Clinical Management Review

Evaluation of Adverse Reactions to Vaccines

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Learning objectives:

1. To describe the role of health and vaccine providers in vaccine pharmacovigilance.
2. To describe the most frequent adverse reactions to vaccines.
3. To discuss the management of patients with a history of possible adverse reaction to vaccines.
4. To recognize absolute and partial contraindications to revaccination depending on the adverse reaction to vaccine reported.

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The development and widespread use of vaccination over the past centuries has been the single most impactful intervention in public health, by effectively preventing morbidity and mortality from infectious diseases. Vaccination is generally well tolerated in the vast majority of the population, and the benefits of vaccination largely outweigh the risk of severe adverse events in the majority of patients. Vaccine hesitancy can be a significant concern and lead to infectious disease outbreaks. All health care providers play an important role in maintaining public confidence in vaccines because their attitude and knowledge is often critical in facilitating acceptance of a vaccine. The purpose of this review is to first, provide an understanding of the basic concepts that are relevant to vaccine pharmacovigilance, and secondly, to provide an overview and discuss management of both immune and nonimmune adverse events after vaccination. **(J Allergy Clin Immunol Pract 2021;9:3584-97)**

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Since the first vaccinia virus (cowpox) vaccine was used by Edward Jenner in 1796 to prevent smallpox, the development and widespread use of vaccines has prevented mortality and morbidity from at least 25 vaccine-preventable diseases.[1] However, before the COVID-19 pandemic, many regions of the world that included high-, low-, and middle-income countries were experiencing a resurgence of measles, a disease that is preventable with a safe and effective vaccine that has been in use for over 50 years.[2] In the same year, the World Health Organization

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Abbreviations used
ADEM- Acute disseminated encephalomyelitis
AEFI- Adverse events following immunization
DT- Diphteria and tetanus
DTaP- Diphteria, tetanus, and pertussis
ELS- Extensive limb swelling
GBS- Guillain-Barré syndrome
ISRR- Immunization stress—related response
ITP- Immune thrombocytopenic purpura
ORS- Oculorespiratory syndrome
PEG- Polyethylene glycol
SIRVA- Shoulder injury related to vaccine administration
SSLR- Serum sickness—like reactions
SSPE- Subacute sclerosing panencephalitis
Td- Tetanus and diphteria toxoid
TTS- Thrombosis with thrombocytopenia syndrome
WHO- World Health Organization

(WHO) listed vaccine hesitancy as one of the 10 most important threats to global health.[3] Vaccine hesitancy is a complex issue with multiple determinants that relate to sociocultural, religious, and historical factors that are influenced by personal, social, and family perceptions but directly related to vaccine and vaccination-specific issues.[4] Within this complex matrix concerns about vaccine safety may often be paramount and be a barrier to vaccine acceptance. With the rapid global deployment of novel COVID-19 vaccines and the subsequent detection of vaccine safety signals, there has been a renewed focus on vaccine safety. The purpose of this review is 2-fold: first, to provide an understanding of the basic concepts that are relevant to vaccine pharmacovigilance and secondly, to provide an overview of adverse vaccine and immunization reactions, including COVID-19 vaccines.

VACCINE PHARMACOVIGILANCE AND THE ROLE OF HEALTH CARE AND VACCINE PROVIDERS

All health care providers play an important role in maintaining public confidence in vaccines because their attitude and knowledge is often critical in facilitating acceptance of a vaccine.[5] Providers should have a thorough knowledge of the common and rare adverse effects of vaccination as well as how the safety of a vaccine is established and monitored. The reason is that health care and vaccine providers play a central and critical role in vaccine pharmacovigilance through postlicensure surveillance and the passive reporting of adverse events following immunization (AEFI). Vaccine safety can only be inferred by the absence of adverse vaccine or immunization reactions. A vaccine reaction refers to a reaction caused by the vaccine product, whereas an immunization reaction refers to the process of immunization and not the vaccine product.[6] Common adverse vaccine reactions are characterized during clinical trials (phases I-III), but as the vaccinated cohort is limited in number (often <20,000), reactions that are rare (frequency <1 in 1000), delayed, or occur in subpopulations are unknown at the time of vaccine licensure. Postlicensure surveillance plays a critical role in determining previously unrecognized reactions but is also important to detect an increased frequency of a known reaction and any immunization errors. Most countries are reliant on passive or spontaneous reporting by health professionals or consumers of an AEFI, which is "any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine." The adverse event may be any "unfavourable or unintended sign, abnormal laboratory finding, symptom or disease."[6] It is important to understand that the reporting of an AEFI is not predicated by a known causal association with the vaccine. The reason for this is that not all reactions will be known at the time of licensure and recent examples of adverse reactions detected after licensure include intussusception after the rotavirus vaccine, narcolepsy after the adjuvanted influenza vaccine, and thrombosis and thrombocytopenia syndrome (TTS) after adenoviral vaccines including the AstraZeneca (AZD1222) COVID-19 vaccine.[7-9]

The detection, reporting, analysis, and communication about AEFI form the basis of vaccine pharmacovigilance, and in most countries, this is the responsibility of the national regulatory authority. As many reported AEFI also occur without prior immunization, it is important to classify an AEFI as being due to a reaction (vaccine or immunization) or a coincidental event. For individual and serious AEFI, the WHO recommends a systematic causality assessment process.[6] This process seeks to classify the event into one of 5 categories (Table I). However, for previously unknown events, epidemiological studies are required to establish a causal association and quantify the extent of vaccine-attributable risk. This can be achieved by comparing background rates to observed rates of the event after immunization, by comparing vaccinated and unvaccinated cohorts or by quantifying risk over different time windows, post immunization.

