Journal of the Egyptian Society of Parasitology, Vol. 53, No.2, August 2023
J. Egypt. Soc. Parasitol. (JESP), 53(2), 2023: 233 – 246
Online: 2090-2549

AN OVERVIEW ON ALLERGIC REACTIONS TO PATHOGENIC VACCINES

By
SARYA MOHAMED HAWAM[1], AMR IBRAHIM ABOU-ELMAGD[2], MOHAMED H. M. ELSHISHTAWY[3] and TOSSON A. MORSY[4]
[1]Department of Microbiology, Military Medical Academy, Cairo, 11291, [2]Department of Gastroenterology, The Armed Forces College of Medicine, Cairo 11711, [3]Specialist of Public Health and [4]Faculty of Medicine, Ain Shams University, Cairo 11566, Egypt (Correspondence:[1]saryahawam@yahoo.co.uk; [2]Amrgit@yahoo.com https://orcid.orh/ 0000.0001=94-6-7889; [3]mshisht94@gmail.com and [4]tossonmorsy @med.asu.edu.eg; morsyegypt2014@gmail.com; Orcid.org/0000-0003-2799-2049)

Abstract

A pathogen is a bacterium, virus, parasite or fungus that inhabits virtually every environment on the planet and can cause diseases to man, animals and plants. Vaccines contain weakened or inactive parts of a particular organism (antigen) that triggers an immune response within the body. Newer vaccines contain the blueprint for producing antigens rather than the antigen itself. Regardless of whether the vaccine is made up of the antigen itself or the blueprint so that the body will produce the antigen, which will not cause the disease in the person receiving the vaccine, but it will prompt the immune system to respond much as it would have on its first reaction to the actual pathogen. They help to create protective antibodies-proteins help in fighting off infections. But, vaccine refusal may result in vaccine-preventable disease in individual and/or outbreaks of vaccine-preventable disease in unvaccinated and vaccinated individuals

However, severe allergic reactions to vaccines are rare but do occur. Local reactions involved redness, swelling or irritation at the injection site. These common reactions typically begin within a few hours of the injection and clear up soon after. Systemic ones, which are less common, but potentially more serious develop sneezing, nasal congestion or hives or even throat swelling, wheezing or chest tightness. Anaphylaxis is a rare life-threatening reaction to allergy shots as low blood pressure and trouble breathing begins within 30 minutes of the injection, or even starts later than that.

The vast majority of microbes are harmless, and many play essential roles in plant, animal and human health. This overview focuses on immediate-type allergic reactions to human vaccines; and delayed reactions are also briefly discussed overview discussed. The overview on allergic reactions to the new developed parasitic vaccines will be given in due time elsewhere.

Key words: Vaccines, Effectiveness, Allergic reactions rarity, Hesitancy, Controlling

Introduction

Severe allergic reactions to vaccines are rare and difficult to predict. An allergic reaction defined as an idiosyncratic reaction caused by an immunologic mechanism. The World Allergy Organization recommended categorizing immunologic reactions to drugs (including vaccines) based upon symptoms appearance times (Johansson *et al,* 2004). Although vaccination programs have as their main goal the protection of the person vaccinated, in some cases the protective effect extends to non-vaccinated persons, producing herd immunity (Lefebvre *et al,* 2015).

This system included two main reaction types: immediate and delayed. This was intended to distinguish IgE-mediated (type I immunologic reactions) accounted for many immediate reactions, from others, due to the life-threatening anaphylaxis risk if the patient was re-exposed (Sampson *et al,* 2006): 1- Immediate reactions begin within an hour of administration or may begin within few minutes, IgE-mediated reactions are likely to present within this time, and 2- Delayed reactions appear many hours to days post administeration. These reactions may be caused by several mechanisms, but rarely the IgE-mediated ones.

Review and Discussion

Clinical manifestations (table): Immediate, IgE-mediated allergic reactions may involve various combinations of up to 40 potential symptoms and signs. The commonest symp-

toms and signs are 1- Cutaneous symptoms, including flushing, itching, urticaria, and angioedema, 2- Respiratory symptoms, such as nasal discharge, nasal congestion, voice change, sensation of throat closure or choking, stridor, cough, wheeze, and dyspnea, & 3- Cardiovascular symptoms, such as faintness, syncope, altered mental status, palpitations, and hypotension

Definition of anaphylaxis: The most severe form of an IgE-mediated allergic reaction is anaphylaxis, defined as a systemic allergic reaction that is rapid in onset and may cause death, but rare, with rates from active surveillance studies ranged from 0.65 to 1.31/million vaccine doses (Bohlke *et al,* 2003).

Diagnostic criteria (table) for anaphylaxis were proposed by National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium (McNeil *et al,* 2016). Anaphylaxis treatment must be based on general life-support principles: Call for help early, use airway, breathing, circulation and disability, exposure (ABCDE) approach to recognize and treat problems. Treat the greatest threat to life first. Give IM adrenaline to treat airway/breathing/circulation problems (Soar *et al,* 2008).

Timing: When anaphylaxis occurs after given a vaccine, patients generally develop symptoms within 30 minutes however the onset may occasionally be delayed up to several hours (Patja *et al,* 2001). Later onset reactions tend to be less severe. Reactions occur hours to days after vaccination could be due to delayed absorption of the allergenic component. Some of the late reactions may not be related to vaccination, but due to exposure to another allergen after vaccination (Cheng *et al,* 2015).

Delayed vaccine reactions: Several types of delayed reactions to vaccines were noted, including common reactions like fever or local swelling, & various rare reactions. These immunologic or non-immunologic may be nature, such as 1- Fever and irritability are common after vaccination and must not preclude additional doses of the same vaccine in future (NCIR, 2011), & 2- Local reactions to vaccination, such as swelling and redness at injection site, are common and self-limited. This must not be considered reasons to avoid given further vaccination. Local reactions can be treated with cool compresses for the first hours after the symptoms appear or with acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs) if pain or swelling is troublesome. But, antipyretics should not be given empirically or prophylactically, as a few studies reported that these medications may reduce vaccination immune response (Broder *et al,* 2006).

