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Anxiety-related adverse events following immunization (AEFI): A systematic review of published clusters of illness

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Abstract

Background: Clusters of anxiety-related adverse events following immunization (AEFI) have been observed in several countries and have disrupted country immunization programs. We conducted a systematic literature review to characterize these clusters, to generate prevention and management guidance for countries.

Methods: We searched seven peer-reviewed databases for English language reports of anxiety-related AEFI clusters (≥ 2 persons) with pre-specified keywords across 4 categories: symptom term, cluster term, vaccine term, and cluster AEFI phenomenon term/phrase. All relevant reports were included regardless of publication date, case-patient age, or vaccine. Two investigators independently reviewed abstracts and identified articles for full review. Data on epidemiologic/clinical information were extracted from full text review including setting, vaccine implicated, predominant case-patient symptoms, clinical management, community and media response, and outcome/impact on the vaccination program.

Results: Of 1472 abstracts reviewed, we identified eight published clusters, from all six World Health Organization (WHO) regions except the African Region. Seven clusters occurred among children in school settings, and one was among adult military reservists. The size and nature of these clusters ranged from 7 patients in one school to 806 patients in multiple schools. Patients' symptoms included dizziness, headache, and fainting with rapid onset after vaccination. Implicated vaccines included tetanus (2), tetanus-diphtheria (1), hepatitis B (1), oral cholera (1), human papillomavirus (1), and influenza A (H1N1)pdm09 (2). In each report, all affected individuals recovered rapidly; however, vaccination program disruption was noted in some instances, sometimes for up to one year.

Conclusions: Anxiety-related AEFI clusters can be disruptive to vaccination programs, reducing public trust in immunizations and impacting vaccination coverage; response efforts to restore

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public confidence can be resource intensive. Health care providers should have training on recognition and clinical management of anxiety-related AEFI; public health authorities should have plans to prevent and effectively manage anxiety-related AEFI clusters. Prompt management of these occurrences can be even more important in an era of social media, in which information is rapidly spread.

Keywords

Mass anxiety; Mass hysteria; AEFI; Mass psychogenic illness

1. Background

Anxiety-related reactions occurring in clusters have alternately been labeled as mass psychogenic illness, mass hysteria or epidemic hysteria. This phenomenon has been considered as a form of mass reaction, the collective occurrence of a constellation of similar physical symptoms among a group of individuals with shared beliefs about the cause of their symptoms [1]. These clusters usually occur in closed, cohesive social settings (e.g., a school) and have been well described following concerns of food poisoning or environmental hazards [2–5].

Anxiety-related reactions are recognized by the Council of International Medical Sciences (CIOMS) as one of the five categories of adverse events following immunization (AEFI); the other four AEFI categories include vaccine product-related reactions, vaccine quality defect-related reactions, immunization error-related reactions and coincidental events [6].

Two types of mass anxiety-related AEFI have been described: an anxiety reaction and a motor reaction. An anxiety reaction frequently presents with rapid onset after the suspected stimulus and symptoms generally include dizziness, fainting, headache, hyperventilation, and weakness. A motor reaction typically has a slower onset after the stimulus and presents with motor agitation, twitching, motor tics, speech impairment, gait disturbances and sometimes pseudo-seizures [7].

Clusters of anxiety-related AEFI following mass vaccination in several countries have received increasing attention in traditional and social media, and these can disrupt country immunization programs [8]. This has prompted an investigation by World Health Organization (WHO) and other international partners to better understand clusters of anxiety-related adverse events following immunization (AEFI) and to review existing terminology and develop guidelines for management [9].

We performed a systematic review of published literature to characterize clusters of anxiety-related reactions following vaccination with respect to patient demographics, vaccines implicated, countries or regions affected, treatments offered, public health response efforts, and impact sustained on vaccination programs. These data can be used to help generate guidance for countries on how best to prevent such occurrences, as well as how to address clusters when they occur to minimize risk to affected patients and vaccination programs.

