IMMUNIZATION STRESS-RELATED RESPONSES

A manual for program managers and health professionals to prevent, identify and respond to stress-related responses following immunization
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The document is based on the principles enshrined in WHO’s Global Manual on Surveillance of Adverse Events following Immunization and the CIOMS Definition and Application of Terms for Vaccine Pharmacovigilance and also on published literature on anxiety-related responses to immunization.
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tr>
<td>AEFI</td>
<td>Adverse Events Following Immunization</td>
</tr>
<tr>
<td>CIOMS</td>
<td>Council for International Organizations of Medical Sciences</td>
</tr>
<tr>
<td>CRPS</td>
<td>Complex Regional Pain Syndrome</td>
</tr>
<tr>
<td>DNSR</td>
<td>Dissociative Neurological Symptom Reaction</td>
</tr>
<tr>
<td>HPV</td>
<td>Human Papillomavirus</td>
</tr>
<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
</tr>
<tr>
<td>ISRR</td>
<td>Immunization Stress-Related Response</td>
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<td>POTS</td>
<td>Postural Orthostatic Tachycardia Syndrome</td>
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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 is a technical document, and users are expected to have a basic understanding of immunization and its use in the broader health system. A shorter simpler synopsis is also available.
INTRODUCTION
1. INTRODUCTION

1.1. Immunization and pharmacovigilance

“Immunization is, and should be recognized as, a core component of the human right to health”³. Immunization prevents over 2.5 million deaths each year; however, as vaccine-preventable diseases become less common, maintaining public trust and support for immunization may be challenging. As the safety of vaccines is often a prime concern, all countries should have a functional, robust safety system. A comprehensive safety monitoring system requires coordination and collaboration between the national regulatory authorities responsible for licensure of drugs and vaccines in each jurisdiction and the immunization programme authorities who implement immunization policy and practice.

Vaccine pharmacovigilance consists of the activities for the detection, assessment, understanding and communication of “adverse events following immunization” (AEFI) and other vaccine- or vaccination-related issues and the prevention of untoward effects of vaccines or vaccination. An essential element of pharmacovigilance is post-licensure surveillance of AEFI, which involves:

• Safety surveillance system for detecting serious AEFI,
• Means for storing and reviewing collated reports of AEFI,
• Process for investigating serious AEFI and clusters of AEFI,
• Process for assessing causality in selected reports and
• Process for further investigation and communication of serious AEFI.

The outcome of the investigation of any serious AEFI should be communicated to all stakeholders, including communities. Some programmatic or regulatory factors might have to be changed to foster public trust in the programme.
1.2. ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

The report of the Council for International Organizations of Medical Sciences (CIOMS) and the WHO Working Group on Vaccine Pharmacovigilance defined an AEFI as

Any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.

Thus, a reported adverse event is not automatically mean that it was caused by the vaccine. CIOMS and WHO have defined five cause-specific AEFI, which differentiate vaccine- and vaccination-related reactions from coincidental events by rigorous assignment of causality:

- **Reaction to a vaccine product:** caused or precipitated by one or more of the inherent properties of a vaccine;
- **Reaction to a defect in vaccine quality:** caused or precipitated by one or more defects in the quality of a vaccine, including its administration with a device provided by the manufacturer;
- **Reaction to an immunization error:** caused by inappropriate handling, prescribing or administration of a vaccine;
- **Reaction related to anxiety:** arising from anxiety about immunization; and
- **Coincidental event:** caused by something other than a vaccine, immunization error or immunization anxiety.

1.3. Terminology: Immunization Stress-Related Response (ISRR)

The term “immunization anxiety-related reaction” is used to describe a range of symptoms and signs that may arise around immunization that are related to “anxiety” and not to the vaccine product, a defect in the quality of the vaccine or an error of the immunization programme. These reactions are described as AEFI arising from anxiety about immunization and include vasovagal-mediated reactions, hyperventilation-mediated reactions and stress-related psychiatric reactions or disorders. The term “anxiety” does not, however, adequately cover the presentation of all these AEFI and anxiety may not manifest during such events. Thus, a new term is proposed that better describes this cause-specific AEFI, which is “immunization stress-related response (ISRR)” (see Annex 1).

The new term is used to cover the entire spectrum of manifestations (symptoms and signs) of a stress response rather than a single symptom, anxiety. Individual responses to stress vary from person to person or may change according to time or context. In this cause-specific definition, stress results from the process of immunization. As for other AEFI, symptoms may occur during or after immunization; however, in contrast to other AEFI, the symptoms of an ISRR may also occur immediately before immunization. In this manual, we explain how individuals respond to stress in relation to immunization according to a conceptual biopsychosocial model used by health professionals, which helps to understand a person’s response to stress and how it may manifest.
1.4. Pathogenesis, diagnosis and management of stress in an individual: the biopsychosocial model

Stress responses are complex, involving a combination of physiological factors within an individual, his or her psychological strengths, vulnerability, knowledge and preparedness and the social context. The reasons for which an individual presents stress symptoms can be understood or explained with the biopsychosocial model. Although a stress response may present both “physical” and “psychological” symptoms, they are interconnected. For example, symptoms that we think of as “psychological” (e.g. depression) often have accompanying physical symptoms or signs (e.g. changes in appetite, sleep and weight loss). Likewise, psychological factors (e.g. anxiety) can influence physiological functioning (e.g. increase the heartbeat, raise the blood pressure). Such responses may occur more commonly in particular social environments, such as peer or occupational groups. Understanding the biological, psychological and social components can help in prevention, diagnosis and management (Annex 2).

1.4.1. Immunization and the biopsychosocial model

As stated above, any stress response that occurs around the time of immunization is influenced by physiological, psychological and social factors (Table 1.1). These factors can be broadly characterized into pre-existing factors and those that occur during or at the time of immunization. The distinction may not, however, be clear, as multiple factors contribute to a stress response. Understanding these factors helps in the prevention, diagnosis and management of an ISRR.

### Table 1.1 Immunization and the biopsychosocial model

<table>
<thead>
<tr>
<th>BIOPSYCHOSOCIAL FACTOR</th>
<th>PRE-EXISTING CONDITIONS (HISTORICAL)</th>
<th>CONDITIONS OCCURRING DURING IMMUNIZATION (DYNAMIC)</th>
</tr>
</thead>
</table>
| Physiological          | • **Age**: adolescence is a period of risk for vasovagal reactions.  
  • **Sex**: females are more predisposed to vasovagal reactions.  
  • **Weight**: lower body mass index increases the risk of vasovagal reactions  
  • Physiological stress response to pain, such as change in heart rate or blood pressure: acute stress response |
| Psychological          | • **Temperament** (personality)  
  • Ability to understand and reason, which depends on developmental age and cognitive understanding  
  • Preparedness: prior knowledge of immunization by injection  
  • Underlying anxiety  
  • Previous experience  
  • Underlying psychological factors (e.g. anxiety and fear) that may affect the perception of symptoms after an injected vaccine, such as pain at the injection site, dizziness due to a vasovagal reaction or fever and lethargy as part of the expected immune response to the vaccine |
| Social                 | • Community trust in health care  
  • Community perceptions, norms and values about immunization  
  • Community and family support for immunization  
  • False or misleading news reports and social media messages about immunization  
  • Experience of peers  
  • Behaviour of health care workers and observers (e.g. family, friends)  
  • Behaviour of others being vaccinated (e.g. during mass or school campaigns) |
1.5. Clusters of Immunization Stress-Related Responses (ISRR)

In a cluster, similar events occur in several individuals within minutes, hours or a few days and/or at the same location. Clustering of individuals experiencing a stress response has been reported for centuries and is due to a variety of inciting events, including immunization (see section 5.2). Various terms have been used to describe such “outbreaks”, including “mass hysteria”, “epidemic hysteria” and “mass psychogenic illness” (5, 6). As outlined in Annex 2, ISRR may spread by direct contact and also via social media, although the risk factors for cluster events continue to remain an important area for research. The Internet has increased the potential for rapid, effective sharing of negative concerns, which spread like a virus.

When ISRR occur in a cluster, they may generate public concern, and, if they are linked to immunization, they may halt or undermine the immunization programme. Although the vaccine is not the underlying cause, the event may be wrongly attributed to it. Halting an immunization programme in such situations will give the impression that the vaccine or the programme is the cause, which will both increase the risk of vaccine-preventable diseases and undermine vaccine acceptance and trust. Proper messaging and transparent communication with communities about the event and its possible causes are important initial steps in reducing the effect of the cluster on community acceptance of vaccines. Mismanagement of individual diagnoses and treatment can lead to iatrogenic complications due to inappropriate use of medications and over-investigation. Such situations are easily exploited by people opposed to immunization programmes.

1.6. Events, disorders or syndromes reported after immunization with currently no confirmed relation to immunization and not considered to be ISRR

A variety of delayed and continuing AEFI have been reported after immunization for which 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 dissociative neurological symptom disorders (also known as conversion disorders) with delayed onset of symptoms, other somatic symptom and related disorders, complex regional pain syndrome (CRPS) type 1 with delayed onset, postural orthostatic tachycardia syndrome (POTS) and chronic fatigue syndrome. The pathogenesis of these conditions is unknown and is the subject of research. Symptoms of CRPS and POTS may overlap with those of other conditions, making diagnosis difficult in both the general population and vaccinated individuals. Given the complexity of the syndromes and probable differences in the approaches to their diagnosis and management among countries and centres, the reported background incidence may differ in different countries.

In some countries, these conditions have been reported as AEFI, raising significant concern in the public and among health authorities. In some areas, such concern has led to reduced uptake of HPV vaccine (8, 9). It is beyond the scope of this manual to review each of these conditions in depth, but summaries of certain conditions with key references are provided below.
1.6.1. Complex regional pain syndrome (CRPS)

CRPS is characterized by continuing pain which is considered to be out of proportion to the severity of the initial injury or event. The clinical diagnostic criteria are pain accompanied by changes or asymmetry in at least three of four symptoms reported by the patient and at least two observable at the time of diagnosis: (i) sensory: hyperalgesia (increased sensation of pain), allodynia (experiencing pain to stimuli that are not usually painful); (ii) vasomotor: temperature differences, skin colour changes or asymmetry; (iii) pseudomotor: oedema or sweating; and (iv) motor or trophic: decreased range of motion and/or motor dysfunction such as weakness, tremor, dystonia and/or changes in hair, nails or skin. CRPS is a clinical diagnosis of exclusion. Most cases of CRPS do not occur in close temporal proximity to immunization.

There have been case reports of CRPS following rubella, tetanus or HPV vaccine. In 2016, the European Medicines Agency reviewed the relation between CRPS, POTS and the HPV vaccines and concluded that the evidence does not support a causal link between the vaccines (Cervarix, Gardasil/Silgard and Gardasil 9) and development of CRPS or POTS. Therefore, there is no reason to change the way the vaccines are used or amend the current product information.

In a review of databases of post-licensure adverse events following immunization with HPV-16/18-adjuvanted vaccine (Cervarix®), the observed incidence of cases of CRPS confirmed by independent expert review was statistically significantly lower than the expected rate.

1.6.2. Postural orthostatic tachycardia syndrome (POTS)

POTS is characterized by an abnormally large increase in the heart rate when changing from a lying down to a standing up position, without any orthostatic hypotension. The excessive increase in heart rate is usually accompanied by various symptoms of orthostatic intolerance, which may include palpitations, light-headedness, weakness, “brain-fog”, peripheral coldness, purplish skin discolouration and blurred vision. Some sufferers also experience syncope. People beyond infancy and early childhood may be affected, but the condition tends to cluster in women of childbearing age. As noted above, the report concluded that the evidence did not support a causal link between the vaccines (Cervarix, Gardasil/Silgard and Gardasil 9) and development of POTS. Therefore, there is no reason to change the way the vaccines are used or amend the current product information.
2. MANIFESTATION AND CLASSIFICATION OF AN IMMUNIZATION STRESS-RELATED RESPONSE

ISRR may manifest as acute stress responses, vasovagal reactions or dissociative neurological symptom reactions or DNSRs (see Fig. 2.1) that may present as non-epileptic seizures. The symptoms of an acute stress response may appear just before, during or immediately after immunization. Thus, unlike other adverse reactions, an acute stress response may precede immunization. The symptoms of a dissociative neurological symptom reaction that may occur after immunization may be delayed by days.