General, routine immunization schedules differ from one country to another (El-Bahnasawy and Morsy, 2015). In the United States, universally recommended vaccines for children and adolescents include hepatitis B; rotavirus; diphtheria, tetanus, pertussis; *Haemophilus influenzae* type b; pneumococcal conjugate; inactivated polio; seasonal influenza; measles, mumps, rubella; varicella-zoster virus; hepatitis A; meningococcus; and human papillomavirus (WHO, 2016). The shorter intervals between vaccine doses were associated with increased rates of local reactions, although studies have now shown that this is not the case. The recommended interval between doses of tetanus-containing vaccines had been ten years. New vaccines were recommended in 2006 to provide not only booster doses for tetanus & diphtheria (Td), but also to pertussis; Tdap (CDC, 2006). Two subsequent studies reported rates of local reactions in patients given the new vaccine. In one, the rates of injection site reactions to Tdap were no different among subjects who had received Td within the past two years, compared with those vaccinated with Td more than two years before (Beytout *et al,* 2009). But, no higher rates of injection site reactions whether a Tdap-containing vaccine was given one month after a Td-containing vaccine or after placebo, and recommended that Tdap must be given to all adolescents and adults regardless the interval since last Td (Talbot *et al,* 2010)

Serum sickness & sickness-like reactions: Serum sickness is a self-limited disease generally alleviated by the discontinuation of the offending agent. But, differential diagnosis of serum sickness includes risky life-threatening disease entities that must be excluded (Rixe and Tavarez**,** 2022). Delayed immunologic reactions as rare cases of persistent itchy injection site nodules to aluminum -containing vaccines related to delayed-type hypersensitivity to aluminum (CDC, 2011a). Encephalopathy/encephalitis following immunization was a rare, but serious adverse event (Tam *et al,* 2020). Also, vaccine administration may elicit vasovagal reactions (fainting), particularly in patients prone to response, vasovagal reactions characterized by hypotension, pallor, diaphoresis, weakness, nausea, vomiting, bradycardia, and if severe, consciousness loss (Kang *et al,* 2008). Vasovagal reactions can mimic anaphylaxis, as both may involve hypotension and collapse, but cutaneous signs and symptoms are usually quite different. Fainting was usually preceded by pallor, whereas anaphylaxis often began with flushing and also included itching, urticaria, and angioedema. In anaphylaxis, tachycardia was commonest than bradycardia. In patient with past fainting in response to vaccinations, it was prudent to administer future vaccines while he was lying supine (Kelso and Greenhawt, 2014).

Sources of information: A list of potential allergens contained in vaccines is maintained by the Institute for Vaccine Safety available on internet, and the US provided tables of excipients contained in vaccines, categorized by vaccine (CDC, 2022)

Gelatin (table) which is added to many vaccines as a stabilizer, causes many anaphylactic reactions to measles, mumps, and rubella (MMR), varicella, and Japanese encephalitis vaccines; the new encephalitis vaccine without gelatin (Sakaguchi *et al,* 1996). Anaphylaxis from gelatin in influenza and zoster vaccines were reported (Sakaguchi *et al,* 2001). Reactions to zoster vaccine were reported in patients sensitized to alpha-gal, a carbohydrate allergen that also causes allergy to mammalian meats (Lasley, 2007).

Allergic reactions to beef and/or pork (i.e. mammalian) meat were considered rarely reported in young atopic children, but now clear that red meat allergy was common in some parts of the world in other ages (Wilson and Platts-Mills, 2019). But, a negative history of an allergic reaction to ingestion of gelatin didn't exclude gelatin as responsible for an allergic reaction when injected with the vaccine, and patients who have experienced a reaction to a vaccine may require testing for gelatin allergy (Stone *et al,* 2017).

Persons who react to gelatin on ingestion must be evaluated by an allergist before vacc ination. If history is consistent with an immediate-type allergic reaction to gelatin with proved by skin tests or serum-specific IgE antibody tests to gelatin, it is prudent to skin test such patients with gelatin-containing vaccines prior to administration (WHO, 2019). If the vaccine skin tests are negative, vaccine can be given as usual, but patient must be observed for at least 30 minutes. If vaccine skin tests are positive, vaccine can be given in graded doses. Gelatin-free brands of some vaccines, such as MMR and varicella, are available in some countries, although not in the United States (Kumagai *et al*, 2001)

The incidence of allergic reactions to gelatin in vaccines was particularly high in Japan, a phenomenon that was subsequently attributed, in part, to the population genetic characteristics (Sakaguchi *et al,* 2002) Japanese manufacturers removed the gelatin from some vaccines and switched to a more thoroughly hydrolyzed gelatin in others, with a dramatic reduction in the rate of reactions, which were variably adopted in other countries and reactions to gelatin in vaccines still occur (Kuno-Sakai and Kimura, 2003).

Egg protein is present in yellow fever, MMR, and some influenza and rabies vaccines. But, potentially of clinical significance amount was only in yellow fever vaccine (O'Brien *et al,* 1971). It is the second most common food allergy in infants and young

children (milk is the most common), responses to proteins in foods and include IgE antibody-mediated allergy and other allergic syndromes, such as atopic dermatitis and eosinophilic esophagitis (Spergel *et al,* 2009).

Yellow fever vaccine is prepared in egg embryos with reported allergic reactions but, this vaccination is a must for travelers entering several countries in endemic areas and a reduced intradermal dose of the yellow fever vaccine induced protective antibody responses in egg-allergic individuals (Roukens *et al,* 2009). Allergy after the ingestion of egg, raw or cooked, must be sought prior to administration, and persons with positive histories must be evaluated by an allergist (Kelso, 2000). Such patients should be skin tested with yellow fever vaccine prior to administration. If the vaccine skin tests are negative, the vaccine can be given in the normal way, but the patient observed for at least 30 minutes afterward. If vaccine skin tests are positive, vaccine can be administered in graded doses.

Casein, an allergenic protein contained in cow's milk is preliminarily implicated in causing anaphylaxis to diphtheria, tetanus, and pertussis vaccines (DTaP or Tdap) in a small number of severely milk-allergic children (Kattan *et al,* 2011). Vaccines are prepared in a medium derived from cow's milk protein, and Nano-gram quantities of residual casein were demonstrated in these preparations. But, the vast majority of even severely milk-allergic patients have no allergic reactions to these vaccines (Franceschini *et al,* 2015). In this cohort, anaphylaxis to red meat was the main cause of food induced anaphylaxis; beef specific IgE and cow's milk was a predisposing factor for vaccine induced anaphylaxis (de Silva *et al*, 2018)

Thimerosal, aluminum, or phenoxyethanol were added to some vaccines as preservatives, but the thimerosal use (contained mercury) in vaccines has decreased dramatically due to theoretical concerned about cumulateve mercury exposure in children (Grabenstein, 1997).

These preservatives were not documented to cause immediate-type allergic reactions to vaccines and immediate-type skin testing was not generally indicated. However, they may cause delayed-type hypersensitivity reactions and contact dermatitis when applied topically to skin (Heidary and Cohen, 2005): 1- Contact sensitivity to them was not a contra-indication to receive these vaccines (Patrizi *et al,* 1999). An adult developed a generalized maculopapular rash to a thimerosal-containing influenza vaccine was thought to be a T cell-mediated allergic response to thimerosal due to a positive patch test to substance (Lee-Wong *et al,* 2005). This was a rare and unpredictable complication, if indeed there is actually a causal relationship. 2- Ability of such agents to cause delayed local reactions after vaccination showed limited evidence exists. Of 125 patients with patch test-positive contact sensitivity to the thimerosal or its derivatives, who were challenged with intramuscular injections of thimerosal, only 4% (five) developed mild local reactions to injection, indicated that these local reactions were uncommon even in contact-sensitized patients (Audicana *et al,* 2002). 3- Rare, aluminum-containing vaccines cause persistent nodules at injection site, possibly by delayed hypersensitivity or other immune responses to aluminum. So, patch testing or any specific testing for suspected sensitivity to the preservatives to assess the patient's ability to tolerate a vaccine containing it is not necessary. Patch testing can be performed to diagnose allergic contact dermatitis, but this was not helpful in relation to vaccination. If a patient with documented contact dermatitis to one of the additives was concerned about receiving a vaccine contained the same agent, then it was prudent to administer a formulation that didn't contain it, if available. Also, if a patient with known contact sensitivity has had a bothersome local reaction to a vaccine contained the preservative in the past and needs another; it would be prudent to give a product free of this preservative, if available. But, if a non-preservative vaccine

is not available, the risk of any local reaction was minimal and should not preclude vaccination (CDC, 2020).