2. Methods

2.1. Search strategy

We searched for articles in seven databases including Pubmed/Medline, Global Health, Embase (OVID), PsychInfo, Scopus, Pro-Quest and Central Cochrane Library. Our search strategy comprised search terms or keywords (and their derivatives) grouped in the following categories: symptom term, cluster term, vaccination term. We also searched phrases collectively used to describe the phenomenon of mass hysteria, mass anxiety or mass psychogenic illness (Table 1).

Titles and abstracts that met eligibility criteria were independently reviewed by two investigators (AL and MM), and a final list was developed and referred for further review of the full article.

2.2. Eligibility criteria

We included English-language published reports of clusters – defined as two or more cases occurring within a two-week time-period in the same location – of anxiety-related reactions following mass vaccination. We excluded papers that reported hysteria about the illness itself (e.g., measles, pandemic influenza), individual case reports of AEFI, prospective or retrospective surveillance studies for AEFI, published reports of cluster anxiety-related AEFI that were in another language, and media reports or commentaries. There were no restrictions on publication date, patient age, or vaccine implicated.

2.3. Article review and analysis

Articles that met eligibility criteria were reviewed using a standard abstraction form for content including: cluster setting, vaccine used, date(s) of vaccination and relative onset of symptoms, index case symptoms, subsequent cases, clinical diagnosis and management, community and media response, and impact on immunization program. Descriptive analysis was conducted to identify common themes in these clusters.

3. Results

3.1. Search and abstraction

The literature search yielded 1670 articles from 1978 to 2015, among which 198 (12%) were duplicates. Of 1472 titles and abstracts, 46 (3%) met criteria for full text review. Among 46 articles, there were eight (17%) published reports of clusters of anxiety-related AEFI. Thirty-eight articles were excluded for the following reasons: general articles describing anxiety-related AEFI (6), media reports (10), non-English language (9), individual case reports (4), AEFI surveillance results (2), commentary article (1), and unrelated to anxiety-related AEFI (6).

3.2. Overview of published reports

Eight published reports of anxiety-related AEFI clusters were included in this review (Table 2). Published reports of anxiety-related AEFI from 1992 to 2010 occurred in high-, middle- and low-income countries. Clusters ranged in size from seven patients in one school to

806 patients in multiple schools. All published clusters described similar anxiety-related symptoms of dizziness, headache, and fainting with rapid onset after vaccination. Seven (88%) of eight clusters occurred in school-age children (ages 12–16) in school settings, and one (12%) affected a group of adult military reservists. Implicated vaccines included: tetanus (2), tetanus-diphtheria (1), hepatitis B (1), oral cholera (1), human papillomavirus (1), and influenza A (H1N1)pdm09 (2). All articles described product investigation of administered vaccine lots, and no investigation implicated unsafe vaccines as the cause of the reaction.

The section below summarizes each of the published anxiety-related AEFI clusters including the following data, if available: cluster setting, vaccine used, date(s) of vaccination and relative onset of symptoms, index case symptoms, subsequent cases, clinical management, community and media response, and impact on immunization program.

3.3. Published reported clusters

1. **1992 – Iran; tetanus toxoid vaccine [10]—**On October 6, 1992, 26 girls (approximately 14 years old) were vaccinated with tetanus toxoid at a school in Hanza, a secluded village with population <1000 persons, as part of routine immunization. Four days later, one girl fainted; she demonstrated symptoms of pseudo-seizure, tremor, blurred vision, headache, and burning sensation on her hands; she was transferred to the local health center. Of note, the child had a known history of syncope and seizure and was being treated with imipramine and perphenazine. Over the next two weeks, nine girls from the same school presented with similar symptoms; the first four cases were sent to a general practitioner and subsequently transferred to a pediatrician and admitted to the university hospital to rule out encephalitis. Multiple laboratory tests were completed on these patients, including lumbar puncture. Finally, the children were diagnosed with “hysteria” and discharged. This cluster raised community concern for “brain disease” caused by “faulty” vaccine, and the vaccination program was halted. Public health officials held community education events and visited patients’ homes to provide reassurance, and routine tetanus vaccination in school resumed the following year.

