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REVIEW

Immune-mediated adverse reactions to vaccines

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Vaccination continues to be the single most important and successful public health intervention, due to its prevention of morbidity and mortality from prevalent infectious diseases. Severe immunologically mediated reactions are rare and less common with the vaccine than the true infection. However, these events can cause public fearfulness and loss of confidence in the safety of vaccination. In this paper, we perform a systematic literature search and narrative review of immune-mediated vaccine adverse events and their known and proposed mechanisms, and outline directions for future research. Improving our knowledge base of severe immunologically mediated vaccine reactions and their management drives better vaccine safety and efficacy outcomes.

KEYWORDS

adverse drug reactions, allergy, drug allergy, hypersensitivity, immunology, vaccines

1 | INTRODUCTION/BACKGROUND

Vaccination is 1 of the most important and successful public health interventions. Globally, vaccines effect immunity in hundreds of millions of individuals each year.[1] The sentinel successes of vaccination include eradication of smallpox, the confinement of polio to a tiny geographic footprint with hopes of eradication, and the aversion of millions of deaths due to measles.[2,3] An estimated 23.3 million global deaths will be averted by vaccination between 2011 and 2020.[2]

Despite, or perhaps because of these successes, increasing attention by the public has been focused on the infrequent risks of vaccination.[4,5] Patients sometimes perceive the risks of vaccination to be of greater concern than the benefits, and some groups currently promote avoidance of specific or all vaccines.[4-6] This has been described previously as a *crisis of confidence* in vaccination.[7-9] Currently, a global resurgence of measles is due in part to parents avoiding routine childhood immunizations for their children.[10]

Parents who report a child having a previous adverse event following immunization have increased hesitancy about future vaccination, although the vast majority of these events are usually the expected sequelae required for immunity, and of low severity.[11] Worldwide, pharmacovigilance for these events is strengthened on a country-by-country basis by the World Health Organization through the Global Vaccine Safety Initiative.[12] In the USA, adverse events are reported either by patients, family members or health care providers to the Vaccine Adverse Event Reporting System (VAERS) and can be evaluated by the multidisciplinary Clinical Immunization Safety Assessment network or the Vaccine Safety Datalink.[13,14] Loughlin *et al*. reported a sample of 100 patients from VAERS who were evaluated using the World Health Organization's adverse events from immunization causality assessment criteria, and only 3% of reported vaccine reactions could be definitely

causally linked to the vaccine received.[15] Of the remaining adverse events, 20% were classified as probably linked, 20% were classified as possibly linked, and the majority (53%) were classified as either unlikely to be linked or unrelated to a vaccine received.[15] However, in light of unnecessary gaps in vaccination coverage it is increasingly important that any major side effects from vaccination should be separated from online myths of adverse effects and made predictable by science. This would ideally include both heightened education and elimination of the adverse effects.

In this paper we perform a systematic literature search and narrative review of immune-mediated vaccine adverse events and their known and proposed mechanisms, and outline directions for future research. The scope of this review focuses on mechanisms of immediate and delayed hypersensitivity to vaccination, adverse outcomes in the immune suppressed, and discusses ways in which the field of vaccinology can move toward a goal of minimizing hypersensitivity reactions and other adverse events that lead to gaps in vaccination on a population level.