Antimicrobials: Many antimicrobials may be added in trace amounts to vaccines, mainly neomycin, polymyxin B and streptomycin (Chung, 2014). For many years, antibiotics (in particular BLs) were considered the most frequent culprit for DIA (Renaudin *et al,* 2013). But, studies have questioned this view. In a nationwide study carried out by allergists in Portugal during a 4-year period, NSAIDs were shown to be the leading cause, followed by antibiotics. Mean age when the reaction occurred from 2 to 89 years, averaged 17.4, indicating that DIA may appear at any age (Faria *et al,* 2014). Persons who experienced encephalopathy within a week after administration of a previous dose of pertussis-containing vaccine not attributable to another identifiable cause must not receive more dose of a vaccine with pertussis (Kroger *et al,* 2013). Severe combined immunodeficiency (SCID) disease and a history of intussusception are contraindications to receive rotavirus vaccines (CDC, 2011b).

Latex: Rubber in vaccine vial stoppers or syringe plungers may be either dry natural rubber latex or synthetic rubber. Those made with latex pose a theoretical risk to latex-allergic patients, either as a result of liquid vaccine solution extracting latex allergens from the stopper by physical contact or by passing the needle via the stopper and retaining latex allergen in or on needle. One anaphylactic reaction after hepatitis B vaccine administered to a latex-allergic patient was due to rubber in stopper (Lear *et al,* 1995). Anaphylaxis patients to latex can safely receive vaccines from vials with non-DNR stoppers. If the only available has latex stopper, it must be removed and vaccine drawn up directly from the vial without passing needle via stopper (Hamilton *et al,* 2005). If the only available vaccine contains latex in the packaging that cannot be avoided, such as in a prefilled syringe, vaccine can still be administered, but patient must be observed for at least 30 minutes afterward. Russell *et al.* (2004) in USA reported database with >160,000 vaccine adverse event data, showed 28 cases of immediate-type hypersensitivity reactions in vaccine recipients with allergy to latex history.

Yeast: Some vaccines contain yeast protein, including Hepatitis B vaccines (up to 25 mg/dose) and 4- & 9-valent human papillomavirus vaccines (<7mcg/dose), but adverse reactions to these, if any, was rare (DiMiceli *et al,* 2006). Nittner-Marszalska *et al.* (2001) in Poland reported that saccharomyces cerevisiae enolase, the major allergen of the baker's yeast, induces allergic immediate response in patients with inhalant allergy sensitized to *Candida albicans* extract. If the vaccine skin tests are negative, vaccine can be given as usual, but patient observed for at least 30 minutes afterward. If skin tests are positive, vaccine can be given in graded doses.

Dextran: Dextran implicated in allergic reactions to a particular brand of MMR vaccine previously used in Italy and Brazil, related to IgG antibodies to dextran and hypothesized to be complement activation and anaphylatoxin release. This vaccine was withdrawn from the market, although dextran was sporadically found in other vaccines (Zanoni *et al,* 2008). The IgE-mediated react to specific vaccines rarely involved anaphylactic reactions to vaccine microbial components.

Diphtheria: There was a report of anaphylaxis after a diphtheria (DT) booster with skin tests and radioallergosorbent tests (RAST) positive to both DT and tetanus toxoids (Martín-Muñoz *et al,* 2002). Generalized hives attributed to IgE directed against the DT component of Di-Te-Pol (diphtheria-tetanus-polio) vaccine occurred (Skov *et al,* 1997). Children with DT reactions to vaccines may lose hypersensitivity by time, and reaction to this vaccine didn't necessarily preclude its future use (Bégin *et al,* 2001).

Hepatitis B vaccine: There were a few reports consistent with anaphylaxis to hepatitis B vaccine, but none confirmed with skin tests or measurement of allergen-specific IgE in serum, literature reviews on adverse reac-

tions to hepatitis B vaccination suggest that the rate of anaphylaxis was < 1 in 100,000 vaccinations (DeStefano *et al,* 2002).

Haemophilus influenza type b (Hib): There were a few reports consistent with anaphylaxis to this vaccine without being confirmed by skin tests or allergen-specific IgE in sera (Demicheli *et al,* 2003). A case of anaphylaxis after Hib-conjugate vaccine was due to DT-conjugating protein that showed the importance of determining specific culprit allergen as other vaccines contained the same conjugating protein (Nelson *et al,* 2000).

Human papillomavirus vaccine: Anaphylaxis aqfter administration of human papillomavirus vaccine was reported (Brotherton *et al,* 2008). It occurred after the initial dose of this vaccine, but few patients developed symptoms after the second dose. Gardasil contains trace yeast proteins and the stabilizer polysorbate 80. But, four patients who had apparent anaphylactic reactions to it were negative skin test to vaccine, baker's yeast, and polysorbate 80. Vaccination in adolescents was associated with a high rate of syncope that accounted for some events diagnosed as anaphylaxis (Brotherton, 2019)

Influenza: Some vaccines contain egg protein, but allergic reactions were due to some other components as well. In Japan in 2011 & 2012, there was a three- to fivefold increase in influenza vaccine-associated anaphylaxis reported in 36 children without egg allergy, of whom 19 were subsequently investigated (Nagao *et al,* 2016). These 19 had abnormally high levels of IgE directed against whole vaccine and against several hemagglutinin proteins, but without egg-specific IgE or IgE directed against various excipients in the vaccines. Skin testing with full-strength vaccine was performed in just three patients, but was positive in all three and negative in 10 control patients, including some with egg allergy. The patients' basophils were activated when incubated with the vaccine. These findings suggest (but do not prove) that the allergen was some component (possibly hemagglutinin) of the vaccine. Interestingly, all reactions were caused by a vaccine from one specific manufacturer, and this preparation was unique in containing the preservative 2-phenoxyethanol (2-PE). IgE to 2-PE was not detected in patients' sera, but they hypothesized that 2-PE may interact with the vaccine components to enhance allergenicity in some way. The manufacturer replaced the 2-PE with thimerosal and reaction rates returned to baseline.

Japanese encephalitis (JE): Some immediate-type anaphylactic reactions were reported with the JE vaccine, including some reactions in which patients had IgE antibodies to gelatin (Elnakib *et al,* 2018). With this vaccine in particular, there were many data of late-onset anaphylaxis hours to 2 weeks after vaccination (Takahashi *et al,* 2000). A new JE vaccine without gelatin, whether or not with a lower rate of adverse reactions must be determined.

