



POINT OF VIEW

True and false contraindications to vaccines



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Received 15 January 2017; accepted 18 February 2017

Available online 8 May 2017

KEYWORDS

Vaccine;
Adverse event;
Anaphylaxis;
Child;
Contraindication;
Precaution;
Management;
Risk;
Recommendations;
Health-care

Abstract Nowadays, the awareness of risks related to infectious diseases has decreased, whereas THE perception of risks related to vaccination is growing. Therefore, it may be difficult for health care providers to convince people of the importance of vaccination and adherence to the immunisation schedule.

Selected situations that might raise uncertainties about vaccine recommendations are discussed in order to help health care providers to identify real and perceived contraindications to vaccines, and cases to be referred to specialised pre-vaccination consultation due to an increased risk of adverse events to vaccines.

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Introduction

Nowadays, the incidence of several infectious diseases and, consequently, awareness of infection-related risks has decreased notably, whereas the perception of risks related

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to health interventions, especially vaccinations, is increasing. Now, more than ever, people want to have an active role in the protection of their own health. Therefore, health-care providers should be able to give people complete information on the importance of immunisation. This is, however, sometimes a difficult task.

The most common clinical conditions which may raise doubts about vaccine recommendations are discussed below. The aim of this review is to facilitate identification of those situations that are true contraindications to vaccination, and disorders requiring specialised pre-vaccination consultation due to an increased risk of adverse events to vaccines.^{1,2}

Contraindications, precautions and warnings

Before administering a vaccine, health personnel must verify if there are diseases that create risks of serious adverse events present in the vaccinee ("Contraindications" – see Table 1), or conditions which are more likely to be associated with adverse events or decreased vaccine efficacy: the vaccination may be offered with precautions in these cases, after assessment of risks versus benefits (see Table 2). Situations should be further identified in which the vaccine is safe and effective, but might interfere with an ongoing, or a recently stopped drug therapy ("Warnings for vaccination" – Table 3). Data on patient's medical history collected according to a standardised, specifically arranged format, are suitable in most cases for this scope. Evidence is lacking regarding the possibility of decreasing the risk of adverse events by clinical evaluation, or any diagnostic tests performed in apparently healthy subjects; therefore they are not recommended.

If true contraindications to vaccination are identified (Table 1), vaccination should be avoided and the patient is to be referred to specialised consultation where available. If a risk/benefit assessment is indicated, health personnel should consider: the vaccinee's risk of contracting the infectious disease to be prevented; incidence and seriousness of complications associated with the infectious disease, taking into account all the patient's individual factors; levels of specific antibody titres to estimate protection; efficacy of the specific vaccine dose to be administered, and incidence and seriousness of adverse events associated with the vaccine. Consulting summaries of vaccine product characteristics and published guidelines, e.g. "Guide to Contraindications of Vaccinations",^{3,4} is useful in decision-making: all contraindications, precautions and warnings are listed in these references. Updates of both general and specific guidelines about vaccinations should be consulted as well.

True contraindications to vaccinations

Contraindications to vaccines (Table 1) are as follows:

1. A personal history of previous anaphylactic reactions to vaccine components or substances used in the vaccine production.^{3,4} This is the only true contraindication applicable to all vaccines. An anaphylactic reaction is defined by a number of symptoms and signs involving

Table 1 Contraindications to vaccination.

For all vaccines

Anaphylactic reactions to vaccine components

Serious adverse events to a previous dose of vaccine

Anaphylactic reactions to the same vaccine or same vaccine components but low/moderate risks due to that specific infectious disease and its complications
If the risk of infection for potentially lethal or disabling diseases is high, and specific antibody titres are not protective, the patient should be referred to an allergist to undergo skin tests with the vaccine and its components.

If vaccine or vaccine component skin test results are positive, the vaccine might still be administered in graded doses according to a standardised protocol, in a hospital setting.