2 | METHODS

We searched PubMed for relevant articles published between January 1945 and August 2018. Articles were selected as relevant if they provided a description of an immune-mediated vaccine adverse event or shed light on a mechanism for an immune-mediated vaccine reaction. We used various combinations of the following terms: 'vaccine', 'vaccination', 'immunization', 'allergy', 'hypersensitivity,' 'Guillain-Barré,' 'adverse' and 'anaphylaxis.' In addition, we added supplemental search terms related to vaccine excipients; specifically: 'gelatin,' 'egg,' 'alpha-gal,' 'latex,' 'milk,' 'chicken,' 'yeast,' 'aluminum,' 'thimerosal,' 'phenoxyethanol,' 'neomycin,' 'polymyxin B,' 'kanamycin,' 'gentamicin,' 'streptomycin,' 'chlorotetracycline,' 'amphotericin B,' 'dextran' and 'polysorbate 80.' In combination with the term 'vaccine' we also searched for reports of 'acute generalized exanthematous pustulosis,' 'erythema nodosum,' 'granuloma annulare,' 'bullous pemphigoid,' 'Sweet's syndrome,' 'Gianotti-Crosti,' 'lichenoid' 'cutaneous lupus,' 'lupus vulgaris' and 'serum sickness.' Additional publications were sourced from the references in individual articles. Relevant articles were selected after reading through all titles and abstracts, and full texts were obtained if the information contained in the title or abstract was insufficient to exclude the study as relevant. Priority on relevance was given to: (i) publications containing cases of post-vaccination immune-mediated adverse events that provided evidence for a mechanism; followed by (ii) publications containing well described cases of postvaccination immune-mediated adverse events and at least probable causality where mechanisms are currently unknown or poorly defined; and (iii) original research articles that examine the epidemiology of postvaccination immune-mediated adverse events. Out of a total of 260 articles initially selected on abstract review as potentially relevant, 169 were included as references in this final narrative review manuscript.

2.1 | Mechanisms of vaccine hypersensitivity

2.1.1 | Antibody mediated hypersensitivity

Immediate hypersensitivity to vaccines is caused by the presence of immunoglobulin (Ig)E in a patient which can precipitate degranulation of mast cells and release of histamine (type I hypersensitivity) in response to an antigen within the vaccine.[16] Although it is now known that there are mechanisms by which mast cell degranulation can occur without the presence of IgE,[17] IgE-mediated anaphylaxis is the most important and severe immediate reaction occurring after vaccination.[18,19] Symptoms have a rapid onset (typically <15 min) and include itching, urticaria, angioedema, nausea, vomiting, diarrhoea, wheezing, shortness of breath, hypotension, loss of consciousness and, in severe instances, death.[16] Treatment of acute symptoms should always include early administration of intramuscular epinephrine.[18,19] Allergy testing using skin prick or intradermal testing read at 15–20 minutes with appropriate histamine and saline controls can be informative to evaluate this type of hypersensitivity.[19] (Figure 1).

Because of the short time between immunization and onset of symptoms, causality assessment of true immediate hypersensitivity is often more straightforward, but there are reactions which may present with similar symptoms and signs which are not true IgE-mediated reactions. Mimics of immediate hypersensitivity do not utilize an IgE

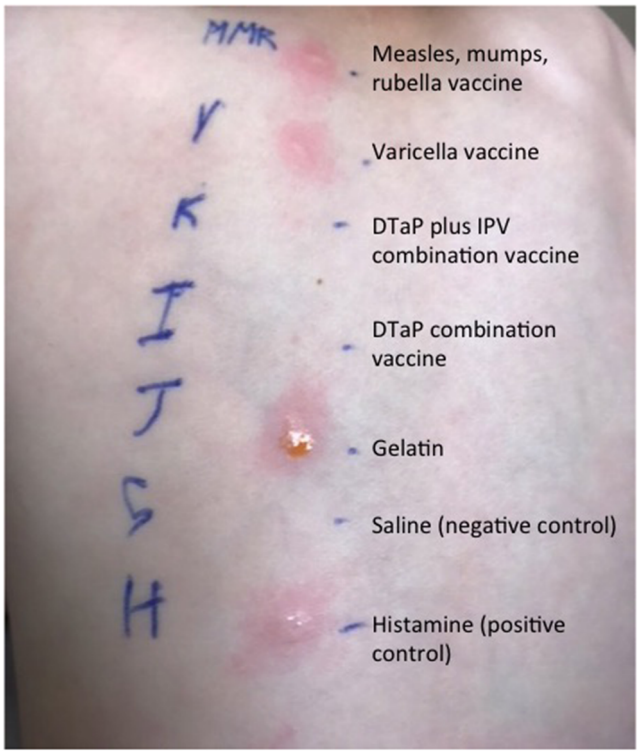


FIGURE 1 Immediate hypersensitivity skin testing in an alpha-gal allergic patient with anaphylaxis after vaccination demonstrates a skin test positive response to gelatine containing vaccines, which were subsequently demonstrated to also contain alpha-gal allergen. Image modified from Stone *et al.*[28,29] DTaP = diphtheria, tetanus, and acellular pertussis; IPV = inactivated polio vaccine