**Fig. 2.1 Classification of stress responses and reactions**

<table>
<thead>
<tr>
<th>Immunization stress-related response – A spectrum</th>
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<tbody>
<tr>
<td>Acute stress response</td>
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<tr>
<td>Vasovagal reaction</td>
</tr>
<tr>
<td>Dissociative neurological symptom reaction (with or without non-epileptic seizures)</td>
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### 2.1. Acute stress response including a vasovagal reaction

Most ISRR occur in the immediate time period surrounding a vaccine administered by the injection. Symptoms may manifest immediately before, during or after immunization. Unlike other types of AEFI, an ISRR may occur before immunization, in anticipation of the procedure. Such responses may be precipitated by pain, fear, prolonged standing, the sight of a needle, the sight of blood, the behaviour of a caregiver or peer or even by being in a crowded or overheated environment. An acute stress response or vasovagal reaction is usually transient and resolves spontaneously.
2.1.1. Acute stress response

An acute stress response is an internal physiological response to a threat in all mammals and is often referred to as a “fight or flight” response. It may manifest with variable severity of symptoms and may range from mild feelings of worry and “butterflies” in the stomach to sympathetic stimulation: increased heart rate, palpitations, difficulty in breathing or rapid breathing (hyperventilation). It occurs by activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenocortical axis, which increases blood flow to the brain, heart, lungs and skeletal muscles and reduces the blood flow to less critical body areas (see Annex 3). An individual’s stress response is affected by a number of factors including their understanding and interpretation of the situation, their emotional response, their memory of previous experiences, genetics, gender and environment. The degree of control that a person perceives as having over the situation may also be important.

Hyperventilation syndrome (rapid 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 the fingers, light-headedness, dizziness and headache. In some individuals, this maybe a recurrent symptom that is not necessarily associated with recent provocative stress. Syncope and non-epileptic seizures characterized by pseudo-absence spells may occur. Adolescent girls are usually affected, and episodes are associated with anxiety or as a component of an anxiety disorder. Episodes often recur, and the diagnosis may be missed and ascribed to cardiac or another life-threatening disorder.

2.1.2. Vasovagal reaction

A vasovagal reaction manifests as symptoms of mild dizziness or a brief loss of consciousness (syncope) because of insufficient blood flow to the brain after loss of blood pressure due to a decreased heart rate or vasodilatation of blood vessels. It may be associated with prodromal symptoms such as nausea, sweating or pallor. Some individuals who experience syncope may also have a syncopal seizure. Vasovagal reactions are usually benign, but injuries may result from falling.

A vasovagal reaction results in bradycardia and/or peripheral vasodilation with hypotension, which reduces the blood flow to the brain. The symptoms experienced include dizziness, blurred vision and syncope. Loss of consciousness usually lasts for less than 20 seconds but may last up to several minutes. Recovery is usually rapid. A vasovagal reaction is considered maladaptive but benign. An initial acute stress response consistent with a fight or flight response (sympathetic involvement with increased heart rate and blood pressure) 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.

2.2. Dissociative neurological symptom reactions, including non-epileptic seizures

Although reports of AEFI in individuals who have shown symptoms consistent with a dissociative neurological symptom reaction (DNSR) after immunization are poorly documented, clusters of such reactions, including non-epileptic seizures, are well documented.
2.2.1. Dissociative neurological symptom reactions (DNSR)

Terminology
Dissociative neurological symptom disorders are grouped in the International Classification of Diseases (ICD), 11th revision, under dissociative disorders, with various sub-codes according to the presenting symptoms. In ICD, 10th revision, these disorders were classified under “conversion disorder”, and the Diagnostic and Statistical Manual of Mental Disorders (DSM) lists it as conversion disorder/functional neurological symptom disorder. These disorders are therefore more commonly known by the older term “conversion”. Annex 1 outlines the problems related to use of this term.

Reactions versus disorders
The term dissociative neurological symptom “reaction” (DNSR) is used in this document rather than “disorder” in order to maintain consistency with ICD-11 but to acknowledge that it is difficult in the short term to meet the requirement that symptoms be severe enough to reach the diagnostic threshold for a disorder. The word “reaction” captures more transient symptoms. For a condition to be considered a disorder, the symptoms should not be transient. Existing research has focused on dissociative neurological symptom disorders/conversion disorders rather than reactions; but for simplicity, we will use the term “dissociative neurological symptom reactions or DNSR”.

Dissociative neurological symptoms and signs can include weakness or paralysis, abnormal movements or limb posturing, gait irregularities, speech difficulties, and non-epileptic seizures with no apparent physiological basis. The symptoms and signs may take hours to days to develop after immunization. DNSRs appear to be more common in females; they are not usually diagnosed in infants. In children, DNSRs usually manifest as single symptoms.

DNSRs are considered to be the result of interaction of numerous factors at various levels: psychological factors (e.g. history of abuse, traumatic experiences), vulnerability (e.g. age, personality, gender, pre-existing anxiety or depression), factors that shape manifestation of symptoms (e.g. witnessing symptoms in others), triggering factors (e.g. situations, circumstances) and factors that explain why symptoms persist (e.g. coping strategies).

2.2.2. Non-epileptic seizures

One type of DNSR is non-epileptic seizures, also often referred to as pseudo-seizures or psychogenic seizures. They are classified as DNSRs, because they are a manifestation of a DNSR and are caused by the mechanism described above. Non-epileptic seizures resemble epileptic seizures but do not involve the characteristic neural discharges associated with epilepsy. Non-epileptic seizures are considered involuntary and may be a response to high autonomic arousal. People who experience non-epileptic seizures may or may not report feeling fearful or anxious before the event that triggers them. Such seizures may manifest as various motor and sensory symptoms, with no neurological signs of an organic basis (see section 3). Non-epileptic seizures are less common in early childhood (the youngest age reported is 5 years), and the prevalence appears to increase in adolescence. This condition is typically a diagnosis of “exclusion”.

DISSOCIATIVE NEUROLOGICAL SYMPTOM REACTIONS (DNSRs), INCLUDING NON-EPILEPTIC SEIZURES

- These reactions occur most commonly in stress events other than vaccination.
- If they are reported post-vaccination, vaccination is best understood as a contributing stress event within a multifactorial etiology.
- A biopsychosocial perspective helps to understand the multiple factors that contribute to their onset and persistence.
- Diagnosis should be made if the symptoms and/or signs meet standard ICD-11 (World Health Organization 2018) criteria for dissociative neurological symptom disorder. The term reaction may be used if impairment in functioning is difficult to determine given transient nature or initial stages.

NON-EPILEPTIC SEIZURES

- These seizures resemble epileptic seizures but do not involve the characteristic neural discharges associated with epilepsy. Non-epileptic seizures are considered involuntary and may be a response to high autonomic arousal. People who experience non-epileptic seizures may or may not report feeling fearful or anxious before the event that triggers them. Such seizures may manifest as various motor and sensory symptoms, with no neurological signs of an organic basis (see section 3). Non-epileptic seizures are less common in early childhood (the youngest age reported is 5 years), and the prevalence appears to increase in adolescence. This condition is typically a diagnosis of “exclusion”.

IMMUNIZATION STRESS-RELATED RESPONSES
Clinical case 1

AG, a 13-year-old girl, received HPV vaccine in a school programme. She had fainted 2 months previously when a blood sample was taken, and, just before receiving the vaccine, she received a Facebook message from a friend complaining about how painful the injection had been. She was the last girl in her class to be vaccinated and had been standing, watching her classmates receive the vaccine. Before being vaccinated, she complained of chest pain, but the vaccinator was in a hurry and did not follow up on this complaint.

Less than 2 minutes after immunization, AG said that she felt light-headed, had blurred vision and was having difficulty in breathing. The vaccinator administered a dose of adrenaline into the left deltoid; however, the shortness of breath persisted, and severe palpitations began. An ambulance was called, and AG was admitted to the local hospital with a diagnosis of anaphylaxis due to the HPV vaccine.

Comment. A history of syncope is a risk factor for a vasovagal reaction. The adverse social media message probably increased AG’s anxiety before and fear during immunization manifested as an acute stress response accompanied by chest pain. Her symptoms immediately after immunization are consistent with an acute stress response (sympathetic system activation), exacerbated by the effect of adrenaline, which is a sympathetic stimulant, and by receiving a second injection, as she was afraid of needles, and by fear transmitted by the vaccinator, who thought this was anaphylaxis.

Interventions that would have been useful include:

1. Before immunization:
   • Identification of individual risk factors,
   • communication about and explanation of stress symptoms and
   • vaccinating her first or in privacy.

2. During immunization:
   • Use of pain management techniques (see section 4.1.6),
   • vaccinating her seated or lying down and allowing her to remain supine for 10–15 minutes after immunization and
   • use of muscle tension to raise her blood pressure and avoid syncope (see section 4.1.7).

3. After immunization:
   • Clinical differentiation between syncope and anaphylaxis to avoid use of adrenaline (another injection) and unnecessary hospitalization and
   • feedback to the vaccinator to avoid mismanagement of similar incidents in the future.

As AG was hospitalized for a serious AEFI, an investigation of the case and an assessment of causality would be indicated, followed by appropriate communication to both the patient and her family and to the vaccinator, with recommendations and interventions to decrease the risk for future misdiagnosis (see section 4.2).
Clinical case 2

FM, a 14-year-old boy, received an injection of tetanus and diphtheria toxoid with acellular pertussis vaccine (Tdap) into the left deltoid after a traumatic injury to his foot. His parents had recently separated, and FM was angry that his father had not come to the hospital to be with him when he was injured. He had recently attended a local clinic with complaints of fatigue, where investigations revealed a normal blood count and normal results in basic screening for chronic inflammatory conditions. He had not received some childhood vaccines, because the family was concerned about vaccine safety. As a child FM had experienced a febrile seizure after receiving diphtheria, tetanus and whole-cell pertussis vaccine (DTwP).

FM felt dizzy immediately after immunization but recovered rapidly when he lay down. He appeared well, but the next day he returned with symptoms of acute intermittent loss of vision, extreme fatigue, headache and an abnormal gait. The results of general and neurological examinations were normal, as were a repeat blood count, electroencephalogram, cerebrospinal fluid and computed tomography scan. His local doctor was uncertain about the diagnosis but thought that he had vaccine-induced encephalitis.

Comment. FM had several biological (e.g. dizziness during the injection), psychological (e.g. separation of his parents, anger at his father) and social (e.g. family concern about the side-effects of vaccines) risk factors. According to the ICD-11, a DNSR can include alterations in sensation (headache and vision disturbance) and control of body movements (abnormal gait) with no identifiable physiological pathology (see section 4).

Interventions that would have been useful include:

1. **Before immunization:**
   - Identification of individual risk factors and
   - Communication about and explanation of stress symptoms.

2. **During immunization:**
   - Use of pain management techniques (see section 4.1.6).

3. **After immunization**
   - Clinical diagnosis of a DNSR triggered by the stress of immunization combined with pre-existing stressors, which should be managed by a thorough explanation, including the mind–body connection, the fact that the diagnosis is well recognized, a management approach to correct the disability and control symptoms and addressing the psychosocial context by therapy and family support; and
   - Feedback to the vaccinator to avoid mismanagement of similar incidents in the future.
EPIEMIOLOGY OF IMMUNIZATION
STRESS-RELATED RESPONSES
ISRR can occur individually or in clusters. This section summarizes the results of epidemiological studies on the rates of ISRR in individuals, while section 5 describes their occurrence in clusters. Some anxiety or fear is a normal part of the response to immunization, and it would be impossible to determine how commonly these minor symptoms occur. The rates of more severe symptoms of an acute stress response, such as a vasovagal reaction with syncope, after immunization have, however, been determined.

