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Frequently asked questions on seven rare adverse events following immunization

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Keywords

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Summary

Routine mass immunization programs have contributed greatly to the control of infectious diseases and to the improvement of the health of populations. Over the last decades, the rise of anti-vaccination movements has threatened the advances made in this field to the point that vaccination coverage rates have decreased and outbreaks of vaccine-preventable diseases have resurfaced. One of the critical points of the immunization debate revolves around the level of risk attributable to vaccination, namely the possibility of experiencing serious and possibly irreversible adverse events. Unfortunately, the knowledge about adverse events, especially rare ones, is usually incomplete at best and the attribution of a causal relationship with vaccinations is subject to significant uncertainties. The aim of this paper is to provide a narrative review of seven rare or very rare adverse events: hypotonic hyporesponsive episode, multiple sclerosis, apnea in preterm newborns, Guillain-Barré syndrome, vasculitides, arthritis/arthralgia, immune thrombocytopenic purpura. We have selected these adverse events based on our experience of questions asked by health care workers involved in vaccination services. Information on the chosen adverse events was retrieved from Medline using appropriate search terms. The review is in the form of questions and answers for each adverse event, with a view to providing useful and actionable concepts while not ignoring the uncertainties that remain. We also highlight in the conclusion possible future improvements to adverse event detection and assessment that could help identify individuals at higher risk against the probable future backdrop of ever-greater abandonment of compulsory vaccination policies.

Introduction

In the last 10 years, great advances have been made in developing and introducing new vaccines and expanding immunization programs. More people than ever before are being vaccinated and access and use of vaccines by age groups other than infants is expanding. As a result of immunization combined with other health care and development interventions – including improved access to clean water and sanitation, better hygiene and education – the annual number of deaths among children under five years of age fell from an estimated 9.6 million in 2000 to 7.6 million in 2010, despite an increase in the number of children born each year [1].

According to World Health Organization (WHO) data, vaccination prevents 2-3 million deaths every year worldwide. At the same time, WHO warns that globally 22 million newborns do not receive basic immunization; among them there are 700,000 newborns belonging to the WHO European Region. Vaccination is perceived as unsafe and unnecessary by a growing number of parents in large part because diseases that were once the cause of many outbreaks and loss of health and life are now rarely seen, because they have been prevented by vaccines. In this perspective, a rare potential for vaccine-induced harm can loom large when people no longer experience the targeted disease, a case of vaccines being the victims of their own success. In fact anti-vaccination movements have been implicated in lowered vaccine acceptance rates and in the increase in vaccine-preventable disease outbreaks and epidemics. In large part, this is caused by mistrust in the medical system and by fear of adverse events (AEs) that doctors are unwilling to talk about. On the contrary, research has shown that exposure to scientific proof can be effective in boosting patients' knowledge; in the USA, the Centers for Disease Control and Prevention (CDC) published information aiming to educate the reader and dispel the most widespread myths [2-5].

In spite of the fact that vaccines currently used in immunization programs are safe, like all medicinal products they have potential health risks and can cause adverse events, defined as harmful and unintended effects following the use of a medicinal substance [6].

Regarding vaccines, an Adverse Event Following Immunization (AEFI) is any harmful clinical event that occurs after vaccine administration and that does not necessarily have a causal relationship with vaccine use.

In this context an AEFI could be an unintentional unfavorable sign, a laboratory test anomaly, a symptom or a disease [7].
It is important to point out that in this definition of AEFI, only a temporal association is considered and no causal relationship is implied; indeed, much of the assessment of AEFIs is devoted to ascertaining whether a causal relationship actually exists (under different degrees of likelihood, i.e. certainly, probably, possibly related or unrelated).
The scientific knowledge about AEFIs is limited because their notification is frequently overlooked by physicians (under-notification) and because the available adverse event data frequently show only temporal relationships between vaccination and the onset of an AEFI. Indeed the establishment of causality is challenging and requires much time and labor. In fact, the largest review of adverse events to date, published in 2012 by the Institute of Medicine of the USA (IOM), explains in the Preface that in the majority of cases, available scientific information was not sufficient to conclude whether a particular vaccine caused a specific rare AEFI [8, 9]. One of the reasons is that even very large epidemiologic studies may not be able to detect or rule out rare (or very rare) AEFIs. An AEFI is conventionally considered rare if it occurs in < 1/1000 but > 1/10000 individuals (very rare if < 1/10000 individuals). There is a residual category of AEFI for which frequency is unknown because they were spontaneously reported after the vaccine was marketed and therefore the denominator required to compute frequency was unavailable [10].
There are many elements to be considered in assessing the risk-benefit balance of vaccine administration. First of all, the advantages of vaccine administration have to be taken into account, in terms of benefits (protection) afforded by each dose administered.
Next, the likelihood of contracting the disease must be considered, which is itself related to the incidence of the disease, to the vaccine coverage rate in the population and to other factors that can increase risk, for example exposure to a case, occupational risk or travels to highly endemic areas.
A thorough assessment of the frequency, severity, and causal relation of AEs (and their complications) is also necessary, especially for Serious Adverse Events (SAEs) [11]. A SAE is any adverse event that either results in death, or is life-threatening, or requires inpatient hospitalization or causes prolongation of existing hospitalization, or results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect, or requires intervention to prevent permanent impairment or damage [12].
The need to answer questions from patients and health care workers (HCWs) and to choose whether to vaccinate an individual or not, based on a risk-benefit assessment that takes into account the susceptibility of the individual (a form of personalized medicine), forms the basis of our review that aims to provide actionable answers to doubts about a selection of rare, very rare or of unknown frequency adverse events.