mediated mechanism, and include vasovagal syncope (especially amongst teenagers) and hypotonic hyporesponsive episodes.[20,21] Delayed onset urticaria, irritability, drowsiness, hypotonia, and febrile seizures are other examples of more adverse events that may be falsely labelled as allergic.[20,21] Within a dedicated Italian vaccine adverse event clinic, Donà *et al*. report that IgE-mediated anaphylaxis accounted for 10% of paediatric referrals, with the remainder comprised of these other causes.[20] Within a random VAERS sample, there was 1 case of reported anaphylaxis out of 100 event reports.[15]

In addition, there are delayed antibody mediated hypersensitivity reactions that have been mechanistically suggested to be related to complement activation, immune complex deposition (type 3 hypersensitivity or an Arthus reaction) or other less-well defined mechanisms, including T-cell mediated processes or, less likely, late activation of the IgE system.[22]

2.2 | Role of vaccine excipients in immediate hypersensitivity reactions

Unlike drugs, excipients represent a major contributor to specific IgE and immediate reactions associated with vaccines. However, immediate hypersensitivity reactions to vaccines which meet definitions for IgE-mediated reactions or anaphylaxis are exceedingly rare, occurring in <1 case per million doses administered.[23] The major common predictor and mechanism of immediate hypersensitivity during vaccination is the presence of pre-existing allergy to a vaccine excipient, such as egg,[24] gelatine[25-27] and, most recently, galactose-α, 1,3, galactose, commonly referred to as *alpha-gal*.[28,29] This differs significantly from anaphylaxis related to drugs where anaphylaxis is usually related to the active drug component and not the excipient.

Ideally, identification and reporting of cases of vaccine excipient anaphylaxis should progress through recognizable stages (Figure 2). Cases should be evaluated using causality assessment and hypersensitivity should be confirmed using published immediate hypersensitivity skin testing strategies[19] to prove immediate reactivity to a vaccine and/or a specific excipient.

We suggest that these criteria also be considered when interpreting the literature of vaccine anaphylaxis, especially when the number of reactions to an excipient is limited to isolated case reports. These criteria were utilized in the creation of Table 1.

2.2.1 | Interventions to reduce excipient mediated immediate hypersensitivity

Intentional efforts to minimize egg protein and careful study have subsequently made the ongoing risk of egg allergy mediated reactions during vaccination with measles–mumps–rubella[30] and influenza vaccines[31] minimal. Efforts to reduce gelatine content in vaccines given in Japan and Germany subsequently reduced allergic vaccine adverse events.[32,33] These success stories provide a framework to consider when there is a need to reduce immediate hypersensitivity to a vaccine excipient.

2.2.2 | T-cell mediated hypersensitivity

Most delayed-type hypersensitivity reactions (type IV hypersensitivity) are T-cell mediated reactions that can be both CD4+ and/or CD8 + dependent, with a target allergen presented via major histocompatibility molecules to T-cell receptors.[16] Activation of CD4+ T cells results in cytokine mediated inflammation which is typically confined to a local area, but can sometimes be widespread.[16] In reactions where CD8+ T cells are involved, the release of perforin and granzyme can lead to bystander cell injury and death by apoptosis.[16] Symptoms of delayed hypersensitivity generally have onset within 6 hours to weeks

