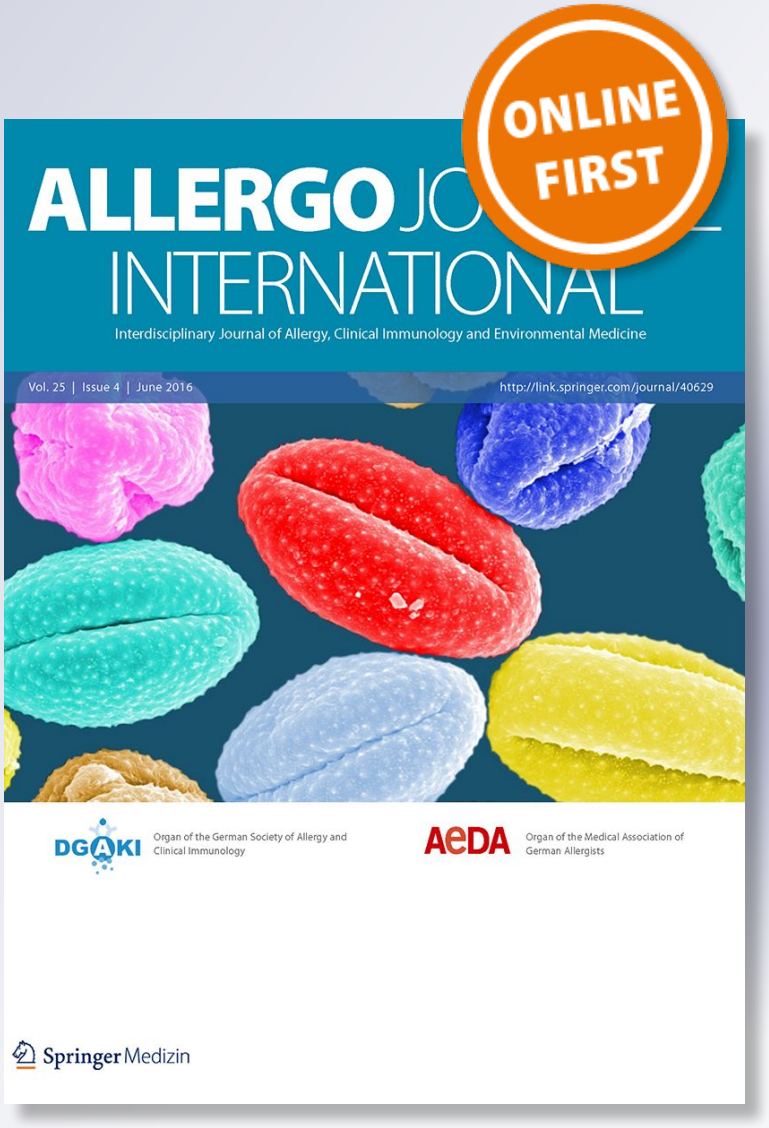
Allergies and vaccination: a myth demystified

Tobias Ankermann, Thomas Spindler, Michael Gerstlauer & Sebastian Schmidt

Allergo Journal International
Interdisciplinary Journal of
Allergy, Clinical Immunology and
Environmental Medicine

e-ISSN 2197-0378

Allergo J Int
DOI 10.1007/s40629-018-0077-8



Springer

review

Allergo J Int
https://doi.org/10.1007/s40629-018-0077-8

CrossMark

Allergies and vaccination: a myth demystified

Tobias Ankermann · Thomas Spindler · Michael Gerstlauer · Sebastian Schmidt

Received: 7 March 2018 / Accepted: 30 April 2018

Abstract
Background Vaccinations are among the commonest and most successful medical measures. Due to the drop in the incidence of vaccine-preventable diseases, rare side effects such as allergic reactions are coming more to the fore. In addition, vaccinations are often associated with the rising prevalence of allergic sensitization and allergic disease. The myth that "vaccinations cause allergies" is being circulated. This article presents the available evidence on the effect of vaccinations on the prevalence of atopic manifestations (sensitization, asthma, allergic rhinitis, food allergy) and atopic dermatitis. Based on position papers, recommendations are given on the approach to vaccinations in children with allergic disease and/or atopic dermatitis as well as on the approach in patients with anaphylactic reactions to vaccines.
Methods A literature search in PubMed and in the reference lists of the identified articles was conducted.
Results There is no evidence that vaccinations increase the risk of specific allergic sensitization or the manifestation of allergic diseases either in high-risk patients (atopy, positive family history) or in patients with no family history of atopy. Vaccinations do not cause allergies! According to experts, atopic children can be vaccinated under standard conditions without a mandatory follow-up observation period. Allergy testing should be performed following allergic reactions to vaccines or vaccine components. Follow-up vaccinations after anaphylactic reactions to vaccines or vaccine components should be performed under monitoring conditions by physicians experienced in the recognition and treatment of anaphylactic reactions.
Conclusion Standard vaccinations do not increase the risk for manifesting allergic disease or specific sensitization to environmental allergens. If individual protection is desired, and taking into account the particular risks and provisos, children with allergic disease and anaphylactic reactions to vaccines can also be vaccinated.

Keywords Allergy · Anaphylaxis · Atopy · Vaccinations · Side effect

Abbreviations

BCG	Bacillus Calmette Guérin (vaccine)
DTP/DTaP	Diphtheria, tetanus, and pertussis (vaccine); a acellular
EAACI	European Academy of Allergy and Clinical Immunology
GPA	German Society for Pediatric Allergology (*Gesellschaft für Pädiatrische Allergologie*)
HDC	Human diploid cell lines
IgE	Immunoglobulin E
ISAAC	The International Study of Asthma and Allergies in Childhood

Parts of this article were already published in 2014 (Pädiatrische Allergologie in Klinik und Praxis 2014;17:11–3).

