyes** |
| **Respiratory** | Persistent cough, noisy breathing as airway constriction: wheeze, stridor. If very severe respiratory arrest. | HYPERVENTILATION Rapid and deep breathing | Normal to deep breaths |
| **Cardiovascular** | ↑ heart rate, ↓ BP, circulatory arrest | ↑ heart rate, normal or elevated systolic Blood Pressure | ↓ heart rate, +/- transient ↓ BP |
| **Gastrointestinal** | Nausea, vomiting Abdominal cramps | Nausea | Nausea, vomiting |
| **Neurological and other symptoms** | Uneasiness, restlessness, agitation, Loss of Consciousness (LOC), little response once supine /flat | Fearfulness, light-headedness dizziness, numbness, weakness tingling around lips, spasm in hands, feet | Transient Loss of Consciousness (LOC), good response once supine /flat +/- tonic-clonic seizure |

It is important to remember that if sudden loss of consciousness is delayed and occurs more than 5-10 minutes after immunization, anaphylaxis should be considered as a possible diagnosis in addition to vasovagal syncope. Since anaphylaxis may be life-threatening, it requires immediate management with intramuscular adrenaline. Thus, it is important to exclude anaphylaxis and secondly define the manifestation of the ISRR to guide proper onsite case management, which is critical to preventing further concerns and possible development of a cluster. Clusters of anaphylaxis have NOT been reported. Therefore, a cluster of multiple individuals presenting with these symptoms and signs, including collapse, is likely to be an ISRR and not anaphylaxis.

Clues that a patient has a dissociative neurological symptom reaction include the disappearance of symptoms or signs when the patient is distracted, signs or symptoms which are not consistent with known neurological disorders, and no response to pharmacological interventions. Symptoms and signs may be intermittent and vary between presentations. For example, there may be inconsistent neurological findings such as unusual gait or postures. The limb power and sensation may be normal lying down but the patient may exhibit an inability to stand and walk. If presenting as seizure, it is important that non-epileptic seizures be differentiated from seizures due to other causes such as epilepsy, meningitis and encephalopathy.

**Management of ISRR**
The key is to differentiate an ISRR from anaphylaxis and other diagnoses. If a vasovagal reaction has developed, 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 immunization error-related reaction. The nature of the symptoms, the fact that they are expected and
not harmful and will resolve spontaneously without any need for medications, should be explained. **Medication and hospitalization should be avoided as much as possible** as experience has shown that they may aggravate the situation and cause additional cases.

Management of a dissociative neurological symptom reaction including a non-epileptic seizure involves a multi-disciplinary approach including medical and psychological assessments that focuses on interventions to reduce the functional disability. As a primary measure, reassure the affected person and others, assist the person to lie down in a calm and well-ventilated place, and importantly, keep calm and confident. Encourage returning to “normal activity”. In general, referral to a health practitioner or a health centre with expertise will be required. Treatments need to be tailored to the symptom constellation and may include physiotherapy, cognitive behavioral therapy and/or pharmacological interventions.

**ISRR occurring as clusters of cases**

In social situations, such as schools or in 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. This pattern can be exacerbated when children or adolescents waiting to be vaccinated can observe others post-vaccination who may be experiencing stress responses.

Clusters of these events following immunization have occurred in both rural and urban settings, as well as in high-, middle- and low-income countries across the world and the extent of the cluster has varied widely from 7 affected individuals in one school to over 800 in multiple schools. Individuals in clusters described similar symptoms of dizziness, headache, and syncope with rapid onset after vaccination. Sometimes abdominal symptoms were reported. Vaccination programs have been negatively affected (and in some instances entire programs suspended) especially when these events are reported in the traditional and/or social media.

Investigations have demonstrated the absence of vaccine product or immunization error. Both males and females were affected, and most published clusters involved adolescents. Different vaccines were implicated; although some of the clusters involved a new vaccine introduction or a change in the routine vaccination program, including a novel vaccine, new age group, or new setting for vaccination.

In some instances, clinical management of cases within the clusters involved invasive testing or treatment that led to even more harm, as the link to 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.

It is also important to keep in mind that, as previously mentioned, it **is extremely rare and almost impossible for anaphylaxis to occur in clusters**. However, in some instances, making a wrong diagnosis of clusters of anaphylaxis has resulted in mismanagement of ISRR clusters resulting in hospitalizations with inappropriate treatment and caused further worsening of the patients’ condition.