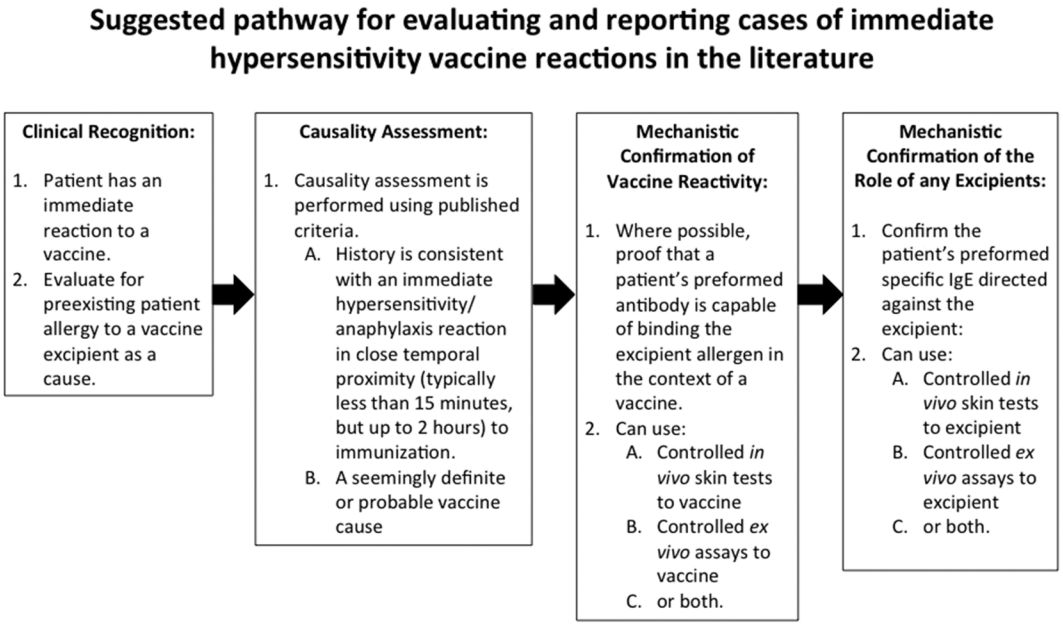


FIGURE 2 Suggested pathway for evaluating and reporting cases of immediate hypersensitivity vaccine reactions in the literature[26-29]

TABLE 1 Immediate and delayed excipient-mediated reactions to vaccines

Pre-existing allergen	Excipient causes immediate vaccine reaction	Excipient causes delayed vaccine reaction	Relevant vaccines
Foods:			• MMR
Gelatine	Yes[25-29,32,114-117]	Not reported	• MMRV • varicella • yellow fever • zoster
Alpha-gal	Yes, in some allergic recipients[28,29,118] alpha-gal may confound the diagnosis for some gelatine allergies, or require co-presence of gelatine allergy to cause reaction.	Not reported	• MMR • MMRV • varicella • zoster Potential concern: • intranasal live attenuated influenza vaccine • yellow fever
Egg	Yes[24,119]	Not reported	Potential concern: • rabies • yellow fever Previous concern, no longer clinically relevant: • influenza[31,120-130] • MMR[30,131,132]
Cow's milk (severe)	Possible[133-135]	Not reported	• DTaP, Tdap • OPV
Chicken	Possible[136]	Not reported	• yellow fever
Yeast	Possible[137]	Not reported	• hepatitis B
Nonfoods:			
Preservatives/adjuvants (aluminium, thimerosal, phenoxyethanol)	Yes, thimerosal in 1 patient with preceding contact allergy[34] Aluminium and phenoxyethanol Possible[138,139]	Reports typically describe large local reaction with positive patch testing.[140-146] Disseminated rash[147,148] and sterile granulomas/abscesses[149-151] also reported.	Various[19,152,153] • aluminium used as adjuvant • Thimerosal used as preservative; overall use is declining • Phenoxyethanol used as preservative
Antimicrobials (neomycin, polymyxin B, kanamycin, gentamicin, streptomycin, chlorotetracycline and amphotericin B)	Possible[154,155]	Reports typically describe large local reaction and positive patch testing.	Various[19,152,153]
Latex	Yes[156,157]	Contact allergy to latex very common but does not appear to increase vaccine reactions.	Vaccines with rubber latex in syringes, vials, diluents, caps or packaging[19] are becoming less common. Most experts recommend vaccination followed by observation.[19]
Dextran	Yes, possibly non-IgE mediated.[158,159]	Not reported	No vaccines containing dextran currently available on the market.
Polysorbates/polyethylene glycols	One case reported.[160] Immediate IgE mediated hypersensitivity has recently been reported and sensitization	Not reported	Various[19,152,153] • HPV vaccine reported[160]

(Continues)

TABLE 1 (Continued)

Pre-existing allergen	Excipient causes immediate vaccine reaction	Excipient causes delayed vaccine reaction	Relevant vaccines
	has been demonstrated with positive vaccine skin test in a sensitized individual.[161-163]		