PD Dr. T. Ankermann (✉)
Department of Pediatric and Adolescent Medicine I, University Hospital Schleswig-Holstein, Kiel Campus, Arnold-Heller-Straße 3, House 9, 24105 Kiel, Germany
ankermann@pediatrics.uni-kiel.de

Dr. T. Spindler
Allergy Campus, Hochgebirgsklinik Davos, Davos Wolfgang, Switzerland

Dr. M. Gerstlauer
Department II of Pediatric and Adolescent Medicine, Augsburg Hospital, Augsburg, Germany

PD Dr. S. Schmidt
Department and Outpatient Clinic for Pediatric and Adolescent medicine, University Hospital Greifswald, Greifswald, Germany

Published online: 18 September 2018

KiGGS	Study on the Health of Children and Adolescents in Germany (*Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland*)
LAIV	Live attenuated influenza vaccine
MAS	Multicenter allergy study
MMR	Measles, mumps, and rubella (vaccine)
OPV	Oral polio vaccine
RR	Riva-Rocci blood pressure measurement
SCIT	Specific subcutaneous immunotherapy
TBE	Tick-borne encephalitis
TIV	Trivalent inactivated influenza vaccine

Introduction

Vaccines are among the most effective and cheapest medical methods to prevent infectious diseases [1]. As with all medical interventions, adverse side effects are also seen with vaccines; however, on the whole, these are rare events. Systematic investigations report an incidence of 4.8–83 adverse events per 100,000 doses of vaccine (reviews in [2, 3]). Having said that, these reactions are generally non-allergic (hypersensitivity)-mediated local reactions at the vaccination site [4]. In contrast, anaphylactic reactions are extremely rare, with a reported incidence of 0.3–3 per million doses of vaccine [5–8]. Anaphylactic reactions are usually seen in patients with no identifiable risk factors. Previous anaphylactic reactions, including those to other allergens, and pre-existing uncontrolled bronchial asthma have been shown to be risk factors for an anaphylactic reaction to vaccines. While systematic investigations demonstrate only a slight risk of repeat adverse side effects following vaccinations, patients with anaphylactic reactions often do not undergo re-vaccination and not all events are reported, meaning that a reliable risk assessment on the basis of epidemiological data is not feasible [9].

Although the prevalence of vaccine-preventable diseases has declined as a result of vaccination programs, awareness of adverse side effects—despite the rarity of serious anaphylactic reactions—has grown among physicians as well as patients and parents [10]. This intensifies concerns about possible anaphylaxis and creates uncertainty as to whether or not to vaccinate. As a result, patients are deprived of individual protection and the vaccination rate drops.

Patients that have experienced anaphylaxis in the past to vaccine components should be subject to special safety measures in the case of further vaccinations and need to undergo a special allergy work-up prior to subsequent vaccinations [2, 3, 11–15]. An open and clearly structured approach to potential allergic reactions following vaccination is important, since adverse side effects and allergic reactions to vaccines and vaccine components are used again and again as an argument against vaccines [16–18]. There is also often uncertainty about how patients at increased risk for developing allergy and/or manifest sensitizations and allergic disorders should be vaccinated (high-risk patients). Therefore, this article discusses the diagnostic and therapeutic approach to further vaccinations in the case of suspected rare severe allergic reaction (equivalent to Ring and Messmer grade II and higher [19]) to the vaccine according to the recommendations of the position papers of the German Society for Pediatric Allergology (Gesellschaft für Pädiatrische Allergologie, GPA; [13]) and the European Academy of Allergy and Clinical Immunology (EAACI; [15]), and explains the recommended approach in risk patients.

In addition to concerns about adverse side effects as a result of vaccine administration, there is also concern among patients, parents, and health care personnel that the implemented vaccination programs can promote the development of sensitization and clinically relevant allergies [20]. This view is reinforced by opinions published on the Internet that are based on deliberate misinformation and misinterpretations [21, 22]. Therefore, this article also discusses the current status of knowledge on the effect of vaccines on the development of specific sensitizations and manifest allergic diseases.

Effect of vaccines on the development of sensitizations and allergic diseases

The prevalence of atopic diseases has risen worldwide over the last 30 years [23]. The short time period in which this development has taken place, together with epidemiological observations, suggests that the change in environmental conditions is responsible for this rise. A modulation of the immune response as a result of reduced immune stimulation in early childhood—due in part to smaller families, less care in daycare facilities, less contact with animals, less contact with pathogenic and non-pathogenic micro-organisms (bacteria, endoparasites), and a general reduction in biodiversity—has been postulated as the cause [24–27]. This observation is referred to as the "hygiene hypothesis". A link to vaccinations is regularly discussed. On the one hand, it could be that vaccines and the resultant elimination of vaccine-preventable diseases deprive the immune system of influencing factors that are important to its development. On the other, antigens contained in vaccines might stimulate the immune system in a positive manner, thereby preventing the development of sensitizations and atopic diseases (reviews in [28, 29]).

The majority of retrospective as well as prospective epidemiological studies found no increased effect of vaccines on the prevalence of allergic diseases [29–39]. Likewise, a multicenter investigation found no increased risk of specific sensitization and severe dermatitis among especially high-risk children with atopic dermatitis and a family history of allergic diseases (2184 children aged 1–2 years; [33]). In that particular study on high-risk children, the severity of dermatitis was inversely correlated with the cumula-

tive number of vaccine doses. A higher cumulative number of vaccine doses was also associated with lower specific sensitization and lower prevalence of bronchial asthma and atopic dermatitis in the German multicenter allergy study (MAS) cohort [32]. This effect for bronchial asthma was still seen at the age of 20 years in the MAS cohort [40]. The International Study of Asthma and Allergies in Childhood (ISAAC; Phase 1) also found an inverse relationship between asthma and immunizations in early childhood [34]. Retrospective analysis of data from the Study on the Health of Children and Adolescents in Germany (Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland, KiGGS) revealed that children fully immunized in the first year of life had a lower risk of developing allergic rhinitis after the age of 1 year (adjusted prevalence ratio [aOR] 0.85; 95% confidence interval [CI] 0.76–0.95). No statistically significantly increased risk was found for bronchial asthma or atopic dermatitis [29].