Measles, mumps, and rubella: Most anaphylactic reactions to measles, mumps, and rubella (MMR) caused by gelatin allergy (Kelso *et al,* 1993), without relation to egg allergy as vaccine contains no, or a minuscule amount of, egg protein. Safety MMR vaccine given to people with egg allergy was detected in 54 children who had never been vaccinated, but with egg allergy (James *et al,* 1995). Skin testing was performed with the vaccine in 17 children, and 3 were positive. All children were given the MMR vaccine as a single full dose and none had immediate or delayed adverse reactions. Measles, mumps, rubella, and varicella (chickenpox) are serious diseases that can lead to serious complications, disability, and death. However, public debate over the safety of trivalent MMR vaccine and the resultant drop in vaccination coverage in several countries persisted, despite its almost universal use and accepted effectiveness (Di Pietrantonj *et al,* 2020).

Meningococcus: Anaphylactic reactions to meningococcal polysaccharide or polysaccharide-protein conjugate vaccines were very rare; one per million doses (Ball *et al,* 2001).

Pneumococcus: There are two anaphylaxis

reports in children who received 23-valent pneumococcal vaccine (Ponvert *et al,* 2010). IgE antibody to vaccine was detected by skin tests or allergen-specific IgE in serum.

Rabies: There were a few anaphylaxis reports, but none confirmed with skin tests or allergen-specific IgE in serum (CDC, 1987). Some late-onset (several days after vaccination) serum sickness-like reactions and urticaria associated with IgE antibodies to beta-propiolactone-altered human serum albumin in the vaccine have also been reported (Swanson *et al,* 1987).

Tetanus: There are a few reports consistent with anaphylaxis (including fatalities) to tetanus vaccines, some of which were supported by positive skin tests and elevated levels of allergen-specific IgE directed against the tetanus and diphtheria (Td) toxoids (Carey *et al,* 1992). However, children with reactions to DT vaccines sometimes lose the hypersensitivity with time, so a childhood reaction to this vaccine does not necessarily preclude its future use (Mayorga *et al,* 2003).

Diphtheria, tetanus, and pertussis vaccines (DTaP or Tdap) may also contain trace (nanogram) quantities of residual casein (an allergenic milk protein) from milk-based medium in which they were produced. The possibility that this residual casein could be responsible for some anaphylactic reactions to vaccines was raised by a case series of eight children who developed anaphylaxis within an hour (six within 20 minutes) of receiving DTaP or Tdap (Ponvert *et al,* 2001). However, the results of this report require more confirmation. Most patients, even those with severe cow's milk allergy, tolerate the vaccines as evidenced by the observations that milk allergy is common in infants and anaphylaxis to these vaccines is rare (Slater *et al,* 2011). Until more information is available, infants with severe milk allergy must be observed for at least 30 minutes after vaccination.

Typhoid: Rare anaphylactic reactions were reported to both the injected VI polysaccharide vaccine and oral live-attenuated Ty21a vaccine (Begier *et al,* 2004). Some of these reports involve the typhoid vaccines administered alone and others when vaccines were co-administered with vaccines as in yellow fever. Two licensed vaccines against typhoid fever (parenteral Vi polysaccharide and oral attenuated S. *typhi* strain Ty21a) are available. The Vi polysaccharide vaccine induced serum anti-Vi-antibodies (Klugman *et al,* 1996). There were several reports of severe reactions to typhoid vaccine within an hour of vaccination not consistent with anaphylaxis, but involved high fever, vomiting, and headache (Hoyt and Herip, 1996). Wahid *et al.* (2014) in USA reported that functional antibodies measurement might be important in assessing immunogenicity of a new generation of typhoid and paratyphoid A vaccines.

Varicella: Anaphylaxis rate was reported as three reactions per million doses. Most anaphylactic reactions to varicella vaccine are due to gelatin allergy (Wise *et al,* 2000).

Yellow fever: Many reports were consistent with anaphylaxis to yellow fever vaccine (Kelso *et al,* 1999). The constituent responsible for these apparently IgE-mediated reactions has not been investigated, but the vaccine contains gelatin as well as egg proteins (El Bahnasawy *et al,* 2015).

Zoster: Zoster vaccine is well-tolerated, but rare anaphylactic events were reported in patients who reacted to gelatin in the vaccine (Tseng *et al,* 2012).

Why parents refuse vaccination? Childhood vaccination is one of the most effective ways to prevent serious illnesses and deaths in children. But, worldwide, many children don't receive all recommended vaccinations (WHO, 2019). Many parents don't see the preventable diseases as serious or life-threatening and would prefer to not put more chemicals into the children's bodies (Fredrickson *et al,* 2004). Others think if the children have healthy diets and lifestyles they would be at a less risk of contracting the preventable childhood diseases (Dubé *et al,* 2014). But, parents' refusals of vaccination were in-

creasing (Harmsen *et al,* 2013). Consequently, as to parents' education, all the healthcare workers by all means must make an effort to be to date up on the recommended vaccines and to understand why those immunizations are indicated (McKee and Bohannon, 2016).

Covid-19 vaccines anaphylaxis: Many adverse reactions were reported for COVID-19 vaccines, classified into very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000), and not known (cannot be estimated from the available data). Currently, due to lack of sufficient confirmed data, following the COVID-19 vaccine BNT162b2 approval, several severe anaphylaxis cases occurred within the first few days after public vaccination (Banerji *et al,* 2021). The European Anaphylaxis Registry includes data from 1,123 patients >65 years old with anaphylactic reactions given by tertiary referral centers specialized in allergology and/or dermatology in Austria, Bulgaria, France, Germany, Italy, Poland, Spain, and Switzerland (Aurich *et al,* 2019). Since anaphylaxis requires immediate treatment, diagnosis is primarily made based on recognition of clinical signs and symptoms. Signs & symptoms in adults and children include respiratory, gastrointestinal, cardiovascular, skin/mucosal, neurologic, sudden secretions increase from eyes, nose, or mouth; urinary incontinence (CDC, 2022). However, patients with a history of allergic diseases must not be excluded from vaccines as their exclusion from vaccination may have a significant impact to reach the goal of herd immunity (Bousquet *et al,* 2021).

Conclusion

Anaphylactic reactions to vaccines are rare, but potentially life-threatening. IgE-mediated reactions are most often due to vaccine constituents rather than microbial products.

Anaphylactic reactions symptoms to vaccines are similar to those of anaphylaxis due to other etiologies. Usually appear within 30 minutes but may rarely up to several hours.

There were rare reports of systemic allergic reactions to nearly every vaccine, although some were more commonly implicated, such as the vaccines for yellow fever, measles, mumps, and rubella (MMR), and tetanus.

Evaluation of a possible vaccine allergy begins with determining if symptoms and timing are consistent with an anaphylactic reaction. Then it discerned if the patient had previous exposure to vaccine or needs more doses of vaccine in question, or the vaccines with common constituents, in the future.

Skin testing to vaccines must be done and interpreted by an allergy specialist. Skin prick test may be done with an undiluted the vaccine solution in question, or with a diluted solution in patients whose reactions were truly life-threatening. If negative, this is followed by intradermal testing with a 1:100 dilution of the vaccine.