MMR = measles, mumps, rubella; MMRV = measles, mumps, rubella, varicella; DTaP= diphtheria, tetanus and acellular pertussis; Tdap = tetanus, diphtheria and acellular pertussis; OPV = oral polio vaccine; HPV = human papilloma virus

and can range widely from localized skin symptoms to disseminated rashes with systemic symptoms and/or blistering of the skin and mucosal surfaces.[34]

Locally confined reactions to vaccines, with prolonged warmth, redness, swelling, rash or malaise is the most common type of immune-mediated reaction after vaccination, and may represent the extreme spectrum of normal immune responses leading to immunity. Low-acuity delayed-type immune-mediated reactions have a typical onset of hours to days of reactions, but can be delayed up to 2–3 weeks, making it difficult to determine definitive causality.[15] The most common type of such reactions reported are delayed onset papular rashes,[35] which can be confusing since these are a very common occurrence in childhood and generally associated with viruses, rather than the vaccine itself. Local delayed hypersensitivity reactions confined to the site of the vaccine are not a contraindication to future vaccination.[36] A rare disseminated papular rash with delayed hypersensitivity features has been described in adult military recruits 10–18 days after receipt of the current smallpox vaccine (ACAM2000; Figure 3).[37]

By contrast, more severe versions of delayed-type hypersensitivity such as Stevens–Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) have been reported in exceedingly rare cases only.[38-40] It is thought in most cases that these are single events related to a response to virotopes present within the vaccine and unlikely to occur in the future. SJS/TEN needs to be differentiated from erythema multiforme major (EMM) which has been associated with a viruses such as herpes simplex virus 1, *Mycoplasma pneumoniae* as well as rarely with vaccines.[41,42] EMM, unlike SJS/TEN, is recurrent in the absence of re-exposure to the initial inciting event.[43]

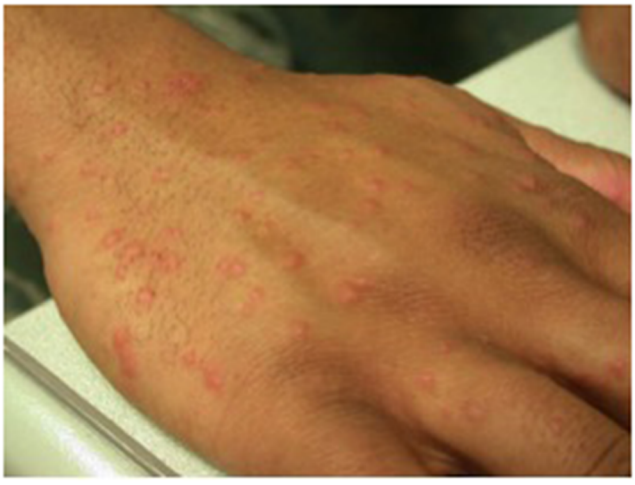


FIGURE 3 Disseminated papular rash after receipt of smallpox vaccine (ACAM2000), without detectable intralesional virus[37]

Other rare delayed cutaneous reactions potentially associated with vaccines have been reported (Table 2) and include acute generalized exanthematous pustulosis,[44,45] erythema nodosum,[46-49] granuloma annulare,[50] bullous pemphigoid,[51-53] Sweet's syndrome,[54-59] Gianotti–Crosti syndrome,[60] lichenoid eruptions,[46,50,61-66] cutaneous lupus,[46,67] lupus vulgaris[68-70] and serum sickness-like reactions.[71-76] Similar to vaccine associated EMM, the presence of an ongoing infection prior to both vaccination and the development of these cutaneous syndromes is frequently reported in these cases. Most reports provide follow-up data that there was no recurrence of symptoms upon subsequent booster doses of the associated vaccines. Causality assessment has only rarely been performed in these reports and underlying host risk factors including genetic predisposition are currently unknown.[77-80]