### 3.1. Vasovagal reaction with syncope

The rates of more severe manifestations of an acute stress response after immunization, specifically vasovagal syncope, have been documented in some countries (Table 3.1), although syncope without injury is not reported in some areas. The rates of reporting of vasovagal syncope depend on case ascertainment, case definitions and the surveillance mechanism used. As shown in the following examples, the reported rates of syncope vary from 0.054 to 88/100,000 vaccine doses depending on factors mentioned above.

- Clinical study of 16,974 adolescents who received meningococcal vaccine, the rate of syncope during the 15 min after immunization was 88/100,000.
- During active surveillance of army recruits, the rate of syncope ranged from 4.1 to 14/100,000 (153,172 vaccine recipients). Events were more commonly reported in individuals under 20 years and in women, irrespective of vaccine type. Injury attributable to falls related to syncope was reported after 6.9% of syncopal episodes after immunization.
- Post-immunization syncope has been reported from licensure surveillance systems in various countries. For example, 463 cases were reported between 1 January 2005 and 31 July 2007 in the USA Vaccine Adverse Event Reporting System. The rate of reports of post-immunization syncope in 2006 among people > 5 years of age was 0.054/100,000 doses distributed. Reports were more frequent in adolescents aged 11–18 years and in females (77%).

Use of post-licensure data to determine rates of syncope is subject to a number of limitations.

- Passive surveillance results in underreporting.
- Incidence rates are difficult to calculate because the denominator (administered doses) is often not available, and the numerator (syncope episodes) may be poorly defined.
- Age- and gender-specific rates cannot be calculated when these parameters are not reported in passive surveillance.
- In clinical trials, the participants do not include all those in a certain age category; therefore, the rates of syncope associated with vaccination may be under- or overestimated.

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**EPIDEMIOLOGY OF INNOCULIZATION STRESS-RELATED RESPONSES**
3.2. Dissociative neurological symptom disorder or reaction (DNSR)

Existing research has typically used the older terminology of «conversion disorder» which would include what we refer to as DNSR. DNSRs have been reported after immunization, even if a causal relationship had not been confirmed. The rates of such reactions (including non-epileptic seizures) after immunization are unknown; however, as DNSRs can occur independently of immunization, a background rate for these events has been determined (Table 3.1).

The rates of DNSRs have been estimated for Australian children < 16 years of age using the following definition:

"the presence of one or more symptoms and/or signs affecting voluntary motor or sensory function that could not be explained by a neurological or other general medical condition, according to the clinical judgment of the treating paediatrician after physical examination and appropriate investigations**.
For simplicity, we use the current dissociative neurological symptom disorder term rather than the older conversion term. The criteria require that the symptoms and/or signs cause significant distress and/or impairment in daily activities. The annual incidence of DNSRs in children < 16 years of age was 2.3/100,000 (95% confidence interval [CI], 2.0;2.6). The reported incidence of DNSRs in children < 10 years seen by paediatric specialists, was lower, 0.8/100,000 (95% CI, 0.6;1.1). DNSRs are less common in early childhood, with 5 years being the youngest age reported (manifesting as non-epileptic seizures).

The background incidence rate of non-epileptic seizures is 1.4–33 per 100,000 individuals, with the highest rates in female adolescents (see Table 3.1).
APPROACHES FOR PREVENTION, DIAGNOSIS AND MANAGEMENT OF IMMUNIZATION STRESS-RELATED RESPONSES
All health care professionals involved in immunization should be informed about and trained in the characteristics of ISRR, including measures to prevent or minimize their occurrence and recognition of the symptoms and signs in order to address them when they occur in one or more vaccine recipients. In some situations, clusters of ISRR can be anticipated, and measures should be taken to prevent them or to identify them rapidly. For example, the frequency of syncope is higher in HPV immunization than for other vaccines\textsuperscript{38, 39}. This is probably because many programs deliver HPV immunization in schools, predominately for adolescent girls. HPV vaccine teams should therefore be prepared, and health care professionals involved in large or mass immunization campaigns should be re-trained or sensitized about ISRR just before they deliver these services.

Prevention begins before immunization, by addressing predisposing risk factors, such as identifying potential vaccinees at high risk of an ISRR in discussions with the potential recipient, parents or teachers, paying special attention to precipitating factors for the expected recipient during immunization. Once identified, it is necessary to follow up with interventions to reduce perpetuation of the risk factors. Environmental factors such as an overheated, crowded waiting area, lack of privacy for immunization and access to negative social media and communications during school and mass immunization campaigns should also be addressed to decrease the risk of ISRR.
4.1. Prevention

4.1.1. Identification of individuals with predisposing risk factors for an ISRR

A rapid, targeted history before immunization can help to identify individuals with predisposing risk factors for an ISRR. The risk factors relevant to immunization include:

- Age 10–19 years (but can occur outside this age group);
- History of vasovagal syncope;
- A previous negative experience (e.g., from pain or vasovagal syncope) and an expressed fear of injections, including blood–injection–injury phobia; and
- Pre-existing conditions such as anxiety disorders and developmental disorders (particularly autism spectrum disorder).

In some circumstances, targeted questions can be posed to identify strong needle fear. Such questions could be included on written consent forms or checklists, when these are used. If the responses to these questions suggest very strong needle fear (without avoidance), consideration should be given to treating the fear before future immunizations or at least taking time to manage the special needs of these individuals. If the fear leads to refusal (i.e., avoidance), additional measures may be required before immunization, such as counselling or behavioural interventions with appropriate health professionals. In selected circumstances of extreme fear and when the expertise is available, a patient might be referred for pharmacological anxiolytics and sedation. In some very rare instances, immunization could be done concurrently with a procedure that requires anaesthesia.

4.1.2. General preventive interventions

Basic measures should be in place to reduce anxiety and fear before, during and after immunization. The approach should be appropriate for age and stage of development and based on evidence. It should target factors such as the environment in which vaccines are given, the health care providers and family communication, physical position and psychological strategies such as distraction to reduce pain. The specific measures should include a focus on the individual being vaccinated and might also include a parent or caregiver if present. Additional measures may be required for individuals with pre-existing factors or when groups of individuals are vaccinated.

4.1.3. Immunization environment and procedure

The immunization environment is important. When possible, vaccines should be administered in a calm, private, planned environment. This may be difficult when vaccines are provided during a short period for large groups of individuals, such as in mass campaigns or a school programme. Additional details on the procedures and techniques to be adopted in such situations are available in the WHO guidance document Immunization in practice, a practical guide for health staff.
4.1.4. Attitude of health care providers and parents

A vaccinator who adopts a friendly, confident, relaxed approach is more likely to allay fear and anxiety. A trusting relationship should be formed, if possible within the time constraints, supported by demonstration of competence and compassion. In some instances, parents may instil fear of needles and of health care professionals in their children, which can aggravate the children’s fear. Such interactions should be discouraged. Training of health care workers in communication can help to build the trust of vaccine recipients.

4.1.5. Communication

Communication can help to mitigate anxiety and fear about immunization. Communication should be directed to both vaccine recipients and any accompanying parent or guardian. Age-appropriate language should be used, and words and phrases that might arouse fear should be avoided (Annex 4). Sometimes, some degree of control can be given to older children, adolescents or adults in their decisions about immunization, including choosing which arm for the injection, if this is not contrary to immunization policy and practice. Brief crying should be regarded as a normal response of infants and young children but may suggest that further measures should be taken to reduce pain. Prior to mass immunization campaigns including school programs, targeted messages and awareness sessions, especially for adolescents, can help alleviate some concerns and with other interventions improve the immunization experience.

4.1.6. Pain and measures to reduce pain associated with injectable vaccines

As most vaccines are given by injection, people may receive nine or more injections between infancy and adolescence. Pain is a complex, subjective experience, with both sensory and emotional components. Sensory nerves in the injected limb are stimulated, but the experience of pain is modified by factors in the central nervous system. Pain also triggers the autonomic nervous system. Many people experience pain when they have an injection. Pain may play an important part in the stress response to immunization because it may be associated with mild to severe psychological distress.

Pain management is considered to be a human right. Although immunization may be considered by some to be “just a little poke”, many children and some adolescents and adults experience significant pain and fear during needle procedures. Unmanaged pain from such procedures can have negative consequences, including longer procedures, syncope, greater distress, exaggerated negative memories, fear of needles and potential future avoidance of health care. General measures to reduce pain and fear are advisable in preparation for injection of a vaccine, which include physical, psychological and pharmacological strategies (see also Annex 4).
4.1.7. Additional interventions for people at risk of ISRR

Once an individual has been identified as at risk for ISRR, additional measures should be taken. This will depend on the available expertise and resources, with wide variation both among countries and situations (e.g. urban or rural, clinic or school programme). Nevertheless, some simple, inexpensive measures can be applied anywhere, such as immunizing a person who is at risk of a vasovagal reaction in a supine position.

A vasovagal reaction may be a severe manifestation of an acute immunization stress response and may rarely result in significant trauma because of a vasovagal syncope. Vaccine recipients who have had previous vasovagal reactions triggered by pain (due to an immunization or not) should have these additional measures instituted.

The risk of syncope can be decreased by use of a strategy called “muscle tension”, designed to maintain the blood pressure to avoid syncope. Reviewing the steps listed below with potential vaccine recipients can also give them a sense of control and distract them from the procedure.

The results of a randomized controlled trial indicated that arm or leg exercise 15 min before or immediately after immunization could decrease minor AEFI, including several that could be classified as ISRR, in adolescents and young adults.

### ADDITIONAL MEASURES TO REDUCE THE RISK OF AN ACUTE IMMUNIZATION STRESS RESPONSE IN PEOPLE IDENTIFIED AS AT RISK

- The presence of a familiar person, such as a trusted family member or friend can be helpful. If this trusted person is anxious or fearful, however, their presence may exacerbate the potential for a stress response.
- When possible, people who are particularly anxious or fearful of injections should not have to wait with others prior to immunization.
- Immunize at the beginning of a clinic, if possible separately from the group.
- Immunization in private will also prevent their peers from observing any negative reaction, which could in turn make others more fearful.

### ADDITIONAL MEASURES FOR PEOPLE AT RISK OF A VASOVAGAL REACTION

- Immunize in a seated or supine position.
- Consider using muscle tension (see right).
- After immunization, allow them to remain seated for 15–30 min or as long as is feasible.
- People who are immunized in the supine position should adopt an upright position only if they have no vasovagal symptoms.
- Ideally, the vaccinator should remain with the vaccine recipient during this period and be alert for early signs or symptoms of a vasovagal reaction.

### MUSCLE TENSION

- Ask the vaccine recipient to tense his or her large muscle groups, such as by clutching a ball in the hand of the arm not used for immunization or tensing the leg and abdominal muscles.
- Ask him or her to maintain the tension for 15–30 seconds, until he or she feels warm or flushed in the face.
- Ask the vaccine recipient to release the tension to the starting point for 15–30 seconds.
- Repeat the tension and releasing cycles before, during and after the vaccination procedure.
4.2. Diagnosis of ISRR

4.2.1. Acute stress response, including vasovagal reaction

Some level of anxiety before and fear during immunization are considered normal at any age. The signs or symptoms of an acute stress response may manifest before, during or shortly after immunization. The onset of symptoms and signs is usually immediate, at the time of or within minutes of immunization; however, vasovagal syncope may occur later if a vaccine recipient was seated or lying down and quickly adopts a standing position.

An acute stress response manifests as a variety of acute cardiovascular, respiratory and neurological symptoms and signs that are due to activation of the autonomic nervous system and particularly the sympathetic nervous system. The symptoms represent a “fight or flight” response and are due primarily to release of adrenaline from the adrenal gland and cortisol from the adrenal cortex (see Annex 3). Some individuals manifest a parasympathetic response, with bradycardia (slow heart rate) and blood vessel dilatation, both of which result in hypotension, reducing the blood flow to the brain and resulting in syncope. A severe reaction may cause cerebral hypoxia and a syncopal seizure. The symptoms and signs of an acute stress response and a vasovagal reaction are listed in the highlight.