If the suspect vaccine contains egg (yellow fever & some influenza), gelatin, latex, or *Saccharomyces cerevisiae* yeast (hepatitis B and 4- & 9-valent human papillomavirus), skin testing to these constituents must also be performed. But, if skin testing with the vaccine is negative; the patient must receive the vaccine in the usual manner. For safety, such patients are usually given the vaccination supervised by the allergy specialist.

If skin testing to a constituent (gelatin, egg. ..etc.), or the vaccine is positive, it may still be possible for the patient to receive vaccine in a graded manner (Fig. 1). But, this must only done after a good assessment of relative risks and benefits of vaccination.

Authors' declarations: They declared that they neither have any conflict of interest nor received any funds.

References

Aalberse, RC, van Ree, R, Danneman, A, Wahn, U, 1995: IgE antibodies to tetanus toxoid in relation to atopy. Int. Arch. Allergy Immunol. 107:169-72.

Aurich, S, Dolle-Bierke, S, Francuzik W, *et al,* 2019: Anaphylaxis in elderly patients-data from the European anaphylaxis registry. Front Immunol. 10:750-9.

Audicana, MT, Muñoz, D, del Pozo, MD, *et al,* 2002: Allergic contact dermatitis from mercury antiseptics and derivatives: Study protocol of tolerance to intramuscular injections of thimerosal. Am. J. Contact Dermat. 13:3-12.

Ball, R, Braun, MM, Mootrey, GT, 2001: Vaccine Adverse Event Reporting System Working Group: Safety data on meningococcal polysaccharide vaccine from the vaccine adverse event reporting system. Clin. Infect. Dis. 32:1273-8.

Banerji, A, Wickner, PG, Saff, R, *et al,* 2021: mRNA vaccines to prevent COVID-19 disease and reported allergic reactions: Current evidence and approach. J. Allergy Clin. Immunol. Pract. 9, 4:1423-37.

Begier, EM, Burwen, DR, Haber, P, *et al,* 2004: Postmarketing safety surveillance for typhoid fever vaccines from the Vaccine Adverse Event Reporting System, July 1990 through June 2002. Clin Infect Dis 2004; 38:771.

Bégin, P, Vu, MQ, Picard, M, *et al,* 2001: Spontaneous resolution of diphtheria-tetanus vaccine hypersensitivity in a pediatric population. Allergy 66:1508-12.

Bergfors, E, Trollfors, B, 2013: Sixty-four children with persistent itching nodules and contact allergy to aluminium after vaccination with aluminium-adsorbed vaccines-prognosis and outcome after booster vaccination. Eur. J. Pediatr. 172:171-6.

Beytout, J, Launay, O, Guiso, N, *et al,* 2009: Safety of Tdap-IPV given one month after Td-IPV booster in healthy young adults: a placebo-controlled trial. Hum. Vaccine 5:315-9.

Bierman, CW, Shapiro, GG, Pierson, WE, *et al,* 1977: Safety of influenza vaccination in alle-

Bohlke, K, Davis, RL, Marcy, SM, *et al,* 2003: Risk of anaphylaxis after vaccination of children and adolescents. Pediatrics 112:815-22.

Bousquet, J, Agache, I, Blain, H, Jutel, M, Ventura, M, *et al,* 2021: Management of anaphylaxis due to COVID-19 vaccines in the elderly. Euro J. Allergy Clin. Immunol. First published: 02 April 2021https://doi.org/10.1111/all.14 838

Broder, KR, Cortese, MM, Iskander, JK, *et al,* 2006: Preventing tetanus, diphtheria, and pertussis among adolescents: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines recommendations of the advisory committee on immunization practices (ACIP). MMWR Recomm. Rep. 55:1-10.

Brotherton, JML, 2019: The remarkable impact of bivalent HPV vaccine in Scotland. BMJ. 2019 Apr 3;365:l1375. doi: 10.1136/bmj.l1375.

rgic children. J. Infect. Dis. 136:S652-8.

Brotherton, JM, Gold, MS, Kemp, AS, *et al,* 2008: Anaphylaxis following quadrivalent human papillomavirus vaccination. CMAJ 179:525-9.

Carey, AB, Meltzer, EO, 1992: Diagnosis and "desensitization" in tetanus vaccine hypersensitivity. Ann. Allergy 69:336-42.

CDC, 1984: Systemic allergic reactions following immunization with human diploid cell rabies vaccine. MMWR Morb. Mortal. Wkly. Rep. 33: 185-94.

CDC, 2006: Preventing tetanus, diphtheria, and pertussis among adults: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine recommendations of the Advisory Committee on Immunization Practices (ACIP) and recommendation of ACIP, supported by the Healthcare Infection Control Practices Advisory Committee (HICPAC), for use of Tdap among health-care personnel. MMWR. Recomm. Rep. 55:1-10.

CDC, 2008: Syncope after vaccination--United States, January 2005-July 2007. MMWR Morb Mortal Wkly Rep. 57:457.

CDC, 2011: Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine from Advisory Committee on Immunization Practices 2010: MMWR Morb. Mortal. Wkly. Rep. 60:13-8.

CDC, 2011b: Addition of history of intussusception as a contraindication for rotavirus vaccination. MMWR Morb. Mortal. Wkly. Rep. 60, 41:1427.

CDC, 2015: Vaccine excipient and media summary excipients included in U. S vaccines, by vaccine. http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/latex-table.pdf

CDC, 2020: Thimerosal and Vaccines https://www.cdc.gov/vaccinesafety/index.html

CDC, 2022: Vaccines and Immunizations https://www.cdc.gov/vaccines/vac-gen/additives.htm

Cheng, DR, Perrett, KP, Choo, S, *et al,* 2015: Pediatric anaphylactic adverse events following immunization in Victoria, Australia from 2007 to 2013. Vaccine 33:1602-8.

Chung, EH, 2014: Vaccine allergies. Clin. Exp. Vaccine Res. 3, 1:50-7.

Demicheli, V, Rivetti, A, Di Pietrantonj, C, Clements, CJ, Jefferson, T.J, 2003: Hepatitis B vaccination and multiple sclerosis: Evidence from a systematic review. Viral Hepat. 10, 5:343