Patient who had complications requiring long-term or invasive treatment after previous vaccination and risks related to the disease to be prevented are low/moderate

Patient with complications without *restitutio ad integrum*, with low/moderate risks related to the disease to be prevented

For live attenuated vaccines:

Agammaglobulinaemic syndrome

Complete T-cell deficiency

HIV immunodeficiency with CD4+ lymphocyte count <15% of total lymphocyte count

Solid or haematological neoplasia during treatment

Transplant within six months

Current therapies

Chemo/radiotherapy up to six months from suspension

High-dose steroids for at least two weeks and up to one month from suspension

High-dose immunosuppressive drugs

Pregnancy

Contraindications concern live attenuated vaccines

Varicella, Measles-mumps-rubella and Calmette-Guerin Bacillus and are related to the paucity of clinical trials.

Accidental administration of Measles-mumps-rubella vaccine in pregnant women did not demonstrate an increase of teratogenic risk and it is not an indication for pregnancy interruption.

at least two organs or systems among skin and cardiovascular, respiratory and gastrointestinal systems.⁵ By definition, an anaphylactic reaction is caused by mastocyte degranulation and it is very likely to occur in the presence of respiratory and/or cardiovascular symptoms. Although an anaphylactic reaction due to vaccines might occur up to 4 h after administration, it generally occurs within 1 h.^{6–8} Since anaphylactic reactions are life-threatening, vaccinations with the same product or vaccines sharing any possibly implicated substances must be avoided when disease-related risks are mild to moderate. If the risk of infection for potentially lethal or disabling diseases is high, and specific antibody titres are not protective, the patient should be referred

Table 2 Precautions to vaccination.

Family history of seizures induced or augmented by fever.
<i>Personal history of</i>
Allergy to milk and egg proteins with immediate symptoms for vaccines containing these components
Mild-to-moderate immune deficiency (e.g. selective IgA deficiency, IgG subclasses deficiency) for live vaccines
Haemato-oncological diseases
Autoimmune diseases in active phase or relapse
Genetic diseases without progressive pattern but possibly associated to immune deficiency (e.g. Down syndrome, Di George syndrome) for live attenuated vaccines
Seizures induced or augmented by fever (febrile seizures, Dravet syndrome)
Unstable neurological diseases or neurological disorders with unknown aetiology
<i>Mild to moderate adverse events to a previous dose of vaccine</i>
Events with non-immediate onset
Hypotonic-hyporesponsive episode
<i>Current therapies</i>
Immunosuppressive therapy (low or maintenance doses) for live vaccines

Table 3 Possible interactions between vaccines and other therapies (warnings).

Vaccine	On-going therapy
Measles-mumps-rubella	Immunoglobulins: vaccine efficacy possibly decreased.*
Varicella	Salicylates: risks for Reye's syndrome possibly increased. Immunoglobulins: vaccine efficacy possibly decreased.* Acyclovir: vaccine efficacy possibly decreased.
Rotavirus	Immunoglobulins: vaccine efficacy possibly decreased.*
Influenza	Carbamazepine, phenytoin, theophylline, warfarin: blood concentration of drugs possibly increased, with overdose symptoms.
Oral typhoid	Amoxicillin, ciprofloxacin, chloramphenicol, doxycycline, sulphamides, proguanil: vaccine efficacy possibly decreased.
BCG	Vaccination contraindicated in patients treated with ethambutol, isoniazid and rifampicin.

* Time intervals between immunoglobulin administration and vaccination vary, depending on kinds of vaccine; refer to guidelines to vaccination for specific time intervals.

to an allergist to perform skin tests with the vaccine and its components.⁷ If vaccine or vaccine component skin test results are positive, the vaccine may still be administered, if necessary, in graded doses. If the full vaccine dose is normally a volume of 0.5 mL, the patient

is first given 0.05 mL of a 1:10 dilution and then given full-strength vaccine (at 15-minute intervals) at doses of 0.05, 0.1, 0.15, and finally 0.2 mL, for a cumulative dose of 0.5 mL. In a patient who is presumed to be allergic to the vaccine being administered, this procedure needs to be performed in a hospital setting under direct medical supervision, with emergency medications and equipment immediately available to promptly treat an anaphylactic reaction should it occur.^{7,9} We recommend an allergological consultancy before immunisation in any cases of possible IgE-mediated reactions to vaccines (e.g., immediate symptoms limited to the skin or mucosae, with or without cardio-respiratory involvement).