When sudden loss of consciousness occurs > 5–10 minutes after immunization, anaphylaxis should be considered a possible diagnosis, in addition to vasovagal syncope. As anaphylaxis may be life-threatening and requires immediate medication, it should be ruled out quickly (see Table 4.1).

Blood pressure, pulse, respiratory rate and peripheral circulation should be measured. The lungs should be auscultated for wheeze or stridor and the skin inspected for rash (urticaria, erythema, swelling). During this examination, the patient should remain supine, on the side, in the recovery position.

The differences between anaphylaxis, general acute stress response and vasovagal reaction with syncope are outlined in Table 4.1.
4.2.2 Dissociative neurological symptom reactions (DNSR) including non-epileptic seizures

Diagnosis of a DNSR, including non-epileptic seizure, requires symptoms that fulfil the case definition or diagnosis (see section 2.2). These reactions can be triggered by stress events other than immunization and as a part of the background rate. Thus, diagnosis of a DNSR (with or without non-epileptic seizures) after immunization does not automatically imply that immunization was the cause. Causality should be assessed systematically with the WHO method and due consideration of all causes (see section 4.2.3).

The history of any co-morbid psychological disorders before immunization should be elicited, such as anxiety or depression, as immunization may precipitate manifestation of the symptoms, which may progress rapidly. The presence of a co-existing or underlying neurological or rheumatological disorder may mask clinical features and findings. Clues to a clinical diagnosis of a DNSR are listed in Table 4.2.

Table 4.2. Clues to diagnosis of a DNSR

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>GENERAL Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Disappearance of symptoms or signs when the patient is distracted</td>
</tr>
<tr>
<td></td>
<td>Signs or symptoms that are not consistent with known disorders</td>
</tr>
<tr>
<td></td>
<td>Symptoms or signs that do not respond to pharmacological interventions (for example, to a bronchodilator given for shortness of breath due to bronchospasm)</td>
</tr>
<tr>
<td></td>
<td>Symptoms and signs that are intermittent and vary between presentations</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dystonia</th>
<th>Inconsistent sustained movements over time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unusual postures</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gait</th>
<th>Fluctuation of gait and stance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal limb power and sensation when lying down but inability to stand or walk</td>
</tr>
<tr>
<td></td>
<td>Sudden buckling of knees without falling</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Myoclonus</th>
<th>Changing pattern of frequency, amplitude and anatomical distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory</td>
<td>Loss of sensory function that is not anatomically consistent with any known sensory disorder</td>
</tr>
</tbody>
</table>

Adapted from reference 51

Table 4.1 Differences between anaphylaxis, general acute stress response and vasovagal reaction with syncope

<table>
<thead>
<tr>
<th>ANAPHYLAXIS</th>
<th>ACUTE STRESS RESPONSE</th>
<th>GENERAL VASOVAGAL REACTION WITH SYNCOPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Usually 5 min after immunization but may be delayed up to 60 min</td>
<td>Sudden, occurs before, during or shortly after (&lt; 5 min) immunization</td>
</tr>
<tr>
<td>System</td>
<td>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</td>
<td>Pale, sweaty, cold, clammy</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Persistent cough, noisy breathing and airway constriction: wheeze, stridor. If very severe, respiratory arrest.</td>
<td>Hyperventilation (rapid, deep breathing)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>↑ heart rate, ↓ blood pressure, circulatory arrest</td>
<td>↑ heart rate, normal or ↑ systolic blood pressure</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea, vomiting, abdominal cramps</td>
<td>Nausea</td>
</tr>
<tr>
<td>Neurological and other symptoms</td>
<td>Uneasiness, restlessness, agitation, loss of consciousness, little response when supine or lying flat</td>
<td>Fearfulness, light-headedness, dizziness, numbness, weakness, tingling around the lips, spasms in hands, feet</td>
</tr>
</tbody>
</table>
4.2.2. Dissociative neurological symptom reactions (DNSR) including non-epileptic seizures

Diagnosis of a DNSR, including non-epileptic seizure, requires symptoms that fulfil the case definition or diagnosis (see section 2.2). These reactions can be triggered by stress events other than immunization and as a part of the background rate. Thus, diagnosis of a DNSR (with or without non-epileptic seizures) after immunization does not automatically imply that immunization was the cause. Causality should be assessed systematically with the WHO method and due consideration of all causes (see section 4.2.3).

The history of any co-morbid psychological disorders before immunization should be elicited, such as anxiety or depression, as immunization may precipitate manifestation of the symptoms, which may progress rapidly. The presence of a co-existing or underlying neurological or rheumatological disorder may mask clinical features and findings. Clues to a clinical diagnosis of a DNSR are listed in Table 4.2.

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>CLINICAL DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Disappearance of symptoms or signs when the patient is distracted</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Symptoms and signs that are intermittent and vary between presentations</td>
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<td>Dystonia</td>
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<td>Gait</td>
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<tr>
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<tr>
<td>Sensory</td>
<td>Loss of sensory function that is not anatomically consistent with any known sensory disorder</td>
</tr>
</tbody>
</table>

Adapted from reference 51

The gold standard for assessing non-epileptic seizures is a video electroencephalograph. This is, however, seldom practicable, and diagnosis of these disorders is usually based on clinical identification of a particular pattern of presentation. Non-epileptic seizures should be differentiated from seizures due to other causes (e.g. epilepsy, meningitis or encephalopathy). Clinical clues for differentiation are listed in Table 4.3.

4.2.3. Role of WHO causality assessment classification

Stress responses can be triggered by several events in daily life. One such trigger is anxiety and fear of pain associated with any needle procedure or injection, including immunization. As the symptoms and signs of a vasovagal reaction generally occur close to the time of immunization, the causality is usually clear. As DNSRs, including non-epileptic seizures, can be triggered by stress events other than immunization and as a part of the background rate, diagnosis of this condition does not automatically attribute causality to immunization. In general, the closer the onset of stress-related symptoms is to the time of the immunization, the more likely it is that immunization is the (or one of the) triggering event(s). Although a precise time cannot be specified, it would seem plausible that the onset of symptoms within 7 days of immunization would be compatible with an ISRR, after consideration of other relevant factors.

DNSRs are considered to be the result of interaction of a number of factors at various levels: psychological factors (e.g. history of abuse, traumatic experiences), vulnerability (e.g., age, personality, gender, pre-existing anxiety or depression), factors that shape the presentation of symptoms (e.g. witnessing symptoms in others), triggering factors (e.g. situations, circumstances) and factors that explain why symptoms persist (e.g. coping strategies). If a dissociative neurological symptom is reported after immunization, immunization may be considered a stress event that contributes to the presentation within a multifactorial etiology. A biopsychosocial perspective should be taken to understand the multiple factors that contribute to onset and maintenance.
The causality of all ISRR should be assessed using the WHO classification. The first step is to determine whether the reported symptoms and signs fulfill the definition of an acute stress response, vasovagal reaction or DNSR. If so, the next step is to formulate the causality question. Unlike other adverse events following immunization that need causality assessment, symptoms of a vasovagal reaction may precede administration of a vaccine; but the symptoms of a DNSR are unlikely to precede immunization.

Other, coincidental causes of the event should be considered simultaneously, with determination of whether it is related to the vaccine product, to a quality defect or to an error in the immunization program or procedure. Expert opinion should be sought from suitable specialists, the evidence reviewed, options debated and causality prioritized and finalized. Even if causality has been assigned, the decision may be changed later as newer evidence appears. (Also see section 6.3).

### Table 4.3. Differentiating a non-epileptic seizure (subgroup of DNSR) from epilepsy

<table>
<thead>
<tr>
<th>Condition</th>
<th>Non-Epileptic Seizures</th>
<th>Epileptic Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Helpful</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration &gt; 2 min</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Eyes and mouth closed</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Resisting eye opening</td>
<td>Common</td>
<td>Very rare</td>
</tr>
<tr>
<td>Visible large bite mark on side of tongue, cheek or lip</td>
<td>Very rare</td>
<td>Occasional</td>
</tr>
<tr>
<td>Fast respiration during attack</td>
<td>Common</td>
<td>Ceases</td>
</tr>
<tr>
<td>Grunting or guttural “ictal cry”</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Weeping or upset after a seizure</td>
<td>Occasional</td>
<td>Very rare</td>
</tr>
<tr>
<td>Recall for period of unresponsiveness</td>
<td>Common</td>
<td>Very rare</td>
</tr>
<tr>
<td>Thrashing, violent movements</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Post-ictal stertorous breathing</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Attacks in medical situations</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Unhelpful</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stereotyped attacks</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Attack on arousing from sleep</td>
<td>Occasional</td>
<td>Common</td>
</tr>
<tr>
<td>Aura</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Incontinence of urine or faeces</td>
<td>Occasional</td>
<td>Common</td>
</tr>
<tr>
<td>Injury</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Report of tongue biting</td>
<td>Common</td>
<td>Common</td>
</tr>
</tbody>
</table>

Adapted from reference 53; see also www.brightoncollaboration.org.
4.3. Management

Identification and initial clinical management of acute stress responses and vasovagal reactions are the responsibility mainly of the vaccinator or health care provider. More complex presentations such as DNSRs may require additional clinical expertise, such as that of a medical generalist or specialist and other health professionals (e.g., psychologists). It is useful to use a biopsychosocial model to understand the factors that contribute to the presentation and to use the understanding to guide management (see Annex 2).

4.3.1. Management of an acute stress response

The general principle of managing an acute stress response such as a vasovagal reaction is calm, reassuring, positive communication with the vaccine recipient and family until the symptoms resolve. The important aspects of management and communication include the following.

- The key is to differentiate an immunization stress-related response from anaphylaxis and other diagnoses (see Table 4.1).
- If a vasovagal reaction has occurred, the individual should be maintained in the supine position and practise muscle tension if appropriate for their age.
- Once an immunization stress response has been identified, the vaccinator should clearly explain that it was not related to the vaccine product or to an immunization program or procedure error.
- The nature of the symptoms and the fact that they were to be expected, are not harmful and will resolve spontaneously without medication should be explained.
- Medication and hospitalization should be avoided if possible, as they may aggravate the situation and result in additional cases.

4.3.2. Management of complex presentations such as DNSR

- A DNSR should be differentiated from other conditions, including neurological diagnoses (see Tables 4.2 and 4.3).
- Management of a DNSR, including a non-epileptic seizure, consists of a multi-disciplinary approach, including medical and psychological assessments and interventions to reduce any functional disability. In general, the patient should be referred to a health practitioner or a health centre with the necessary expertise. Treatment should be tailored to the symptom constellation and may include physiotherapy, cognitive behavioural therapy or pharmacological interventions.
- The immediate steps should include the following.
  - Reassure the affected person, others in the vicinity and the parent or caregiver where applicable that short-term anxiety and fears about insects, storms, heights, water, blood and needles are normal, as are similar worries about immunization.
  - In a clinic or school programme, segregate the affected person, assist him or her in lying down in a calm, well-ventilated place, manage crowd flow and minimize the presence of unnecessary staff, services and noise.
  - Keep calm and confident to comfort the patient, help him or her to breathe slowly and advise use of the muscle tension technique (see section 4.1.7) if necessary.
  - Once the patient’s questions have been answered and if he or she is relatively calm, distraction e.g. listening to music, talking about something else, drawing etc) may help to further decrease stress.
  - Encourage a return to “normal activity”. Continue the session as planned, making sure that groups waiting for immunization are not in contact with the affected person.
5.

APPROACH TO CLUSTERS OF IMMUNIZATION STRESS-RELATED RESPONSES

The simultaneous appearance of similar symptoms in a group of people with no identifiable physiological cause has been the focus of attention over hundreds of years; it is generally thought that the affected individuals share beliefs about the cause of their symptoms\cite{footnote}. The transmission and spread of the response may be enhanced by the environment (e.g. transmitted from person to person by sight or by social media), transmitted by a more senior (trusted, experienced) to a less experienced (more vulnerable) person, by a response by others (e.g. emergency personnel, parents), media and social media\cite{footnote,footnote2}. Usually, the spread of such situations and their resolution are relatively rapid\cite{footnote3}. ISRR clusters are common for some age groups only; there are no documented clusters in infants and small children, while they are common among adolescents and young adults.