2. **1995 – Italy; hepatitis B vaccine [11]—**On September 28–29, 1995, twenty-four 7th and 8th grade students were vaccinated with hepatitis B vaccine in two groups (separated by grade) in a local health care center in Castelfranco, a small village in Southern Italy. Seven of 24 vaccinated students developed symptoms of dizziness, headache, fainting, and paresthesias; onset of symptoms occurred approximately 30 min following vaccination, when the student returned to class. All case-patients were in the 7th grade. Five students were sent to the emergency room, and four were admitted for observation. A case-control study was conducted, which showed adverse events were more frequent among children with prior hospitalization, needle phobia, and prior history of chills and paresthesia. It is unclear from the report if this vaccine was part of the country’s routine childhood immunization schedule or if it was a new introduction. Community or media response and impact on the vaccination program were not reported.

3. **1998 – Jordan; tetanus-diphtheria vaccine [12]—**Tetanus-diphtheria (Td) toxoid is routinely administered to all children in 1st grade (age around 7 years) and 10th grade

(age around 15 years) during September at the start of the school year. On September 29, 1998, 160 10th grade students were vaccinated in a school in Amman, by groups of 10 at the school library. After school, several students had complaints of headache and dizziness; the next morning, one ill student tripped and fell in the school hallway, and this was initially suspected to be a syncopal episode. Later, 20 additional students complained of feeling faint. Teachers contacted the civil defense ambulance and emergency team to assist with suspected infectious disease outbreak in the school. All ill students were sent to the hospital via ambulance; 55 students were admitted, routine blood testing demonstrated normal results, and patients received treatment including hydrocortisone and antihistamine.

The Minister of Health, Minister of Education, and television and newspaper media staff were dispatched to the school, and concerns about reactions to the vaccine were expressed. The Minister of Health stated on television that all children with any symptoms after vaccination should be admitted to the hospital for observation, irrespective of clinical assessment. The Minister of Education authorized stopping vaccination at all schools.

Over the next few days and weeks, more students from other schools reported similar symptoms of chest tightness, dizziness and feeling faint. An official public health investigation was initiated to survey all vaccinated students. Among 25,667 students vaccinated across multiple schools, 806 reported symptoms; 110 were first graders and 696 were tenth graders, and 47% were female.

The World Health Organization (WHO) assisted the Ministry of Health (MOH) to restore public confidence in vaccination; surveillance for vaccine adverse events was initiated and a response system was established. The report concluded that multiple factors caused a small cluster in one school to lead to this large country-wide outbreak. There was prior distrust of the government due to recent alleged contamination of the water supply, and public officials reacted with strong statements on national television. There also appeared to be secondary gain for some students from the events; teachers reported “some students laughed as they queued up to be examined, hoping for a ride to the hospital rather than having to endure a day at school.” Hospital staff also stated “it was difficult to discharge some students because they were enjoying their stay too much.” Media coverage implied that the vaccine was ‘faulty and dangerous’.

4. 2001 – India; tetanus toxoid [13]—Two hundred girls in the 10th grade class (age around 15–16 years) at school in a small village in northern India were vaccinated with tetanus toxoid. Students were not informed in advance of the vaccination plan, and some students were on a religious fast. One student reported dizziness and fainted post-vaccination; soon after, several other students complained of headache and several collapsed in school. Students were rushed to the local health center and the primary care provider diagnosed anaphylaxis. Therapy included antihistamines and steroids, which caused bradycardia, hypotension and further syncope. Forty-five of 58 affected students were admitted for testing and observation. There were several adverse media reports and public outrage. The community blamed ‘defective or adulterated vaccine,’ and there was added hostility over inappropriate medical management. “The situation resolved in two

weeks;" however, details of the public health response and outcome on the vaccination program were not described further in the report.