We focused on the issues regarding risk assessment, risk communication and risk management for seven AEFIs:
- Hypotonic Hyporesponsive Episode (HHE);
- Multiple Sclerosis (MS);
- Apnea in the pre-term newborn (APTN);
- Guillain-Barré Syndrome (GBS);
- Vasculitides;
- Arthritis/Arthralgia (AA);
- Immune Thrombocytopenic Purpura (ITP).

Methods and search results

We performed a literature search on Medline using PubMed up to August 26th 2016. We applied neither language nor date of publication restrictions and we performed the search using the following search terms individually and in combination: vaccin*; immuniz*; immunis*; thrombocytopenia; apnea; hypotonic hyporesponsive; Guillain Barré; multiple sclerosis; arthritis; arthralgia; vasculitis.

Tab. I. Search strategy and results.

Search item	Search terms (S)	Number retrieved (Numbers in brackets used in combined searches)
S1	Vaccin*	(323853)
S2	Immuniz*	(165606)
S3	Immunis*	(11117)
S4	Thrombocytopenia	(64342)
S5	Apnea	(46708)
S6	Hypotonic hyporesponsive	47
S7	Guillain Barré	(8165)
S8	Multiple Sclerosis	(70531)
S9	Arthritis	(281729)
S10	Arthralgia	(13873)
S11	Vasculitis	(97428)
S12	S1 AND S4	644
S13	S1 AND S5	125
S14	S1 AND S7	615
S15	S1 AND S8	999
S16	S1 AND S9	2057
S17	S1 AND S10	223
S18	S1 AND S11	533
S19	S2 AND S4	878
S20	S2 AND S5	82
S21	S2 AND S7	345
S22	S2 AND S8	1333
S23	S2 AND S9	2791
S24	S2 AND S10	63
S25	S2 AND S11	433
S26	S3 AND S4	42
S27	S3 AND S5	20
S28	S3 AND S7	33
S29	S3 AND S8	59
S30	S3 AND S9	184
S31	S3 AND S10	9
S32	S3 AND S11	19

We also used the report of the Institute of Medicine [8] for reference.

We have chosen to answer for each AEFI the following frequently asked questions (FAQs) based on the requests for information that HCWs routinely ask:

- definition and incidence of the adverse event;
- biological plausibility based on the existence of pathophysiological mechanisms that lead to adverse event onset, and causality assessment;
- risk factors for AEFI onset after vaccination;
- types of vaccines possibly associated with the adverse event and AE management;
- special considerations in vaccine administration to patients:
  - who experienced the AEFI following a previous immunization.
  - who suffer from or have had episodes of the disease in question (In this context we use the term "disease" when the AEFI corresponds to a well-recognized disease and we consider the disease to be a possible risk factor for its own exacerbation after immunization).

For the AEFI, we used validated case definitions where available and, as regards pathophysiology, we reported the main hypotheses according to current scientific knowledge. Selection of information on the vaccines potentially implicated in the various AEFIs, on the main risk factors and on the recommendations for immunization of individuals who previously experienced the AEFI, was also performed based on the reports available from the literature. The results obtained from the search strategy are shown in Table I.

Frequently Asked Questions (FAQs)

Hypotonic Hyporesponsive Episode (HHE)

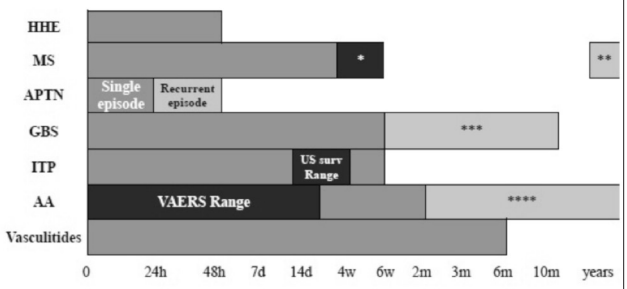
How is a case of HHE defined and how frequent is it?

HHE is a clinical condition which has the following features: reduced muscle tone, hyporesponsiveness and change of skin color, in the absence of cardiologic (particularly of heart rhythm), electroencephalographic and glycemic alterations [13]. Apart from the clinical triad of signs there are no further investigations helpful in confirming the diagnosis of HHE [14-16]. The reported rates following a whole cell pertussis vaccine ranges from 0 - 291 per 100,000 doses [17, 18]. The median time to onset of signs after immunization is 3–4 h but ranges from immediately to 48 h post-immunization, while the median duration of the triad signs is 6–30 min [16] (Fig. 1).

What are the pathophysiological mechanisms underlying HHE?

Pathophysiology of HHE is currently unknown. It was hypothesized in the first studies about this AE, that the pathophysiological mechanism could be an exaggerated vagal response, but the timing of onset of HHE and the lack of ECG, EEG and glycemic alterations led to refuting this hypothesis and, at the present time, no new hypotheses have been put forward. The main efforts have been put into defining correctly HHE in order to avoid mistakes in diagnosis and notification [16, 19, 20].