5.1. Definition of a cluster

A cluster of AEFI is two or more cases of the same adverse event related in time, place or vaccine administered. It represents the aggregation of relatively uncommon events or diseases in space and/or time at a frequency that is believed or perceived to be greater than could be expected by chance. Anxiety and fear can be contagious\cite{footnote}. In social situations such as schools or in places where people congregate, one person’s syncope may trigger syncope in others around them. Situations in which large numbers are involved and/or the symptoms appear to be exaggerated are often referred to as “mass psychogenic illness” or “mass hysteria” in the literature; however, patients may find the term demeaning, which may exacerbate the problem. In addition, as noted above, a biopsychosocial framework is necessary to fully capture the complexities (see Annex 2). When investigating ISRR clusters, other causal factors must be excluded, as outlined in section 6.3.
5.2. Epidemiology

Clusters of reactions consistent with mass ISRR have been reported in several countries. They usually occur in closed, cohesive social settings, such as in schools or during mass campaigns. Clusters have been receiving increasing attention in both traditional media and social media and in some instances have led to disruption of a country’s immunization programs. The true prevalence of such events is difficult to determine, as there appears to be general reluctance to publish reports on such events in the peer-reviewed literature once the situation is resolved and the immunization programme resumed. Another problem in examining such events has been lack of standardized terminology (see section 1.5.2).

In a 2018 review of mass ISRR, clusters of these events after immunization were described in both rural and urban settings and in high-, middle- and low-income countries throughout the world. The size of the clusters ranged from 7 affected patients in one school to 806 in several schools. Similar symptoms were described in all the clusters, consisting of dizziness, headache and syncope of rapid onset after immunization. Abdominal complaints were also reported in some clusters. Seven of eight clusters occurred in adolescents (aged 12–16 years) in schools and one (12%) in a group of adult military reservists, who were predominately males.

Investigations revealed no error in the vaccine product or immunization program or procedure. Males and females were affected equally. Several different vaccines were implicated. Some clusters were associated with introduction of a new vaccine or a change in the routine immunization programme, such as a new age group or a new setting for immunization. Of the vaccines implicated, three were tetanus-containing vaccines, one was to prevent hepatitis B, one was an oral cholera vaccine, one was HPV vaccine, and two were vaccines to prevent influenza A (H1N1).

The clinical management of cases in clusters that involved invasive testing or treatment was reported in some cases to be harmful. Small clusters in one group setting (usually a school) may spread rapidly to others, often due to media reports. Elements that differentiate such incidents after immunization from similar events are the prevalence of high levels of needle fear and stress-related reactions, including vasovagal syncope among children, adolescents and adults. This pattern can be exacerbated when children or adolescents who were waiting to be immunized observed others experiencing stress responses after immunization.

Clinicians should consider this possibility and the impact of social media in its spread in making a differential diagnosis when the symptoms present before, during or after immunization, especially if more than one child or adolescent is involved. Such mass ISRR are expected to continue to occur with the introduction of new vaccines and new target ages and during routine immunization campaigns with currently available vaccines.

ISRR in clusters should not be misdiagnosed as anaphylaxis. Anaphylaxis is extremely rare. For vaccines as it is < 1/1,000,000, it is almost impossible for anaphylaxis to occur in clusters and have not been described. A wrong diagnosis of clusters of anaphylaxis can, however, result in clinical mismanagement, result in hospitalization with inappropriate treatment and further worsen patients’ condition.
A 2018 study has pointed out that social media may be useful for identifying clusters of anxiety-related AEFI and that sole reliance on the published literature may result in serious underestimates of the occurrence of such events. In this study, 20 cluster events were identified through social media that had not been reported in mainstream media. The events involved children and immunization programmes in schools or national immunization campaigns. Six immunization programmes were reportedly stopped because of these events.

### Table 5.1. Eight published reports of clusters of anxiety-related AEFI

<table>
<thead>
<tr>
<th>YEAR</th>
<th>COUNTRY, SETTING</th>
<th>NO. VACCINATED</th>
<th>NO. (%) OF CASES</th>
<th>AGE OR SCHOOL GRADE</th>
<th>NO. (%) FEMALE</th>
<th>VACCINE</th>
<th>SYMPTOMS</th>
<th>CLINICAL MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>Islamic Republic of Iran, school</td>
<td>26</td>
<td>10 (38)</td>
<td>14 years</td>
<td>10 (100)*</td>
<td>Tetanus</td>
<td>Pseudo-seizure, tremors, blurred vision, headache, syncope</td>
<td>Hospitalized, multiple laboratory examinations, including lumbar puncture</td>
</tr>
<tr>
<td>1995</td>
<td>Italy, school</td>
<td>24</td>
<td>7 (29)</td>
<td>7th grade</td>
<td>4 (57)</td>
<td>Hepatitis B</td>
<td>Dizziness, headache, syncope, paraesthesia</td>
<td>Hospitalized</td>
</tr>
<tr>
<td>1998</td>
<td>Jordan, schools</td>
<td>25,667</td>
<td>806 (3)</td>
<td>10th grade</td>
<td>379 (47)</td>
<td>Tetanus–diphtheria</td>
<td>Headache, dizziness, chest tightness, pyrexia, hypotension, feeling faint</td>
<td>Hospitalized, blood tests, treated with steroid and antihistamine</td>
</tr>
<tr>
<td>2001</td>
<td>India, school</td>
<td>200</td>
<td>58 (29)</td>
<td>10th grade</td>
<td>58 (100)*</td>
<td>Tetanus</td>
<td>Headache, syncope, giddiness, falling, nausea, vomiting</td>
<td>Hospitalized, treated with steroid and antihistamine</td>
</tr>
<tr>
<td>2001</td>
<td>Viet Nam, school</td>
<td>234</td>
<td>97 (41)</td>
<td>12 years</td>
<td>49 (51)</td>
<td>Oral cholera</td>
<td>Cold extremities, headache, nausea, abdominal pain, pruritis</td>
<td>Emergency department, treated with intravenous fluid, oral rehydration solution and/or antihistamine</td>
</tr>
<tr>
<td>2007</td>
<td>Australia, school</td>
<td>720</td>
<td>26 (4)</td>
<td>12–17 years</td>
<td>26 (100)*</td>
<td>HPV</td>
<td>Dizziness, syncope, weakness, palpitations, aphasia</td>
<td>Emergency department, testing included neuroimaging</td>
</tr>
<tr>
<td>2009</td>
<td>Taiwan (China), schools</td>
<td>9,115</td>
<td>350 (4)</td>
<td>12–15 years</td>
<td>237 (68)</td>
<td>H1N1 influenza</td>
<td>Dizziness, nausea, headache, hyper-ventilation</td>
<td>Not reported</td>
</tr>
<tr>
<td>2010</td>
<td>USA, military reserve</td>
<td>201</td>
<td>14 (7)</td>
<td>≥ 20 years</td>
<td>6</td>
<td>H1N1 influenza</td>
<td>Weakness, headache, dizziness</td>
<td>Hospitalized, nerve conduction tests for index patient</td>
</tr>
</tbody>
</table>

Adapted from reference 24

* Only girls were vaccinated, either because the school was only for girls school or the vaccine was indicated only for girls (HPV vaccine).
5.3. Identification of predisposing risk factors

During mass immunization, individuals with risk factors for ISRR (see section 4.1.1) should not be vaccinated with the rest of the group but should have a separate appointment several days later. If this is not practicable, these individuals should be vaccinated separately, in private, even just behind a screen. Pain management techniques should also be used (see Annex 4).

5.4. Specific issues in mass immunization campaigns: Prevention, diagnosis and management

Once a cluster of cases is identified, the affected individuals should be separated from each other and from healthy vaccine recipients. Health care professionals involved in planning or conducting mass immunization campaigns should be aware that, during such campaigns, vaccine providers may be under pressure to vaccinate many people in a short time which may increase the occurrence of ISRR. (Several individuals grouped for the purpose of receiving an immunization can be considered a “mass” in this context.) Therefore, during the micro-planning phase of mass immunization campaigns or programs for immunizing groups, ISRR in clusters needs to be anticipated and plans prepared in advance to address the same. Preventive measures include mitigating environmental factors known to contribute to clusters of ISRR, such as an overheated, crowded waiting area, prolonged standing, lack of privacy for immunization and access of those being vaccinated to e-communication (e.g. text messaging, social media). The “local setting” of mass vaccine administration including the waiting areas prior to and post immunization needs to be assessed.

The presence of local community leaders and local health workers who are familiar to those being immunized can reassure them and support the immunization team. Privacy should be available to recipients for immunization by injection (even in mass campaigns), and the local culture and sensitivity with regard to dress and gender must be respected.

Emergency kits, information, education and communication messages, job aids or posters showing the differences between anaphylaxis and an acute stress response, including vasovagal syncope, should be available to health workers (see Table 4.1). Primary responders (with addresses, phone numbers and transport plans) to an event or a cluster of events should be identified. After immunization, recipients should be advised to wait for 30–60 min in a well-lit waiting area with basic distractions and a relaxing ambience.

All health care professionals involved in a campaign should be educated and reminded about ISRR. A communication plan (see section 7.2) must be established and a spokesperson nominated as the focal point of information for the media and the public if a cluster of ISRR occurs."
Panic has been reported not only in people who have been immunized but also among the parents/caregivers of immunized children. For example, in January 2016, parents panicked during an oral polio immunization campaign in Kashmir after it was rumoured that children had died after receiving oral polio vaccine. The rumour spread rapidly on social networking sites, WhatsApp and mobile phones. Despite immediate clarifications by health care professionals on radio, television and Twitter, that no child had died, that the report was just a rumour and “fake news”, the concern was not resolved, and long lines continued outside hospitals.68
REPORTING MECHANISMS AND SUPPORT STRUCTURES FOR IMMUNIZATION STRESS-RELATED RESPONSES
A functioning, responsive AEFI surveillance system will improve the transparency of the activities of a national immunization programme on vaccine safety and increase the trust of staff and the public in the programme. Cases of ISRR may be events of interest that need to be reported to a country or jurisdiction’s immunization program. Immunization providers should be familiar with the immunization safety monitoring programme of the country in which they are working.

A response should be initiated to prevent potential clustering, increased community concern about a vaccine and subsequent loss of trust in the vaccine or the immunization programme. As with the general recommendation to investigate AEFI cases defined as serious, it may be appropriate in certain circumstances to investigate such cases of ISRR. Mismanagement of the response to such events, especially if they occur in clusters, has led to serious loss of confidence and decreased vaccine coverage in both developed and developing countries.

ISRR are AEFI, and the principles of surveillance – detection, notification, reporting, investigation, analysis, causality assessment, management and communication of individual cases and clusters (Fig. 6.1) – are similar to those for monitoring and responding to any AEFI. There are, however, certain important characteristics that set ISRR apart. This section provides an overview of the surveillance of AEFI and of the handling of cases of ISRR by national immunization programmes.
6.1. Surveillance of adverse events following immunization (AEFI)

The goal of surveillance of immunization safety is early detection and analysis of relevant adverse events and an appropriate, rapid response in order to minimize the impact on the health of individuals and on the immunization programme. Most AEFI are identified by patients, parents or caregivers or health care providers and are then notified to the health care system (passive surveillance). Details of such notified AEFI are reported to the immunization programme and the health authorities on a standard AEFI reporting form, preferably within 24 hours of notification. The signs and symptoms observed and the basic clinical features should be documented on the form.

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 (even of minor events), the authorities should initiate a detailed investigation.

As mentioned above, ISRR are a category of AEFI; therefore, their surveillance (which includes case detection, notification, reporting, investigation, record-keeping and maintenance of a database - line list), will be similar to that of other AEFI, and they will be included in the line list of AEFI. Investigation of serious cases (see below) follows the same guidelines as for other AEFI.