2.3 | Excipient allergies and delayed vaccine hypersensitivity

Delayed type hypersensitivity reactions against vaccine excipients have also been described (Table 1) and may present as a generalized reaction or a contact reaction over the site of the vaccine. In general, these reactions are of lesser severity and localized, but some reported excipient-mediated vaccine reactions are consistent with disseminated cutaneous rashes or other symptomatology. Currently there have not been any major attempts to determine how often or the mechanism by which delayed hypersensitivity responses against a vaccine excipient occurs, due to the typically lower severity. There are currently no validated testing strategies for ascertaining cases of delayed hypersensitivity to a vaccine. Subsequent causality assessment should attempt to prove the likeliness of the role of the vaccine or excipient.[81] If a vaccine excipient is suspected in particular there is a potential role for delayed intradermal skin testing and/or patch testing with the vaccine and the excipient separately (Figure 4).[34]

2.3.1 | Guillain–Barré syndrome

Immunologically mediated neurological complications such as Guillain–Barré syndrome and other demyelinating neuropathies (Bell's palsy, acute disseminated encephalomyelitis, etc.) are a known and reported adverse event related to immunization,[13] but such events are exceedingly rare, occurring after <1 per million doses of vaccines administered.[23,82-85] Guillain–Barré syndrome suspected as a

TABLE 2 Immunological reactions to vaccines, by associated vaccine

Reaction	Associated vaccines
Immediate hypersensitivity[164]	Hepatitis B Influenza Measles, mumps and rubella (MMR) Tetanus toxoid containing vaccines Varicella Yellow fever Zoster
Serum sickness or serum sickness-like[71-76]	Hepatitis B Influenza Influenza (H1N1) Pneumococcal Rabies Tetanus
Severe delayed cutaneous hypersensitivity (SJS or TEN)[38-40]	Hantavirus Influenza MMR Rabies Smallpox
Erythema multiforme major[38-40]	Diphtheria and tetanus (DT) Diphtheria, pertussis and tetanus (DPT) Haemophilus influenza B Hepatitis B Human papillomavirus (HPV) Influenza (H1N1) MMR Meningococcal Inactivated polio vaccine (IPV) Oral polio vaccine (OPV) Smallpox Varicella
Guillain-Barré syndrome[86,89-93,164]	Influenza OPV Rabies Tetanus toxoid containing vaccines
Risk for disseminated/prolonged infection in severe cellular immunodeficiency[107-109]	Bacille Calmette–Guérin (BCG) Live attenuated influenza MMR OPV Oral typhoid vaccine Rotavirus Smallpox Varicella Yellow fever
Risk for disseminated/prolonged infection in severe humoral immunodeficiency[107-109]	Live attenuated influenza Oral typhoid vaccine OPV Smallpox Yellow fever
Acute generalized exanthematous pustulosis[44,45]	DPT Influenza MMR Pneumococcal vaccine
Erythema nodosum[47-49,165,166]	BCG DT Hepatitis B HPV Rabies Tetanus, diphtheria, and acellular pertussis (TDaP) Typhoid
Granuloma annulare[50,167-169]	BCG DT Hepatitis B
Bullous pemphigoid[51-53]	Hepatitis B DT DPT Influenza MMR Meningococcal Pneumococcal Smallpox
Sweet's syndrome[54-59]	BCG Influenza Influenza (H1N1) Pneumococcal
Gianotti-Crosti syndrome[60]	DPT Hepatitis A Hepatitis B Influenza Japanese encephalitis MMR
Lichenoid eruptions[46,50,61-66]	BCG Hepatitis B HPV Influenza Pneumococcal Yellow fever
Cutaneous lupus[46,67]	Hepatitis B Influenza
Lupus vulgaris[68-70]	BCG

SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis

vaccine-associated event through case reports.[36,86,87] Symptoms include progressive neuromuscular weakness, usually beginning in the extremities and then centrally, with potential progression toward respiratory failure or cranial nerve weakness.[88] Onset of symptoms is considered as possibly linked to vaccination if it occurs within 6 weeks after a dose of tetanus,[89,90] oral polio,[86] rabies[91] or influenza[92,93] containing vaccines. Postvaccination Guillain–Barré syndrome, similar to that occurring after an acute infection, is thought to be a mixed, delayed immune-mediated reaction, which probably represents a T cell response where CD4+ and CD8+ T cells cross-recognize specific virotopes and similar self-antigens in the nervous system, leading to either an axonal or demyelinating clinical subtype.[91] This mixed delayed inflammatory reaction is not easily characterized but has a high level of severity; 20–30% of cases develop respiratory failure.[91] Due to the delayed onset of symptoms, a more thorough understanding of Guillain–Barré events is crucial for their diagnosis