Fig. 1. Time frame of attribution of selected AEs to vaccination.



Legend:

: Time frame of AE onset during which the AE is commonly attributed to vaccination

HHE: Hypotonic Hyporesponsive Episode [16].
MS: Multiple Sclerosis; Dark grey box [27];
Black box: * trend identified only in a small sample of cases [27];
Light grey box: ** trend identified by some authors but not confirmed [28].
APTN: Apnea in Pre-Term Newborns; Dark grey box: single episode [34-37,42,43];
Light grey box: recurrent episode [41,52]
GBS: Guillain-Barré Syndrome; Dark grey box [28,67,78];
Light grey box: *** extension of time window of onset suggested by some authors [60].
ITP: Immune Thrombocytopenic Purpura; Dark grey box [127];
Black box: range identified by US postmarketing surveillance [132].
AA: Arthralgia and Arthritis; Black box: range identified by VAERS [104];
Dark grey box: [105];
Light grey box: **** extension of time window of onset suggested by some authors [90].
Vasculitides: Dark grey box [84,92].

Which are the vaccines associated with HHE onset?

The first cases were reported in children under 5 years of age following administration of whole-cell pertussis vaccine [15, 16]. Over the last 20 years, cases of HHE have been reported following administration of diphtheria, tetanus, *H. influenzae B*, Hepatitis B Virus, 13-valent pneumococcal, acellular pertussis vaccines. In the latter case, the frequency appears to be lower than with the whole-cell vaccine [13, 16, 21].

What are the risk factors for HHE and how can it be managed?

No risk factors have been identified and so there are no specific precautions to be taken.

According to studies based on the follow-up of HHE relying on parental reporting and neurodevelopmental testing, HHE is a self-limiting event without long-term sequelae [16], so it is important to reassure the parents that it is an event that does not lead to complications.

What is the recommended action regarding immunization in case of a previous episode of HHE?

According to a recent Polish study, in a group of 49 children who experienced HHE following diphtheria-tetanus-whole cell pertussis vaccination (DTwP), 2 children experienced a second episode of HHE after a second consecutive dose of DTwP [22]. According to this study, it seems that HHE can recur more frequently in children who have already experienced it compared to the general population. In spite of this observation, no contraindications to subsequent vaccination exist for these children.

Multiple Sclerosis (MS)

How is a case of MS defined and how frequent is it?

Multiple Sclerosis (MS) is an acquired chronic immune-mediated inflammatory condition of the central nervous system (CNS), affecting both the brain and spinal cord. It is the most frequent cause of serious physical disability in working age people. The person affected by MS typically develops symptoms in their late 20s, experiencing visual and sensory disturbances, limb weakness, gait problems and symptoms which affect urinary and gastrointestinal tracts. The clinical course is often characterized at the beginning by a partial recovery, but over time MS tends to evolve toward increasing disability [23]. In 2007, globally, the median estimated prevalence of MS was 30 per 100,000 while regionally, the median estimated prevalence of MS was greatest in Europe (80 per 100,000), followed by the Eastern Mediterranean (14.9), the Americas (8.3), the Western Pacific (5), South-East Asia (2.8) and Africa (0.3). The total estimated number of people diagnosed with MS was approximately 1.3 million [24].

What are the pathophysiological mechanisms underlying post-vaccination MS?

Pathophysiology of post-vaccination MS is uncertain. The first hypothesis was based on the discovery, in 1985, of a molecular mimicry phenomenon between Hepatitis B Virus (HBV) polymerase and myelin basic protein, but in light of subsequent research, today this association appears to be far less significant [25, 26]. Currently the most plausible mechanism seems to be hyperstimulation of the immune system that acts as an enhancer of a pre-existing autoimmune vulnerability [27].

Which are the vaccines associated with MS onset?

According to a case-control study in France in a pediatric population, it was observed that in the three years following HBV vaccination the odds for developing an MS flare were 1.5 but this result was not statistically (95%CI) significant [28]. In a subsequent case-control study in California, a possible increase in central demyelination risk in the first 30 days after any vaccination was reported in subjects under 50 years of age. A trend towards an association of MS and any type of vaccination within 42 days (6 weeks) after immunization was identified (OR: 2.32; 95%CI: 1.18-4.57), but this result was obtained in a small sample of cases and cannot be generalized at the present time (Fig. 1). Moreover, since this association has not been observed in the longer term in the above study, it is hypothesized that vaccination could act as a trigger for underlying MS [27].

Which are the risk factors for MS and how do they affect immunization?

There are several risk factors (15-60 years of age, female gender, family history, Epstein Barr Virus infection, etc.) for MS but they do not affect routine immunization practice since the association between MS and vaccination has not been demonstrated in spite of numerous studies on this topic [8].

What is the recommended action regarding immunization in case of previous or ongoing acute episodes of MS?

Inactivated vaccines are generally considered safe while live ones can require further analyses of risk and benefit, especially for patients on immunosuppressive agents in whom usually live attenuated vaccines should be avoided. On the contrary, Varicella Zoster Virus (VZV) vaccination is required before initiating treatment with certain disease modifying treatments, such as glucocorticoids, methotrexate and biologics [29]. Moreover, as far as tetanus vaccine is concerned, there is evidence that it can reduce the probability of MS relapse [30].

