Vaccinations and allergies

I. De Schutter, A. Malfroot
UZ Brussel
The following are true allergic (IgE-mediated) reactions?

A anaphylaxis  
B serum sickness  
C Arthus reaction  
D urticaria  
E itching nodules  
F local (painful) swelling and erythema

1. A + C + D + F  
2. A + C + D + E + F  
3. B + C + D + F  
4. A + C + F  
5. A + D
Hypersensitivity reactions

- Immediate reactions (type 1 hypersensitive reactions)
  - IgE-mediated
  - minutes up to 4h after vaccine
  - urticaria, angio-edema, resp. distress, anaphylaxis

- Delayed reactions (type 3 hypersensitive reactions)
  - immune complexes, T-cell mediated (?)
  - hours to days (up to 2-3 weeks) after vaccine
  - rashes (urticaria, erythema multiforme), Arthus reaction, angio-edema, arthritis,…

- Non immunologic:
  - hard itching nodules < adjuvans ex. Aluminium
The following symptoms are common in anaphylaxis

A. itching erythema or urticaria
B. pallor
C. coughing
D. bradycardia
E. urinary loss
F. unconsciousness

1. A + B + C + F
2. A + C + D + E + F
3. B + C + D + F
4. A + C + F
5. A + C + D + F
Anaphylaxis <-> pseudo allergic reactions

- **Anaphylaxis:**
  - acute allergic reaction (resp tract, and/or cardiovascular sympt and/or cutaneous sympt)
    - laryngeal oedema/ bronchospasme
    - shock (volume deficit due to increased vascular permeability)
    - urticaria, angio-edema

- **Syncope:**
  - palor, hypotension, nausea, (vomiting), muscle weakness, bradycardia

- **Hyperventilation**
The following statements are correct

A  A non-allergic person may go home immediately after any vaccination
B  In a non-allergic person, observation for 15 min. is only necessary after vaccination with a life-attenuated vaccine
C  Observation for at least 15 min. is necessary for any person following any vaccination
D  An egg allergic person must be observed during 30 min. after YF-vaccination

1. A + D
2. B + D
3. C + D
4. C
5. None is correct
Risk of adverse reactions following vaccination

Syncope

- Incidence: unknown
- 77.4% in persons < 20y (45.5% in 10-19y)
- Morbidity related to fall

- FDA: 2000-2006: 107 reports of syncope/presyncope/unintended injury on day of vaccination
  - 100/107 within 20’ after vaccination
  - 105/107 falls; 2 motor cycle collisions
  - 83/107: 2-17y old
  - 3/107 severe head injuries (2 fatal cases)
  - 65/107: moderate to minor injuries of the head or extremities
  - 39/107: falls without any injuries

1 C. Vandermeulen Tijdschr. Voor Geneeskunde 2004; 60 (20): 1456-61
Risk of adverse reactions following vaccination

Anaphylaxis
- Anaphylaxis in children/ ado’s
  → 0.65 cases/ $10^6$ doses – 1.53 cases/ $10^6$ doses
- Estimated incidences:
  - DTP: 2/ 100.000
  - HBV: 0.16/ 100.000
  - MMR: 0.016 - 0.35/ 100.000
  - YF vaccine: 0.76/ 100.000 (40/5.236.820 doses)

Other
- YF-vaccine associated neutropenic disease
  → 0.4/ 100.000
- YF-vaccine associated viscerotropic disease
  → 0.3/ 100.000

2 Plotkin 2008
4 N.P. Lindsey et al. Vaccine 2008; 26: 6077-6082
Anaphylaxis

- **onset**
  - minutes up to 4h after vaccination

- **respiratory symptoms**
  - larynx edema
  - bronchospasm, coughing

- **cutaneous symptoms**
  - urticaria
  - pruritus
  - angio-edema

- **cardiovascular symptoms**
  - hypotension (persistent)
  - tachycardia

- **neurological symptoms**
  - unconsciousness (persistent)

Syncope

- **onset**
  - before
  - during
  - up to 15 min after vaccination

- **no respiratory symptoms**

- **cutaneous symptoms**
  - pallor
  - sweating

- **cardiovascular symptoms**
  - hypotension (short)
  - bradycardia

- **neurological symptoms**
  - unconsciousness (short)
  - urinary loss

Adapted from “Handboek Vaccinaties” Van Gorcum 2007
Increased risk for anaphylaxis is associated with

A  Contact allergy for neomycin
B  dyspnoea after ingestion of eggs
C  swelling of the limb after formal vaccination (Arthus reaction)
D  urticaria after formal vaccination

1. A + B + D
2. B + D
3. B + C + D
4. All of the above
Prevention of anaphylaxis

- Identification of patients at increased risk through anamnesis
  Previous reactions (edema of mouth / larynx, dyspnoe, cardiovascular signs) after contact with
  - any vaccin,
  - latex,
  - antibiotics (neomycin, polymyxine),
  - eggs,
  - yeast,
  - other
- Other evaluations if “+” anamnesis: ID test, skin test, ...
- Patients with increased risk => vaccination in hospital setting with rescusitation possibilities
- Always 15 min. observation after any vaccination
Suspected IgE-mediated reaction: work-up

● **Evaluation of IgE-mediated reaction**\(^1\)
  → skin prick tests: 1/10 ; full strength
  → specific serum IgE
  → intradermal tests: 1/100 ; 1/10
    ● If “-”: IgE-mediated allergy very unlikely
  → basophil activation test (BAT)\(^2\)
    ● IgE-mediated allergy for in- and outdoor allergens, food allergies, latex allergy, hymenoptera venom allergy, some drug allergies
    ● no routine analysis

● **IgG-level**\(^1\)
  → if level consistent with protection from disease => consider withholding additional doses