A consideration of the role of specific vaccines in the mediation of allergies put the pertussis vaccine repeatedly in focus, given that transient IgE formation to vaccine antigens was detected [41]. However, the follow-up investigation of a prospective vaccine trial showed no increased prevalence of allergic diseases at the age of 7 years following pertussis vaccination [42]. Similarly, a Swedish database analysis found no increased use of asthma medication at the age of 15 in adolescents vaccinated against pertussis in infancy [43]. These results are supported by a British retrospective analysis [37]. Another retrospective investigation, this time in the Netherlands, showed a risk reduction for allergic diseases following pertussis vaccination [44]. One study showed that measles infections were associated with fewer allergic symptoms, but that the vaccination showed neither a positive nor a negative correlation with allergic symptoms [45]. This lack of either risk-reducing or risk-increasing effects for the measles vaccine (and the combined MMR vaccine) has been confirmed in other investigations, in particular for asthma [32, 46]. A birth cohort in the Faroe Islands, in contrast, showed a risk reduction for asthma in MMR-vaccinated children aged 5 years (odds ratio [OR] 0.33; 95% CI 0.12–0.90), which was still detected at the age of 13 years (OR 0.22; 95% CI 0.08–0.56). In this cohort, MMR vaccination was not significantly associated with an increased or a reduced risk for atopic dermatitis, allergic rhinitis, or the detection of specific sensitization in skin prick testing [47]. Meta-analyses show that the Bacillus Calmette Guérin (BCG) vaccine is also not linked to an increased prevalence of allergic diseases and that the postulated positive effects are transient [35, 48]. However, some investigations have shown an increased risk for allergic disease following vaccinations. For example, a retrospective study demonstrated an increased rate of atopic dermatitis following MMR or measles vaccination [49]. A combined diphtheria and tetanus vaccine in the first year of life in an Australian cohort was associated with an increased risk of asthma (relative risk [RR] 1.76; 95% CI 1.11–2.78) [50]. To summarize the data, there is no evidence that vaccinations increase the risk of specific allergic sensitization or the manifestation of allergic diseases either in high-risk patients (atopy, positive family history) or in patients with no family history of atopy.

A further subject of discussion is whether delayed vaccinations or late vaccinations are able to reduce the risk of allergic disease. A reduced risk for allergic rhinitis was found in children that received their second diphtheria and tetanus vaccine with a 2-month delay. However, the authors explained this effect by confounders (e.g., more intercurrent effects in the group vaccinated late) [51]. A retrospective analysis of 11,531 fully DTP-vaccinated Canadian children revealed that the risk for asthma was reduced up to the age of 7 years if there had been a delay in the administration of the first three doses (low risk [LR] 0.4; 95% CI 0.2–0.9; [52]). Likewise, a cross-sectional survey (117 infants and young children in the US; DTP, oral polio vaccine [OPV], and MMR (4:3:1 series) at the age of 24 months) showed that these subjects had fewer visits to a subspecialist following delayed immunization [53]. In contrast, an investigation of two preschool cohorts in Great Britain (8 years apart) showed that delayed vaccination was associated with higher asthma risk [54]. Spycher et al. also found that delayed vaccination did not result in a reduced risk for allergic diseases [55]. A retrospective analysis in another British cohort of 29,238 children aged up to 11 years found no link between vaccinations and physician visits for allergic disease [39]. In an Australian population-based cohort (HealthNuts, Melbourne), the delayed administration of diphtheria-tetanus-acellular pertussis (DTaP) showed no increased risk for food allergies (aOR 0.77; 95% CI 0.36–1.62; $p = 0.49$) or specific allergic sensitizations (aOR 0.66; 95% CI 0.35–1.24; $p = 0.19$). However, a reduced incidence of atopic dermatitis and lower drug use to treat dermatitis emerged as secondary outcome parameters [56].

To summarize the data, there is no evidence that the delayed administration of vaccinations results in

Summary

Vaccinations do not promote the development of specific allergic sensitization to environmental allergens, nor do they promote the development of allergic disease (asthma, allergic rhinitis, food allergies) and neurodermatitis.

There is no evidence to suggest that the delayed administration of recommended vaccinations prevents specific allergic sensitization to environmental allergens and allergic disease (asthma, allergic rhinitis, food allergies) and neurodermatitis.

Table 1 Possible allergen sources in vaccines. (Modified from [2])

Allergen source/group	Individual factor
Active vaccine antigen	Toxoids, toxins
	Other vaccine antigen (native, recombinant)
Contamination from culture media	Chicken egg
	Chicken embryo
	Horse serum
	Cell components of mice, apes, and dogs
Other impurities	Latex
Additives (groups)	*Additives (active substances)*
Antibiotics	Neomycin
	Kanamycin
	Tetracycline
	Gentamicin
	Streptomycin
	Polymyxin B
	Amphotericin B
Preservatives	Formaldehyde
	Thimerosal
	Thimerfonate sodium
	2-Phenoxyethanol, PE
	Octoxynol
Stabilizers	Gelatin
	Lactose
	Polysorbate 80/20

a higher or lower prevalence or incidence of specific sensitizations and allergic diseases.

Immunization in atopic children or children with allergic diseases (asthma, allergic rhinitis, food allergy, atopic dermatitis)

Systematic prospective investigations that enable an individual risk assessment or that identify relevant risk markers are lacking. All practical guidelines recommend the vaccination of atopic children or children with allergic diseases under standard conditions. In the case of acute disease, vaccination should be delayed until disease resolution. If an underlying disease is unstable (e.g., uncontrolled asthma), vaccination should be considered on a case-by-case basis. As a first step, the disease should be stabilized if possible. In the case of on-going subcutaneous allergen-specific immunotherapy (SCIT), vaccinations should be carried out at the midpoint of the maintenance phase with the greatest possible interval between individual SCIT injections [13].

Immunization in children with known allergy to vaccine ingredients

Allergens in vaccines can include the vaccine antigen itself, additives such as stabilizers and preservatives, as well as contamination during the production process (Table 1; [2]). The most frequently described causal allergens in allergic vaccine reaction include chicken protein and, in the past, gelatin [57]. Using a gelatin-free vaccine is recommended in the case of clinically manifest allergy to gelatin. If this is not possible, one can follow the procedure described for yellow fever vaccination (see below) following an individual risk–benefit assessment. Allergies to other components such as latex, traces of casein (cow milk allergy), antibiotics, yeasts, thimerosal, aluminum, and phenoxyethanol are much rarer (Table 2 provides an overview of the approach in the case of these potential allergens (from [13])).