The management of a vaccinee who experiences an AEFI, which is often initiated by the vaccinating physician or allied health professional, should focus on the nature and severity of the symptoms and implement appropriate management. As part of the initial management, it is critical to document the event in detail including the temporal onset of symptoms and the presence of any coexisting or coincidental conditions. Reporting of the AEFI to public health authorities in a timely and accurate manner contributes to vaccine pharmacovigilance. A subsequent review is important to determine if the event was an adverse reaction (vaccine or immunization) or a coincidental event. Such an assessment must first start with a clear diagnosis of what the event was and then a secondary assessment of the role of the vaccine. Careful evaluation is also essential to guide the approach to future vaccination. Figure 1 depicts the allergist's approach to a patient referred for AEFI. The first step consists in determining whether the presentation is compatible with an allergic reaction or not. In many regions, specialist immunization and allergy services have been established to provide such assessments and to provide revaccination under a medically supervised environment.[10-12]

IMMEDIATE ALLERGIC REACTIONS

Immediate allergic reactions to vaccines are mediated by the presence of preformed IgE antibodies on mast cell surfaces, which causes the release of histamine and other mediators on contact with a specific allergen contained in the vaccine. Mast cell degranulation may also be triggered by inflammatory stimuli independent of IgE, such as activation of the complement system, which elicit the same clinical presentation.[13]

Symptoms of an IgE-mediated reaction or release of histamine and other mediators range from urticaria to anaphylaxis, including angioedema, dyspnea, gastrointestinal symptoms such

as abdominal pain, vomiting, and diarrhea, hypotension, or altered consciousness.[14] Most reactions occur within the first 20 minutes of exposure to the vaccine, although some can occur up to 4 hours after injection. Potentially life-threatening anaphylactic reactions have been reported to occur in 1 per 1 million doses.[15] Many potential allergens are present in vaccines and should be considered before proceeding to further immunization.

Potential allergens found in vaccines include food derivatives, antimicrobials, residual media, extrinsic substances such as latex, carrier proteins, and microbial antigens.[15-17] More recently, molecules such as polyethylene glycol (PEG) and polysorbate have been suspected of eliciting anaphylactic reactions, although it is not clear if these reactions are IgE-mediated.[17] Preservatives and adjuvants seem to be rarely associated with such reactions.

Food derivatives

Food derivatives that can be found in vaccines include egg protein, gelatin, bovine serum albumin, and milk proteins (Table II).[15-17] Egg proteins, mainly ovalbumin, have been a main concern as an etiology of vaccine anaphylactic reaction. Whereas some vaccines are grown in hen's eggs, others are propagated in chick embryo fibroblasts and contain very small amounts of egg protein if any at all. In recent decades, many published reports have revealed that the very low amount of egg proteins contained in vaccines is well tolerated by egg-allergic people.[18-23] Skin testing with influenza vaccine is no longer recommended as it was found to be irritative and it does not accurately predict the risk of an allergic reaction on readministration.[17-21,24] Although this might also be the case with yellow fever and rabies vaccines, studies are needed to confirm their innocuity in egg-allergic patients.[25-27]

Gelatin is an animal protein of bovine or porcine origin that has clearly been associated with vaccine anaphylactic reactions.[15] It is found in significant amounts in some vaccines such as MMR, varicella, older zoster, some influenza, some yellow fever, and typhoid, and in lower amounts in older Japanese encephalitis and oral typhoid vaccines (capsules).

Bovine serum albumin has been used in very low amounts as a stabilizer in many vaccines,[15] and vaccine anaphylaxes have been attributed to this component. A case series also suggested that milk proteins, notably casein, could be associated with vaccine anaphylaxis in 8 children with severe cow's milk allergy.[28] Amounts of casein lower than 18 ng/mL have been found in diphteria-tetanus-pertussis vaccines.[29] However, because this is the only case series and vaccination is well tolerated in cow's milk–allergic children, this did not impact vaccination recommendations.[15,16]

Antimicrobials

Trace amounts of different antimicrobials such as neomycin, polymyxin B, gentamicin, streptomycin, chlortetracycline, and amphotericin B can be found in some vaccines.[15-17] Antimicrobials are used during the production process of vaccines to prevent bacterial and fungal growth. Even if these are potential allergens, allergic reactions to these components seem very rare with a single report of anaphylaxis after vaccination attributed to the neomycin component of the vaccine.[30]

Residual media

Some residual media constituents, such as yeast, have been suspected in some anaphylactic vaccine reactions.[15] The allergens are recombinant proteins expressed by *Saccharomyces cerevisiae* (Baker's yeast). Yeast protein can be found in very low amounts in hepatitis B, human papillomavirus, and one type of meningococcal conjugate vaccine.[31]

Latex

Natural latex can be found in the tip caps of prefilled syringes of some vaccines and also on the tip caps of prefilled oral applicators of some rotavirus oral vaccines.[31] Water-soluble proteins in natural latex are expected to induce an allergic reaction mostly when a large area of surface mucosal membranes is exposed to these proteins, which is not really the case with vaccine vials. However, there are reports that justify caution in patients with a history of severe latex allergy.[32] Fortunately, synthetic rubber, which is not allergenic, has replaced natural latex in most products.

Microbial antigens

On rare occasions, the microbial antigen itself has been suspected as the culprit of vaccine hypersensitvity, namely with tetanus and diphteria toxoids, pneumococcus, and *Bordetella pertussis* antigens.[33,34] However, these cases were poorly documented. More recently, there was a report of anaphylactic reaction after pneumococcal conjugate vaccine (13-valent) administration, for which the carrier protein CRM197, a nontoxic mutant diphteria toxin, was suspected to be the allergen, supported by a positive skin test and basophil activation test.[35] Even if very infrequent, allergy to carrier protein should be kept in mind when investigating anaphylactic reactions to conjugated or combined vaccines.

PEG and polysorbate

The COVID-19 pandemic has given rise to several new forms of vaccines, including the mRNA vaccines. PEG is used as a stabilizer in the lipid coat of these vaccines to increase its hydrosolubility.[17] A total of 2.5 to 11.1 episodes of anaphylaxis per 1 million doses administered have been reported, which is higher than usually observed with other vaccines.[36-38] PEG is widely used in pharmaceutical, food, and cosmetology industries, but its molecular weight varies depending on the product, giving different properties to the molecule.[39] The exact mechanism associated with COVID-19 vaccine anaphylaxis is not yet known, and the role of PEG has to be confirmed. Polysorbate is a molecule structurally related to PEG and also found in some vaccines. Polysorbate and its degradation products are known to be anaphylactogenic and are suspected to explain some reports of vaccine anaphylaxis.[40]

Preservatives and adjuvants

To prevent bacterial growth in multidose vials, thimerosal, 2-phenoxyethanol, and phenol are added to vaccines.[15] Since 2001, thimerosal has been removed in vaccines used in young children by precaution concerning potential mercury toxicity. Although delayed-onset contact dermatitis have been reported with thimerosal, there have been no clear anaphylactic reactions linked to this preservative.