-4.
de Silva, NR, Dasanayake, WMDK, Karunatilake, C, Wickramasingha, GD, De Silva, BD, *et al,* 2018: Etiology of anaphylaxis in patients referred to an immunology clinic in Colombo, Sri Lanka. Allergy Asthma Clin. Immunol. Nov. 8;14:81. doi:10.1186/s13223-018-0295-0
DeStefano, F, Verstraeten, T, Chen, RT, 2002: Hepatitis B vaccine and risk of multiple sclerosis. Expert. Rev. Vaccines 1, 4:461-6.
Di Pietrantonj, C, Rivetti, A, Marchione, P, Debalini, M, Demicheli, V, 2020: Vaccines for measles, mumps, rubella, and varicella in children. Cochrane Datab. Syst. Rev. 4, 4:CD004407.
DiMiceli, L, Pool, V, Kelso, J, *et al,* 2006: Vaccination of yeast sensitive individuals: Review of safety data in the US vaccine adverse event reporting system (VAERS). Vaccine 24:703-10.
Dreskin, SC, **Halsey, NA, Kelso, JM, Wood, R A, Hummell, DS, *et al,* 2016:** International Consensus (ICON): Allergic reactions to vaccines. World Allergy Organ. J. 9, 1:32. Doi: 10.1186/ s40413-016-0120-
Dubé, E, Gagnon, D, Nickels, E, *et al,* 2014: Mapping vaccine hesitancy: Country-specific characteristics of a global phenomenon. Vaccine 32, 49:6649-54.
El-Bahnasawy, MM, Morsy, TA, 2015: Beyond immunization: Travelers' infectious diseases. 1- Diarrhea. JESP 45, 1:29 -42
El-Bahnasawy, MM, Megahed, LA, Saleh, H AA, Morsy, TA, 2015: Training program for the nursing staff regarding the viral hemorrhagic fevers (VHFs) in a fever hospital. JESP 45 2: 249-72
Elnakib, MM, Abdel Fadil, EE, Morsy, TA, 2018: The arthropod-borne encephalitis viruses the neglected serious diseases. JESP 48, 3:13-28
Faria, E, Rodrigues, JC, Gaspar, E, *et al,* 2014: Drug-induced anaphylaxis survey in Portuguese Allergy Departments. J. Investig. Allergol. Clin. Immunol. 24:40-8.
Franceschini, F, Bottau, P, Caimmi, S, Crisafulli, G, Lucia, L, *et al,* 2015: Vaccination in children with allergy to non-active vaccine components**.** Clin. Transl. Med. 4:3. doi:10.1186/s40169-014-0043-0
Fredrickson, DD, Davis, TC, Arnould, CL, *et al,* 2004: Childhood immunization refusal: Provider and parent perceptions. Fam. Med. 36, 6: 431-9.
Grabenstein, JD, 1997: Clinical management of hypersensitivities to vaccine components. Ho-sp. Pharm. 32:77-82.
Hamilton, RG, Brown, RH, Veltri, MA, *et al,* 2005: Administering pharmaceuticals to latex-allergic patients from vials containing natural rubber latex closures. Am. J. Hlth. Syst. Pharm. 62:1822-8.
Harmsen, IA, Mollema, L, Ruiter, R, *et al,* 2013: Why parents refuse childhood vaccination: A qualitative study using online focus groups. BMC Publ. Hlth.13:1183-8.
Heidary, N, Cohen, DE, 2005: Hypersensitivity reactions to vaccine components. Dermatitis 16: 115-9.
Hoyt, RE, Herip, DS, 1996: Severe systemic reactions attributed to acetone-inactivated parenteral typhoid vaccine. Mil. Med. 161:339-44.
James, JM, Burks, AW, Roberson, PK, Sampson, HA, 1995: Safe administration of the measles vaccine to children allergic to eggs. N. Engl. J. Med. 332:1262-6.
Johansson, SG, Bieber, T, Dahl, R, *et al,* 2004: Revised nomenclature for allergy for global use: Report of the nomenclature review Committee of the World Allergy Organization, October 2003. J. Allergy Clin. Immunol. 113: 832-40.
Kang, LW, Crawford, N, Tang, ML, *et al,* 2008: Hypersensitivity reactions to human papillomavirus vaccine in Australian schoolgirls: Retrospective cohort study. BMJ 337:a2642-8.
Kattan, JD, Konstantinou, GN, Cox, AL, *et al,* 2011: Anaphylaxis to diphtheria, tetanus, and pertussis vaccines among children with cow's milk allergy. J. Allergy Clin. Immunol. 128:215-20.
Kelso, JM, 2000: Raw egg allergy-a potential issue in vaccine allergy. J. Allergy Clin. Immunol. 106:990-8.
Kelso, JM, Li, JT, 2009: Practice Parameters: Adverse reactions to vaccines. Ann. Allergy Asthma Immunol. 103, 2:S1-14.
Kelso, JM, Greenhawt, MJ, 2014: Adverse reactions to vaccines in infectious diseases. In: Middleton's allergy: Principles and practice, 8th ed, Adkinson NF, Bochner BS, Burks AW, *et al* (Eds.), Elsevier, Philadelphia.
Kelso, JM, **Jones, RT, Yunginger, JW, 1993:** Anaphylaxis to measles, mumps, and rubella vaccine mediated by IgE to gelatin. J. Allergy Clin. Immunol. 9, 4:867-72
Kelso, JM, Mootrey, GT, Tsai, TF, 1999a: Anaphylaxis from yellow fever vaccine. J. Allergy Clin. Immunol. 103:698-702.

Kelso, JM, Cockrell, GE, Helm, RM, Burks, AW, 1999b: Common allergens in avian meats. J. Allergy Clin. Immunol.104:202-9.

Kelso, JM, Greenhawt, MJ, Li, JT, *et al,* 2012: Adverse reactions to vaccines practice parameter 2012 update. J. Allergy Clin. Immunol. 130:25-30.

Klugman, KP, Koornhof, HJ, Robbins, JB, Le Cam, NN, 1996: Immunogenicity, efficacy and serological correlate of protection of *Salmol. typhi* Vi capsular polysaccharide vaccine three years after immunization. Vaccine 14:435-8.

Kroger, A, Atkinson, W, Pickering, L, 2013: General immunization practices. In: Plotkin, S, Orenstein, W, Offit, P, eds. Vaccines. 6th Ed. China: Elsevier Saunders

Kumagai, T, Yamanaka, T, Wataya, Y, *et al,* 2001: A strong association between HLA-DR9 and gelatin allergy in the Japanese population. Vaccine 19:3273-9.

Kuno-Sakai, H, Kimura, M, 2003: Removal of gelatin from live vaccines and DTaP-an ultimate solution for vaccine-related gelatin allergy. Biological 31:245-51.

Lasley, MV, 2007: Anaphylaxis after booster influenza vaccine due to gelatin allergy. Pediatr. Asthma Allergy Immunol. 20:201-8.

Lear, JT, English, JS, 1995: Anaphylaxis after hepatitis B vaccination. Lancet 345:1249-52.

Lee-Wong, M, Resnick, D, Chong, K, 2005: A generalized reaction to thimerosal from an influenza vaccine. Ann. Allergy Asthma Immunol. 94:90-6.

Lefebvre, CDS, Terlinden, A, Standaert, B, 2015: Dissecting the indirect effects caused by vaccines into the basic elements. Hum. Vaccines Immunother. 11:2142-57.

Mark, A, Björkstén, B, Granström, M, 1995: Immunoglobulin E responses to diphtheria and tetanus toxoids after booster with aluminium-adsorbed and fluid DT-vaccines. Vaccine 13:66-9.

Martín-Muñoz, MF, Pereira, MJ, Posadas, S, *et al,* 2002: Anaphylactic reaction to diphtheria-tetanus vaccine in a child: Specific IgE/IgG determinations and cross-reactivity studies. Vaccine 20:3409-14.