Chicken protein is an important causal allergen, since viruses in some widely used vaccines are cultured in a chicken fibroblast cell culture, while other

Table 2 Approach in rare allergies to defined vaccine components. (From [13])[a]

Vaccine component	Procedure
Latex	If there is a history of anaphylaxis following contact with latex allergens, a preparation without latex in the stopper should be used. If latex-free stoppers are not available, the vial stopper should be removed prior to drawing the vaccine. Following vaccination, the patient should be monitored for at least 30 min; the possibility for immediate and appropriate anaphylaxis treatment must be ensured. Patients with latex contact allergy can undergo regular vaccination
Cow's milk allergy (traces of casein)	The relevance of traces of casein in the culture medium in the production of vaccines to diphtheria, tetanus, and pertussis in terms of risk is unknown
	In the case of manifest cow's milk allergy with respiratory/circulatory symptoms, a non-fractional vaccine followed by at least 30 min monitoring is recommended
Antibiotics	Contact dermatitis to antibiotics contained in vaccines is not a contraindication. Vaccination is performed under standard conditions
Yeasts	Residual yeast protein in hepatitis B and papilloma virus vaccines can pose an increased risk of allergic reaction to vaccine in patients allergically sensitized to *Saccharomyces cerevisiae* and clinically manifest allergy to baker's or brewer's yeast. Following an individual risk–benefit assessment, fractional vaccination can be used as in the procedure described for yellow fever vaccination
Thimerosal	In the case of contact sensitization without manifest clinical symptoms, vaccination is performed under standard conditions. In the case of manifest contact dermatitis, a vaccine that does not contain thimerosal should be used if possible
Aluminum	In the case of contact sensitization without manifest clinical symptoms, vaccination is performed under standard conditions. In the case of contact dermatitis or the appearance of aluminum cysts or granulomas, a vaccine that does not contain aluminum should be used if possible
Phenoxyethanol	In the case of contact sensitization without manifest clinical symptoms, vaccination is performed under standard conditions. In the case of manifest contact dermatitis, a vaccine that does not contain phenoxyethanol should be used in the future if possible

[a]In the case of allergies to vaccine components, the possibility for immediate and appropriate anaphylaxis treatment must be ensured

vaccines are produced using incubated chicken eggs. Vaccines with viruses cultured in chicken fibroblast cell cultures (MMR, rabies, tick-borne encephalitis [TBE]) contain at least traces of chicken protein (in the nanogram range). Various studies have shown that children with a known history of chicken protein allergy can be vaccinated against measles, mumps, and rubella [58, 59]. Chicken protein allergy is no longer listed as a contraindication for this vaccine in international and national guidelines [13–15]. Therefore, children with manifest chicken egg allergy involving reactions limited to the skin can receive the MMR vaccine under standard conditions. Children with respiratory, circulatory, or gastrointestinal reactions should be immunized by a physician experienced in the recognition and treatment of anaphylactic reactions in children (single dose, minimum monitoring period of 2 h; [13]).

Only a small number of vaccines are produced using incubated chicken eggs (e. g., some vaccines against influenza and yellow fever vaccines). As a result of the production process, these vaccines may contain higher quantities of chicken protein (up to the 1 µg range in influenza vaccines; [60]). A number of studies have shown that the use of tri- and tetravalent inactived influenza vaccines (TIV) is safe in egg-allergic patients [61–63]. In Germany, however, TIV and live attenuated influenza vaccines (LAIV) are formally contraindicated to date in patients with symptoms of chicken egg allergy. In their place, a vaccine produced using human diploid cell lines (HDC) that contains no chicken protein can be used in adults While this vaccine is not approved for children in Europe, it is approved in the US for children from the age of 4 years.

From an allergologist perspective, influenza vaccination with TIV is possible in individuals with manifest egg allergy. In the case of exclusively cutaneous reactions to chicken egg, vaccination with TIV can be performed in the physician's office (single, unsplit dose, minimum monitoring period of 2 h); in the case of respiratory/circulatory reactions or gastrointestinal symptoms to chicken protein, TIV vaccination should be performed by a physician experienced in the treatment of anaphylactic reactions (unsplit dose, minimum monitoring period of 2 h; [13]). Balanced but comprehensive written patient information is required on the contraindication stated in the product information in the case of chicken protein allergy (off-label use). Since the German statutory healthcare insurances are not obliged to bear the costs of these vaccinations, inquiries regarding reimbursement should be made beforehand. Given that there is no recommendation on a national level, the state is not liable for vaccination damage (no liability in accordance with § 60 of the German infection Protection Act [Infektionsschutzgesetz, IfSG]).

Large quantities of residual ovalbumin are found in the yellow fever vaccine (up to the milligram range). As such, the indication for yellow fever vaccination should be reviewed carefully in the case of manifest chicken protein allergy. If the indication is reliably established, and once the patient has been fully informed about the existing formal contraindication, skin prick testing with the yellow fever vaccine should be performed. If the patient tests negative in the skin prick test, the vaccine can be split (10 and 90% of the dose) under inpatient monitoring, which offers the option of immediate anaphylaxis treatment. In the case of a positive skin prick test, the vaccine should be administered in fractional doses (Fig. 3) under the same inpatient conditions [12, 13].

Diagnostic approach in suspected allergic reactions to vaccines

Predictive allergy testing for potential vaccines or vaccine components is not recommended—not least since sensitization can be expected far more frequently than can a resultant clinically relevant allergic reaction. The diagnostic algorithms published to date have not been evaluated in prospective or retrospective investigations and the approaches have not been standardized [2, 11, 12, 64–68]. Following an allergic reaction to vaccine, it is essential to carry out a risk–benefit assessment in consultation with the parents, while taking the severity of the reaction into consideration, before any diagnostic steps are taken. Diagnostic testing only makes sense if other vaccinations with the respective vaccine antigen or vaccines potentially containing allergenic components are indicated. An overview of possible allergen sources in vaccines is provided in Table 1.

The first diagnostic step is to take a thorough patient history. Cardinal questions include the following: the point in time at which the reaction occurred (immediate-type—within a maximum of 4 h—or delayed reaction), extent (local or systemic), precise description of the clinical reaction, and identification of the vaccine ingredients that are possible triggers. In the case of a delayed reaction, further information on patient history is required in particular to differentiate other possible causes or cofactors (Table 3 for important patient history information in the case of suspected allergic reaction to vaccine).

Further diagnostic tests are only beneficial in the case of systemic immediate-type reactions. No diagnostic testing is required for isolated, even extensive, local reactions [13, 15]. There is no evidence to date to demonstrate whether an atopy patch test for risk stratification prior to further vaccinations is suitable.