5. 2001 – Vietnam; oral cholera vaccine [14]—A cholera vaccination campaign was initiated as part of public health response to a potential outbreak after cases of cholera were detected in Ca Mau Province in southern Vietnam in mid-November 2001. On December 18, 2001, oral cholera vaccine was administered to 599 children in classrooms in two primary schools. One hour following vaccination, three boys aged 12 years complained of nausea, trembling and headache. They were transported through the school courtyard, in view of other classrooms, to the library for observation. Of 234 vaccinated students in School #1, 97 students presented to health facilities with symptoms of cold extremities, headache, abdominal pain, pruritus, and dizziness. Mean age was 9.6 years, and 49 were female (43%). No cases were reported from School #2. Clinical management of case-patients included intravenous fluid, oral rehydration solution, antipyretics and/or antihistamines. No invasive testing was done, and patients were discharged the same day. There were several adverse media reports indicating a 'poisoning incident' at the school. Several domestic public health partners were involved in the initial investigation, which concluded the symptoms were caused by anxiety reaction.

An international partner, International Vaccine Institute, conducted a case-control study which found that affected patients were younger than controls by approximately 6 months, and risk was similar for boys and girls.

Vaccinations resumed in two weeks, after it was concluded that the students' symptoms were due to anxiety reactions; however, acceptance for the second dose was lower than for the first dose at School #1. Further community and media response was not described in the report.

6. 2007 – Australia; human papillomavirus (HPV) vaccine [15,16]—Quadrivalent HPV vaccine was included in Australia's national immunization program starting in April 2007. On May 7th, 720 girls aged 12–17 years received HPV vaccine at an all-girls school in Melbourne. Each vaccine was administered to a seated student privately, with separate entrances and exits to the vaccination room. Within 2 h following vaccination, 26 girls presented to the school sick bay with dizziness, syncope and aphasia. Ill students were directed to the sick bay through the school's central quadrangle, in view of other classrooms. Four students were taken to the emergency room for further management, including neuroimaging. No additional invasive testing or specific treatments were done.

Media interest and public anxiety heightened, and extensive public health efforts were undertaken to reassure the community about vaccine safety, including radio interviews with the federal health minister and Victorian state premier. Further comments on the impact of this event on the vaccination program and resolution of HPV vaccination were not discussed in this report.

7. 2009 – Taiwan; influenza A (H1N1)pdm09 vaccine [17]—Taiwan began in-school vaccination for pandemic influenza (H1N1) for 1st–12th grade students in November

2009, as part of public health outbreak response. On November 23, 2009, a cluster of 46 (7%) of 692 vaccinated students aged 12–15 years presented with dizziness, nausea, headache and hyperventilation within two hours of vaccination. Surveillance was initiated and identified 23 clusters of students with similar symptoms (total of 350 students) in schools across Taiwan, between November 2009 and January 2010. Each cluster involved between 2 and 46 ill students; 237 (68%) were female and the median age was 13 years (range 6–16 years). The public health authority responded by briefing the media with key messages to inform and reassure the public regarding vaccine safety. A guidance document was sent to school staff and immunization organizers. The author of this report commented that the country's mandate to vaccinate all students in two months gave limited time for patient education, resulting in public distrust and subsequent decline in influenza H1N1 vaccination coverage.

8. 2009 – United States; influenza A (H1N1)pdm09 vaccine [18]—On February 19, 2009, 201 military reservists were vaccinated with influenza A (H1N1)pdm09 vaccine, as part of influenza outbreak response efforts. The following day, a 23-year old male reservist presented to an emergency room with progressive lower to upper extremity weakness, and he was diagnosed with possible Guillain-Barré Syndrome (GBS). The Commanding Officer advised other reservists to report symptoms, and 13 additional reservists presented to the hospital with non-specific complaints; symptoms resolved, and they were discharged with only supportive therapy. The index patient was admitted for two days, and nerve conduction studies were done; GBS diagnosis was excluded, and he was discharged with a diagnosis of 'generalized weakness' and fully recovered.