Adjuvants help to enhance the immune response to vaccines. The most common adjuvants used in vaccines are aluminum hydroxide and aluminum phosphate. Anaphylaxis to these components has not been reported, but the delayed occurrence of nodules is well documented. Finally, an increased rate of anaphylaxis was observed in Canada with the use of AS03 (trade name for a squalene-based adjuvant) during influenza A vaccination in 2009, but the exact role of the adjuvant was not clear.[41]

TABLE I. Council for International Organizations of Medical Sciences/World Health Organization cause specific definition of adverse events following vaccination (AEFI)

Vaccine product–related reaction	An AEFI that is caused or precipitated by a vaccine due to 1 or more of the inherent properties of the vaccine product
Vaccine quality defect–related reaction	An AEFI that is caused or precipitated by a vaccine that is due to 1 or more quality defects of the vaccine product including its administration device as provided by the manufacturer
Immunization error–related reaction	An AEFI that is caused by inappropriate vaccine handling, prescribing, or administration
Immunization anxiety–related reaction	An AEFI arising from anxiety about the immunization
Coincidental event	An AEFI that is caused by something other than the vaccine product, immunization error, or immunization anxiety

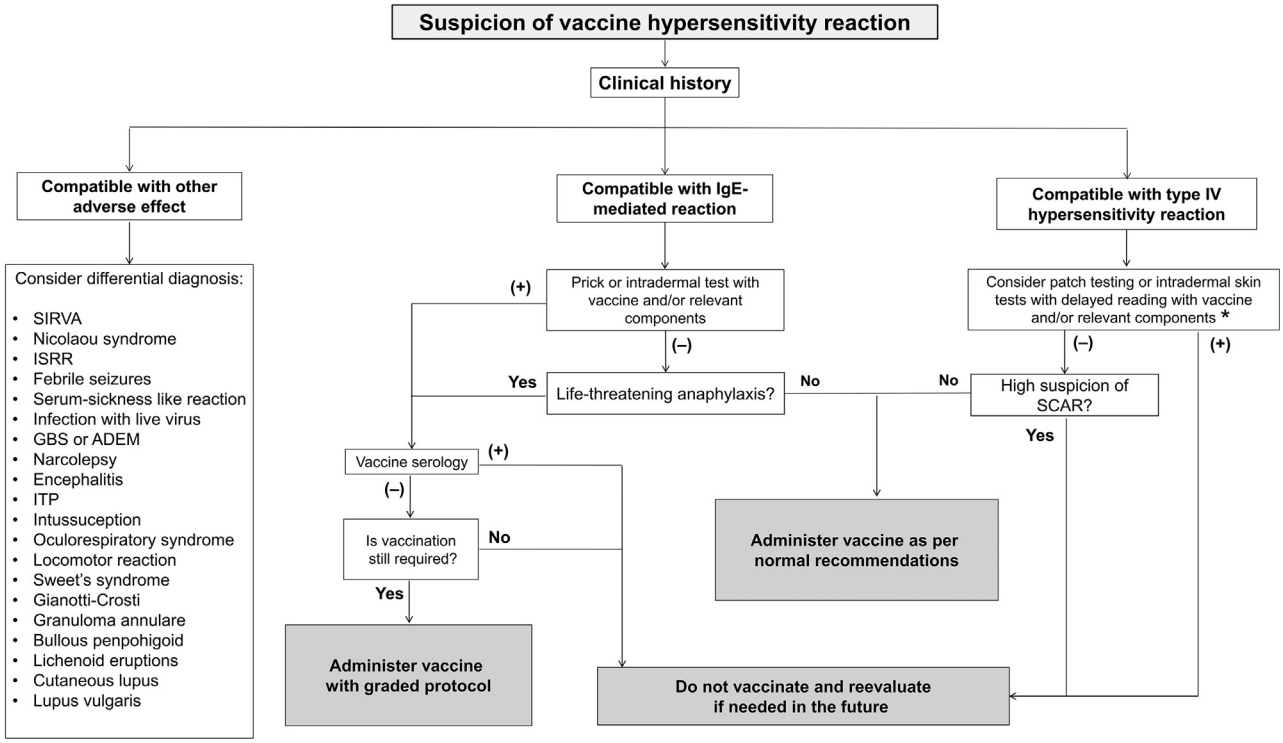

FIGURE 1. Clinical management of suspected vaccine hypersensitivity reaction. *Local injection site reactions that may be compatible with type IV hypersensitivity are in most cases not a contraindication to future doses and would not warrant testing. *ADEM*, Acute disseminated encephalomyelitis; *GBS*, Guillain-Barré syndrome; *ITP*, idiopathic thrombocytopenic purpura; *ISRR*, immunization stress–related reaction; *SCAR*, severe cutaneous adverse reactions, which include drug reaction with eosinophilia and systemic symptoms, acute generalized exanthematic pustulosis, Stevens-Johnson syndrome, or toxic epidermal necrolysis; *SIRVA*, shoulder injury related to vaccine administration.

Clinical approach to suspected IgE-mediated reaction to a vaccine

For immediate reactions suspected to be IgE-mediated, clinical evaluation should focus on previous reactions to vaccines or vaccine components and pre-existing food and drug allergies. Even if not reported, concomitant occurrence of new diagnosis of food or drug allergy should be explored. Preschool children frequently introduce new food allergens in their diet during the first year of the immunization calendar or receive nonsteroidal anti-inflammatory drugs as antipyretical prophylaxis.

Skin prick tests using the undiluted vaccine and relevant components should be performed (Tables II and III). If negative, an intradermal skin test with the vaccine diluted 1:100 in normal saline is then performed. In most vaccines, the 1:100 dilution is reported to be nonirritative.[42] Even if the sensitivity and specificity of vaccine skin testing have not been well documented, in clinical practice, the negative predictive value of a negative intradermal skin test to vaccine appears very good. When skin testing is negative, the risk of an allergic reaction to the vaccine is minimal and the patient can generally be revaccinated using 1 single dose, although an observation period of 30 minutes after vaccination is warranted as a precaution (Figure 1).

On the other hand, a positive skin prick test or intradermal test supports an IgE-mediated mechanism and increases the risk of reaction on readministration of the vaccine. In that situation, the risk-benefit ratio of vaccination should be discussed.