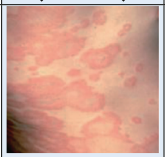
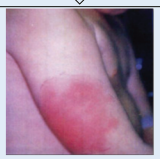
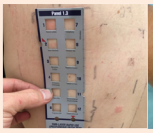
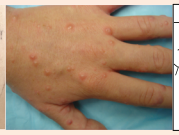
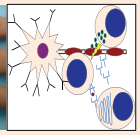
	Off Target						On Target
Mechanism Category	Antibody mediated		T cell mediated or mixed			Immune deficiency	Normal Response
Antigen	excipient / vaccine	vaccine	excipient	vaccine	vaccine	Failed immune control of live vaccine strain	vaccine
Adverse event (mechanism)	 Immediate hypersensitivity (IgE mediated)	 Local vasculitis (IgG immune complexes)	 Delayed hypersensitivity	 Delayed hypersensitivity	 Mixed - CD4+, CD8+ T & B cell mediated inflammation	 Infection due to live vaccine strain	Local tenderness, warmth, fever, irritability
Examples	Egg, gelatin, or alpha-gal immediate hypersensitivity	Arthus Reaction	Metal, antimicrobial contact allergy	Delayed smallpox reaction	Guillain- Barré syndrome, other demyelinating conditions	Disseminated rotavirus, varicella	Large local reaction
Predisposing factors	Pre-existing allergy to component of vaccine (see table 3)	Previous receipt of certain vaccines, shallow injection technique	Pre-existing allergy to component of vaccine (see table 3)	Possible genetic variation in antigen presentation/processing		Pre-existing primary or secondary immunodeficiency	Normal response
Evaluation	Thorough history and causality assessment						
	Skin testing to vaccine and relevant excipients (19)	Physical examination	Consider patch testing to vaccine and relevant excipients (19)	Consider contacting regional experts for genetic analysis and biobanking of specimens		• Confirm vaccine strain organism • Workup for cellular/humoral immunodeficiency (139)	Physical examination
Strategies for re-exposure to vaccine	• Alternative vaccine without implicated excipient • Split dose re-challenge • Desensitization	Deeper future injection technique	Low severity reactions are not contraindications for future use	Generally not a contraindication Strict avoidance if causality assessment indicates a higher likelihood and reaction is a severe cutaneous adverse reaction	Generally not a contraindication	Avoid relevant live vaccines depending upon type of underlying immunodeficiency	Reassurance and supportive care

FIGURE 4 Mechanism category, adverse events, examples, predisposing factors, evaluation and strategies for management of immune-mediated adverse events to vaccines. The blue column represents immediate-type reactions, the pink columns represent delayed-type reactions, and the green column represents failure to control live vaccine strain leading to a prolonged or disseminated vaccine strain infection[19,108]

and to assess whether vaccination was in the causal pathway.[13,15] Other patient specific factors need to be taken into account, such as preceding infections with *Campylobacter jejuni*, cytomegalovirus, Epstein–Barr virus, influenza A virus, *Mycoplasma pneumoniae* or *Haemophilus influenzae* that could be the actual trigger.[94-96] Interestingly, it is unknown whether the influenza vaccine may be protective against the subsequent development of Guillain–Barré during natural influenza A infection.[91] It is known that influenza vaccination after a previous episode of Guillain–Barré syndrome does not precipitate recurrence of symptoms.[97]

