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Adverse Events Related to Vaccination (VAEs): How to Manage the Further Doses of Immunization and Parents' Hesitancy

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Abstract

This study supports the evidence that after vaccine-related reactions, it is still possible to carry out the immunization protocol.

Out of more than 1000 patients per year evaluated for potential vaccine-related risks (patients with chronic/serious diseases and events connected with vaccination), 76 (6%) presented previous vaccine adverse events (VAEs). The decision about whether to continue child vaccination is made evaluating different factors: absence of specific contraindications, parents' counseling, adequate hospital setting, choice of an appropriate and individualized schedule. None of the 76 children vaccinated after VAEs presented further side effects.

Our data demonstrate that VAE is not a recurring event. The real risk of a new VAE is mostly associated with the serious allergic reactions (IgE-mediated anaphylaxis) and parents should be aware of this information, so that the widespread fear of VAE recurrence can be contained. Indeed, this type of concerns represents one of the main reasons for vaccination hesitancy, which leads to incomplete vaccination schedules.

Conclusions: This chapter encourages clinicians to take advantage of the available VAE assessment algorithms to objectively evaluate real vaccine risk of VAE and provide parents with correct information, considering that VAEs are rare and severe reactions are extremely rare.

Keywords: vaccine, adverse event, side effect, re-vaccination, causality assessment, VAE

1. Introduction

A vaccine adverse event (VAE), also referred to as an adverse event following immunization, has been defined as “a medical incident that takes place after immunization, causes concern and is believed to be caused by the immunization” [1, 2]. These events are individual reactions usually induced by a direct effect of the vaccine or one of its components and are related with underlying medical conditions or idiosyncratic responses of the recipient. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom, or disease [3]. However, any untoward medical occurrence, which follows immunization and which does not necessarily have a causal relationship with the administration of the vaccine, is considered as VAE. These include also those conditions that would have occurred later on in life but are triggered earlier by the vaccination, like febrile seizures.

The adverse event may be a true adverse reaction that is induced by the vaccine, or may be caused by the way it is administered. Some events result from inappropriate practices, such as wrong dose, route, site or technique of administration, inappropriate intervals, incorrect preparation or amount of diluent, contamination, wrong storage, or ignored contraindications.

Other VAEs may be coincidental and would have occurred regardless of vaccination. These are purely temporally associated, because vaccines in children are given at an age when they are susceptible to many diseases. When a VAE is coincidental, the event would have occurred even if the individual had not been immunized. Sudden infant death syndrome (SIDS), for example, is an event clearly unrelated to vaccination; however, serious clinical events may be blamed to the vaccine by parents or community because of its close temporal association with immunization, especially if the vaccinated individual was previously healthy.

A vaccine safety surveillance program named Vaccine Adverse Event Reporting System (VAERS), run by the Center of Diseases Control and Prevention and Food and Drug Administration, has been instituted in 1990 in the US to collect information about VAEs [4]. In 1999, the World Health Organization (WHO) established the Global Advisory Committee of Vaccine Safety to respond promptly, efficiently, and with scientific rigor to vaccine safety issues of potential global importance. The last committee report edited on December 2015 is published and available online [5].

The main concern for both clinicians and people is to be able to distinguish between a real VAE and another health problem that is just temporally coincidental and not related to vaccination. This is particularly true in our era of vaccine skepticism: due to parents' frequent hesitation or outright refusal to accept some or all of the recommended vaccines, vaccination coverage is progressively decreasing [6]. The main reasons why people refuse vaccinations include ignorance about how vaccines work, which leads to an inappropriate criticism due to misunderstandings [7], and the negative influence by the media about vaccination safety and efficacy [8]. Whatever the cause, VAEs can upset people to the point of refusing further vaccination for their children [9].

To correctly interpret VAEs, the following characteristics need to be evaluated: the time correlation between vaccination and symptoms, the general health conditions of the subjects, and in particular their predisposition to allergies, and the known correlations between specific vaccines and clinical manifestations. In 2013, WHO edited the “User Manual for the revised classification on Causality assessment of adverse events following immunizations,” a guide to a systematic and standardized causality assessment process for VAEs [10]. The manual suggests to adopt a systematic approach considering both the population (i.e., statistical strength of association between vaccine and VAE, biological plausibility, and coherence of the association) and the individual (i.e., relationship between vaccine and VAE, clinical and/or laboratory proof of the association, and exclusion of alternative explanations) levels. Recently, some authors have proposed other “causality assessment schemes” to help clinicians distinguish between VAEs whose association with the vaccination is consistent, indeterminate, or inconsistent [11].