TABLE II. Potential vaccine allergens: food derivatives

Excipient	Function	Vaccine type	Vaccine name	Amount per 0.5 mL dose
Albumin bovine				
Bovine	Stabilizer	HepA	Vaqta	$<10^{-4}$ mcg
Bovine serum	Stabilizer	JE	Ixiaro	≤100 ng/mL
		DTaP+IPV+Hib	Pentacel	≤50 ng
		DTaP+IPV	Quadracel	≤50 ng
		DTaP+IPV+Hib+HepB	Vaxelis	≤50 ng
		Rabies	RabAvert	Small quantities
Calf serum	Stabilizer	DTaP+IPV	Kinrix	VERO cell culture growth
		DTaP+IPV+HepB	Pediatrix	VERO cell culture growth
		Zoster	Zostavax	Trace amounts
		IPV	Ipol	<50 ng
Fetal bovine serum	Stabilizer	Rotavirus	Rotateq	Trace amounts
		Varicella	Varivax	Trace amounts
Egg protein				
Ovalbumin	Residual medium	Influenza	Afluria Quad	≤1 mcg
			Fluvirin	≤1 mcg
			Flulaval Quad	≤0.3 mcg
			Fllumist Quad	≤0.24 mcg
			Fluarix	≤0.05 mcg
		Rabies	RabAvert	≤3 ng
Egg protein		Influenza	Fluad	<0.4 mcg
		Yellow fever	YF-Vax	≤4.42 mcg/mL
Gelatin				
Porcine hydrolyzed	Stabilizer	Varicella zoster	Zostavax	15.58 mg
Gelatin hydrolyzed	Stabilizer	MMR	MMR-II	14.5 mg
		Varicella	Varivax	12.5 mg
		MMRV	ProQuad	11 mg
		Influenza	FluMist Quad	2 mg/0.2 mL dose
Bovine	Stabilizer	Rabies	RabAvert	<12 mg polygeline
Gelatin	Manufacturing residue	JE	JE-Vax	500 mcg/1 mL dose
	Gelatin capsule	Typhoid	Vivotif	Gelatine capsules
	Stabilizer	Yellow fever	YF-Vax	Amount not specified
Milk (casein)[28]		Tdap, DTap	Infanrix	≤18.3 ng/mL
			Adacel	≤17.3 ng/mL
			Daptacel	≤10 ng/mL
Yeast	Medium nutrient	HepB	Engerix-B	≤5% yeast protein
			Heplisav-B	≤5% yeast protein
		DTaP+HepB+IPV	Pediarix	≤5% yeast protein
		HepA+HepB	Twinrix	≤5% yeast protein
		HepB	Recombivax	≤1% yeast protein
		HPV	Gardasil	<7 mcg yeast protein
			Gardasil 9	<7 mcg yeast protein/dose
		Pneumococcal 13-valent	Prevnar 13	Ingredients in growth medium
		Meningococcal	Menveo	Amount not specified

Adapted from www.vaccinesafety.edu. For simplicity, information is presented for a few brands only. Further information on other brands is available at www.vaccinesafety.edu.

Performing serology to determine the immune status obtained by prior vaccinations is useful to allow the patient to make an informed decision. If the patient has IgG antibody levels that already confer protection against the disease, an adequate option would be to withhold or delay the vaccination. As protective antibody titers may decline over time, skin testing should be repeated some years later to assess spontaneous resolution of the allergy (eg, tetanus and diphtheria booster dose).[43] If the skin tests are still positive and the benefits to receive the vaccine outweigh the risks, the booster dose of the vaccine should administered in graded doses under observation (Table IV). It should be noted that some vaccines are irritating and can cause false-positive results. This is the case for influenza vaccine, for which skin testing is no longer recommended in egg-allergic patients due to its low sensitivity and specificity.[17,20,44]

TABLE III. Potential vaccine allergens: nonfood derivatives

Excipient	Function	Vaccine type	Vaccine name	Amount per 0.5 mL dose
Antibiotics				
Amphotericin B	Antimicrobial	Rabies	RabAvert	≤20 ng
Chlortetracycline			RabAvert	≤200 ng
Gentamycin sulfate		Influenza	Fluarix Quad	≤0.15 mcg
			FluMist Quad	<0.015 mcg/mL
Neomycin		MMR	MMR-II	25 mcg
		MMRV	ProQuad	≤16 mcg
		Rabies	RabAvert	<10 mcg
		Influenza	Fluvirin	≤2.5 mcg
			Fluad	≤0.02 mcg
		IPV	IPOL	<5 ng
		DTaP+IPV	Kinrix	≤0.05 ng
		DTaP+HepB+IPV	Pediarix	≤0.05 ng
		DTaP+IPV+Hib	Pentacel	<4 pg
		HepA	Vaqta	<10 ppb (residual)
		Varicella	Varivax	Trace amounts
		Varicella zoster	Zostavax	Trace amounts
Neomycin sulfate		Rabies	Imovax	<150 mcg/mL
		Influenza	Afluria Quad	≤81.8 ng
		HepA	Havrix	≤40 ng
		HepA+HepB	Twinrix	≤20 ng
Polymyxin		Influenza	Fluvirin	≤3.75 mcg
Polymyxin B		Polio	IPOL	25 ng
		Inflluenza	Afluria Quad	≤14 ng
		DTaP+IPV	Kinrix	≤0.01 ng
		DTaP+HepB+IPV	Pediarix	≤0.01 ng
Polymyxin sulfate		DTaP+IPV+Hib+HepB	Vaxelis	<25 ng
		DTaP+IPV+Hib	Pentacel	<4 pg
		DTaP+IPV	Quadracel	<4 pg
Streptomycin		Polio	IPOL	200 ng
Latex				
	Pharmaceutical closure	DTaP	Infanrix	Tip caps of prefilled syringes
		DTaP+IPV	Kinrix	
		DTaP+HepB+IPV	Pediarix	
		Tdap	Boostrix	
		Td	Tenivac	
		HepB	Engerix-B	
		HepA	Havrix	
		HepA+HepB	Twinrix	
		Influenza	Fluvirin	
		Rotavirus	Rotarix	Tip caps of prefilled oral applicator
Polyethylene glycol				
	Lipid	COVID-19	Moderna	1.93 mg PEG 2000
			PfizerBioNtech	0.05 mg PEG 2000/0.3 mL dose
Polysorbate				
Polysorbate 20	Surfactant	HepA	Havrix	0.05 mg/mL
		Influenza	Flublok Quad	≤27.5 mcg
		HepA+HepB	Twinrix	Amount not specified
Polysorbate 80		Influenza	Fluad	1.175 mg
			Fluarix Quad	≤0.55 mg (Tween 80)
		HepB	Heplisav-B	0.1 mg/mL
		Zoster	Shingrix	0.08 mg
		Meningococcal group B	Trumenba	0.018 mg
		Influenza	Flucelvax Quad	≤1500 mcg