In the case of systemic immediate-type reactions that, given the clinical picture, are consistent with an IgE-mediated reaction (Table 3), skin testing with the specific vaccine is recommended. If this proves positive, an attempt should be made to identify the most likely causal agent. In order to detect allergic sensitization to single allergens (e.g., ovalbumin,

Table 3 Important patient history information in suspected allergic reactions to vaccine

Subject	Patient history information
Timing	Immediate (within 4 h)
	Delayed-type
Extent	Local
	Systemic
Symptoms	Urticaria/angioedema
	Rash
	Rhinoconjunctivitis
	Obstructive ventilatory disorder
	Circulatory reaction (tachycardia, drop in blood pressure)
	Vomiting, nausea
	Defecation
Duration	Hours
	Days
	Longer or fluctuating
Resolution	Spontaneous
	Under medication (which?)
Cofactors	Infection
	Recent contact with other potential allergens
Vaccination history	Previous allergic reactions to vaccine?
	Further vaccination required?
Vaccine	Preparation
	Ingredients
	Batch
Other known allergies/ disorders	Dermatitis, asthma, rhinoconjunctivitis
	Urticaria
	Food allergy
	Drug allergy
	Contact allergic

gelatin) contained in the vaccine, serum IgE tests (except for vaccine antigens) or skin prick tests are recommended. Fig. 1 provides an overview of the possible diagnostic work-up in such cases. Skin testing (skin prick tests and intradermal tests) should be carried out according to the current recommendations by physicians experienced in the performance and evaluation of skin tests, since irritant, nonspecific reactions are not uncommon with these tests (in particular intradermal testing with 1:10 dilution; [69]).

Approach to subsequent vaccinations following allergic reactions to vaccine

The decision on whether or not to perform subsequent vaccinations should only be made following a thorough risk–benefit assessment in consultation with the parents. Where appropriate, vaccine titers that have already been reached should be considered in the decision-making process. Against the background of previous reactions to vaccines, it is mandatory that parents and patients be provided with comprehensive information during a personal consultation and that this consultation is documented prior to renewed vaccination. An attempt should always be made to perform the vaccination using an alternative vaccine that does not contain the identified or suspected allergen [13, 15].

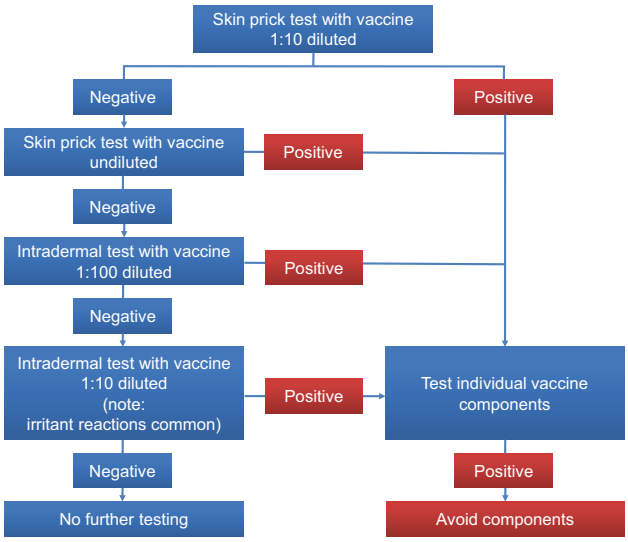


Fig. 1 Skin testing following an immediate-type allergic reaction. (Same procedure as in immediate-type reactions to chicken egg and vaccines with high ovalbumin content, e.g., yellow fever vaccine)

The following pragmatic approach for further vaccinations (not systematically evaluated; Fig. 2) is recommended in children with confirmed local immediate-type reactions (not life-threatening anaphylaxis or systemic reactions). Mild local reactions require neither diagnostic testing nor particular monitoring [13, 15]:

- Negative skin test: vaccine administration followed by observation for 1 h in the medical practice.
- Positive skin test: fractional vaccine administration (Fig. 3). Observation for at least 1 h in the medical practice.
- Skin testing either not feasible or unequivocal: vaccine administration followed by observation for at least 1 h in the medical practice.

The following pragmatic approach for further vaccinations (not systematically evaluated; Fig. 2) is recommended in children with confirmed systemic immediate-type reactions:

- Skin test negative (or unfeasible/unequivocal), but known previous reaction, life-threatening anaphylactic reaction, or systemic reaction: administration of 10% vaccine dose. Observation for 30 min. If no reaction is observed: administration of the remaining dose (90%) and further inpatient observation for at least 120 min.
- Anaphylactic or systemic reaction to polyvalent vaccines, skin testing unfeasible or unequivocal: vac-

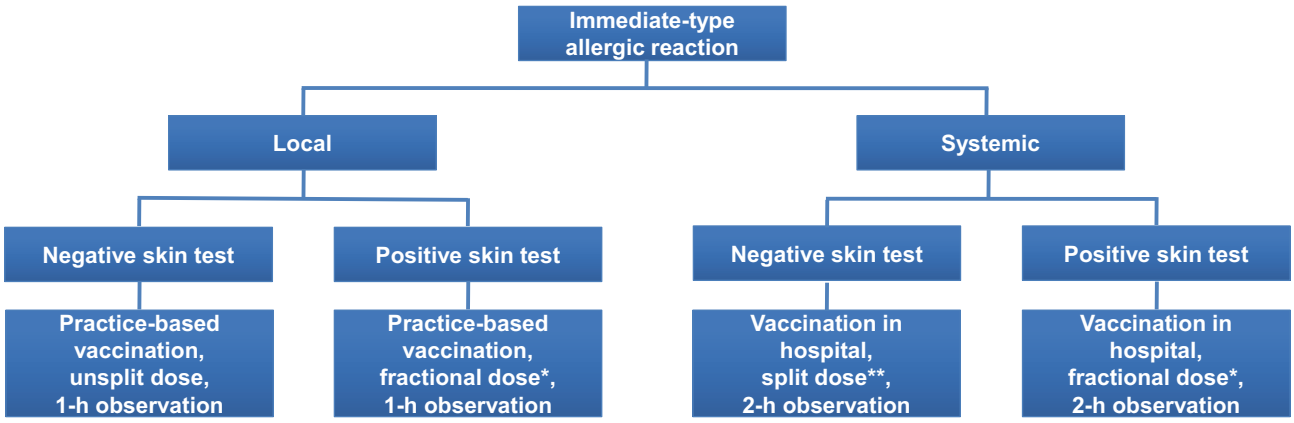


Fig. 2 Diagnostic approach following allergic reactions to vaccines. (*Split doses according to Fig. 3. **Split doses 10%, 90%)