1.1. Kinds of VAEs

The most typical and worrisome VAEs are allergic reactions, since reactions to the next dose of the same vaccine may be more immediate and severe than the first one, sometimes also life threatening [12]. Immediate allergic reactions are the most severe. These are relatively easy to identify because they are IgE-mediated and can be detected either by skin prick tests (SPTs) or *in vitro* by specific IgE assay [13]. One of the most serious VAEs is anaphylaxis, which could have life-threatening features: circulatory failure (altered level of consciousness, low blood pressure, weakness or absence of peripheral pulses, cold extremities due by reduced peripheral circulation, flushed face, and increased perspiration), with or without respiratory difficulties (bronchospasm and/or laryngospasm/laryngeal edema), normally with rapid onset (minutes), an unpredictable clinical course, and variable severity. Over 80–90% of anaphylaxis also presented skin and mucous membrane manifestations. Diagnosis of anaphylaxis is supported by the presence, following administration of a vaccine to a healthy recipient, of two or more of the above system signs and symptoms, which occur with a rapid onset. Anaphylactic reactions to vaccines are extremely rare but have the potential to be fatal.

It should be highlighted that the incidence of severe allergic reactions is very low, ranging between 0.5 and one cases/100,000 doses [14]. Currently, in Australia and US, anaphylaxis and encephalopathy are the only conditions determining absolute contraindication to revaccination with the suspect vaccine [15, 16]. Allergic children can also be at risk of reactions against non-active vaccine components, such as eggs/gelatin/antibiotics. Schemes with recommendations for vaccination of such allergic children have been developed [17].

A kind of VAEs that are particularly worrisome for parents is hypotonia-hyporesponsiveness episode (HHE), which is characterized by the sudden onset of pallor or cyanosis, decreased level or loss of responsiveness, and decreased level of muscle tone, occurring within 48 h of vaccination, normally transient and self-limiting. These episodes have been described to

occur after vaccination with hexavalent vaccine and are considered to be related to the pertussis component [18]. A review of Canadian tertiary-care hospitals has shown that HHE accounts for less than five cases per 100,000 admissions to hospitalization, the majority of whom are discharged within 24 h [19]. Current evidences do not suggest that HHEs are associated with long-term morbidity or mortality.

Febrile seizures are among VAEs of particular parents' concern. However, febrile seizures are relatively common in children between 6 months and 5 years, and are more frequent in subjects with familiar and/or individual predisposition.

Other systemic reactions are fever, malaise, myalgia, irritability, headache, and loss of appetite. Inconsolable continuous crying lasting at least 3 h accompanied by high-pitched screaming can occur. The arthralgia usually including the small peripheral joints is infrequent but can be persistent lasting longer than 10 days. Rarely rubella vaccine can cause an acute arthropathy that lasts 10 days. Guillain-Barré syndrome (GBS): acute onset of rapidly progressive, ascending, symmetrical flaccid paralysis, without fever and with sensory loss could occur after 30–60 days after immunization. Encephalopathy/encephalitis occurs within 72 h to 4 weeks after vaccination, as an acute onset of seizures or severe alternation in the level of consciousness and/or distinct change in behavior lasting 1 day or more. Idiopathic thrombocytopenic purpura (ITP) often follows measles vaccines. The timing and severity of these systemic reactions varies according to the characteristics of the vaccine received, the age of the recipient, and the individual biological response to each vaccine: it can start within a few hours to several days after vaccine.

A different kind of VAEs is represented by local reactions. These are frequently reported as “hypersensitivity reactions”: pain, swelling, or redness at the site of injection usually starting within a few hours are generally mild and self-limiting. These are not allergic reactions, but may be due to a direct effect of the vaccine product, or be related to a higher antibody titers. Also, errors in vaccine preparation, in handling, or administration can cause local adverse effects, as purulence, inflammation, and positive Gram stain culture. Nodules at the injection site are relatively frequent and are constituted by a small well-defined mass or a lump at the injection site, which are indicated as a subcutaneous nodule, antigen cysts, or granulomas, in the absence of abscess formation, erythema, and warmth. Local reactions are generally of moderate entity but can be significant at times, making parents and patients antonyms to revaccination. Local reactions are commonly observed following tetanus, pertussis, and diphtheria vaccine: reports demonstrated that the rate and severity increase with booster compared with primary doses of these antigens [20–25].