The surveillance programme should be monitored continuously to detect trends.

In general, ISRR that are individual acute stress responses (such as anxiety, needle phobia etc) need not be reported in AEFI surveillance, with the exception of a vasovagal reaction with syncope. Any injury resulting from syncope should also be reported as an AEFI. Dissociative neurological symptom reactions, including non-epileptic seizures, may develop later, at home or in school or the workplace and when notified to the health system, should be reported.

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DEFINITION OF A SERIOUS AEFI

- Requiring hospitalization or prolongation of existing hospitalization.
- Persistent or significant disability or incapacity.
- Life-threatening.
- Causing serious concern in the community.
- Death.
- Congenital anomaly or birth defect.
6.2. Case investigation

Investigation of ISRR differs from routine AEFI investigations. One of the key elements the investigator specifically makes detailed enquires about is the time of occurrence of the event in relation to immunization. Other AEFI are of interest only if they occur after immunization, while ISRR (acute stress response and/or vasovagal reaction) may occur immediately before, during or after immunization. During the investigation, probing questions should be posed to the relevant people and evidence collected to determine whether the event was a stress response related to immunization. Specific biopsychosocial aspects and other potential triggers for individual patients or for all the patients in a cluster and the environmental context of the immunization site should be collected for investigation of ISRR (Annex 2). A visit to the place where the event occurred, interviews with parents, teachers, support staff, vaccinators and health care providers may be required, especially for investigation of clusters. The investigator should have good understanding of the entire spectrum of stress responses to immunization, as outlined in section 4.2, and make enquiries accordingly.

Analysis of the core variables on the reporting form should identify patterns in the timing, location, patient profile and the clinical features of such events. Clusters may be observed in single or, rarely, in several locations. Such “signals” should be identified early and appropriate measures taken to identify the triggers (Fig. 6.2).

Fig. 6.2. Approach to investigating clusters of AEFI, including ISRR

* In some clusters of ISSRs may see patients with the symptoms who were not immunized: symptoms developed when heard about the cases or maybe coincidental event. 6.3
6.3. Assessment of causality

ISRR commonly manifest immediately before, during or after immunization as an acute stress response, with tachycardia, hyperventilation, dryness of the tongue or vasovagal syncope; DNSRs may manifest later after immunization. All such events should be differentiated from other coincidental events as well as rare vaccine-related events. Thus, the clinical manifestation of the AEFI and a detailed investigation after the event must be documented to arrive at a case definition and creation of a suitable question for causality assessment. Once the investigation is complete, a systematic causality assessment should be conducted with the WHO method, which includes a standard checklist to differentiate classes of AEFI. Causality assessment of AEFI for individual cases in a cluster must be done separately and cannot be grouped. So each case must be separately investigated.

If causality for an ISRR has been assessed on the basis of the diagnosis and exclusion of coincidental events, it may be classified as “consistent with a causal association to immunization” in the category immunization anxiety-related reactions (Fig. 6.3). The triggering factors should be determined and addressed to prevent additional cases. For all such events, the diagnosis and the cause should be communicated to all stakeholders and, if necessary, the media, as described in section 7.

Fig. 6.3. Final classification of an AEFI causality assessment

* B1: This is a potential signal and maybe considered for investigation.
6.4. Reporting ISRR during immunization campaigns
Immunization campaigns are fertile ground for both individual and clusters of ISRR. During campaigns, a large cohort may be immunized in a relatively short time, often in “unconventional” settings. A high prevalence of ISRR may be misinterpreted as due to the vaccine. Prior to campaigns, health care providers should be trained in recognizing the potential triggering mechanisms of ISRR, their prevention and diagnosis and the response and reporting mechanisms for such events. AEFI investigations must be conducted rapidly and the findings communicated to stakeholders and the media to avoid any immunization crisis.

6.5. Global support for monitoring vaccine safety
As outlined in the Global manual on surveillance of AEFI, national systems for post-licensure monitoring of vaccine safety vary in structure, methods and performance. The WHO global vaccine safety team has prepared harmonized tools, methods and capacity-building to assist countries in monitoring vaccine safety.
COMMUNICATION STRATEGIES FOR PREVENTING AND ADDRESSING IMMUNIZATION STRESS-RELATED RESPONSES
If an ISRR is not well managed, it can significantly erode trust in immunization and in the health authorities delivering it, especially if ISRR occur in clusters. A new vaccine, a new site of delivery, a mass campaign or a new target age group all increase the risk for ISRR, singly and in clusters. To prevent and mitigate the negative impact of ISRR, a strong communication plan must be in place to reduce fear and uncertainty by providing information on the real cause of an ISRR, focusing on the age-specific pattern of ISRR clusters. To anticipate, prepare for and respond effectively to ISRR, countries should have ready communication plans and activities to:

- Build and maintain a strong programme that sustains trust in vaccines and immunization;
- strengthen support for immunization and the programme, thereby increasing uptake of vaccines and resilience to any scares and rumours;
- assess and respond immediately to any event that may erode trust;
- ensure engagement of stakeholders to establish consistent facts about immunization and a supportive environment; and
- avoid personal blame and stigmatization; rather, acknowledge the importance of preventing such cases by establishing a supportive environment of care and confidence in immunization staff and the immunization services they provide.

Together, these actions may prevent escalation of a situation into a crisis and minimize the damage of a crisis if one occurs. This section proposes a simple step-wise procedure for using communication to mitigate an ISRR and to plan activities to respond to the risks posed by an isolated ISRR or a cluster. Communities may not accept the truth, and various misconceptions and interpretations may circulate. Therefore, communication of evidence to exclude other potential causes is equally important. This may require expertise in fields such as toxicology, allergy, neurology and psychology.
7.1. Tailoring communication programmes to prevent ISRR

Immunization programmes must prepare comprehensive plans to improve acceptance and support for immunization, establish strong trust in vaccines and make populations resilient to scares about vaccine safety. Such plans should always include the prevention of ISRR (see section 4.1). This will include the necessary staff training and support in structuring immunization service delivery to minimize elements that might be associated with ISRR.

All plans should have a budget endorsed at the appropriate levels of senior management, be kept up to date and involve all stakeholders who play a role in implementation. The plan should include a template for crisis communication, as timelines will be short and multiple competing priorities may arise in a crisis. In the case of ISRR, the crisis plan will need to support a timely, appropriate response involving all the necessary stakeholders and thus mitigate any negative impact on immunization. Efficient, effective communication can make the difference between mitigation and escalation of a crisis.

Prevention is the cornerstone of risk management. Prevention is anticipating and analysing the short- and long-term risks associated with vaccines and the strategies for delivering them and then tailoring communications or programmatic interventions to eliminate or mitigate those risks (Table 7.1). Annex 5 outlines the information to be collected for planning communications to prevent risks. Communication to prevent ISRR can be broadly divided into primary and secondary strategies.

7.2. Communications response to any type of ISRR

Implementing a well-planned crisis communications strategy will help to maintain the public’s trust in vaccines, the national immunization programme and the health authorities. This is particularly important in a crisis emerging from an ISRR that was not precipitated by a vaccine or an immunization program or procedure error. An effective communication response is essential to continue or restart immunization programmes with the full confidence of the public and all stakeholders. An effective communications strategy contributes to sustaining high national immunization coverage and preventing a resurgence of vaccine-preventable diseases.

7.2.1. Responding to an ISRR

The goal of communication is rapid on site management and local de-escalation of a situation to avoid spread to further individuals.

Health care providers and other staff should be ready and able to take the necessary steps to tactfully isolate the person concerned (“index case”) to prevent transmission of fear and anxiety to others and to reduce stress.

Patients with stress-related AEFI must be managed by professionals who are qualified and experienced in diagnosing and managing such reactions (sections 4.2 and 4.3). Cultural sensitivity must be taken into consideration during case management as this can vary from one context to another.
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Table 7.1. Primary and secondary prevention communication strategies for ISRR

<table>
<thead>
<tr>
<th>PRIMARY</th>
<th>AT POPULATION LEVEL AT A VERY EARLY STAGE IF RISK FACTORS ARE PRESENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Programme:</td>
<td></td>
</tr>
<tr>
<td>• Continue to explain the importance and safety of vaccines and immunization.</td>
<td></td>
</tr>
<tr>
<td>• Collect and analyse data on the situation as it becomes available.</td>
<td></td>
</tr>
<tr>
<td>• Develop, pre-test and pre-position key messages and tools.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SECONDARY</th>
<th>AT LOCAL LEVEL, TO DETECT AND RESPOND TO INITIAL CHANGES FROM ROUTINE ACTIVITIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary strategies, plus the following:</td>
<td></td>
</tr>
<tr>
<td>Programme:</td>
<td></td>
</tr>
<tr>
<td>• Activate a communications team.</td>
<td></td>
</tr>
<tr>
<td>• Decide if, when and what to communicate.</td>
<td></td>
</tr>
<tr>
<td>• If necessary, implement the crisis communication plan.</td>
<td></td>
</tr>
<tr>
<td>• Provide ongoing information to stakeholders, especially the media, when necessary.</td>
<td></td>
</tr>
<tr>
<td>• Monitor public sentiment, media coverage and social media where applicable.</td>
<td></td>
</tr>
<tr>
<td>• Counteract any spread of rumours.</td>
<td></td>
</tr>
</tbody>
</table>

| Health care providers: |
| • Train health care providers in communication and interpersonal skills and in the importance of staying calm in the case of an event. |
| • Test and retrain health care providers in understanding of AEFI and ISRR. |
| • Structure immunization sessions to avoid waiting groups observing people being immunized. |
| • Emphasize techniques for relaxing, connecting with and increasing the trust of recipients before immunization. |
| • Ensure that the processes and timelines for reporting events and follow-up actions are clear. |

Adapted from reference 69.
Table 7.2. Steps in analysis of ISRR to determine the breadth and depth of the communication response

<table>
<thead>
<tr>
<th>STEP 1: DEFINE THE TYPE OF ISRR AND POTENTIAL IMPACT ON THE TRUST ON VACCINES</th>
</tr>
</thead>
</table>
| **Low-impact event:**  
Event is not serious or receives little or no attention in the media or among the public.  
*Example:* An isolated incident of syncope in a child during routine immunization |
| **Medium-impact event:**  
Event is serious, relevant in the country or context and can be expected to arouse media attention.  
*Example:* Several parents complain that a mass immunization session was poorly organized, with reports of syncope in some adolescents. |
| **High-impact event:**  
Event is serious, of unknown cause, includes clusters of reactions, may be memorable or dramatic, and has attracted high media attention.  
*Example:* Reports of syncope in many adolescents after immunization, with considerable negative media reports. |

<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• The AEFI monitoring and reporting system</td>
</tr>
</tbody>
</table>
• local health care providers |
• experts from the immunization programme and the ministry of health |
• laboratory, monitoring, surveillance, procurement and logistics staff |
• relevant ministries, such as ministries of education or children |
• national regulatory authorities |
• if immunization was done at a school, principals and/or teachers. |

| STEP 3: ASSESS THE POTENTIAL IMPACT ON TRUST IN HEALTH AUTHORITIES.  
WHAT FACTORS MIGHT INCREASE THE IMPACT? |
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Uncertainty, negative emotions, fears</td>
</tr>
</tbody>
</table>
• mass immunization campaign |
• extensive media attention |
• involvement of children or pregnant women |
• credibility of the story and its source |
• similarity to previous events that caused a crisis |
• lack of trust in the immunization programme and/or the health system or government. |

<table>
<thead>
<tr>
<th>STEP 4: DEFINE THE COMMUNICATION RESPONSE.</th>
</tr>
</thead>
</table>
| **Low-impact event**  
Routine communication, but monitor the public debate and ensure the availability of  
• A communication strategy and contingency plan  
• an effective AEFI monitoring and reporting system  
• strong links with media partners  
• advocacy for vaccines. |
| **Medium-impact event**  
Restricted communications. Do not communicate to a wider public audience yet, however start preparing:  
• Collect more facts.  
• Engage stakeholders, and inform spokespeople.  
• Prepare messages and share them with partners, especially those likely to be contacted by the media or the public. |
| **High-impact event**  
Respond immediately:  
• Gather the communications team.  
• Understand the problem.  
• Liaise with key stakeholders.  
• Communicate externally proactively. |
Monitoring and evaluation of communication after an ISRR

To track progress and demonstrate the outcomes – both intended and unintended – the impact of implementing communication interventions should be monitored and evaluated. The communications plan should include a system for monitoring the process, outputs and outcomes and evaluating the results.