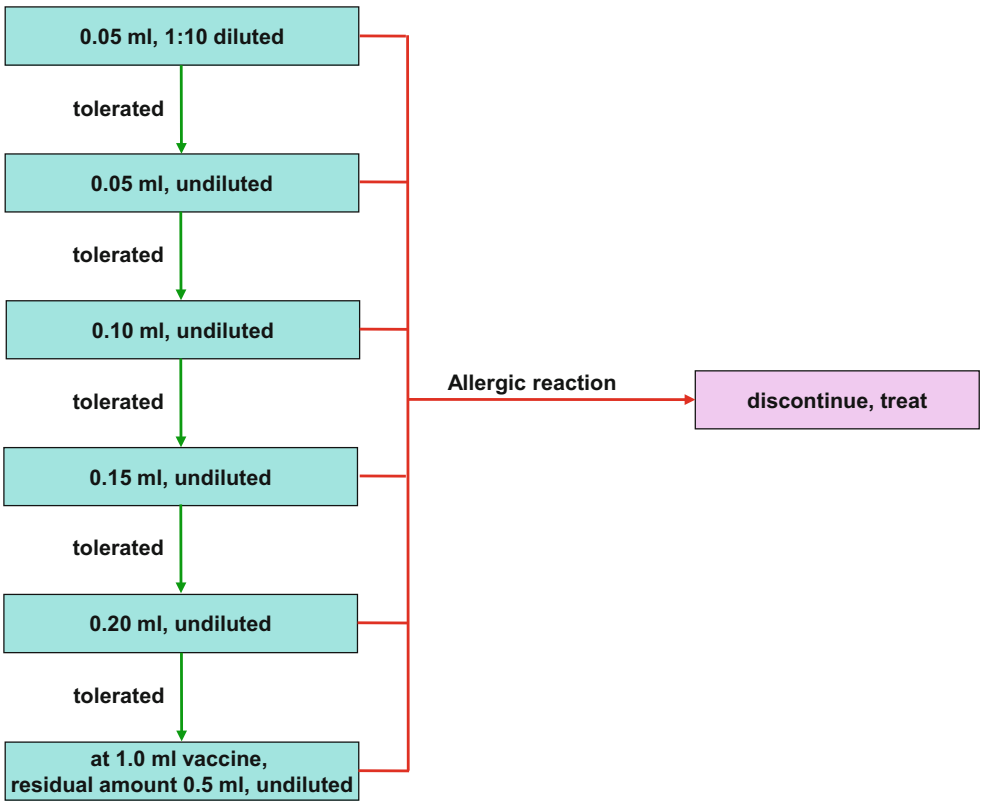


Fig. 3 Vaccination in the case of high allergic risk using fractional vaccine doses and dose escalation (dose interval: 30–60 min)

cine administration, if possible with single components. Consider fractional vaccine administration.

- Positive skin test: vaccination under clinical observation (in hospital), fractional vaccine administration according to Fig. 3. Follow-up observation under intensive monitoring (monitor, pulse oximetry monitoring, RR measurement, clinical observation) for at least 120 min. Inpatient stay of at least 12 h.

Following systemic allergic immediate-type reactions to previous vaccinations, (inpatient) monitoring of patients for at least 12 h is recommended in order for possible delayed anaphylactic and allergic reactions to be promptly recognized and treated by appropriately trained personnel. From a pragmatic perspective, inpatient observation overnight is recommended. The recommended intensive monitoring time for immediate-type allergic reactions (monitor, RR measurement) is 2 h.

Children that have experienced delayed reactions to vaccinations can be revaccinated under standard conditions. The methods currently available do not permit risk assessment.

Fractional administration and dose escalation can be carried out if vaccination is absolutely essential in patients with previous systemic immediate-type re-

Summary

Allergy testing should be performed following vaccine-induced anaphylaxis in order to minimize the risk of future anaphylactic reactions.

In the case of previous anaphylactic reactions to vaccines or anaphylaxis induced by a vaccine component (e.g., chicken egg protein), follow-up vaccinations should be carried out under inpatient supervision (i.v. access, fractional dose, minimum monitoring time of 2 h following final partial dose) by a physician experienced in recognizing and treating anaphylactic reactions in children. If possible, the triggering allergen should be avoided.

actions ([64]; Fig. 3). This injection protocol should be carried out under monitoring conditions (blood pressure measurement, monitor, pulse oximetry, i.v. access in place) with the possibility of intensive care intervention. Another option is to administer the vaccine dose or fractional vaccine under premedication with antihistamines and/or glucocorticoids, as used in patients allergic to iodinated radiocontrast media [70]. However, this approach has not been systematically investigated.

Summary

To summarize the data, there is no evidence that vaccinations increase the risk of specific allergic sensitization or the manifestation of allergic diseases either in high-risk patients (atopy, positive family history) or in patients with no family history of atopy. Vaccinations do not cause allergies! According to the available evidence, the delayed administration of vaccines compared with recommended times has no effect on subsequent specific sensitization or allergic diseases. According to experts, atopic children can be vaccinated under standard conditions without a mandatory follow-up observation period. Allergy testing should be performed following allergic reactions to vaccines or vaccine components. Follow-up vaccinations after anaphylactic reactions to vaccines or vaccine components should be performed by physicians experienced in the recognition and treatment of anaphylactic reactions.

Acknowledgements The authors would like to thank Christoph Grüber for formulating the basis for this work and for kindling the authors' enthusiasm for the topic allergy and immunization. He is missed.

Conflict of interest T. Ankermann, T. Spindler, M. Gerstlauer and S. Schmidt declare that they have no competing interests.