Apnea in pre-term newborns (APTN)

How is a case of APTN defined and how frequent is it?

An apneic episode is usually defined as a cessation of breathing for 20 seconds or longer or a shorter breathing pause accompanied by bradycardia (< 100 bpm), cyanosis or pallor [31].

It is a significant clinical problem manifested by an unstable respiratory rhythm reflecting the immaturity of respiratory control systems. Anatomically the immaturity is manifested as decreased synaptic connections, decreased dendritic arborization and poor myelination. The condition should be considered a developmental disorder rather than a disease state because it resolves with maturation [32]. All infants born at ≤ 28 weeks' gestation were diagnosed with apnea, while 85% of those born at 30 weeks and 20% of those born at 34 weeks were diagnosed with apnea [31].

Regarding post-immunization APTN, some authors estimate an incidence rate of post-immunization cardiorespiratory events (apnea, bradycardia and/or desaturation) between 7 and 47% [33-35], whereas for apnea alone the incidence varies between 10 and 20% [36, 37].

What are the pathophysiological mechanisms underlying APTN?

Pathophysiological hypotheses are uncertain and not related to a specific vaccine or to adjuvants. An increase in systemic inflammatory response after immunization interacting with an immature nervous system in the preterm newborn has been postulated. In support of this hypothesis studies have shown that there is a temporal correlation between immunization and an increase in interleukin 6 (IL-6) and C-reactive protein (CRP) [38-41].

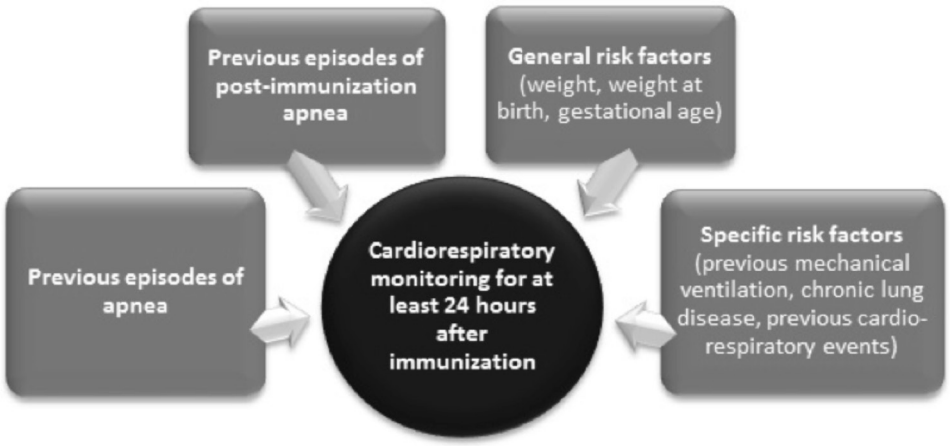
Which are the vaccines associated with APTN onset?

Vaccines associated with APTN are: diphtheria-tetanus-whole cell pertussis, *H. influenzae b*, Hepatitis B Virus, Inactivated Polio Virus, Meningococcal C conjugate (DTwP, DTwP-Hib, DTwP-Hib-HBV-IPV and MenC) [34-37, 42, 43]. As far as pertussis vaccine is concerned, it has recently been shown that the incidence of APTN post-diphtheria-tetanus-acellular pertussis (DTaP) immunization is similar to the post-DTwP incidence of APTN [44-46].

What are the risk factors for APTN and how do they affect immunization?

Several risk factors have been identified: age [35, 43, 44], weight [34, 37, 43], gestational age [44], previous mechanical ventilation [34, 35], presence of chronic pulmonary pathology [34], history of cardiorespiratory events [44, 46], pre-immunization apnea episodes [47]. Some studies have highlighted that the association between apnea and immu-

Fig. 2. Main factors affecting the need for cardiorespiratory monitoring after immunization.



nization is significant if immunization occurred before 67 days of age, whereas significance disappears for immunization after this time period [47, 48]. It is therefore advisable to perform cardiorespiratory monitoring after vaccination of all pre-term infants with risk factors [47].

What is the recommended action regarding immunization in case of previous episodes of APTN?

As with all preterm newborns, immunization is very important and should be performed according to chronological age. If possible the first vaccination should be performed before the discharge from the hospital [49-51].

It is advisable to perform cardiorespiratory monitoring after vaccination particularly for those who experienced pre-immunization apnea who are at 25-fold risk of developing post-immunization apnea compared to those who did not [47]. In order to avoid recurrent episodes in preterm infants who experienced post-immunization apnea, cardiorespiratory monitoring for at least 24 hours after vaccination is recommended [41] (Fig. 1). However, the episodes of post-vaccination apnea are self-limiting and do not cause long-term sequelae [44, 52] (Fig. 2).

Guillain-Barré Syndrome (GBS)

How is a case of GBS defined and how frequent is it?