Mayorga, C, Torres, MJ, Corzo, J, *et al,* 2003: Immediate allergy to tetanus toxoid vaccine: Determination of immunoglobulin E & immunoglobulin G antibodies to allergenic proteins. Ann. Allergy Asthma Immunol. 90:238-42.

McKee, C, Bohannon, K, 2016: Exploring the reasons behind parental refusal of vaccines. J. Pediatr. Pharmacol. Ther. 21, 2:104-9.

McNeil, MM, Weintraub, ES, Duffy, J, *et al,* 2016: Risk of anaphylaxis after vaccination in children and adults. J. Allergy Clin. Immunol. 137:868-74.

Miller, JR, Orgel, HA, Meltzer, EO, 1983: The safety of egg-containing vaccines for egg-allergic patients. J. Allergy Clin. Immunol. 71:

Nagao, M, Fujisawa, T, Ihara, T, Kino, Y, 2016: Highly increased levels of IgE antibodies to vaccine components in children with influenza vaccine-associated anaphylaxis. J. Allergy Clin. Immunol. 137:861-6.

NCIR, 2011: National Center for Immunization and Respiratory Diseases: General recommendations on immunization recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm. Rep. 60:1-12.

Nelson, MR, Oaks, H, Smith, LJ, *et al,* 2000: Anaphylaxis complicating routine childhood immunization: Hemophilus Influenza b conjugated vaccine. Pediatr. Asthma Allergy Immunol. 14: 315-20.

Nittner-Marszalska, M, Wójcicka-Kustrzeba, I, Bogacka, E, Patkowski, J, Dobek, R, 2001: Skin prick test response to enzyme enolase of the baker's yeast (*Saccharomyces cerevisiae*) in diagnosis of respiratory allergy. Med. Sci. Monit. 7, 1:121-4.

O'Brien, TC, Maloney, CJ, Tauraso, NM, 1971: Quantitation of residual host protein in chicken embryo-derived vaccines by radial immunodiffusion. Appl. Microbiol. 21:780-6.

Patja, A, Mäkinen-Kiljunen, S, Davidkin I, *et al,* 2001: Allergic reactions to measles-mumps-rubella vaccination. Pediatrics 107:E27-32.

Patrizi, A, Rizzoli, L, Vincenzi, C, *et al,* 1999: Sensitization to thimerosal in atopic children. Contact Dermatitis 40:94-8.

Ponvert, C, Ardelean-Jaby, D, Colin-Gorski, AM, *et al,* 2001: Anaphylaxis to the 23-valent pneumococcal vaccine in child: A case-control study based on immediate responses in skin tests and specific IgE determination. Vaccine 19: 4588-94.

Ponvert, C, Scheinmann, P, de Blic, J, 2010: Anaphylaxis to the 23-valent pneumococcal vaccine: A second explored case by means of immediate-reading skin tests with pneumococcal vaccines. Vaccine 28:8256.

Rixe, N, Tavarez, MM, 2022: Serum Sickness StatPearls [Internet]. Last Update: August 29.

Renaudin, J, Beaudouin, E, Ponvert, C, *et al,*

2013: Severe drug-induced anaphylaxis: Analysis of 333 cases recorded by the allergy vigilance network from 2002 to 2010. Allergy 68:929-37

Roukens, AH, Vossen, AC, van Dissel, JT, Viser, LG, 2009: Reduced intradermal test dose of yellow fever vaccine induces protective immunity in individuals with egg allergy. Vaccine 27: 240-8.

Russell, M, Pool, V, Kelso, JM, Tomazic-Jezic, VJ, 2004: Vaccination of persons allergic to latex: A review of safety data in the Vaccine Adverse Event Reporting System (VAERS). Vaccine 23, 5:664-7.

Sakaguchi, M, Miyazawa, H, Inouye, S, 2001: Specific IgE and IgG to gelatin in children with systemic cutaneous reactions to Japanese encephalitis vaccines. Allergy 56:536-42.

Sakaguchi, M, Nakayama, T, Inouye, S, 1996: Food allergy to gelatin in children with systemic immediate-type reactions, including anaphylaxis to vaccines. J. Allergy Clin. Immunol. 98: 1058-64.

Sakaguchi, M, Nakayama, T, Kaku, H, *et al,* 2002: Analysis of HLA in children with gelatin allergy. Tissue Antigens 59:412-6.

Sampson, HA, Muñoz-Furlong, A, Campbell, RL, *et al,* 2006: Second symposium on the definition and management of anaphylaxis: Summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J. Allergy Clin. Immunol. 117:391-9.

Skov, PS, Pelck, I, Ebbesen, F, Poulsen, LK, 1997: Hypersensitivity to the diphtheria component in the Di-Te-Pol vaccine. A type I allergic reaction demonstrated by basophil histamine release. Pediatr. Allergy Immunol. 8:156-9.

Slater, JE, Rabin, RL, Martin, D, 2011: Comments on cow's milk allergy and diphtheria, tetanus, and pertussis vaccines. J. Allergy Clin. Immunol. 28:434-9.

Soar, J, Pumphrey, R, Cant, A, Clarke, S, Corbett, A, *et al,* 2008: Emergency treatment of anaphylactic reactions--guidelines for healthcare providers. UK Resuscitation 77, 2:157-69.

Spergel, JM, Brown-Whitehorn, TF, Beausoleil, JL, *et al,* 2009: 14 years of eosinophilic esophagitis: Clinical features and prognosis. J. Pediatr. Gastroenterol. Nutr. 48:30-8.

Stone, CA Jr, Hemler, JA, Commins, SP, *et al,* 2017: Anaphylaxis after zoster vaccine: Implicating alpha-gal allergy as a possible mechanism. J. Allergy Clin. Immunol. 139:1710-15.

Swanson, MC, Rosanoff, E, Gurwith, M, *et al,* 1987: IgE and IgG antibodies to beta-propiolactone and human serum albumin associated with urticarial reactions to rabies vaccine. J. Infect. Dis. 155:909-12.

Takahashi, H, Pool, V, Tsai, TF, Chen, RT, 2000: Adverse events after Japanese encephalitis vaccination: Review of post-marketing surveillance data from Japan and the United States: The VAERS Working Group. Vaccine 18:2963-9.

Talbot, EA, Brown, KH, Kirkland, KB, *et al,* 2010: The safety of immunizing with tetanus-diphtheria-acellular pertussis vaccine (Tdap) less than 2 years following previous tetanus vaccination: Experience during a mass vaccination campaign of healthcare personnel during a respiratory illness outbreak. Vaccine 28:8001-8.

Tam, J, Tran, D, Bettinger, JA, Moore, D, Sauvé, L, *et al,* 2020: Review of pediatric encephalitis and encephalopathy cases following immunization reported to the Canadian Immunization Monitoring Program Active (IMPACT) from 1992 to 2012: Canadian Immunization Monitoring Program Active Investigators. Vaccine 38, 28:4457-63.

Tseng, HF, Liu, A, Sy, L, *et al,* 2012: Safety of zoster vaccine in adults from a large managed-care cohort: A vaccine safety data-link study. J. Intern. Med. 271:510-8.