Another event that often occurs after vaccination is fainting. It is considered a vasovagal response and usually takes place in older children and adolescents who are prone to this kind of reaction. It is not considered to be a serious reaction and never represents a contraindication to continue vaccination schedule. Canadians have proposed immunization guidelines on pain mitigation to help clinicians to prevent the aforementioned situations [26].

In our vaccine unit at the Bambino Gesù Pediatric Hospital in Rome, we visit about 1000 patients per year and we evaluate those who have one or more risk factors for vaccination.

About 6% of patients at risk for vaccination has a history of VAE. The decision on the opportunity to continue the vaccination schedule is made upon the evaluation of various factors. In case specific contraindications are not highlighted, we administer vaccines following a patient-individualized schedule.

Here, we present the results of the analysis of data on patients with history of VAEs that came to our attention between September 2014 and February 2016.

2. Materials and methods

We included in our analysis all children who have been vaccinated at the Vaccine Unit of Bambino Gesù Children Hospital from September 10, 2014, until February 18, 2016. On a total of 1367 enrolled subjects, 76 children (6%) came to our unit with a previous history of one or more VAEs. In case of more than one VAEs, these were classified as “main event” and “secondary event” depending on the severity of reported symptoms.

We recorded patients’ familial and personal history, predisposition to allergies, time correlation between vaccine administration and VAE, severity of referred VAE (i.e., grade 1: mild; grade 2: moderate; grade 3: severe), if the previous VAE has caused hospitalization, VAE duration, and sequela of the previous VAE.

Based on this general evaluation, we decided whether patients could continue to be vaccinated or not. For those who were, we created a personalized vaccine schedule and provided them with a vaccination follow-up plan in our unit.

3. Results

3.1. Previous, referred VAE

Patients’ characteristic: The median age of the 76 patients affected by a previous VAE was 3.9 ± 4 years.

VAEs type: The most common was urticaria/angioedema, which was referred by 31 out of 76 patients (41%). Other common VAEs were hypotonia/sleepiness (11 patients = 14%), local symptoms (7 patients = 9%), high fever (6 patients = 8%), and low fever (5 patients = 7%). In our sample, seizures were relatively rare (3 patients = 4%). Anaphylaxis, the most severe VAE, was referred only by 1 patient after hexavalent vaccine administration. Guillain-Barré syndrome, another severe adverse event, was referred by 1 patient after mumps, measles, and rubella (MMR) vaccine (**Table 1**). Sixteen patients (21%) reported positive personal and/or familiar history regarding allergies. In all cases, the referred VAE was supposedly of allergic nature and the patient or his/her parents were allergic.

VAEs entity: The main referred VAE was classified as mild in 13 out of 76 patients (17%), moderate in 54 (71%), and severe in 9 (12%) patients. The mean time interval between vaccination

	N reported events	% on reported events ^a	% on observed patients ^b
Primary event			
Local symptoms	7	9	0.5
Unusual crying	3	4	0.2
Urticaria/angioedema	31	41	2.3
Fever >40.5	6	8	0.4
Fever 38–40	5	7	0.4
Hypotonia/hyporesponsiveness	11	14	0.8
Seizures within 72 h	3	4	0.2
Guillain-Barré within 6 weeks	1	1	0.1
Purpura	3	4	0.2
Neurological symptoms other than seizures	3	4	0.2
Anaphylaxis	1	1	0.1
Gastrointestinal symptoms	1	1	0.1
hypothermia	1	1	0.1
Concomitant event			
None	62	82	4.5
Local symptoms	2	3	0.1
Unusual crying	1	1	0.1
Urticaria/angioedema	1	1	0.1
Fever >40.5	2	3	0.1
Fever 38–40	4	5	0.3
Hypotonia/hyporesponsiveness	1	1	0.1
Seizures within 72 h	2	3	0.1
Gastrointestinal symptoms	1	1	0.1
VAEs characteristics			
Severity grade 1	13		17
Severity grade 2	54		71
Severity grade 3	9		12
Time interval Mean, $\pm$ SD	26 h		72 h
Time interval Median, range	6 h		10 min to 480 h
VAE duration Mean, $\pm$ SD	82 h		189 h
VAE duration Median, range	48 h		30 min to 24 h
N. hospitalization	19		25

	N reported events	% on reported events ^a	% on observed patients ^b
N. vaccinated that reported sequelae	0		-
N. positive familiar history for VAEs	16		21

^aPercentage of events with respect to the number of patients with VAE (n. 76).
^bPercentage of events with respect to the observed at-risk patients (n. 1367).