Guillain-Barré syndrome (GBS) is a rare condition in which a person's immune system attacks their peripheral nerves. The syndrome can affect the nerves that control muscle movement as well as those that transmit feelings of pain, temperature and touch, determining muscle weakness and loss of sensation in the legs and/or arms. It is more common in adults and in males; however, people of all ages can be affected. Around 3-5% of GBS patients die from complications like paralysis of the muscles of respiration, blood infection, lung embolus or cardiac arrest [53, 54]. Etiology of GBS is still unknown, but infections from influenza, Cytomegalovirus, Zika Virus and *C. jejuni* can act as triggers for the onset of GBS [55-59].

What are the pathophysiological mechanisms underlying GBS?

Mechanisms are uncertain, but thought to be immune mediated and based on auto-immune reactions: immunological similarity [60-62], production of anti-myelin or anti-axonal glycoproteins antibodies induced by vaccine epitopes [63]. Alternatively it is also hypothesized that vaccine components can interfere directly with peripheral nervous system structures [64]. The time frame of onset considered for possible vaccine-induced GBS is commonly up to 6 weeks after vaccination, but some authors consider a longer time-frame (Fig. 1).

Which are the vaccines associated with GBS onset?

Several studies investigated the correlation between influenza vaccine and GBS occurrence, with mixed results (Tab. II).

Over the last years cumulative evidence on the increased incidence of GBS following H1N1 influenza vaccination in the 2009-2010 season was reported with a significantly higher risk for non-adjuvanted *vs* adjuvanted vaccine [68, 70]. A European multinational case-control study on the same vaccine showed an increased risk of GBS post-vaccination, but after adjusting for upper respiratory tract infections, influenza-like illness or influ-

Tab. II. GBS incidence in different influenza seasons (vaccinated vs non vaccinated subjects).

Influenza seasons	GBS incidence in vaccinated subjects (per million)
1976 (H1N1)	7.2 cases per million in the vaccinated group vs 0.79 cases per million in the non-vaccinated group [64]
1991-1999	0.95 cases per million in the group vaccinated against influenza vs 0.22 cases per million in the group vaccinated against diphtheria-tetanus [65]
1990-2005	0.7 cases per million vaccinated subjects [66]
2000	0.86 cases per million vaccinated subjects [67]
2001	1.21 cases per million vaccinated subjects [68, 69]
2009 (H1N1)	1.6 excess cases per million vaccinated subjects [68, 69]

enza vaccination, the association was no longer significant [68, 71].
In this regard, epidemiological data from the available literature note that the relative risk (RR) of GBS following vaccination is far lower than the one following an infectious disease (RR 1.41 *vs* 7.35 [68, 72-75]), especially in the case of influenza [76].
According to a recent simulation, assuming a typical influenza season and a typical vaccine effectiveness, influenza vaccination would reduce the individual risk of GBS [77, 78] (Tab. II).
In 2011, the Institute Of Medicine (IOM) could not confirm nor refute the causal relationship between GBS and anti measles, mumps, rubella, varicella, Hepatitis A Virus, Hepatitis B Virus, Human Papilloma Virus (HPV), influenza, diphtheria, tetanus and acellular pertussis vaccines because of inadequacy of available data. In 2004 the IOM confirmed the causality between the 1976 influenza vaccine and GBS [8].

What are the risk factors for GBS and how do they affect immunization?

Concerning risk factors for post-vaccination GBS, the main one identified to date is the previous occurrence of GBS or the presence of GBS at the time of immunization [79, 80]. Therefore it is important to collect an adequate clinical history asking for previous occurrences of GBS.

What is the recommended action regarding immunization in case of previous episodes of GBS?

In individuals with a history of GBS, the risk of recurring GBS requiring hospitalization after vaccine administration is estimated at 1.18% in a study [81] and at 3.7% in another [80]. At the present time, the ability of influenza vaccination to cause GBS is not an established scientific finding. However, as a precautionary measure, it is advised not to administer vaccines to individuals who have experienced GBS in the previous 6 weeks unless they are at high risk for severe influenza complications; alternatively, the possibility of antiviral chemoprophylaxis can be considered in these subjects [79, 80]. For all other patients with a history of GBS outside of the 6 weeks interval, the decision to vaccinate should be based on risk-benefit balance assessment.

Vasculitides

How is a case of vasculitis defined and how frequent is it?

Vasculitides are a group of related disorders characterized by inflammation of blood vessels leading to tissue or end-organ injury with diverse and only partially understood etiology and with a wide spectrum of clinical manifestations and prognoses [82].
Vasculitis in children is rare. The annual incidence is estimated at about 53/100,000 subjects [83]. The type of vasculitis depends primarily on age: in pediatric populations the most frequent vasculitides are Henoch-Schönlein purpura (annual incidence: 10-20/100,000) and Kawasaki disease (annual incidence: 1-19/100,000; around 1/100 in Japanese newborns); in adults the most common is hypersensitivity vasculitis. Regarding the epidemiology of the different forms of vasculitis, variations are found depending on ethnic and geographic factors: Microscopic Polyangiitis occurs more frequently in Asia, Wegener's granulomatosis in North America and northern Europe, Takayasu arteritis in Japan and Horton's arteritis in Europe and North America. Almost all types of vasculitides have been tentatively implicated as AEs but only in a few there is evidence supporting this association [84].

What are the pathophysiological mechanisms underlying post-immunization vasculitides?