Documentation of lessons learnt, good practices and innovations in communications about events such as ISRR and other AEFI will benefit many aspects of immunization programmes. Stories may be accompanied by individual accounts, stakeholder narratives, photos and include reflections on different forms of communication. For example, giving a voice to health care providers or community members directly implicated in an event may bring a positive light to their experience, build their capacity as advocates for immunization and contribute to counteracting any rumours or negative messages.

Documentation of lessons and good practices will contribute to:
- Conducting a critical analysis of reports from the monitoring process;
- adjusting and revising the communications plan and related budgets;
- support sharing, active discussion and feedback from and to communities that have been affected to improve future collaboration;
- empowering local champions for immunization to foster trust in vaccines; and
- enhancing coordination with partners and the media, with potential implications for future resource mobilization.

Relationships built with key stakeholders and the media should be maintained after such events to ensure that these groups continue to be strong programme partners and contribute to sustaining trust in vaccines and the authorities delivering them.

The following references may be useful in guiding proactive, reactive communications planning:
- Communicating risk in public health emergencies. A WHO guideline for emergency risk communication (ERC) policy and practice;
- WHO emergency risk communication training modules;
- Effective communications: participant handbook: communications programme training for WHO staff;
- Immunization and trust. How concerns arise and the role of communication in mitigating crises;
- Safety events: planning the immediate media response (World Health Organization vaccine safety supporting document).

POINTS TO REMEMBER

- Be prepared to respond to ISRR, with “holding statements” and trained spokespeople.
- ISRR can cause widespread anxiety and fear in the public and may be broadly publicized, which can feed back into the original situation in a cycle of escalation.
- Any response – even if there is initial uncertainty – should be transparent and include an explanation of how the event is being investigated and how information will be shared.
- Monitoring of media and public reactions is critical.
- Frontline workers involved in handling ISRR must be well briefed on the event to avoid any conflicting statements.
- Be tactful. Remember that ISRR are not the patient’s “fault”, nor are they “crazy”. They are responses to the stress of the event as perceived by the patient.
RESEARCH GAPS AND WAY FORWARD
ISRR have been recognized only recently as factors that might have a significant impact on immunization programmes, in both developed and developing countries. Further research on ISRR will provide information about trends in stress and its risk factors, the outcomes of interventions and public health responses, functionality, patterns of care and health care utilization and costs. Some areas for research are listed in Table 8.1.

Table 8.1 Areas for research on ISRR

<table>
<thead>
<tr>
<th>AREA</th>
<th>EXAMPLE RESEARCH QUESTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology and reporting</td>
<td>• What are the prevalence and incidence of ISRR and of mass or cluster ISRR (general, by sex, by age group)?</td>
</tr>
<tr>
<td></td>
<td>• What is the prevalence of DNSRs and disorders after immunization?</td>
</tr>
<tr>
<td></td>
<td>• Why are countries hesitant in reporting clusters, and how can their hesitancy be overcome?</td>
</tr>
<tr>
<td></td>
<td>• What is the long-term outcome of large clusters of cases? Can different trajectories be identified? What is the role of the media?</td>
</tr>
<tr>
<td>Risk factors and effects on immunization programmes</td>
<td>• What are the most influential risk factors (biological, psychological, social) for an ISRR (isolated or in a cluster)? And in what contexts?</td>
</tr>
<tr>
<td></td>
<td>• What is the impact of clusters of ISRR on perceptions of immunization programmes, public trust and immunization coverage?</td>
</tr>
<tr>
<td>Assessment and screening</td>
<td>• What are the best means for rapid screening for high level needle fear and other risk factors for ISRR?</td>
</tr>
<tr>
<td>Interventions</td>
<td>• How can interventions for high level needle fear be adapted and implemented in low- and middle-income countries?</td>
</tr>
<tr>
<td></td>
<td>• What is the effectiveness of the suggested interventions (e.g. muscle tension, privacy, health care provider training and education) in the context of mass immunization?</td>
</tr>
</tbody>
</table>
REFERENCES & ANNEXES


ANNEX 1. GLOSSARY OF TERMS AND DEFINITIONS

Anxiety

• **Definition:** an uneasy or apprehensive emotional state about a future or anticipated threat (1, 2, 3; note: references for annex are in separate list from rest of manual).

• **Features:** a feeling of dread (emotion), helplessness (thoughts), restlessness (observable activity), internal physiological effects such as increased heart rate and hyperventilation and sometimes behaviour to avoid the focus of anxiety.

• **Spectrum:** can range from a normal adaptive response to one that is more problematic and interferes with functioning.

• **Immunization context:** As immunizations via injection cause pain at the time of injection and because immunizations are the most frequent needle-related procedures for most infants and children, anxiety about immunizations is quite common. A low level of anxiety is considered normal, whereas a high level of anxiety can lead to avoidance of immunizations and even other medical consequences, such as a visit to a general practitioner.

Fear

• **Definition:** an alarm reaction that occurs in an actual threat context, either real or perceived.

• **Features:** physical and mental changes (“fight or flight response”). Fear can lead to efforts to escape the feared situation.

• **Spectrum:** Fear occurs on a spectrum from low to high and may be adapted to the threat.

• **Immunization context:** Low levels of fear of immunizations are normal throughout the lifespan, but the intensity changes with age. High levels of fear can result in freezing, intense distress, escape behaviour and/or crying. Some degree of fear of needles is common in children (> 60%) and also in adults (> 20%); extreme needle fear is present in 5–10% of the population.

Phobias and anxiety disorders

• **Definition:** Phobic anxiety disorder or phobia is a clinical diagnosis made by an experienced health care professional. In ICD-11, a specific phobias are coded as 6B03 under Anxiety or fear related disorders.

• **Features:** Strong fear and anxiety are present when a situation results in avoidance or extreme distress. Fear and anxiety about the situation are out of proportion to the actual danger posed and are beyond what would be expected for the individual’s age and development. Such anxiety and fear are long-lasting rather than transient.

• **Spectrum:** Not applicable, as phobias by definition are characterized by strong fear, anxiety and avoidance.
• **Immunization context:** Anxiety about immunization and fear of needles that is sufficiently strong to be diagnosed is listed under specific phobias in ICD-11 and the DSM, 5th edition (DSM-5), and further subtyped as blood-injection-injury phobia. Individuals with this phobia are likely to either avoid immunizations or show extreme distress when receiving immunizations. Over time, fear and anxiety may spread to related situations such as visits to a dentist or general practitioner. Individuals with blood-injection-injury phobia have a higher rate of vasovagal reactions than the general population; however, these reactions is not necessary for diagnosis of the phobia. Variants of blood-injection-injury phobia (e.g. needle phobia, injection phobia) have also been studied. The prevalence of blood-injection-injury phobia is estimated to be 3–4.5%. The condition begins at 5–10 years of age.

**Acute stress response**

See section 2.1 of this document.

**Dissociative neurological symptom reaction or disorder**

(also known as conversion; see section 2.2)

• **Definition:** A dissociative neurological symptom disorder is a clinical diagnosis made by an experienced health care professional. In ICD-11, it is classified under dissociative disorders; in ICD-10, it was referred to as “conversion disorder”. The diagnosis in DSM-5 is “conversion disorder (functional neurological symptom disorder)”, which is classified under somatic symptoms and related disorders. DNSRs are characterized by disruptions in sensation and control of bodily movements with no identifiable organic cause. We have elected to use the term “DNSR” in this document to maintain consistency with ICD-11, which uses the term dissociative neurological symptom disorder but to acknowledge that the symptoms may not be long-lasting. The symptoms of a disorder are not usually transient.

• **Features:** The symptoms and signs can include weakness or paralysis, abnormal movements or limb posturing, gait irregularities, speech difficulties and non-epileptic seizures with no apparent physiological basis. The symptoms and signs may take hours to days to develop after immunization. Dissociative neurological reactions or disorders appear to be more common in females. They are not typically diagnosed in infants; in children, DNSRs typically manifest with a single symptom.

• **Spectrum:** DNSRs or disorders are the result of interactions of numerous factors at various levels: psychological factors (e.g. history of abuse, traumatic experiences); vulnerability (e.g. age, personality, gender, pre-existing anxiety or depression); factors that shape manifestation of symptoms (e.g. witnessing symptoms in others); triggering factors (e.g. situations, circumstances) and factors that explain why the symptoms persist (e.g. coping strategies).

• **Immunization context:** The process of immunization may trigger dissociative neurological symptoms, depending on biopsychosocial factors.
Non-epileptic seizures

**Definition:** Non-epileptic seizures, also often referred to as pseudo seizures or psychogenic seizures, are a manifestation of a DNSR. They are classified as DNSRs. Non-epileptic seizures resemble epileptic seizures but without the characteristic electrical discharges associated with epilepsy. Non-epileptic seizures are considered to be involuntary and may be a response to strong autonomic arousal.

**Features:** Individuals experiencing non-epileptic seizures may report feeling fearful or anxious before the event. The seizures may manifest as various motor and sensory symptoms without neurological signs of an organic basis *(see section 3)*. Non-epileptic seizures are less common in an early acute stress response.

**Spectrum:** may depend on the manifestation.

**Immunization context:** As non-epileptic seizures are a manifestation of dissociative neurological symptom disorders, see above for the immunization context. Non-epileptic seizures have been reported in both immunization and other contexts.
ANNEX 2. BIOPSYCHOSOCIAL CONCEPTUALIZATION OF IMMUNIZATION STRESS-RELATED RESPONSES

The figure below depicts the biopsychosocial conceptualization of an ISRR. This model moves beyond the reductionist biomedical view to acknowledge the complex interplay among biological, psychological and social factors, rather than presenting reactions as “physical/organic” or psychological/psychiatric/functional”.

- **Times:** The diagram is organized according to three broad times: pre-immunization (past predisposing factors), peri-immunization (precipitating factors, initial response) and post-immunization (delayed response influenced by perpetuating factors).

- **Risk factors:** The shapes filled with a pattern contain examples of potential risk factors for experiencing an ISRR; gears are used to represent the dynamic interactions among the risk factors. Additional risk factors (psychological, social) present during mass immunization are noted.

- **Progression:** The person being vaccinated is represented at various times with examples of risk factors that can lead to a cascade of symptoms (initial response, continuing response) consistent with an ISRR; however, not everyone progresses from one stage to another step by step or in a linear fashion. For example, a DNSR does not necessarily follow an acute stress response.

- **Social media:** The potential for social media to provide negative information before immunization (pre-existing) and around immunization (peri-immunization) and to provide widescale communication of adverse events and perpetuate reactions is highlighted.

- **Bottom panel:** The panel beneath the grey line shows the dimensionality of constructs related to ISRR, with examples.
BEFORE VACCINATION
(predisposing)

- Biological
  - Age
  - Genetics
    (e.g. vulnerability to anxiety, vasovagal response, acute stress response)
  - Low body mass

- Psychological
  - Predispose to negative needle experiences
  - Anxiety about vaccination medical situations
  - History of acute stress response

- Social
  - Receive negative information from family, friends, media, others
  - Witness others’ negative reactions
  - Cultural beliefs

PERI-VACCINATION
( precipitating)

- Biological
  - Prolonged standing
  - Vasovagal response
  - Experience of pain

- Psychological
  - Expectations
  - Fear

- Social
  - Behavior and attitude of clinicians, caregivers, expressing pain

INDIVIDUAL

- Biological
  - Cascade of stress response symptoms
  - Hypothalamic-pituitary axis sensitization

- Psychological
  - Catastrophic interpretations
  - Fear
  - Hypervigilance to body experiences

- Social
  - Behavior, confidence, attitude of others (e.g. clinicians, authorities, family, peers, community)
    - Media

MASS

- Biological
  - Concern about evaluation by peers, authority figures

- Psychological
  - Witnessing peers’ adverse reactions
  - Behavior, attitude of others in same context expressing pain in front of peers

- Social
  - Witnessing peers’ adverse reactions

Acute Stress Response
including vasovagal reaction
Dizziness, Vasovagal syncope, Heart racing, Nausea, Blurred vision, Sweating, Hyperventilation

POST-VACCINATION
(perpetuating)

- Biological
  - Age
  - Genetics
  - Low body mass

- Psychological
  - Experience of pain

- Social
  - Hypervigilance to body experiences

Dissociative neurological symptom reaction

Social media

56 IMMUNIZATION STRESS-RELATED RESPONSES
ANNEX 3. PHYSIOLOGICAL EFFECTS OF AN ACUTE STRESS RESPONSE

A perceived threat
(physical, psychological, environmental, etc.)