2.3.2 | Disseminated infections in immunocompromised populations

Disseminated or prolonged vaccine-strain infections are an exceedingly rare complication after receiving a live vaccine. Symptoms are typically consistent with a primary infection from the organism, but with progression to a more severe outcome into an immunocompromised host. Such infections have been reported with smallpox,[37] varicella,[98] rotavirus,[99-101] yellow fever,[102] measles–mumps–rubella,[103] oral polio[104] and Bacille Calmette–Guérin (BCG) vaccines.[105] While these cases are exceedingly rare amongst the general population, they are more common amongst those with either primary or acquired immunodeficiencies.[98,104,106] Severe T-cell immunodeficiency or a household member with a similar immunodeficiency is therefore a strict contraindication to immunization with any form of live vaccines (Figure 4).[107,108] Similarly, vaccination with mucosally-administered vaccines (oral typhoid, oral polio, live attenuated influenza) and yellow fever vaccines is contraindicated in severe humoral immunodeficiency.[109] Adverse outcomes of this type highlight the importance of newborn screening programmes for severe combined immunodeficiencies.[99-101] Ideal case ascertainment should confirm detection of a vaccine strain organism in a patient with a confirmed immune deficiency and a confirmed vaccine receipt. Conversely, identification of a vaccine strain infection after receipt of a live vaccine should prompt evaluation for immune deficiency.

3 | DISCUSSION

Adverse reactions to vaccines that are the result of either an immune-mediated reaction to the vaccine excipient, the active components of the vaccine or related to host immunodeficiency are rare and occur in <1 per million vaccines administered. At the same time, increasing attention by the public is focused on these infrequent risks of vaccination.[4,5] The previously described *crisis of confidence* in vaccination largely centres around an overemphasis upon these rare events or upon a fear of other events such as autism for which an evidence base exists to show them as unrelated to vaccination.[7-9,110-112] The current unpredictability of vaccine-related adverse events contributes to their occurrence and provides the opportunity for mistrust amongst segments of the public. With risk factor and mechanism identification comes the opportunity to avoid adverse events by alteration of vaccines or use of risk stratifying vaccination strategies, as has been demonstrated with egg and gelatine allergy.[30-33] There are excellent methods in place for assessing the causality of vaccine associated events in most countries. We believe that the future direction of this field will require strengthening these networks to include biobanking of specimens along with additional epidemiological, mechanistic and genetic study of true adverse events.[43,113] Such infrastructure will serve as the vehicle by which to drive the field of immunization ever closer to the patient centred goals of predictability, personalized medicine and minimized adverse vaccine reactions.

Given the importance of vaccination to public health, a nonspecific diagnosis of *immediate vaccine allergy* is too imprecise to guide efforts at quality and safety improvement, and may do more harm than good. Hence, as future cases of hypersensitivity emerge, we believe they should be evaluated with increasingly stringent criteria that require initial causality assessment followed by in vivo or in vitro assessment of mechanisms. Validated and widely accepted approaches for mechanistic assessment need to be defined. From the patient perspective, understanding and knowledge of the cause of a reaction provides reassurance and can guide selection of future vaccination approaches.

Postvaccination delayed-type hypersensitivity reactions and immunologically mediated neurological conditions are currently understudied, and there are no a priori predictors or diagnostic tools available for these conditions. Future research directions involve understanding the immunopathogenesis of these reactions and appropriate biobanking of DNA and cellular materials for future genetic and mechanistic studies.

Similarly, while there are already criteria in place for administration of vaccines in immune deficient patients,[19] additional mechanistic research into immune deficiency related postvaccination adverse events should be targeted toward identifying host immune risk factors that predict adverse events and lead to improved screening programmes.

The ability of the healthcare system and vaccine safety researchers to evolve in these future directions will help bolster trust in 1 of the most important public health interventions ever created.

4 | CONCLUSIONS

In summary, adverse reactions to vaccines that are either the direct result of an immune-mediated reaction to the vaccine excipient, the active components of the vaccine or related to host immunodeficiency are rare (Table 2) and fortunately defined diagnosis and management strategies exist (Figure 4). Although many immune-mediated vaccine reactions lack risk factors and mechanisms, excipient allergy and immune deficiency are 2 known mechanisms by which the immune system precipitates adverse events after vaccination. The specific mechanisms and immunological risk factors by which T-cell mediated illnesses such as SJS/TEN or inflammatory neurological conditions such as Guillain–Barré can occur after vaccination are not known but may be less commonly related to a vaccine than the natural viral illness. Where predictability has been obtained and the implementation of mitigation strategies was performed (egg, gelatine allergy), there have been associated increases in safety and confidence. Improved understanding of mechanistic risk factors for severe immunologically mediated vaccine reactions and a shift toward mechanistic causality assessment are crucial future directions for maintaining this vital public health intervention.

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COMPETING INTERESTS

There are no competing interests to declare.

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