Table 1. List of characteristics and types of VAEs.

and referred VAE was 26 ± 72 h. The mean duration of referred VAE was 82 ± 189 h. The longest referred VAEs were obviously Guillain-Barré syndrome, which lasted 60 days. Nineteen out of 76 patients (25%) had been hospitalized after the previous VAE. No patient reported permanent sequela after the referred VAE (**Table 1**).

Correlation between specific vaccine(s) and kind of VAE: We found that the coadministration of hexavalent and PCV13 is the most commonly reported VAE (47 patients, 62.7%), followed by hexavalent alone (7 patients, 9%), MMR (5 patients, 6.7%), and DTaP (4 patients, 5%) (**Table 2**).

Type of reaction caused by specific vaccine(s): Coadministration of hexavalent and PCV 13 was most commonly associated with urticaria/angioedema (21 patients) and hypotonia/hyporesponsiveness (8 patients). Administration of hexavalent alone was associated with various kinds of VAE (hypotonia/hyporesponsiveness, local symptoms, urticaria/angioedema, fever >40.5 grades, anaphylaxis, and fever 38–40 grades). MMR administration was associated with urticaria/angioedema, fever 38–40 grades, fever >40.5 grades, and Guillain-Barré syndrome. DTaP administration was followed by local symptoms in 2 patients, and irritability or urticaria/angioedema in 1 patient each (**Table 2**).

Type of reaction	Hexavalen	DTaP/ IPV	Hex+PCV	PCV13	MenB	MMR	Var	MeC cayw	Flu	HPV	tot
Local symptoms	1	2	4	1	1	-	-	-	-	-	9
Unusual crying	-	-	4	-	-	-	-	-	-	-	4
Urticaria/ angioedema	1	1	21	-	2	3	1	3	-	-	32
Fever >4.5	1	-	6	-	-	-	-	-	1	-	8
Fever	3	-	5	-	-	1	-	-	-	-	9
Hypotonia/ hyporesponsiveness	1	-	9	-	-	1	-	-	-	1	12
Seizures within 72 h	-	-	4	-	-	-	-	-	1	-	5
Guillain-Barré within 6 weeks	-	-	-	-	-	1	-	-	-	-	1

Type of reaction	Hexavalen	DTaP/ IPV	Hex+PCV	PCV13	MenB	MMR	Var	MeC cayw	Flu	HPV	tot
Purpura	-	-	1	1	-	-	-	1	-	-	3
Irritability	-	1	2	-	-	-	-	-	-	-	3
Anaphylaxis	1	-	-	-	-	-	-	-	-	-	1
Gastrointestinal symptoms	-	-	2	-	-	-	-	-	-	-	2
Hypothermia	-	-	1	-	-	-	-	-	-	-	1
Total events by vaccine type	8	4	59	2	3	6	1	4	2	1	90
Percentage of events by type	8.9	4.4	65.5	2.2	3.3	6.7	1.1	4.4	2.2	1.1	%

Table 2. Vaccine adverse events by the type of vaccine.

3.2. Revaccination in Bambino Gesù Children Hospital

All patients that came to our unit with a history of VAE were evaluated for eligibility to continue the vaccination schedule or to be revaccinated with further dose of the same vaccine. Out of the total number of 76 patients, 31 (41%) patients described a VAE of suspected allergic origin (i.e., urticaria/angioedema, anaphylaxis). Our approach to revaccination in patients that referred VAEs of suspected allergic nature is summarized in Table 3. All of these 31 patients underwent a skin prick test before revaccination with the same or a different vaccine: all skin tests resulted negative. All patients within our sample were further vaccinated one or more times. None experienced adverse events again.

Type of VAE	N° VAEs (%)	Vaccine causing the referred VAE	N°	Same vaccine	Subunit of the same vaccine	Different type of vaccine	Same vaccine or subunit + different vaccine	Recurrent VAE
Urticaria/ angioedema	32 (42%)	Hexavalent + PCV13	21	4	6	5	6	None
		DTaP	1	0	0	1	0	None
		Hexavalent	1	0	0	1	0	None
		MenB	2	2	0	0	0	None
		MenC	2	0	0	0	2	None
		MMR	3	0	0	3	0	None
		Varicella	1	0	1	0	0	None
		Men ACWY + B	1	0	0	0	0	None
Anaphylaxis	1 (1%)	Hexavalent	1	0	0	1	0	None

Table 3. Immunization of allergic patients with a previous VAE.