A causality relationship has not been established with certainty; the main hypothesis rests on the concept of molecular mimicry associated with circulating immune-complex deposition [85].
Notwithstanding the uncertainty on the basic pathophysiological mechanism, in some cases of arthritis/arthralgia and vasculitides a mechanism can be found.
In 2011 the term Autoimmune/inflammatory Syndrome Induced by Adjuvants (ASIA) [86] was coined to describe a group of autoimmune-derived clinical conditions with similar symptoms, that occur after vaccination, supposedly induced by adjuvants [86-88]. Underlying the onset of ASIA, an individual predisposition [89] and an environmental triggering factor (endogenous or exogenous) are necessary conditions. Molecular mimicry and overstimulation of the immune system are the pathophysiological mechanisms thought to be responsible for ASIA occurrence [90].

Which are the vaccines associated with vasculitides onset?

Over the last years several articles have been published on the correlation between vaccinations and vasculitides. The most frequently considered immunizations were influenza, Hepatitis B Virus, Bacillus Calmette-Guérin, Human Papilloma Virus, Meningococcal C conjugate and Hepatitis A Virus vaccines, while potentially correlated vasculitides were mostly cutaneous vasculitides, Henoch-Schönlein Purpura (HSP), Kawasaki Disease (KD). Fewer studies were performed on Systemic Lupus Eritematosus (SLE), ANCA-Associated Vasculitides (AAV), Giant Cell Arteritis (GCA) and Polyarteritis Nodosa (PAN) [82].
At the present time the only associations that have not been rejected in evidence reviews are the following [84]:

- influenza vaccine and cutaneous vasculitides [91];
- influenza vaccine and GCA [92];
- Hepatitis B Virus (HBV) vaccine and Polyarteritis Nodosa (PAN) [85].

In particular, the association between vaccination and Kawasaki Disease, which is the second most frequent pediatric vasculitis [83] has been investigated in depth in the last few years. However, this possible association has been rejected based on assessments of Vaccine Adverse Events Reporting System (VAERS) data in 2009 [93] that demonstrated the absence of a temporal relationship between any vaccination and onset of KD symptoms. In spite of this evidence, the fear of an association of this disease with vaccination has remained high and pushed the Food and Drug Administration (FDA) to include it in the pentavalent anti Rotavirus vaccine adverse events re-

porting, following the occurrence of 5 cases out of over 36,000 vaccinated children during phase 3 research [94]. Another vaccination that has been associated with KD is Meningococcal B vaccine for which regulatory authorities have requested ad-hoc post-marketing safety studies [95].

Finally, in 2015 a multicentric study was unable to demonstrate an association between specific vaccinations and KD [96].

What are the risk factors for post-immunization vasculitides and how do they affect immunization?

Individual predisposition appears to be fundamental in the onset of these disorders [84].

A personal or family history of autoimmunity can represent a risk factor for certain vasculitides [97]. For precautionary reasons, it is advisable to follow subjects at risk for Giant Cell Arteritis (GCA) or Polymyalgia Rheumatica, depending on gender or age, for 2-6 months after influenza vaccination [92] (Fig. 1).

What is the recommended action regarding immunization in case of previous or current episodes of vasculitides?

There is mounting evidence that some infections can act as triggers for the onset of vasculitides, particularly Hepatitis B and C (HBV and HCV) viruses for PAN and respiratory tract infections for Henoch-Schönlein Purpura (HSP). Infections have also been implicated in the relapse of some vasculitides, so that influenza and pneumococcal vaccinations are recommended in affected subjects [98, 99], while in France a successful campaign of vaccination against HBV was followed by a decrease in the incidence of Polyarteritis Nodosa (PAN) [98].

Arthritis/Arthralgia (AA)

How is a case of AA defined and how frequent is it?

The term arthralgia is used in the medical literature to indicate articular pain in general; in some cases arthralgia refers to a non-inflammatory condition of the joint, but this is not consistent in the literature. Among the causes of arthralgia are traumatic injury, degenerative processes of the joint, systemic inflammatory disorders, lupus, rheumatoid arthritis and vaccinations [100].

The word arthritis is used by clinicians to specifically mean inflammation of the joints, while it is used in public health to refer more generally to more than 100 rheumatic diseases and conditions that affect joints, the tissues that surround the joint, and other connective tissue, and typically characterized by pain and stiffness in or around one or more joints. The pattern, severity, location of symptoms, involvement of the immune system and other internal organs varies depending on the type of disease [101]. In 2012 in the US 52.5 million adults aged ≥ 18 years had self-reported or doctor-diagnosed arthritis, and 22.7 million reported arthritis-attributable activity limitation [102].

What are the pathophysiological mechanisms underlying post-immunization AA?

Several models have been proposed: a direct mechanism through polyclonal B cells activation and functional alteration of immune-regulatory cells and an indirect mechanism through the production of cytokines, molecular mimicry and immune-complex formation [103]. However, pathophysiological mechanisms post-immunization remain uncertain, as well as the period of onset (Fig. 1).

Possible mechanisms that have been postulated to cause in some cases the onset of post-immunization AA are the ones at the root of ASIA (See the section: "What are the pathophysiological mechanisms underlying post-immunization vasculitides?")

Which are the vaccines associated with AA onset?