(continued)

TABLE III. *(Continued)*

Excipient	Function	Vaccine type	Vaccine name	Amount per 0.5 mL dose
			Flulaval Quad	≤887 mcg
		Pneumococcal 13-valent	Prevnar 13	100 mcg
		DTaP	Infanrix	≤100 mcg (Tween 80)
		DTaP+IPV	Kinrix	≤100 mcg
		DTaP+HepB+IPV	Pediarix	≤100 mcg
		TdaP	Boostric	≤100 mcg (Tween 80)
		HPV	Gardasil	50 mcg
		HPV	Gardasil 9	50 mcg
		JE	JE-Vax	<0.0007%
		DTaP+IPV	Quadracel	10 ppm
		DTaP+IPV+Hib	Pentacel	10 ppm
		Rotavirus	Rotateq	Amount not specified
Sodium taurodeoxycholate				
	Protein purifier	Influenza	Afluria Quad	≤10 ppm (residual)
Thimerosal				
	Preservative	Influenza	Fluvirin	25 mcg mercury/dose in multidose; ≤1 mcg/dose mercury in prefilled syringe
			Fluzone Quad	25 mcg mercury/dose in multidose; none in single dose
			Afluria Quad	24.5 mcg mercury/dose in multidose; none in single dose
		Meningococcal	Menomune	25 mcg mercury/dose in multidose; none in single dose
		Td	TDVAX	≤0.3 mcg mercury, trace amounts
		JE	JE-Vax	0.007%

Adapted from www.vaccinesafety.edu. For simplicity, information is presented for a few brands only. Further information on other brands is available at www.vaccinesafety.edu.

DELAYED ALLERGIC REACTIONS

Extensive limb swelling

Mild local reactions are frequently observed after vaccination and are considered nonspecific immune reactions. Patients can also present with large local reactions, which tend to occur 24 to 72 hours after vaccination. Some patients can present extensive limb swelling (ELS), defined as a large local reaction that extends at least to the elbow or knee of a vaccinated extremity. Vaccines most commonly associated with ELS are polyvalent pneumococcal, tetanus and diphteria toxoid (Td, DTaP, DTP), influenza, and hepatitis B vaccines.[45] In children, the risk of ELS has been shown to increase according to the number of previous doses of DTP and DTaP vaccines received, reaching 1% to 2% after the fifth booster of DTaP.[15,45] Various factors have been associated with ELS, including the injection technique (ie, subcutaneous instead of intramuscular injection), diphteria toxoid content in the case of DTaP, and high prevaccination antibody levels.[46]

Vaccines containing aluminum adjuvants can also induce chronic subcutaneous nodules at the injection site.[47-50] These include diphteria, tetanus, and pertussis vaccines (alone or in combination with other vaccines), as well as human papilloma virus and hepatitis A and B vaccines. The risk of this complication is estimated to be around 0.03% to 0.83%.[51] The nodules typically appear after a median of 3 months of vaccination and may last many years (median: 3-4 years). They can be associated with intense itching leading to local eczema, hypertrichosis, and discoloration. The underlying mechanism appears to be contact allergy to aluminum (type IV hypersensitivity), which has been documented in a significant proportion of these patients and appears to disappear over time.[50,52] Aluminum contact hypersensitivity can be confirmed in clinic by patch testing.

Toxidermias such as Stevens-Johnson syndrome, toxic epidermal necrolysis (type IVc hypersensitivity),[53-55] and acute generalized exanthematous pustulosis[56] (type IVd hypersensitivity) have also rarely been reported as vaccine adverse events. The mechanisms underlying these delayed vaccine reactions are not well established, although pre-existing allergy to vaccine components or possible genetic variations in antigen presentation or processing may be predisposing factors.

MANAGEMENT OF A SUSPECTED DELAYED REACTION

The general approach of a suspected delayed reaction is similar to immediate reactions. The main objective of management is to identify the culprit allergen, so as to allow the vaccine scheduled to resume while avoiding that culprit, if possible. The approach is mainly empirical as there is very little literature on the diagnostic value of allergy testing. In most cases, ELS is not a contraindication to future vaccine doses. In patients with ELS, intradermal skin tests with delayed reading and patch tests to the vaccines and their different components (Table III) may be useful to guide future vaccine selection, particularly in severe cases that are believed to represent type IV—mediated reactions.[57] If no alternative is available and vaccination is warranted by suboptimal serologic response, potential options include combining vaccination with analgesics and antihistamines if necessary.

TABLE IV. Graded administration of vaccine

Recommendation for graded vaccine administration
The following successive doses should be administered subcutaneously at 15- to 20-min intervals:
1. 0.05 mL of 1:10 dilution
2. 0.05 mL of full strength
3. 0.10 mL of full strength
4. 0.15 mL of full strength
5. 0.20 mL of full strength.
Desensitization should only be performed under the direct supervision of a physician experienced in the management of anaphylaxis with necessary emergency equipment immediately available.

YF-Vax Package insert (https://www.fda.gov/vaccines-blood-biologics/vaccines/yf-vax).

Systemic corticosteroids may be used only if a reaction is particularly bothersome or severe given that they may suppress immune responsiveness.

For severe toxidermia, it is preferable to start with a patch test before proceeding to intradermal testing. Although the sensitivity and specificity of these tests are not well documented, they remain a useful tool to help guide the approach to future vaccination in these patients.[58,59] However, if a severe cutaneous adverse reaction is thought to be related to vaccination, this would generally contraindicate future doses.

OTHER IMMUNE ADVERSE REACTIONS

Serum sickness–like reactions

Serum sickness–like reactions (SSLR) have been reported with hepatitis B,[60] influenza,[61-63] pneumococcal,[64] rabies,[65] and tetanus[66] vaccines. The diagnosis of SSLR is generally based on history with typical manifestations of rash and arthralgia. Systemic symptoms are often associated, including fever, malaise, lymphadenopathy, headache, myalgia, abdominal pain, nausea, or vomiting. Contrary to true serum sickness, which is a type III immune complex-mediated hypersensitivity caused by the formation of immune complexes, the exact physiopathological mechanisms underlying SSLR are not well documented. The symptoms occur several days after exposure to the trigger, which is usually a drug or a viral infections and rarely vaccination. A recent study on SSLR after treatment with antibiotics reported a 25% recurrence of symptoms after retreatment, which suggests that such reactions may also have the potential to reoccur after revaccination.[67] Unfortunately, more data are required as there are no published reports at this time of revaccination after suspected SSLR caused by vaccines. The presence of IgE and IgG against vaccine components has been reported in cases of SSLR after rabies vaccination, with skin biopsies demonstrating leukocytoclastic vasculitis.[65] Graded challenges are not useful in this context because the reaction will not occur immediately. Serologic testing for immunity and the possibility of alternative vaccine use should be explored when evaluating risk-benefit of revaccination.