Community and media response, as well as impact on the vaccination program, were not discussed further in this report.

4. Discussion

This review describes eight clusters of anxiety-related AEFIs occurring in both rural and urban settings, as well as in high-, middle- and low-income countries across most WHO regions. Among the patients, males and females were affected equally, and most were school-aged. Several different vaccines were implicated, although specific clusters involved a new vaccine introduction or a change in the routine vaccination program, including a novel vaccine, new age group, or new setting for vaccination. Clinical management involving invasive testing or treatment, in some reports, caused harm [10,12,13]. In two reports, a small cluster which started in one group setting quickly spread to become a larger outbreak, often escalated by media reports. Public health response efforts varied across these reports, as did the impact on vaccination programs.

These reports describe patterns of symptoms that are similar to those documented in the literature for mass anxiety-related illness following other stimuli (e.g., environmental toxin, food poisoning) [3,19–24]. However, there are specific factors that make these incidents following vaccination unique. Prevalence of needle injection phobia among children has been well documented [25]. Vaccination anxiety-related reactions, including vasovagal syncope, has also been described [26]. More specifically, vaccination-related syncope

can occur when needle phobia and subsequent pain of injection can result in autonomic nervous system stimulation causing decreased heart rate and vasodilation, resulting in brain hypoperfusion and temporary loss of consciousness. As seen in several of the reports, this pattern can be exacerbated when individuals are receiving vaccination in a group setting, specifically when children waiting to be vaccinated can observe others post-vaccination who may be experiencing anxiety reactions [8].

This review of the literature is limited by the small number of reports. There is also potential publication bias favoring reports in which the situation resolved and vaccination program resumed, resulting in unmeasured underreporting bias. There are many examples of anxiety-related AEFI clusters that remain unpublished but are documented in social media (personal communication with Suragh) or in investigative reports from WHO or other partner missions to countries. In addition, this literature review is complicated by the fact that there is no standardized terminology for these occurrences. There is a need to identify and clarify terminology that describes the continuum of anxiety-related AEFI and provides for classification. For example, stress reactions and exaggerated stress response may more accurately reflect many of the reactions at the less severe end of the continuum. Through personal communication, we were informed about published papers that described anxiety-related AEFI clusters, but did not appear in our search strategy (e.g. not in the database or used different keywords or reports were embedded in the manuscript content) [27,28]. Finally, our review was limited to English-language reports.

Although there were a limited number of published reports, this review of the literature suggests commonalities and potentially modifiable predisposing factors, which when planned for and addressed can help countries prevent and manage anxiety-related AEFIs occurring in clusters. There is a need for evidence based guidelines on prevention and management of anxiety-related AEFIs during mass vaccination or vaccine introductions, including clinical recognition and assessment of suspect cases, and management of clusters to mitigate further spread. To better manage anxiety-related AEFI clusters, healthcare providers and public health officials may benefit from innovative training approaches incorporating activities such as role-playing under various scenarios and use of nationally trained AEFI investigative teams to support local public health staff during these events.

During microplanning for a vaccine introduction or other changes to a vaccination program, it is important to anticipate and plan for anxiety-related AEFIs. Time pressure, particularly during an outbreak situation, may hamper appropriate community and health provider communication. In addition, the selected setting for mass vaccination activities may limit options for privacy at delivery and pain mitigation interventions. Immediately following vaccination, it is recommended to allow for a 15–30 min post-vaccination observation period, to observe for severe allergic reaction and prevent syncopal episode [29,30]; however, this may not be feasible or routinely followed in a crowded vaccination setting.

Importantly, health providers should be able to recognize symptoms of anxiety-related AEFIs and be able to distinguish these symptoms from other acute AEFIs, most importantly anaphylaxis, to avoid aggressive and potentially harmful clinical interventions. Although anaphylaxis, syncope and anxiety-related reactions all can occur soon after vaccination

and have some overlapping symptoms, there are important distinguishing characteristics; clinicians should be trained to recognize these characteristics. While treatment for anaphylaxis requires rapid administration of epinephrine and possibly antihistamine or corticosteroids, anxiety reactions should be managed by having the patient sit or lie down and take slow deep breaths (Table 3). Treating an anxious patient with corticosteroids and antihistamines may exacerbate symptoms.