References

1. Hajj Hussein I, Chams N, Chams S, El Sayegh S, Badran R, Raad M, et al. Vaccines through centuries: major cornerstones of global health. Front Public Health. 2015;3:269.
2. Fritsche PJ, Helbling A, Ballmer-Weber BK. Vaccine hypersensitivity—update and overview. Swiss Med Wkly. 2010;140:238–46.
3. Caubet JC, Rudzeviciene O, Gomes E, Terreehorst I, Brockow K, Eigenmann PA. Managing a child with possible allergy to vaccine. Pediatr Allergy Immunol. 2014;25:394–403.
4. Mentzer D, Keller-Stanislawski B. Daten zur Pharmakovigilanz von Impfstoffen aus dem Jahr 2014. Bull Arzneimittelsicherh. 2016;2:12–9. URL: http://www.pei.de/SharedDocs/Downloads/bulletin-einzelartikel/2016-daten-pharmakovigilanz-impfstoffe-2014.pdf?__blob=publicationFile&v=2.
5. Zent O, Arras-Reiter C, Broeker M, Hennig R. Immediate allergic reactions after vaccinations—a post-marketing surveillance review. Eur J Pediatr. 2002;161:21–5.
6. Bohlke K, Davis RL, Marcy SM, Braun MM, DeStefano F, Black SB, et al. Risk of anaphylaxis after vaccination of children and adolescents. Pediatrics. 2003;112:815–20.
7. McNeil MM, Weintraub ES, Duffy J, Sukumaran L, Jacobsen SJ, Klein NP, et al. Risk of anaphylaxis after vaccination in children and adults. J Allergy Clin Immunol. 2016;137:868–78.
8. Oberle D, Pavel J, Rieck T, Weichert S, Schroten H, Keller-Stanislawski B, et al. Anaphylaxis after immunization of children and adolescents in Germany. Pediatr Infect Dis J. 2016;35:535–41.
9. Zafack JG, De Serres G, Kiely M, Gariepy MC, Rouleau I, Top KA. Risk of recurrence of adverse events following immunization: a systematic review. Pediatrics. 2017;140:120163707.
10. Chen RT. Vaccine risks: real, perceived and unknown. Vaccine. 1999;17(Suppl3):S41–S6.
11. Wood RA, Berger M, Dreskin SC, Setse R, Engler RJ, Dekker CL, et al. An algorithm for treatment of patients with hypersensitivity reactions after vaccines. Pediatrics. 2008;122:e771–e7.
12. Kelso JM, Greenhawt MJ, Li JT, Nicklas RA, Bernstein DI, Blessing-Moore J, et al. Adverse reactions to vaccines practice parameter 2012 update. J Allergy Clin Immunol. 2012;130:25–43.
13. Grüber C, Ankermann T, Bauer CP, Bruns R, Eigenmann P, Fischer PJ, et al. Pädiatrische Allergologie in Klinik und Praxis. In: Gesellschaft für Pädiatrische Allergologie und Umweltmedizin, editor. Sonderheft „Allergie und Impfen". Bonn: ikomm; 2015.
14. Dreskin SC, Halsey NA, Kelso JM, Wood RA, Hummell DS, Edwards KM, et al. International Consensus (ICON): allergic reactions to vaccines. World Allergy Organ J. 2016;9:32.
15. Nilsson L, Brockow K, Alm J, Cardona V, Caubet JC, Gomes E, et al. Vaccination and allergy: EAACI position paper, practical aspects. Pediatr Allergy Immunol. 2017;28:628–40.
16. Davies P, Chapman S, Leask J. Antivaccination activists on the world wide web. Arch Dis Child. 2002;87:22–5.
17. Betsch C, Sachse K. Debunking vaccination myths: strong risk negations can increase perceived vaccination risks. Health Psychol. 2013;32:146–55.
18. Yaqub O, Castle-Clarke S, Sevdalis N, Chataway J. Attitudes to vaccination: a critical review. Soc Sci Med. 2014;112:1–11.
19. Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. Lancet. 1977;1:466–9.