2. Conditions of severe immunodeficiency: Severe primary or acquired immunodeficiency, such as agammaglobulinaemia, complete T-cell deficiency, HIV infection with CD4+ count less than 15% of total lymphocyte count, pharmacologically-induced immune depression (chemotherapy and radiotherapy up to 3–6 months upon suspension, high-dose steroids for 2 weeks and up to 1 month upon suspension, chronic therapy with immunosuppressive drugs), patients within 6 months of organ transplants.^{10,11} Contraindications refer to live attenuated vaccines, due to risks of clinically relevant infections by vaccine strain viruses in these patients.¹⁰ In less severe, or mild immunodeficiency disorders (e.g. selective IgA deficiency, partial Di George syndrome), live attenuated vaccines may be administered after an accurate risk/benefit assessment.
3. Previous serious, adverse reactions to vaccination different from anaphylaxis. Vaccine adverse events are considered serious if they result in death, or are life-threatening, require hospitalisation or prolongation of existing hospitalisation, result in persistent or significant disability/incapacity, or required intervention to prevent permanent impairment or damage.¹² Examples of serious adverse events are thrombocytopenia, Guillain-Barré syndrome, or brachial neuritis. In these cases, further doses of the same vaccine should be avoided, unless benefits clearly overcome risks.³ The vaccination might be offered with personalised precautions, if risks for a potentially lethal or disabling disease are high and patients give their informed consent.

Misconceptions or need for precautions?

Misconceptions are conditions erroneously perceived as contraindications, although they do not imply an increased risk due to vaccination. Table 4 reports examples of misconceptions. When a personal history of disease is reported, a detailed medical history is required in order to distinguish false contraindications from hidden, true contraindications or conditions deserving additional precautions. In general, a family history of diseases or adverse events to vaccines are not considered contraindications in healthy subjects,³ but family history should always be investigated for specific conditions which need precautions (e.g. if febrile seizures occurred in relatives, separation of measles-mumps-rubella vaccine from varicella vaccine is indicated).

Table 4 False contraindications. Modified from: Ref. [4].

	Misconceptions
General for all vaccines	Mild acute illness with or without fever Mild-to-moderate local reaction (i.e., swelling, redness, soreness) Low-grade or moderate fever after previous dose Lack of previous physical examination in well-appearing person Current antimicrobial therapy* Convalescent phase of illness Preterm birth (hepatitis B vaccine is an exception in certain circumstances) † Recent exposure to an infectious disease History of penicillin allergy, other non-vaccine allergies, relatives with allergies, or receiving allergen extract immunotherapy
DTaP	Fever of $<40.5^{\circ}\text{C}$, fussiness or mild drowsiness after a previous dose of DTP/DTaP Family history of seizures Family history of sudden infant death syndrome Family history of an adverse event after DTP or DTaP administration Stable neurologic conditions (e.g., cerebral palsy, well-controlled seizures, or developmental delay)
Tdap	Fever of $\geq 40.5^{\circ}\text{C}$ for <48 h after vaccination with a previous dose of DTP or DTaP Collapse or shock-like state (i.e., hypotonic hyporesponsive episode) within 48 h after receiving a previous dose of DTP/DTaP Seizure <3 days after receiving a previous dose of DTP/DTaP Persistent, inconsolable crying lasting >3 h within 48 h after receiving a previous dose of DTP/DTaP History of extensive limb swelling after DTP/DTaP/Td that is not an arthus-type reaction Stable neurologic disorder History of brachial neuritis Latex allergy that is not anaphylactic Breastfeeding Immunosuppression
IPV	Previous receipt of ≥ 1 dose of oral polio vaccine
Hepatitis B	Pregnancy Autoimmune disease (e.g., systemic lupus erythematosus or rheumatoid arthritis)