Thalamus and frontal lobes
integrate sensory information and evaluate significance of stimulus

Limbic system
generates an emotional response

Hypothalamus

Activates sympathetic
nervous system

Activates HPA axis

Impulses activate
glands and smooth muscle

Activates adrenal medulla
to release
Adrenaline and noradrenaline

Hypothalamus

Corticothrophin-
releasing hormone

Anterior pituitary gland

Adrenocorticotrophic
hormone

Adrenal cortex

Cortisol

↑ Heart rate
↑ Blood pressure
↑ Breathing rate
(potential hyperventilation)
ANNEX 4. DEVELOPMENTAL APPROACH TO PREVENTING AND REDUCING PAIN

Approach for newborns, infants and pre-school age children

The strategies presented below are derived from both the WHO position paper and publications on reducing pain during vaccine injections. Consideration should be given to the cultural acceptability of the strategy (e.g. breastfeeding in public) and the feasibility of systematic use, including cost (e.g. topical anaesthetics).

<table>
<thead>
<tr>
<th>Immunization environment and health care provider</th>
<th>NEWBORN</th>
<th>INFANT (1–35 MONTHS)</th>
<th>PRE-SCHOOL AGE (3–5 YEARS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not aspirate when injecting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Give most painful vaccine last</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(or simultaneous injection)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inject into anterolateral thigh</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Communication                                      |         |                      |                           |
| Use neutral words to signal the start of the procedure to the caregiver holding the infant |         | Use neutral words to signal the start of the procedure to the caregiver holding the infant | Use neutral words to signal the start of the procedure to the caregiver holding the infant |
| Use a soft, calm voice                            |         |                      |                           |

**NEWBORN INFANT (1–35 MONTHS)**

| Physical positioning                               |         |                      |                           |
| Best cradled in parent’s arms                     |         |                      |                           |
| Breastfeeding if appropriate before, during and after |       |                      |                           |
| Skin-to-skin position before, during and after    |         |                      |                           |

| Distraction and breathing                          |         |                      |                           |
| Age-appropriate strategies: toy, video with encourage-ment from adults to pay attention to the distraction |         |                      |                           |

| Identification of those at risk                    |         |                      |                           |
| Does the parent appear calm?                      |         |                      |                           |
| Screen for strong needle fear in parent*          |         |                      |                           |

*See section 4.1.1 for screening questions
Approach for school-age children, adolescents and adults

The strategies are derived from both the WHO position paper\(^1\) and publications on reducing pain after injections\(^2\). Consideration should be given to the cultural acceptability of the strategy (e.g. breastfeeding in public) and the feasibility of systematic use, including cost (e.g. topical anaesthetics).

<table>
<thead>
<tr>
<th>Immunization environment and health care provider</th>
<th>SCHOOL-AGE CHILD (6–12 YEARS)</th>
<th>ADOLESCENT (13–18 YEARS)</th>
<th>ADULT (≥ 19 YEARS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not aspirate when injecting</td>
<td>Use neutral words to signal</td>
<td>Use neutral words to signal</td>
<td>Use neutral words to signal</td>
</tr>
<tr>
<td></td>
<td>the start of the procedure</td>
<td>the start of the procedure</td>
<td>the start of the procedure</td>
</tr>
<tr>
<td>Explain the procedure</td>
<td>Explain the procedure</td>
<td>Explain the procedure</td>
<td>Explain the procedure</td>
</tr>
<tr>
<td>Do:</td>
<td>Signal the start of the</td>
<td>Signal the start of the</td>
<td>Signal the start of the</td>
</tr>
<tr>
<td></td>
<td>procedure: “Here we go. Tell</td>
<td>procedure: “Here we go. Tell</td>
<td>procedure: “Here we go. Tell</td>
</tr>
<tr>
<td></td>
<td>me about... [distraction topic</td>
<td>me about... [distraction topic</td>
<td>me about... [distraction topic</td>
</tr>
<tr>
<td></td>
<td>from below]”.</td>
<td>from below]”.</td>
<td>from below]”.</td>
</tr>
<tr>
<td>Do not:</td>
<td></td>
<td>Talk about topics other</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>than the procedure (distraction):</td>
<td></td>
</tr>
<tr>
<td>Say it won’t hurt</td>
<td></td>
<td>favourite toys, foods,</td>
<td></td>
</tr>
<tr>
<td>Give repeated, excessive reassurances</td>
<td></td>
<td>events, school, etc.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical positioning</td>
<td>Upright (unless history of</td>
<td>Upright (unless history of</td>
<td>Upright (unless history of</td>
</tr>
<tr>
<td></td>
<td>syncope, then lying down,</td>
<td>syncope, then lying down</td>
<td>syncope, then lying down</td>
</tr>
<tr>
<td></td>
<td>on a bench, mat or floor and,</td>
<td>and using muscle tension;</td>
<td>and using muscle tension;</td>
</tr>
<tr>
<td></td>
<td>if ≥ 7 years, using muscle</td>
<td>see box p. 33)</td>
<td>see box p. 33)</td>
</tr>
<tr>
<td></td>
<td>tension; see box p. 33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Parent present if possible</td>
<td>For those at high risk and</td>
<td></td>
</tr>
<tr>
<td></td>
<td>and if child agrees</td>
<td>if resources are available:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>For those at high risk and if</td>
<td>topical anaesthetic applied</td>
<td></td>
</tr>
<tr>
<td></td>
<td>resources are available:</td>
<td>before (check product</td>
<td></td>
</tr>
<tr>
<td></td>
<td>topical anaesthetic applied</td>
<td>instructions); external</td>
<td></td>
</tr>
<tr>
<td></td>
<td>before (check product</td>
<td>vibrating device with cold</td>
<td></td>
</tr>
<tr>
<td></td>
<td>instructions); external</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>vibrating device with cold</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Identification of those at risk</td>
<td>Screen for strong needle fear</td>
<td>Screen for strong needle</td>
<td>Screen for strong needle</td>
</tr>
<tr>
<td></td>
<td>in child*</td>
<td>fear in adolescent*</td>
<td>fear in adult*</td>
</tr>
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<td></td>
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<td></td>
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</tr>
</tbody>
</table>

*See section 4.1.1 for screening questions
ANNEX 5. INFORMATION TO BE COLLECTED FOR PLANNING COMMUNICATIONS TO PREVENT IMMUNIZATION STRESS-RELATED RESPONSES

The vaccine:
- The disease prevented by the vaccine and its basic epidemiology
- Target age group, vaccine schedule, number of doses
- Route of administration (intramuscular, subcutaneous, intradermal, etc.)
- Type of vaccine (live, live attenuated, inactivated, conjugate, toxoid, etc.)
- How the immune system responds to it
- The composition of the vaccine
- Contraindications and false contraindications

Possible adverse events:
- List of all previously described adverse events with the vaccine and their frequency
- Detailed information about the signs and symptoms of selected adverse events of interest, including possible time after immunization
- ISRR observed in other countries that introduced the vaccine, including rumours, misperceptions and media stories

Background rates of possible AEFI:
- Frequency of AEFI in the target group during the relevant time of year

Situation and setting:
- The recommended local ambience in which the vaccine should be administered, including the degree of privacy, opportunity for interpersonal communication and access to a comfortable place for lying down in case of an event.
- Information about the routine programme or the supplementary immunization activities or campaigns, target cohort and sites of immunization
- Overview of AEFI reported with other vaccines, recently or during the past year
- Any misperceptions or rumours circulating about the vaccine that is to be introduced, e.g. on social media
- Culturally and linguistically appropriate advocacy and messaging strategies
- The media landscape

ANNEX 6. RESPONDING TO THE MEDIA: COMMON QUESTIONS, PREPARING A HOLDING STATEMENT AND MESSAGE MAPPING

Questions the media are likely to ask
According to the “5 Ws and 1 H” principle of journalism:
- Who is responsible for the event?
- Why was this badly managed? If the vaccine is safe, why are so many vaccinated children affected? Why are you providing a bad or expired vaccine?
- What happened? What is the national immunization programme doing to monitor the safety of vaccines?
- When did this happen? What are you going to do about it?
- Where did it happen? Will it happen again?
- How did this happen? How did you allow this to happen?
Holding statement

In case of an ISRR, especially in a cluster, the public has the right to know what happened. A holding statement provides the media with the basic facts about the incident and demonstrates that you are actively dealing with the situation.

Examples of what the statement could include:

- Acknowledge the facts about the event with the 5 Ws and 1 H of journalism.
- Sympathize, by expressing concern and sympathy about what happened.
- Mention that you are in contact with, for example, the child’s family and the school.
- State that it is unlikely that the vaccine is responsible and emphasize the value of vaccines.
- Say that you are investigating the incident, giving it high priority and will report back.
- Provide a time when you will address the media again and how the media can contact you for more information.
- You might add that you will be reviewing the procedures and making any necessary improvements to prevent a repetition of the incident.
- State that you will immediately act on any recommendations.

Be quick, and use all possible media. Time is of the essence. Use all available communication channels, including the Internet, Intranet, social media and mass notification. Be tactful. Emphasize that the incident is not due to the vaccine, the vaccine programme or the patient. The signs and symptoms of an ISRR are responses to a situation that the patient perceived as stressful, either overtly or covertly.

Preparing and using a message map

<table>
<thead>
<tr>
<th>KEY MESSAGE #1</th>
<th>KEY MESSAGE #2</th>
<th>KEY MESSAGE #3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supporting message 1a</td>
<td>Supporting message 2a</td>
<td>Supporting message 3a</td>
</tr>
<tr>
<td>Supporting message 1b</td>
<td>Supporting message 2b</td>
<td>Supporting message 3b</td>
</tr>
<tr>
<td>Supporting message 1c</td>
<td>Supporting message 2c</td>
<td>Supporting message 3c</td>
</tr>
</tbody>
</table>

Example of a message map used for an ISRR

1. IT IS UNLIKELY THAT THE VACCINE CAUSED THE REACTION
   1a. An expert team, including psychologists, will investigate and try to assess what we can do to prevent this in future.
   1b. After millions of doses have already been administered worldwide, there has never been a proven link between the vaccine and the stress related symptoms.
   1c. The diseases that vaccines prevent still pose a real threat to your child.

2. VACCINES ARE THE MOST EFFECTIVE WAY TO PROTECT YOUR CHILD FROM LIFE-THREATENING ILLNESSES
   2a. Immunisation currently prevents an estimated 2-3 million deaths every year. But about 22 million infants worldwide are still missing out on vaccines.
   2b. Measles for example (a vaccine preventable disease) can lead to pneumonia, brain damage and death.
   2c. Vaccines save lives.

3. THE SAFETY OF VACCINES IS OF FUNDAMENTAL CONCERN TO THE HEALTH DEPARTMENT
   3a. The safety of vaccines is closely monitored by surveillance, thereby the safety of vaccines an immunisation is ensured.
   3b. All vaccines have safety profile, meaning they have expected minor reactions but these are usually mild and temporary.
   3c. It is much safer to be vaccinated that to go get the disease.
REFERENCES FOR ANNEXES