All eight published reports reviewed here describe anxiety-related AEFI symptoms; however, motor symptoms occurring in clusters following vaccination have been reported in the media (personal communication with Suragh), so clinicians must be aware of this entity and consider it in their patients' differential diagnosis. Providers should be equipped with knowledge and tools for appropriate clinical management and reporting of AEFI, as set out by the Brighton Collaboration [31]. In addition, providers need guidance, and perhaps oversight, so that patients with anxiety-related reactions are not hospitalized, a practice that can lead to further increase in numbers of cases and exacerbation of symptoms in those hospitalized.

Prior to initiating a large vaccination campaign, public health authorities should have a crisis management plan detailing how they will manage AEFI cases or clusters, if they occur. In addition to providing guidance for specific management of affected patients, the crisis management plan should include a communication plan that identifies a program spokesperson to respond to requests for information from the media and the community including through social media. Immunization programs should partner with media to deliver appropriate communication messages and mitigate the spread of rumors; indeed, training of media contacts on an ongoing basis on topics related to vaccination and vaccine safety may help to create an effective channel for positive communication when AEFI events do occur.

To prevent and effectively manage these clusters, there is a need for improved identification and reporting of vaccination-related anxiety within the current AEFI surveillance infrastructure, as well as appropriate measures to facilitate consideration of vaccination-related anxiety when investigating AEFIs to assess causality. Preliminary data from our ongoing review of clusters of AEFI from social media suggests that these clusters have been underreported in the scientific literature (personal communication with Suragh). To provide a robust evidence base, it is important that countries and WHO publish reports of these clusters or large-scale vaccination anxiety-related outbreaks when they occur, including details of the impact on vaccination programs and mitigating actions taken. Focused research initiatives to better understand precipitating factors for anxiety-related reactions in the context of vaccination will be key to developing strategies for anticipation, prevention, and response to such clusters. In addition to targeted research activities and development of guidelines, international partners must reach consensus on appropriate terminology and sub-classification for such events, to avoid further confusion and mismanagement.

With the continued introduction of new vaccines and new age platforms or during routine vaccination campaigns with available vaccines, we can expect anxiety-related AEFI clusters to continue to occur. Some vaccines in development (e.g. Ebola) already face public distrust

and will be under further scrutiny during implementation [32]. Vaccination programs need to plan for and become experienced in effectively responding to unfounded and damaging rumors, especially in an era of increasing social media use, to effectively mitigate the impact of anxiety-related AEFI that may occur.

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Table 1

Keywords and data sources for a systematic review of English language published reports of anxiety-related AEFI clusters.

Keywords				Databases
Symptom term	**Cluster term**	**Vaccine term**	**Cluster AEFI Phenomenon term/phrase**	
Psych	Outbreak	Vaccine	Adverse event following immunization (AEFI)	Pubmed/Medline
Psychogenic	Cluster	Immunization/Immunisation	Mass psychogenic illness after vaccination (MPIV)	Global Health
Psychological	Cases	Vaccination	Vaccination anxiety-related reaction	Embase (OVID)
Sociogenic	Mass	Vaccine-related	Psychogenic movement disorder	PsychInfo
Illness	Epidemic	Immunization-related	Psychosomatic illness	Scopus
Somatic	Collective	Injection	Somatization disorder	ProQuest Central
Symptoms			Epidemic hysteria	Cochrane Library
Reaction				
Hysteria				
Paranoia				
Anxiety				
Anxiety-related				
Conversion disorder				
Panic				

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Table 2

Eight published reports of anxiety-related AEFI clusters.