**ISRR during mass immunization campaigns**

In the case of mass immunization, health care workers should anticipate and take measures to avoid or minimize ISRR. During the planning phase itself, the “local setting” of mass vaccine administration including the waiting areas prior to vaccination should be assessed.
Emergency kits and information, education and communication (IEC) messages should be readily available. Of importance, job aids or posters differentiating anaphylaxis from an acute stress response including vasovagal syncope should be available to health workers. Planning should also incorporate the different primary responders (with address, phone numbers and transportation plans) to an individual event as well as a cluster of events and ensuring that they are aware of the possibility of being called in the event of an ISRR and responding appropriately. Mitigation of environmental factors known to contribute to clusters such as an overheated and crowded waiting area, prolonged standing, lack of privacy and availability of e-communication tools amongst those being immunized (e.g., for text messaging, social media) needs to be considered.

If vaccination requires injections, privacy needs to be offered to individual vaccine recipients keeping in consideration the local culture and sensitivities regarding dress code and gender. Individuals with risk factors for ISRR should especially be separately immunized. General pain management techniques should also be used. If a cluster of cases has already occurred, de-escalation by separating affected individuals from each other and from healthy vaccine recipients is key.

Having local community leaders and local health workers familiar to the vaccine recipients is helpful. This can increase calmness and comfort in the vaccine recipients and thereby support the immunization team. After vaccination, the vaccine recipients should be advised to wait for a period of 30 minutes to an hour at a waiting area that is well illuminated, providing basic distractions and a relaxing ambience.

**ISRR as a component of AEFI surveillance**

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

The standard country AEFI reporting form should be used and the signs and symptoms observed, and the basic clinical features should be documented. 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, responsible authorities should initiate a detailed investigation of the concerned event or cluster of events. During investigation, it is important to ask probing questions of the relevant stakeholders and collect evidence on the biopsychosocial aspects to determine if the event could be a stress response related to immunization.

Causality for all ISRR should be assessed using the WHO causality assessment classification for AEFI. The first step should be to see if the reported symptoms and signs fulfill a case definition for an acute stress response, vasovagal reaction or dissociative neurological symptom reaction. If so, the causality assessment process should be followed. The next step is to formulate the causality question. However unlike other adverse events, for an acute stress response, symptoms may sometimes precede the actual administration of the vaccine. When assessing causality, after excluding coincidental events, such cases may be currently classified as “consistent with causal association to immunization” under the category of ISRR.
Communication aspects of ISRR

It is essential for countries to have a strong communication plan in place to anticipate, prepare for, and respond effectively to ISRR. Based on an assessment of background information, communication interventions to help prevent ISRR may be broadly divided into ‘primary prevention’ or ‘secondary prevention’ strategies.

Primary prevention strategies are implemented at a population level, at a very early stage when risk factors are present. Strategies include continuing to explain the importance and safety of vaccines and immunization, gathering and analyzing ongoing data on the situation and developing and testing key messages and tools. Simultaneously, health care providers should be trained in communication and interpersonal skills, and the importance of staying calm in the case of any event. They should be provided refresher courses on AEFI and ISRR and be urged to plan immunization sessions to avoid long waiting periods for a person being vaccinated and avoid persons watching those being vaccinated. In addition, they should emphasize techniques for relaxing vaccine recipients by connecting with and increasing their confidence prior to vaccination. They should also be trained on the processes and timelines for reporting events and follow-up actions.

Secondary prevention strategies are implemented at a local level on detecting and responding to ISRR. In addition to the components outlined in primary prevention strategies, secondary prevention strategies include activating the communications team and deciding if, when, and what to communicate and implement according to the crisis communication plan. It is important to simultaneously provide ongoing information to stakeholders, especially the media when necessary, and also monitor public sentiment that would include both the media coverage and social media where applicable, and then counteract any spread of rumors. Health care providers need to share lessons from experience with previous ISRR and review the structure of the immunization environment looking for any immediate adjustments that may be needed such as increased privacy, less waiting times etc.

When individual cases occur, the major goal of communication is rapid on-site 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 and able to take all the necessary steps to tactfully isolate the person concerned (“index case”) in order to help 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”. The reactions are responses to the stress of the event as perceived by the patient. It is absolutely critical to ensure that patients with stress-related AEFI are managed by professionals who are qualified and experienced in diagnosis and managing such reactions. Cultural sensitivities also need to be taken into consideration during case management as this can vary from one context to another.

Monitoring and evaluation are complementary to the communication plan and should include a system to monitor the process, outputs, and outcomes, and evaluate the results. The documentation of lessons learnt, good practices, and innovations in ISRR related communications and other AEFI will benefit many aspects of immunization programmes. It is important to continue to maintain relationships built with key stakeholders and 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 delivering them.