20. Heininger U. An internet-based survey on parental attitudes towards immunization. Vaccine. 2006;24:6351–5.
21. Müller A. Impfen macht krank. 2009. www.gesundheitlicheaufklaerung.de/impfen-macht-krank. Accessed 05.02.2018.
22. Reitemeyer F. Impfen? Nein, Danke!, letzte Änderung 18. Oktober 2016. 2014. www.impfen-nein-danke.de/krankheiten-von-a-z/allergien. Accessed 05.02.2018.
23. Pawankar R. Allergic diseases and asthma: a global public health concern and a call to action. World Allergy Organ J. 2014;7:12.
24. Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. N Engl J Med. 2002;347:911–20.
25. Ege MJ, Mayer M, Normand AC, Genuneit J, Cookson WO, Braun-Fahrländer C, et al. GABRIELA Transregio 22 Study Group. Exposure to environmental microorganisms and childhood asthma. N Engl J Med. 2011;364:701–9.
26. Ege MJ. The hygiene hypothesis in the age of the microbiome. Ann Am Thorac Soc. 2017;14(Supplement_5):S348–S53.
27. von Hertzen L, Beutler B, Bienenstock J, Blaser M, Cani PD, Eriksson J, et al. Helsinki alert of biodiversity and health. Ann Med. 2015;47:218–25.
28. Grüber C, Nilsson L, Björkstén B. Do early childhood immunizations influence the development of atopy and do they cause allergic reactions? Pediatr Allergy Immunol. 2001;12:296–311.
29. Schlaud M, Schmitz R, Poethko-Müller C, Kuhnert R. Vaccinations in the first year of life and risk of atopic disease—Results from the KiGGS study. Vaccine. 2017;35:5156–62.
30. Koppen S, de Groot R, Neijens HJ, Nagelkerke N, van Eden W, Rümke HC. No epidemiological evidence for infant vaccinations to cause allergic disease. Vaccine. 2004;22:3375–85.
31. Matheson MC, Walters HE, Burgess JA, Jenkins MA, Giles GG, Hopper JL, et al. Childhood immunization and atopic disease into middle-age—a prospective cohort study. Pediatr Allergy Immunol. 2010;21:301–6.
32. Grüber C, Illi S, Lau S, Nickel R, Forster J, Kamin W, et al. Transient suppression of atopy in early childhood is associated with high vaccination coverage. Pediatrics. 2003;111:e282–e8.
33. Grüber C, Warner J, Hill D, Bauchau V, EPAAC Study Group. Early atopic disease and early childhood immunization—is there a link? Allergy. 2008;63:1464–72.
34. Asher MI, Stewart AW, Mallol J, Montefort S, Lai CK, Aït-Khaled N, et al. Which population level environmental factors are associated with asthma, rhinoconjunctivitis and eczema? Review of the ecological analyses of ISAAC Phase One. Respir Res. 2010;11:8.
35. Balicer RD, Grotto I, Mimouni M, Mimouni D. Is childhood vaccination associated with asthma? A meta-analysis of observational studies. Pediatrics. 2007;120:e1269–e77.
36. Martignon G, Oryszczyn MP, Annesi-Maesano I. Does childhood immunization against infectious diseases protect from the development of atopic disease? Pediatr Allergy Immunol. 2005;16:193–200.
37. Spycher BD, Silverman M, Egger M, Zwahlen M, Kuehni CE. Routine vaccination against pertussis and the risk of childhood asthma: a population-based cohort study. Pediatrics. 2009;123:944–50.
38. Maher JE, Mullooly JP, Drew L, DeStefano F. Infant vaccinations and childhood asthma among full-term infants. Pharmacoepidemiol Drug Saf. 2004;13:1–9.
39. McKeever TM, Lewis SA, Smith C, Hubbard R. Vaccination and allergic disease: a birth cohort study. Am J Public Health. 2004;94:985–9.
40. Grabenhenrich LB, Gough H, Reich A, Eckers N, Zepp F, Nitsche O, et al. Early-life determinants of asthma from birth to age 20 years: a German birth cohort study. J Allergy Clin Immunol. 2014;133:979–88.
41. Nilsson L, Grüber C, Granström M, Björkstén B, Kjellman NI. Pertussis IgE and atopic disease. Allergy. 1998;53:1195–201.
42. Nilsson L, Kjellman NI, Björkstén B. Allergic disease at the age of 7 years after pertussis vaccination in infancy: results from the follow-up of a randomized controlled trial of 3 vaccines. Arch Pediatr Adolesc Med. 2003;157:1184–9.
43. Vogt H, Bråbäck L, Kling AM, Grünewald M, Nilsson L. Pertussis immunization in infancy and adolescent asthma medication. Pediatrics. 2014;134:721–8.
44. Bernsen RM, de Jongste JC, van der Wouden JC. Lower risk of atopic disorders in whole cell pertussis-vaccinated children. Eur Respir J. 2003;22:962–4.
45. Rosenlund H, Bergström A, Alm JS, Swartz J, Scheynius A, van Hage M, et al. PARSIFAL Study Group. Allergic disease and atopic sensitization in children in relation to measles vaccination and measles infection. Pediatrics. 2009;123:771–8.
46. Hviid A, Melbye M. Measles-mumps-rubella vaccination and asthma-like disease in early childhood. Am J Epidemiol. 2008;168:1277–83.
47. Timmermann CA, Osuna CE, Steuerwald U, Weihe P, Poulsen LK, Grandjean P. Asthma and allergy in children with and without prior measles, mumps, and rubella vaccination. Pediatr Allergy Immunol. 2015;26:742–9.
48. Linehan MF, Nurmatov U, Frank TL, Niven RM, Baxter DN, Sheikh A. Does BCG vaccination protect against childhood asthma? Final results from the Manchester Community Asthma Study retrospective cohort study and updated systematic review and meta-analysis. J Allergy Clin Immunol. 2014;133:688–695.e14.
49. Olesen AB, Juul S, Thestrup-Pedersen K. Atopic dermatitis is increased following vaccination for measles, mumps and rubella or measles infection. Acta Derm Venereol. 2003;83:445–50.
50. Thomson JA, Widjaja C, Darmaputra AA, Lowe A, Matheson MC, Bennett CM, et al. Early childhood infections and immunisation and the development of allergic disease in particular asthma in a high-risk cohort: A prospective study of allergy-prone children from birth to six years. Pediatr Allergy Immunol. 2010;21:1076–85.
51. Bremner SA, Carey IM, DeWilde S, Richards N, Maier WC, Hilton SR, et al. Timing of routine immunisations and subsequent hay fever risk. Arch Dis Child. 2005;90:567–73.
52. McDonald KL, Huq SI, Lix LM, Becker AB, Kozyrskyj AL. Delay in diphtheria, pertussis, tetanus vaccination is associated with a reduced risk of childhood asthma. J Allergy Clin Immunol. 2008;121:626–31.
53. Chung EK, Casey R, Pinto-Martin JA, Pawlowski NA, Bell LM. Routine and influenza vaccination rates in children with asthma. Ann Allergy Asthma Immunol. 1998;80:318–22.
54. Kuehni CE, Davis A, Brooke AM, Silverman M. Are all wheezing disorders in very young (preschool) children increasing in prevalence? Lancet. 2001;357:1821–5.
55. Spycher BD, Silverman M, Kuehni CE. Timing of routine vaccinations and the risk of childhood asthma. J Allergy Clin Immunol. 2008;122:656. author reply 657–8.
56. Kiraly N, Koplin JJ, Crawford NW, Bannister S, Flanagan KL, Holt PG, et al. Timing of routine infant vaccinations and risk of food allergy and eczema at one year of age. Allergy. 2016;71:541–9.
57. Sakaguchi M, Inouye S. IgE sensitization to gelatin: the probable role of gelatin-containing diphtheria-

tetanus-acellular pertussis (DTaP) vaccines. Vaccine. 2000;18:2055–8.
58. Fox A, Lack G. Egg allergy and MMR vaccination. Br J Gen Pract. 2003;53:801–2.
59. Baxter DN. Measles immunization in children with a history of egg allergy. Vaccine. 1996;14:131–4.
60. McKinney KK, Webb L, Petersen M, Nelson M, Laubach S. Ovalbumin content of 2010–2011 influenza vaccines. J Allergy Clin Immunol. 2011;127:1629–32.
61. Webb L, Petersen M, Boden S, LaBelle V, Bird JA, Howell D, et al. Single-dose influenza vaccination of patients with egg allergy in a multicenter study. J Allergy Clin Immunol. 2011;128:218–9.
62. Fung I, Spergel JM. Administration of influenza vaccine to pediatric patients with egg-induced anaphylaxis. J Allergy Clin Immunol. 2012;129:1157–9.
63. Des Roches A, Paradis L, Gagnon R, Lemire C, Bégin P, Carr S, et al. Egg-allergic patients can be safely vaccinated against influenza. J Allergy Clin Immunol. 2012;130:1213–1216.e1.
64. American Academy of Pediatrics. Active immunization. In: Pickering LK, Baker CJ, Long SS, McMillan J, editors. Red book: 2006 report of the committee on infectious diseases. 27th ed. Elk Grove Village: American Academy of Pediatrics; 2006. pp. 446–8.
65. Georgitis JW, Fasano MB. Allergenic components of vaccines and avoidance of vaccination-related adverse events. Curr Allergy Rep. 2001;1:11–7.
66. Grüber C, Niggemann B. A practical approach to immunization in atopic children. Allergy. 2002;57:472–9.
67. Kroger AT, Atkinson WL, Marcuse EK, Pickering LK, Advisory Committee on Immunization Practices (ACIP). General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). Mmwr Recomm Rep. 2006;55(RR-15):1–48.
68. Vanlander A, Hoppenbrouwers K. Anaphylaxis after vaccination of children: review of literature and recommendations for vaccination in child and school health services in Belgium. Vaccine. 2014;32:3147–54.
69. Wood RA, Setse R, Halsey N, Clinical Immunization Safety Assessment (CISA) Network Hypersensitivity Working Group. Irritant skin test reactions to common vaccines. J Allergy Clin Immunol. 2007;120:478–81.
70. Canter LM. Anaphylactoid reactions to radiocontrast media. Allergy Asthma Proc. 2005;26:199–203.