Many vaccines, such as anti-Hepatitis A and B Viruses, measles, mumps, rubella, Varicella Zoster Virus and Human Papilloma Virus (HAV, HBV, MMR, VZV and HPV), have been implicated in the occurrence of AA as they can function as an exogenous trigger for the development of autoimmune disorders [100, 105]. However, the role of vaccinations as possible causative agents of AA has not been established with sufficient evidence. In spite of this, many isolated cases or series of cases of arthritis following vaccination have been reported. These cases tend to be very infrequent and usually only short-term outcomes are described [106]. In fact, the occurrence of post-vaccination arthritis/arthralgia (AA) is usually self-limiting and of moderate intensity [90, 104, 105].

What are the risk factors for post-immunization AA and how do they affect immunization?

In the case of rubella vaccination, possible risk factors are: advanced age, Human Leucocyte Antigens (HLA) dependent predisposition and female gender. Further studies however, found no evidence of increased risk for chronic arthropathy among women vaccinated against rubella.

However, in the absence of scientific evidence of the causal relationship between vaccination and AA and considering the overall risk-benefit balance, it can be stated that vaccination for the overwhelming majority of patients carries no risk of systemic autoimmune disease and should be administered according to current recommendations [105, 107, 108].

What is the recommended action regarding immunization in case of previous episodes of AA?

Previous occurrence of episodes of AA or the presence of AA at the time of immunization is an important risk factor for the onset of post-immunization AA. However, for individuals suffering from AA, vaccination is still recommended because natural infection can cause a relapse of the AA symptoms. In order to give more information on timing and vaccination type to be administered, several studies were conducted in recent years [109-115]:

- vaccination should be performed during the remission phase of the disorder and can be done in patients taking Disease Modifying Anti-Rheumatic Drugs (DMARDs) and anti-Tumor Necrosis Factor (TNF) drugs;
- vaccination should be performed before starting therapy with anti-B cells drugs;

- the administration of live attenuated vaccines, such as BCG, should be avoided, particularly in immunosuppressed individuals;
- some studies have shown efficacy and safety of non-live vaccines in subjects whose condition is under pharmacologic control, even in those taking biologic drugs; influenza and pneumococcal vaccines are strongly recommended in these patients and the choice of vaccine should be as personalized as possible since different Human Leucocyte Antigens (HLA) genetic polymorphisms cause inter-individual variation in terms of efficacy and toxicity.

It should be noted that, although vaccination is strongly recommended in these subjects, post-immunization relapse or symptoms exacerbations can occur, possibly through a mechanism of polyclonal activation of B-cells or through cross-reactivity [90].

Immune Thrombocytopenic Purpura

How is a case of Immune Thrombocytopenic Purpura (ITP) defined and how frequent is it?

The term refers to an autoimmune disorder of unknown etiology characterized by a platelet count < 100,000/μl and by the presence of small areas of hemorrhage (purpura).

Data from surveillance system reports indicate that the frequency and severity of vaccine induced immune thrombocytopenic purpura (VI-ITP) is much lower than after natural infection from vaccine-preventable diseases [116-119].

The incidence of VI-ITP is probably underestimated because mild to moderate and asymptomatic cases often do not come to the attention of physicians and are therefore not diagnosed and reported [120, 121].

What are the pathophysiological mechanisms underlying vaccine induced immune thrombocytopenic purpura (VI-ITP)?

The occurrence of thrombocytopenia has been convincingly related to the production of antibodies that cross-react with platelet antigens that can be detected in about 80% of cases [117-122]. In the case of thrombocytopenia that occurs after anti measles-mumps-rubella (MMR) vaccination, the presence of anti-rubella and anti-measles IgG antibodies that cross-react with platelet antigens has been consistently detected [123-125]. For these reasons the pathophysiological mechanisms underlying VI-ITP can be considered certain.

Which are the vaccines associated with VI-ITP onset?

Specific studies have been performed to assess VI-ITP associated with measles-mumps-rubella (MMR) and Hepatitis B Virus (HBV) vaccination, since the occurrence of immune thrombocytopenic purpura (ITP) is a possible complication of measles and HBV infection. Regarding HBV vaccine, VI-ITP can occur after any dose of the vaccine and, in case of recurring episodes, the clinical picture tends to worsen, thus requiring specific treatment [126]. VI-ITP that occurs after MMR vaccination has an onset within 6 weeks of vaccine administration and presents with a higher platelet count than ITP after natural infection [127] and with clinical manifestations such as petechiae of moderate severity [128], although rarely there have been reports of gastrointestinal (GI) and/or pulmonary hemorrhage [129], hematuria [130] and the need for splenectomy [131] (Fig. 1). The forms of VI-ITP that require hospitalization have a lower average duration of hospitalization than those caused by natural infection (3 *vs* 5 days) [133-135] and no deaths strictly correlated with VI-ITP after MMR vaccination have been reported, unlike in the case of natural infection [117-121]. In the majority of cases (about 90%), VI-ITP is self-limiting within 6 months of diagnosis and only 10% turns into a chronic condition [127-128], whereas ITP after viral infection can become chronic in about 25% of cases on top of having a more severe clinical course [136]. A study performed on a cohort of 1.8 million children and adolescents (age range: 7 weeks to 17 years of age) investigated the correlation between all vaccinations and the onset of ITP, considering a time frame from the date of immunization to 6 weeks after immunization. The results indicate an increase in risk after Hepatitis A Virus and Varicella Zoster Virus vaccinations performed between the 7th and 17th year of age and the 11th and 17th respectively [137] (Tab. III).