Table 4 (Continued)

MMR§	Positive tuberculin skin test Simultaneous tuberculin skin testing** Breastfeeding Pregnancy of recipient's mother or other close or household contact Recipient is female of child-bearing age Immunodeficient family member or household contact Asymptomatic or mildly symptomatic HIV infection Allergy to eggs
Varicella	Pregnancy of recipient's mother or other close or household contact Immunodeficient family member or household contact†† Asymptomatic or mildly symptomatic HIV infection Humoral immunodeficiency (e.g., agammaglobulinaemia)
TIV	Non-severe (e.g., contact) allergy to latex, thimerosal, or egg Concurrent administration of coumadin or aminophylline
LAIV	Health-care providers that see patients with chronic diseases or altered immunocompetence (an exception is providers for severely immunocompromised patients requiring care in a protected environment) Breastfeeding Contacts of persons with chronic disease or altered immunocompetence (an exception is contacts of severely immunocompromised patients requiring care in a protected environment)
PPSV	History of invasive pneumococcal disease or pneumonia
HPV	Immunosuppression Previous equivocal or abnormal Papanicolaou test Known HPV infection Breastfeeding History of genital warts
Rotavirus	Prematurity Immunosuppressed household contacts Pregnant household contacts
Herpes Zoster	Therapy with low-dose methotrexate (≤ 0.4 mg/kg/week), azathioprine (≤ 3.0 mg/kg/day), or 6-mercaptopurine (≤ 1.5 mg/kg/day) for treatment of rheumatoid arthritis, psoriasis, polymyositis, sarcoidosis, inflammatory bowel disease, or other conditions Health-care providers of patients with chronic diseases or altered immunocompetence

Table 4 (Continued)

Contacts of patients with chronic diseases or altered immunocompetence
Unknown or uncertain history of varicella in a U.S.-born person

DT, diphtheria and tetanus toxoids; DTP, diphtheria toxoid-tetanus toxoid, and pertussis; DTaP, diphtheria and tetanus toxoids and acellular pertussis; HBsAg, hepatitis B surface antigen; Hib, *Haemophilus influenzae* type b; HPV, human papillomavirus; IPV, inactivated poliovirus; LAIV, liveattenuated influenza vaccine; MCV4, quadrivalent meningococcal conjugate vaccine; MMR, measlesmumps, and rubella; MPSV4, quadrivalent meningococcal polysaccharide vaccine; PCV, pneumococcal conjugate vaccine; PPSV, pneumococcal polysaccharide vaccine; Td, tetanus and diphtheria toxoids; Tdap, tetanus toxoid-reduced diphtheria toxoid, and acellular pertussis; TIV, trivalent inactivated influenza vaccine.

* Antibacterial drugs might interfere with Ty21a oral typhoid vaccine and certain antiviral drugs might interfere with varicella-containing vaccines and LAIV.

† Hepatitis B vaccination should be deferred for infants weighing <2000 g if the mother is documented to be HBsAg-negative at the time of the infant's birth. Vaccination can commence at chronological age one month or at hospital discharge. For infants born to HBsAg-positive women, hepatitis B immune globulin and hepatitis B vaccine should be administered within 12 h after birth, regardless of weight.

§ MMR and varicella vaccines can be administered on the same day. If not administered on the same day, these vaccines should be separated by at least 28 days. HIV-infected children should receive immune globulin after exposure to measles. HIV-infected children can receive varicella and measles vaccine if CD4+ T-lymphocyte count is >15%. (Source: Adapted from American Academy of Pediatrics. Passive immunisation. In: Pickering LK, ed. Red book: 2009 report of the Committee on Infectious Diseases. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009.)

** Measles vaccination might suppress tuberculin reactivity temporarily. Measles-containing vaccine can be administered on the same day as tuberculin skin testing. If testing cannot be performed until after the day of MMR vaccination, the test should be postponed for at least 4 weeks after the vaccination. If an urgent need exists to skin test, do so with the understanding that reactivity might be reduced by the vaccine.