Year	Country	Setting	Number vaccinated	Number of case-patients (%)	Age group or grade in school	Number of females (%)	Vaccine involved	Symptoms	Clinical management characteristics
1992	Iran	School	26	10 (38)	Age 14 years	10 (100)[a]	Tetanus	Pseudoseizure, tremors, blurred vision, headache, fainting	Hospitalized; multiple labs done (including lumbar puncture)
1995	Italy	School	24	7 (29)	7th grade	4 (57)	Hepatitis B	Dizziness, headache, fainting, paraesthesia	Hospitalized
1998	Jordan	Multiple schools	25,667	806 (3)	10th grade	379 (47)	Tetanus-diphtheria	Headache, dizziness, chest tightness, pyrexia, hypotension, feeling faint	Hospitalized; blood testing done; treated with steroid and antihistamine
2001	India	School	200	58 (29)	10th grade	58 (100)[a]	Tetanus	Headache, fainting, giddiness, falling, nausea, vomiting	Hospitalized; treated with steroid and antihistamine
2001	Vietnam	School	234	97 (41)	12 years	49 (51)	Oral cholera	Cold extremities, headache, nausea, abdominal pain, pruritis	Emergency room visit; treated with intravenous fluid, oral rehydration solution, and/or antihistamine
2007	Australia	School	720	26 (4)	Age 12–17 years	26 (100)[a]	HPV	Dizziness, fainting, weakness, palpitations, aphasia	Emergency room visit; testing included neuroimaging
2009	Taiwan	Multiple schools	9115	350 (4)	Age 12–15 years	237 (68)	H1N1 influenza	Dizziness, nausea, headache, hyperventilation	Not reported
2010	United States	Military reserve	201	14 (7)	Age 20+	6 (43)	H1N1 influenza	Weakness, headache, dizziness	Hospitalized; index patient completed nerve conduction studies

[a]Only girls were vaccinated, either because vaccination took place at an all-girls school or vaccine only indicated for girls (eg. HPV, tetanus).

Table 3

Clinical presentation and management of anaphylaxis, syncope, and anxiety reactions following vaccination.[a]

	Anaphylaxis	Syncope	Anxiety
Onset	Soon (5–30 min) after vaccination	Before, during or soon after vaccination	Before, during or soon after vaccination
General Clinical Presentation & Behavior	Uneasiness, restlessness, agitation	Fearfulness, light-headedness, dizziness, numbness, weakness	Fearfulness, light-headedness, dizziness, numbness, hyperventilation ± tingling
Symptoms by system			
Skin	Hives, swollen eyes and face, generalized rash	Pale, sweaty, cold, clammy	Pale, sweaty, cold, clammy
Respiratory	Noisy breathing with airway constriction - wheezing, stridor	Normal to deep breathing	Rapid and shallow (hyperventilation)
Cardiovascular	↑ heart rate, ↓ blood pressure, dysrrthymias, cardiac arrest	↓ heart rate, ±transient ↓ blood pressure	↑ heart rate, normal or elevated systolic blood pressure
Gastrointestinal	Nausea, vomiting, abdominal cramps	Nausea, vomiting	Nausea, vomiting
Neurologic	Loss of consciousness, little response once supine	Transient loss of consciousness, good response once supine, tonic/clonic seizure	Pseudoseizure, tremor, weakness, tingling sensation on face or extremities
Occur in Clusters	No	Yes	Yes
Clinical Management	1. Epinephrine	1. Place on side	1. Have patient sit or lie down
	2. Assess airway, breathing, circulation	2. Open airway by tilting head back	2. If patient hyperventilating, coach to take slow deep breaths
	3. Intravenous fluid	3. Monitor breathing and pulse	
	4. Antihistamine	4. Check for injury	
	5. Corticosteroids	5. Address underlying cause	
	6. Hospital admission		

[a]Adapted and expanded from the New Zealand Ministry of Health Immunization Handbook, 2014. http://www.health.govt.nz/system/files/documents/publications/immunization-handbook-2014–2nd-edn-apr16.pdf. Presented at the Global Advisory Committee on Vaccine Safety, December 2015 [9].