What are the risk factors for VI-ITP and how do they affect immunization?

The main risk factor for the onset of an episode of VI-ITP is a previous episode of Immune Thrombocytopenic Purpura (ITP) or VI-ITP or the presence of ITP/VI-ITP at the time of immunization [117-121] (see below).

Tab. III. Increase of cases of Immune Thrombocytopenic Purpura (ITP) and their clinical course by selected vaccines.

Vaccine	Age range during which an increase in cases after vaccination occurred	Clinical course
MMR [137]	12th-19th month of age, 1 additional case every 40,000 doses (p = 0.006); no changes with MMVR use	Usually moderate severity, in exceptional cases GI and/or pulmonary hemorrhage. If hospitalization required, hospital stay shorter than in post-infection ITP
HAV [137]	7th-17th year of age (p = 0.001)	*
VZV [137]	11th-17th year of age (p = 0.04)	*
HBV [126]	Inadequate evidence	Lack of guidelines; episodes appear to recur and become more severe after each vaccine administration

*Number of cases is insufficient to describe a typical clinical course.

What is the recommended action regarding immunization in case of previous episodes of ITP or VI-ITP?
In subjects with a history of ITP or post-measles-mumps-rubella (MMR) vaccine VI-ITP, with a normal platelet count at the time of immunization, MMR vaccine appears to be safe and well tolerated [117-121], although relapse of ITP can occasionally occur [138, 139]. Recent studies claim that the first MMR dose does not normally trigger a relapse of ITP and that the booster dose is not followed by relapse within 6 weeks of administration [117-121]. However, the assessment of antibody titer against measles, mumps and rubella is recommended in patients with chronic ITP or with previous post-MMR VI-ITP to avoid further vaccine doses if the antibody titer is protective [119, 140, 141].
International guidelines on immune thrombocytopenia management recommend vaccination against *S. pneumoniae*, *H. influenzae B* and *N. meningitides* before splenectomy [142].

Commentary and conclusions

As shown in this review, the issue of adverse events in the field of immunization is subject to a lot of uncertainties, especially as regards rare and very rare ones; indeed, it is often not possible to conclude with sufficient scientific rigor on causal relationships (or the lack thereof) between vaccines and adverse events [8]. This poses a significant problem in risk communication and risk management as health care workers need to provide fair and balanced information to patients while at the same time not discouraging immunization. Unfortunately, the asymmetry between the knowledge about benefits and the knowledge about risks is common throughout medicine.
It is important to keep in mind that the adverse events we have covered occur rarely or very rarely but that, at the same time, the benefits are not directly experienced by the individual who is vaccinated and that the tolerance for risks (real or perceived) in our societies is relatively low [143].
With many additional vaccines being developed and introduced in vaccination schedules, and with the requirement to be immunized in order to be able to attend kindergarten and schools increasingly introduced or suggested to fight vaccine hesitancy [144], the emphasis on vaccine safety and adverse event monitoring becomes increasingly important. It is also crucial to correctly identify, as far as possible, those individuals who are at higher risk for adverse events and require the adoption of additional precautions and follow-up after immunization, and the few who need to be exempted for medical reasons. On the other hand, the current trend is against compulsory immunization (also on the basis of new evidence showing poor results obtained where both compulsory and voluntary vaccinations are simultaneously present in vaccine schedules) [145], while it is advised to counsel individuals in order to provide correct information on benefits and risks, thus empowering them to make an informed choice.
For these reasons, as some important scientific bodies have suggested, it would be vital to obtain greater knowledge on adverse events, possibly through the widespread use of electronic medical records that would enable a far higher sensitivity in epidemiologic assessments of rare/very rare adverse events. Collecting evidence that fulfills causality criteria [146] will help both risk communication and decision making.
Furthermore, the additional knowledge accumulated through "mechanistic" biomedical research can help elucidate in greater detail the pathophysiological mechanisms of vaccine induced harm and possibly help identify in advance the subjects at risk for harm, moving more and more towards tailored medicine.
Since there is no gold standard in risk communication in the field of vaccination, it is advisable to perform studies aimed at determining a more effective medium of communication [147]. It is important to bear in mind that vaccination risks should not be omitted both because it is unethical, and because considering a vaccine unsafe does not necessarily imply having doubts on its efficacy, therefore perceptions of vaccine importance may mitigate losses in vaccination uptake [148].
Trust in institutions such as Public Health and Government has effects on trust in immunization, and vice-versa [147, 148]; it is necessary to develop a new strategy of risk communication that, rather than showing lists of adverse events, disease complications and their incidence, makes use of widely intelligible instruments and language, in order to clearly answer the questions of both Health Care Workers and Public Health services users.

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Conflicts of Interest
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GLD'A, ET, EZ received reimbursement for participating to one scientific meeting and fee for giving scientific presentations by Sanofi Pasteur.
AC, GG, LZ declare absence of conflicts of interest.

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