†† If a vaccinee experiences a presumed vaccine-related rash 7–25 days after vaccination, the person should avoid direct contact with immunocompromised persons for the duration of the rash.

Precautions are measures specifically adopted to rapidly identify, and properly treat, any predictable adverse events after vaccination, thereby decreasing the risks of these events evolving into serious ones.

A delay in vaccine administration is recommended in subjects with ongoing diseases who are likely to recover soon (e.g. infections), in order not to attribute symptoms incorrectly to the provided vaccination, which are really due to diseases. Whenever possible, completing an ongoing diagnostic work-up for suspected contraindications before the vaccine administration is also recommended. Indeed, the risk/benefit assessment is a priority in the decision-making in every single case.

The following situations are commonly encountered in clinical practice.

Preterm birth represents a false contraindication to vaccinations for children in stable conditions; however, associated disorders (e.g. cardiac diseases, bronchopulmonary dysplasia, neurologic disorders, recurrent infections, apnoea, chronic drug therapies...) may require precautions and a specialised pre-vaccination consultation.^{13–15} Similarly, patients with a *non-progressive neurological disease* should be evaluated for any concomitant disorders (e.g. cardiac diseases, immunodeficiency, autoimmune diseases, epilepsy...), possibly requiring additional precautions or personalised vaccine schedules.^{10,16,17} *Allergy* may represent an issue: a personal history of allergy to substances not included in that specific vaccine, or well-controlled asthma are clearly misconceptions. Conversely, a *personal history of hypersensitivity to vaccine components* requires an evaluation of the kind of manifestation, usually cutaneous, or the time interval between allergen administration and symptom onset, in order to discriminate between immediate (likely IgE-mediated) and delayed reactions (non IgE-mediated).

Depending on the clinical features of vaccinees, examples of precautions which may be adopted are: an immunological evaluation before administration of live vaccines in subjects with recurrent infections, or complex malformative syndromes; body temperature monitoring after vaccination in subjects with a personal history of seizures induced or augmented by fever; the monitoring of pulse oximetry in periods at risk for apnoea in babies with personal history of apnoea, or very preterm birth, low birth weight and respiratory distress in the perinatal period; programming vaccine administration according to the phase of any underlying diseases, as well as the type, dose and pharmacokinetics of drugs in long-term treatments. When IgE-mediated reactions to vaccines occur, a specialised consultation is recommended (see above). It is to be remembered that indications and contraindications may differ depending on kinds of vaccines and vaccine products, since amounts of allergens may differ. In case of egg protein allergy, measles-mumps-rubella vaccine and flu vaccine can be routinely administered without preliminary testing. A suggested precaution is to keep the patient under observation for at least 30 min (only in case of anaphylaxis after egg protein ingestion).⁹

Delayed hypersensitivity reactions to vaccine components (i.e. injection site reactions, dermatitis) are not contraindications to vaccination.⁹

Conclusions

Vaccines are biological products that are mainly offered to healthy individuals. Therefore, the highest standards of safety are guaranteed in every step of production and marketing. Nevertheless, none of these are completely devoid of adverse events, and efficacy cannot be assured in all cases. Furthermore, while benefits of vaccination extend from the single individual to the whole society, the single individual is specifically concerned about risks of serious adverse events.

Health-care providers should be aware that potentially increased risks, as well as rare true contraindications to vaccination, exist in selected cases where specialised

evaluation may be needed. Vaccine personnel should also be trained to recognise conditions that are mistakenly considered as contraindications, and to discuss real or perceived risks of adverse reactions in order to avoid missed vaccinations due to unfounded fears.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

The authors are components of the Committee for Drug and Vaccine Allergies of the Italian Society for Paediatric Allergy and Immunology (SIAIP).

All authors have equally collaborated in the design and drafting of this review. All authors read and approved the final manuscript.

Acknowledgements

Authors are indebted to Dr. Andrew Tenore for editing the English version of the manuscript. We thank our colleague Roberto Bernardini for fruitful discussions and a critical revision of the manuscript.

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