Guillain-Barré syndrome and acute disseminated encephalomyelitis

Guillain-Barré syndrome (GBS) and other demyelinating neuropathies such as acute disseminated encephalomyelitis (ADEM) are rare vaccine-related adverse events.[68] The incidence of GBS after vaccination is estimated to 1 to 3 cases per million vaccinations compared with its global incidence of 0.8 to 1.9 cases per 100,000 persons per year.[68] It has been shown to occur after influenza vaccines in adults but not in children. A possible link is usually suspected when the onset of symptoms occurs within 6 weeks after vaccination. On the other hand, influenza vaccination has been shown to reduce the occurrence of GBS by protecting against natural influenza infection. GBS has also, albeit even more rarely, been reported with tetanus, oral polio, and older formulations of rabies vaccines.[69-71] A cross-recognition of specific virotopes and similar self-antigen in the nervous system by CD4+ and CD8+ T cells is the mechanism presumably leading to demyelinating reaction. It should be kept in mind that intercurrent infections seem to be the trigger of GBS much more frequently than vaccines, with *Campylobacter jejuni* infection found in 25% to 50% of adult GBS patients. Cytomegalovirus, Epstein-Barr virus, *Mycoplasma pneumoniae*, and *Haemophilus influenzae* are other infections associated with GBS and should be taken into account in the investigation.

Concerning ADEM, the only clear pathological association ever demonstrated was with the Semple rabies vaccine.[14] However, a temporal association has been described with Japanese encephalitis, yellow fever, measles, influenza, varicella, and hepatitis vaccines.[72-74]

Encephalopathy or encephalitis

Measles, mumps, and varicella vaccines have been rarely associated with the occurrence of encephalitis. Natural infections with these viruses are well known to cause encephalitis. Measles encephalitis is estimated to occur in 1 case per 1000 to 2000 patients naturally infected with measles.[75] This virus can also cause a persistent infection of the brain resulting in subacute sclerosing panencephalitis (SSPE), which occurs at a rate of approximately 22 cases of SSPE per 100,000 reported cases of measles.[76] Rare cases of encephalitis have been reported after MMR and varicella vaccines.[77-80] As they are live attenuated vaccines, particular caution should be taken to exclude immunodeficiency before vaccination.

Finally, no association has been found between the occurrence of autism spectrum disorder and vaccines, nor with their thimerosal content. This lack of association has been confirmed by many epidemiologic studies, as described in systematic reviews[81,82] and a meta-analysis.[83]

Narcolepsy

An increase in the incidence of narcolepsy was observed following the 2009 influenza pandemic.[84] The same phenomenon was also observed and associated with AS03-adjuvanted 2009 pandemic H1N1 influenza vaccine (trade name: Pandemrix), as confirmed by a meta-analysis.[85] The relative risk of narcolepsy after vaccination with Pandemrix increased 5- to 14-fold in children and adolescents and 2- to 7-fold in adults. The vaccine-attributable risk in children and adolescents was reported to be approximately 1 per 18,400 doses of vaccine.[85] There seems to be a genetic predisposition to this disorder, as almost all patients were HLA DQB1*0602 positive.[86,87] H1N1 cross-reactive T cells are thought to be involved in hypocretin cell destruction, which is linked to narcolepsy.[88]

Immune thrombocytopenic purpura

Measles-containing vaccines have been associated with immune thrombocytopenic purpura (ITP) which occurs rarely,

TABLE V. Examples of rates of local and systemic nonspecific reactions reported to common vaccines based on monographs or package inserts

Vaccine	Monograph	Local reaction (redness, swelling, tenderness)	Fever	Other nonspecific reaction*
DTaP+IPV+Hib	Pediacel	6.8%-33%	13.4%-19.6%	3.3%-46.8%
	Pentacel	7.1%-56.1%	5.8%-16.3%	24.1%-76.9%
DTaP+IPV	Quadracel	0.9%-28.8%	18%-24%	2.3%-51.3%
	Kinrix	26%-57%	16%	16%-19%
MMR	MMR II	0.6%	8.8%	NS
Varicella	Varivax III	19.3%	14.7%	NS
Pneumococcal	Prevnar 13	<5-year-old: ≥1/10 ≥5-year-old: 19.3%-32.5%	<5-year-old: ≥1/10 ≥5-year-old: 9.5%-14.7%	<5-year-old: ≥1/10 ≥5-year-old: 5.7%-31.2%
	Pneumovax 23	16.4%-77.2%	1.4%-2%	2.7%-18.1%
Hepatitis B	Engerix B	≥10%	≥1% and <10%	≥10%
	Recombivax HB	≥10%	≥1% and <10%	≥1% and <10%
Influenza	Fluzone Quadrivalent	0.5%-66.6%	0%-14.3%	8.9%-54%
HPV	Gardasil	25.6%-89.9%	2.7%-5%	0.7%-14.6%
Meningococcal	Menveo	<2-year-old: 8%-31% ≥2- to ≤10-year-old: 13%-45% >10-year-old: 13%-41%	<2-year-old: 3%-9% ≥2- to ≤10-year-old: 2% >10-year-old: 2%	<2-year-old: 6%-57% ≥2- to ≤10-year-old: 3%-18% >10-year-old: 3%-30%
	Menectra	0%-2.6%	0.4%-0.8%	0%-4.5%
	MenQuadfi	Toddler: 16.1%-31.2%	Toddler: 8.1%	Toddler: 5.5%-38%
	Bexsero	<2-year-old: 3%-15% ≥2- to ≤10-year-old: 0%-35% >10-year-old: <1%-17%	<2-year-old: <1% ≥2- to ≤10-year-old: 0%-3% >10-year-old: 0%	<2-year-old: <1%-3% ≥2- to ≤10-year-old: 0%-8% >10-year-old: 0%-7%
Haemophilus influenza B	Act-Hib	5%-30%	1.5%-27.7%	0%-51.8%
	Hiberix	≥10%	≥10%	≥10%
	Pedvax HIB	0.9%-2.5%	14.1%-18.1%	NS