Wahid, R, **Zafar, SJ, McArthur, MA, Pasetti, MF, Levine, M, *et al,* 2014:** Live oral *Salmonella enterica* serovar *Typhi* vaccines Ty21a and CVD 909 induce opsonophagocytic functional antibodies in humans that cross-react with *S. paratyphi* A and *S. paratyphi* B. Clin. Vacc. Immunol. 21, 3:427-34.

WHO, 2019: PRIORIX combined measles, mumps and rubella vaccine, live, attenuated lyophilized powder for injection Meets WHO requirements Active immunizing agent against infection by measles, mumps & rubella. Glaxo SmithKlineInc. 7333 Mississauga Road Mississauga, Ontario L5N 6L4

WHO, 2016: Reducing pain at the time of vaccination: WHO position paper, September 2015-Recommendations. Vaccine 34:3629.

WHO, 2019: Ten threats to global health. www.who.int/emergencies/ten-threats-to-globalhealth.

Wise, RP, Salive, ME, Braun, M, *et al,* 2000: Postlicensure safety surveillance for varicella vaccine. JAMA 284:1271-4.

Wilson, JM, **Platts-Mills, TAE, 2019:** Red meat allergy in children and adults. Curr. Opin. Al-

lergy Clin. Immunol. 19, 3:229-35.

Wood, RA, Setse, R, Halsey, N, 2007: Clinical Immunization Safety Assessment (CISA) Network Hypersensitivity Working Group: Irritant skin test reactions to common vaccines. J. Allergy. Clin. Immunol. 120:478-82.

Zanoni, G, Puccetti, A, Dolcino, M, *et al,* 2008: Dextran-specific IgG response in hypersensitivity reactions to measles-mumps-rubella vaccine. J. Allergy Clin. Immunol. 122:1233-9.

Table 1: Gell and Coombs classification of immunologic drug reactions

Type	Description	Mechanism	Clinical pictures
I- Immediate reaction within an hour	IgE-mediated, immediate-type hypersensitivity	Antigen exposure causes IgE-mediated activation of mast cells and basophils, with release of vasoactive substances, such as histamine, prost aglandins, and leukotrienes	Anaphylaxis Angioedema Bronchospasm Urticaria (hives) Hypotension
II	Antibody-dependent cytotoxicity	An antigen or hapten that intimately associated with a cell binds to anti-body, leading to cell or tissue injury.	Hemolytic anemia Thrombocytopenia Neutropenia
III	Immune complex disease	Damage caused by formation or deposition of antigen-antibody complexes in vessels or tissue. Deposition of immune complexes causes complement ac-tivation and/or recruitment of neutrophils by interaction of immune complexes with Fc IgG receptors	Serum sickness Arthus reaction
IV	Cell-mediated or delayed hypersensitivity	Antigen exposure activates T cells that mediate tissue injury. Depending upon type of T cell activation & other effector cells recruited, different subtypes differ-entiated (types IVa to IVd).	Contact dermatitis, Some morbilli-form reactions, Severe exfoliative dermatoses (SJS/TEN), AGEP, DRESS/DiHS, Interstitial nephritis, Drug-induced hepatitis, Others

Table 2: Symptoms and signs of anaphylaxis

Skin	Feeling of warmth, flushing, itching, urticaria, angioedema, & hair standing on end (pilor erection)
Oral	Itching or tingling of lips, tongue, or palate
	Edema of lips, tongue, uvula, metallic taste
Respiratory	Nose - Itching, congestion, rhinorrhea, and sneezing
	Laryngeal - Itching and "tightness" in throat, dysphonia, hoarseness, stridor
	Lower airways - Shortness of breath (dyspnea), chest tightness, cough, wheezing, and cyanosis
Gastrointestinal	Nausea, abdominal pain, vomiting, diarrhea, and dysphagia (difficulty swallowing)
Cardiovascular	Feeling of faintness or dizziness; syncope, altered mental status, chest pain, palpitations, tachycardia, bradycardia or other dysrhythmia, hypotension, tunnel vision, difficulty hearing, urinary or fecal incontinence, and cardiac arrest
Neurologic	Anxiety, apprehension, sense of impending doom, seizures, headache and confusion; young children may have sudden behavioral changes (cling, cry, become irritable, cease to play)
Ocular	Periorbital itching, erythema and edema, tearing, and conjunctive erythema
Others	Uterine cramps in women and girls

Table 3: Diagnostic criteria for anaphylaxis (Anaphylaxis highly likely when any one fulfilled following three criteria)

Acute onset of an illness (minutes to several hours)	Respiratory compromise (dyspnea, wheeze-bronchospasm, stridor, hypoxemia)
	Reduced BP or associated symptoms of end-organ dysfunction (hypotonia, collapse, syncope, incontinence)
Two or more after exposure to a likely allergic patient (minutes to several hours):	Skin mucosal tissue (generalized hives, itch-flush, swollen lips-tongue-uvula)
	Respiratory compromise (dyspnea, wheeze-bronchospasm, stridor, hypoxemia)
	Reduced BP* or associated symptoms (hypotonia, collapse, syncope, incontinence)
	Persistent gastrointestinal symptoms (cramp abdominal pain, vomiting)
Mild BP exposed to an al-lergic patient (minutes to hours):	A. Infants and children - Low systolic BP (age-specific)* or > 30% decrease in systolic BP
	B. Adults - Systolic BP < 90 mmHg or greater than 30% decrease from that person's baseline

Table 4: Egg content of vaccines (subject to change - check package inserts)

Vaccine	Grown in	Egg protein content	Approach in egg-allergy
Measles and mumps	Chick embryo fibroblast cell cultures	Picograms to nanograms	Administer in usual manner
Purified chick embryo rabies	Chick embryo fibroblast cell cultures	Picograms to nanograms	Administer in usual manner
Influenza (killed injected & live attenuated nasal)	Chick extra-embryonic allantoic fluid	<1 microgram	*
Yellow fever	Chick embryos	Micrograms	Skin test with vaccine prior to administration

Table 5: Gelatin content of USA available vaccines* (subject to change-refer to local prescribing information)

Vaccine (United States brand name and manufacturer)	Gelatin content in micrograms per dose
Influenza (Flumist Quadrivalent 2017-2018, Medimmune vaccines)*	2000 micrograms per 0.2 mL dose
Measles, mumps, rubella (M-M-R-II, Merck)	14,500 micrograms per 0.5 mL dose
Measles, mumps, rubella, varicella (ProQuad, Merck)	11,000 micrograms per 0.5 mL dose
Rabies (RabAvert, Novartis)	≤12,000 micrograms per 1 mL dose
Varicella (Varivax, Merck)	12,500 micrograms per 0.5 mL dose
Yellow fever (YF-Vax, Sanofi Pasteur)	6250 micrograms per 0.5 mL dose¶
Zoster (Zostavax, Merck)	15,580 micrograms per 0.65 mL dose
Typhoid oral Ty21a (Vivotif, Crucell Vaccines)	Capsule

*US/FDA, 2017: Vaccines Licensed for Use in the United States; approved product information (package insert) available at https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093833.htm

Fig. 1: Suggested approach to suspected anaphylaxis to a vaccine.