4. Discussion

In this report, we describe our experience with patients having a history of VAE who come to medical attention for vaccination counseling. In agreement with literature data, our findings show that VAEs are not common and that severe reactions are particularly rare [27]. Our data also demonstrate that VAEs are not recurring events, in general. This information should be shared with parents and patients, since they are often worried that VAE might reappear after subsequent vaccination events. Indeed, this is the most common reason leading to revaccination refusal [9] and noncompletion of vaccination schedules [28].

The only specific risk of repeated VAEs regards those of allergic nature, in particular VAEs that can be interpreted as acute allergic reactions (i.e., IgE-mediated). For this reason, it is important to perform accurate anamnesis and SPT in patients with referred VAEs of suspected allergic nature, using particular caution with patients who exhibit positive SPT (none in our sample). In 2010, Fritsche et al. have accurately described a diagnostic and therapeutic approach toward children with suspected vaccine allergy, highlighting the important role of STP and exposing the desensitization criteria to be employed for revaccination [29]. Based on our experience, when first reactions occur at a very young age and with more than one vaccine, revaccinations are best approached “step by step,” with no more than one vaccine per visit, even in cases of negative SPT.

Our analysis indicates that the most “reactogenic” vaccine is hexavalent coadministered with PCV13. This could be explained both in terms of intrinsic immunogenicity of the vaccine itself and/or with the young age of the patients [13]. It has also been demonstrated that infants who receive hexavalent plus PCV7 have almost twofold higher incidence of reactions than those who received each vaccine alone [30, 31].

VAEs were described to be severe by 12% of parents and patients in our sample, a surprisingly high number. However, we deem as important to point out that we have frequently observed that a large gap exists between parents’/patients’ opinion and clinical evaluation about VAEs severity. People are often biased against and skeptical toward vaccines, and parents tend to interpret any child’s symptom that appears after immunization as worrisome. This phenomenon acts as a statistical bias because probably we overestimated VAEs severity.

Two of our patients came with a history of very important VAEs. The first was a 12-year-old girl who referred a history of anaphylaxis after the third dose of hexavalent vaccine. The reaction occurred 1 h after vaccination and presented with urticaria, breathing and swallowing difficulty, and vomiting. The patient was brought to an emergency department where she was treated with epinephrine, fluids, and steroids. She was discharged after 3 days of hospitalization, in good health conditions. She and her parents denied any history of allergy. After this episode, her vaccine calendar was interrupted. In our vaccine unit, she was re-vaccinated with MMR, after STP with the vaccine had resulted to be negative. Although she did not experience any VAE, she will be re-evaluated to decide whether she can undergo re-vaccination with DTaP. The second patient who referred to our center with a history of serious VAE was a 7-year-old girl with a previous history of Guillain-Barré syndrome, which had occurred after the administration of the second dose of MMR. The syndrome appeared 3 weeks after

vaccination with leg weakness that led to walking impossibility within a few hours. She was admitted to the neurology department of our hospital, where she was promptly diagnosed and received immunoglobulin treatment. She was discharged after a period of 20 days in good general condition and did not experience any sequela nor relapse of the syndrome. After this episode, she did not receive any other vaccine. In our unit, she was re-vaccinated following the routinary vaccination calendar and did not experience any further VAE.