*Asthenia, headache, myalgia, and gastrointestinal discomfort.

within 6 weeks of vaccination.[89-92] The incidence of this adverse event has been estimated at 1 to 3 cases per 100,000 doses after receiving MMR,[90,91] which is significantly lower than rates occurring after natural infection. Incidence of ITP is estimated to 1 per 3000 natural rubella infection, and incidence is estimated to be higher with natural measles infection.[90] One hypothesis has been that virus-platelet aggregates could lead to the generation of neoantigens, and to the production of antiplatelet antibodies.[76]

Thrombosis with thrombocytopenia syndrome

TTS, also referred to as vaccine-induced prothrombotic immune thrombocytopenia, is a newly described syndrome with symptom onset occurring 4 to 30 days after the ChAdOx1 nCoV-19 (Oxford-AstraZeneca) and Ad26.COV2.S (Johnson and Johnson) adenoviral vector COVID-19 vaccines.[9,93-98] A case definition has been proposed by the Brighton Collaboration, which includes both the acute onset of venous or arterial thrombosis and new onset thrombocytopenia.[99] Thrombosis, which is at unusual sites (central venous sinus or splanchnic vessels), needs to be demonstrated by imaging studies, thrombectomy or pathology (biopsy/autopsy), and thrombocytopenia is defined as a platelet count of less than 150,000/μL. The diagnosis is supported by an elevated D-dimer, shortened PT, PTT, and positive platelet factor 4 heparin antibodies.[9,99] The syndrome resembles heparin-induced thrombocytopenia, but the described vaccinated patients are not known to have received heparin.[9] TTS affects all ages but is less likely to occur in the older age groups (greater than 50 years of age), affects females predominately (approximately 80% with ChAdOx1 nCoV-19 and with the Ad26.COV2.S all described cases have been female), and occurs almost exclusively after the first dose of an adenoviral vector vaccine.[96] The absolute rate, as determined by postlicensure surveillance, varies but is estimated to be around 1 in 100,000 vaccinated individuals. Specific immunosuppressive management (intravenous gamma-globulin, steroids) and non-heparin anticoagulation is currently recommended based on guidelines from expert hematology groups.[100,101] The exact pathogenesis and efficacy of management are all areas of urgent and active research.

Oculorespiratory syndrome

The oculorespiratory syndrome (ORS) was first reported during the 2000 to 2002 influenza season in Canada and is characterized by conjunctivitis, cough, wheeze, chest tightness, difficulty breathing, sore throat, or facial swelling that occur within 24 hours of vaccination.[102-104] The symptoms are generally mild and resolve within 48 to 72 hours. The adverse event was mostly described with Fluviral and Vaxigrip vaccines. The estimated incidence was up to 2.9 cases per 100 vaccinations.[104] Recurrence of ORS was observed between 15% and 35% of revaccination with those vaccines during the 2002 to 2003 influenza vaccination season.[103] No anaphylaxis was reported and most recurrences were benign.[103] The mechanisms underlying ORS are not well understood but are not IgE-mediated as demonstrated by negative skin testing.[103] This adverse event has decreased significantly after changes made to

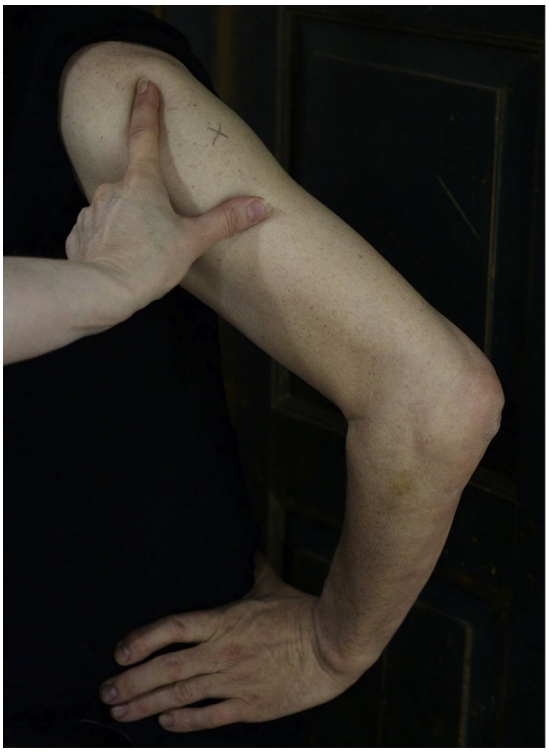

FIGURE 2. Cook injection technique for intramuscular administration of vaccine in the deltoid. Have the patients put their hand on their hip with the shoulder extended about 60°. Put your index finger on the acromion and thumb at the deltoid insertion at the middle of the humerus. Administer the vaccine in the middle of the triangle using an appropriate needle length for the patient (www.vaccinesafety.edu).

vaccine formulations. Since then, ORS-like reactions have been rarely reported with inactivated influenza vaccines.[105] As symptoms may have some similarities with immediate hypersensitivity reactions, it may be advisable to perform skin testing in patients in which symptoms occurred rapidly after vaccination or to revaccinate under supervision.

Musculoskeletal

After MMR vaccine, 10% to 25% of adult females report mild, acute, transient arthralgia or arthritis. Symptoms occur 1 to 3 weeks after vaccination and persist up to 3 weeks.[106] No significant association has been found with other vaccines. The mechanism underlying that reaction is not clearly determined, but environmental factors such as infection and predisposing host factors may contribute.[106] Some cases of arthritis after HPV, HB, and influenza vaccines have been reported, but the causality has not been clearly demonstrated.

Dermatologic

Various specific skin syndromes have been reported after vaccination, including Sweet's syndrome, Gianotti-Crosti, granuloma annulare, bullous pemphigoid, lichenoid eruptions, cutaneous lupus, and lupus vulgaris.[107] However, the role of the vaccine and the underlying mechanisms are not well documented.

INFLAMMATORY REACTION

Nonspecific inflammatory reactions

Mild local reactions are frequently observed after vaccination and consist of redness, swelling, and/or tenderness at the injection site (Table V). They are caused by nonspecific inflammation from injection of foreign molecules and can be prevented in part by using appropriate needle length.[108,109] Systemic signs and symptoms of immune activation such as fever, tiredness, headache, myalgia, and gastrointestinal discomfort occurring within the 48 to 72 hours after vaccination are considered expected side effects and do not contraindicate future vaccination.

Febrile seizures

Febrile seizures are a relatively frequent and benign condition, which can nevertheless be frightening for parents. They occur in 2% to 5% of children during their first 5 years of life (240-480 per 100,000 person-years in this age group).[110] They are usually triggered by fever caused by natural infection. Because all vaccines can cause fever in young children, they are all associated with a small risk of febrile seizures. The incidence of febrile seizures would be 1 per 1250 to 2500 doses after the first dose of measles-containing vaccines.[111] MMRV is associated with a higher risk of febrile seizures than MMR and varicella vaccines given separately the same visit and caregivers can be offered either option. The incidence of febrile seizures with simultaneous administration of inactivated influenza vaccine and PCV13 (pneumococcal) vaccine is 17.5 per 100,000 doses, compared with 5 per 100,000 doses when administrated separately.[112] The incidence of febrile seizures with the DTaP-IPV-Hib vaccine in Denmark was 4 per 100,000 doses.[113] Vaccines have not been associated with persistent epilepsy or infantile spasm.[114]

Intussusception

The rate of intussusception in the first year of life has been estimated to be approximately 34 per 100,000 infants in the United States. However, an increased risk of intussusception in the 21 days after the first dose of vaccination with RotaTeq has been documented with excess cases estimated at 1 to 1.5 per 100,000 vaccinated.[115]

Even if the pathogenesis of intussusception in infants is poorly understood, the role of an inflammatory process is suspected because of the presence of mesenteric lymphadenopathy or inflamed Peyer's patches in a significant proportion of cases. It is possible that some serotype-specific rotaviral enterotoxins are more likely to induce lymphoid hyperplasia and increased intestinal peristalsis.[116,117]

Infection related to vaccine

The risk of infection after vaccination is rare, but care should be taken in people with primary or acquired immunodeficiency, leukemia, or other malignant neoplasms affecting the bone marrow or lymphatic systems and in those receiving systemic immunosuppressive therapy. In general, live viruses should be avoided in immunocompromised patients, but the advice from their immunologist is important, because depending on the type of deficiency, certain live vaccines may be allowed. Disseminated or prolonged infection has been reported in severe cellular immunodeficiencies with the Bacille Calmette-Guérin (BCG),[118] varicella,[119] and oral polio[120] vaccines. Even in individuals without immunodeficiency, varicella-like rash at the injection site or generalized rash is reported in 3.7% and 3.8% of recipients of

varicella vaccine, respectively.[121] Mild zoster (shingles) illness resulting from a latent infection with varicella vaccine virus has also been reported. Even though severe combined immunodeficiency is usually diagnosed during the first year of life or so, prior to varicella vaccination, a clinical and family history suggesting a risk of immune deficiency should be ruled out before vaccination. Similar precautions should also be taken for people receiving zoster vaccine. Infections related to live vaccines have also been reported with smallpox,[122] measles,[123] yellow fever,[124] and rotavirus vaccines.[125-127]

NONIMMUNE REACTIONS TO VACCINATION

Shoulder injury related to vaccine administration

Shoulder injury related to vaccine administration (SIRVA) is another type of local adverse reaction from vaccination, resulting from an improper injection technique. The main risk factor for SIRVA is injection in the upper third of the deltoid, which can cause bursitis, tendonitis, tears, or fluid accumulation in rotator cuff, adhesive capsulitis, or subcortical bone osteitis. Vaccine injected too low can cause nerve injuries. SIRVA lead to pain and reduced range of motion that typically develop within a few hours after vaccination, but can sometimes be delayed up to 4 days. It can be prevented by positioning the patient using the Cook injection technique, injecting in the middle of the deltoid, at a 90° angle, with an appropriate length needle[128-131] (Figure 2).

Inadvertent intravascular injection of vaccine can lead to Nicolau syndrome, which presents as thrombosis and vessel wall inflammation.[132] This was the rationale for the previous practice of performing aspiration before injection. However, this is no longer recommended as there are no large vessels in vaccination sites and aspiration can be painful.[133] The risk of intravascular injection is extremely low with the proper vaccination technique.

Immunization stress–related responses

Immunization stress–related responses (ISRR) describe a variety of symptoms that are triggered by the process of immunization and not a reaction to the vaccine product. Symptoms range from those of an acute stress response with stimulation of the sympathetic nervous system (palor, sweating, tachycardia, palpitations, shortness of breath, etc) and an overcompensation of parasympathetic stimulation that can result in a vasovagal reaction.[134,135] Vasovagal reaction is a frequent nonimmune reaction, which can occur after vaccination but also with other potential stimuli such as venipuncture or at the sight of blood. Some characteristics of the vasovagal reaction that help to distinguish it from the anaphylactic reaction are the presence of bradycardia, normal respiration, pale, sweaty, cold, clammy skin, and self-limited loss of consciousness with a good response to prone positioning.[16] To prevent potential injury from vasovagal reaction, it is recommended to administer the vaccines while the patients are in a seated or lying position and to keep them under surveillance for 15 minutes. Delayed ISRR may manifest as dissociative neurological symptom reactions (conversion reactions) that may include pseudoseizures. Such events may occur in clusters as part of a mass psychogenic illness that often disrupt immunization programs and lead to challenges in restoring public confidence in the safety of immunizations.[136,137]

CONCLUSION

Although vaccine efficacy and effectiveness is of concern to public health authorities because this determines disease control, community and health care provider perceptions of vaccine safety is a major determinant of vaccine acceptability. This is most apparent for novel vaccines but can affect vaccines that have been used for decades and have an established safety record. Vaccine safety is defined by the absence of vaccine or immunization reactions, and at the time of licensure of a novel vaccine safety data are incomplete. Postlicensure health care provider reporting of AEFI is critical to vaccine pharmacovigilance, and allergists are expected to be involved in the evaluation of patients with suspected reactions to vaccines. Health care and vaccine providers should be familiar with common vaccine side effects as well as rare adverse reactions. Fortunately, severe adverse vaccine reactions are rare, but if they do occur, then appropriate investigation and management is required so that patients can be counseled on revaccination or if this is contraindicated on alternate methods of postexposure prophylaxis, if appropriate.

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