Recent reports discuss the classification of VAEs and clarify the correct interpretation of the linkage between an adverse event and previous vaccination [11]; some authors propose algorithms to assess the linkage between VAE and vaccine [32]. According to those indications, a VAE is defined to be caused by the immunization if it is linked to a vaccine product-related reaction, a vaccine quality defect-related reaction, an immunization error-related reaction, and an immunization anxiety-related reaction. Other VAEs are defined as indeterminately related with the immunization, inconsistently related with the immunization and unclassifiable. WHO published a causality assessment manual in which it is possible to follow a causality assessment checklist to clarify the linkage between events and immunizations [10]. Indian guidelines classify VAEs in five broad categories: programmatic error, vaccine reaction, injection reactions, coincidental, and unknown [33]. It is particularly important to distinguish between VAEs that are actually related to the vaccination (i.e., caused by the vaccination, indeterminately related to it, programmatic error, vaccine reaction, or injection reaction) and others, because the second are not reproducible and do not represent a contraindication to re-vaccination. Clinicians should be familiar with these differences and encourage parents and patients to re-vaccination when they refer VAE of the coincidental type. Following those schemes, patients in our sample reported VAEs that could be interpreted as being related to the vaccination, such as allergic and local reactions, as well as VAEs with indeterminate relation with the vaccination, such as fever and unusual crying. It must be empathized that the first group comprises VAEs that are potentially reproducible and patients who should always be studied before re-vaccination (by anamnesis, physical findings, and SPT). Conversely, the second group includes VAEs that are rarely reproduced and patients that can almost always be safely re-vaccinated. As far as our two cases of severe VAE are concerned, anaphylaxis was related to vaccination and Guillain-Barré syndrome had an indeterminate relation with it. Both patients were re-vaccinated, but we considered it to be important to make SPT before re-vaccination of the first patient and have not administered the causative vaccine of anaphylaxis yet. Notably, both patients had interrupted their vaccine calendar before coming to our attention, but re-vaccination resulted to be safe and neither of them experienced any complication.

5. Conclusion

In conclusion, we wish to empathize the concept that a history of VAE does not necessarily represent a contraindication to re-vaccination, as well as encourage clinicians to take advantage of algorithms for VAEs assessment to evaluate the risk of reproducibility. It should be underlined that no classification provides certain proof in favor or against the existence of an association between an event and an immunization. Nevertheless, they provide valuable assistance to clinicians in the determination of the level of likelihood of specific associations.

To maintain public confidence in vaccines, it is important that advanced immunization programs include pre- and postvaccination counseling for subjects at risk [34, 35].

In Italy, VAEs surveillance is mandatory and spontaneous reports of Adverse Events Following Immunization (AEFI) are collected by the National Network of Pharmaco-vigilance, which includes the Italian Medicine Agency, the 20 regions and autonomous provinces of Trento and Bolzano, 204 local health units, 112 hospitals, 38 research institutes, and 561 pharmaceutical industries [36]. Every clinician and vaccine service should contribute to this surveillance and have access to all required data for accurate counseling to parents and patients, and to reassure them about the safety and importance of vaccines. In this era of widespread skepticism about vaccines, easily accessible as well as rigorous counseling is required more than ever.

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Glossary

VAE: any medical incident that takes place after immunization and is believed to be caused by the immunization itself. It is considered any unfavorable or unintended sign, and any abnormal laboratory finding, symptom, or disease

Causality assessment: linkage between a medical incident and a vaccine. Many authors have proposed causality assessment schemes that can be applied to help clinicians distinguish between events whose association with the vaccination is consistent, indeterminate, or inconsistent

Event caused by the immunization: an event that is attributable to a vaccine product-related reaction, a vaccine quality defect-related reaction, an immunization error-related reaction, and an immunization anxiety-related reaction

Coincidental adverse event: medical event that occurs after immunization but it is not caused by immunization itself, and would have occurred independently from the vaccination. In the case of coincidental adverse events, the relation between event and vaccine is only temporally

Temporal association: time interval between the vaccination and the adverse event. Temporal association is independent from causality and events that are temporally associated with vaccines that may or may not be caused by the vaccines

Serious VAE: any VAE that causes a potential risk to the life/health of the recipient, that leads to hospitalization, and that causes disability/incapacity/congenital anomaly or birth defect.

Minor VAE: an event that is not serious and has no potential risk to the health of the recipient of the vaccine

Reproducibility risk: risk that a VAE could reappear after another dose of the same/of another vaccine. The reproducibility risk is mostly significant for VAEs of allergic nature.

Vaccine pharmaco-vigilance: the science of detection, assessment, understanding, and communication of VAEs and other vaccine-related issues

Immunization anxiety-related reaction: an event that arises from anxiety about immunization

Immunization error-related reaction: an event that is caused by an inappropriate vaccine handling, prescribing, or administration

Vaccine product-related reaction: an event that is attributable to one or more properties of the vaccine product, whether the active component or one of the other components of the vaccine (adjuvants, preservatives, stabilizers)

Vaccine quality defect-related reaction: an event that is attributable to one or more quality defects of the vaccine product, including defects of the administration devices

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