---

\(^1\) Kelso J. et al. Ann Allergy Asthma Immunol 2009; 103: S1-14

\(^2\) Ebo D. et al. Cytometry Part B 2008; 74B: 201-210
Table 1. Levels of Antibody Associated With Protection From Vaccine-Preventable Diseases

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Protective level of IgG antibody ≥</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria</td>
<td>0.1 IU/mL¹¹</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em> type B</td>
<td>0.15 μg/mL⁹⁹</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>10 mIU/mL³⁰</td>
</tr>
<tr>
<td>Hepatitis B surface antibody</td>
<td>10 mIU/mL³¹</td>
</tr>
<tr>
<td>Measles (rubeola)</td>
<td>120 mIU/mL (PRN titer)³²</td>
</tr>
<tr>
<td>Polio (inactivated)</td>
<td>1:8 neutralizing antibody titer³³</td>
</tr>
<tr>
<td>Rabies</td>
<td>0.5 IU/mL (VNA titer)³⁴</td>
</tr>
<tr>
<td>Rubella</td>
<td>10 IU/mL⁸⁰</td>
</tr>
<tr>
<td>Tetanus</td>
<td>0.1 IU/mL¹¹</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>0.7 IU/mL²⁹</td>
</tr>
</tbody>
</table>

Abbreviations: IU, international units; mIU, milli-international units; PRN, plaque reduction neutralization; VNA, virus-neutralizing antibodies.
Algorithm for management of suspected allergic reactions to vaccines

1. **Case report**
   - History consistent with immediate hypersensitivity? (Y/N)
     - **Y**
       - Related to vaccine(s)? (Y/N)
         - **Y**
           - Additional doses of vaccine indicated? (Y/N)
             - **Y**
               - Serologic testing for immunity
             - **N**
               - Immunize if indicated or evaluate under causality algorithm if concerned about reaction severity
       - **N**
         - Immune
         - Susceptible or serological testing unavailable, impractical or not indicated
           - Skin testing
             - High risk for target disease? (Y/N)
               - **Y**
                 - Immunize under controlled conditions. Use alternative vaccines if available
               - **N**
                 - Reconsider risk benefit analysis. Immunize if indicated. Observe for reaction.
         - Not indicated or impossible
           - Reconsider risk benefit analysis. Immunize if indicated. Observe for reaction.
     - **N**
       - Immunize if indicated or evaluate under causality algorithm if concerned about reaction severity
Adrenaline (epinephrine) IM (1:1000 sol.) in m. quadriceps.

Dosis: $0.01\text{mg/kg} = 0.01\text{ml/kg}$ max. 0.5 mg

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Dose (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 year</td>
<td>0.05-01 ml</td>
</tr>
<tr>
<td>1-2y (~10kg)</td>
<td>0.1 ml</td>
</tr>
<tr>
<td>2-3y (~15kg)</td>
<td>0.15 ml</td>
</tr>
<tr>
<td>4-6y (~20kg)</td>
<td>0.20 ml</td>
</tr>
<tr>
<td>7-10y (~30kg)</td>
<td>0.30 ml</td>
</tr>
<tr>
<td>11-12y (~40kg)</td>
<td>0.40 ml</td>
</tr>
<tr>
<td>≥13y</td>
<td>0.40-0.50 ml</td>
</tr>
</tbody>
</table>

Repeat dose after 5 min. if no clinical response
An egg-allergic person may be vaccinated under normal conditions with:

A YF-vaccine
B MMR
C hepatitis A vaccine
D influenza vaccine
E japanese encephalitis vaccine

1. A + B + C
2. B + C + E
3. C + D + E
4. B + C + D
5. B + C + D + E
The following statements are true

A Gelatine is a major allergen in MMR and JE-vax
B latex allergy is a contra-indication for any vaccine
C yeast allergy is associated with adverse events following hepatitis A vaccine
D contact allergy for neomycin is a contra-indication for vaccination with neomycin containing vaccines
E thiomersal is a major cause of anaphylaxis after vaccination

1. A + B + D + E
2. A + C + E
3. A + B + C
4. A + C
5. A
6. None of the above
Egg allergy

- **MMR** ¹, ²
  → culture on chicken embryo fibroblasts
    - no special precautions necessary
- **Influenza and YF-vaccin** ¹, ²
  → culture on chicken eggs
    - **serious or life-threatening allergy**
      - skin testing
      - desensitisation (if skin test +)
    - **less severe or local manifestations of allergy**
      - no skin testing
      - vaccination in 2 steps ³ (evaluated for influenza vaccines)
        1° 10% of dose SC - 30 min observation
        2° 90% of dose SC - 30 min observation

¹ Plotkin 2008; ² Red Book 2006
Yellow fever vaccine and serious or life-threatening egg allergy

- **Flow chart (3 steps)\(^1\)**
  - Skin prick test (“+” if wheal \(\geq 3\)mm larger than control + surrounding flare)
  - ID-test (“+” if wheal \(\geq 5\)mm or larger than control)
  - SC administration of reduced dose vaccine

  - no reaction: -> continue vaccination
  - reaction: - stop vaccination
    - desensitisation if vaccine really warranted

- **Protected seroimmunity after reduced dose**
  - Roukens A et al. Vaccine 2009; 27: 2408-09

\(^1\) Red book 2006
Flowchart: Vaccination in patients with serious or life threatening egg allergy

- Skin prick test
  - vaccine (1:10; 1:1)
  - histamine
  - saline 0.9%

- SPT neg
  - administer vaccine
  - observe 30 min
  - no immediate reaction
    - administer 0.4 ml of vaccine
  - immediate reaction
    - stop administration (unless vaccination is really necessary)

- SPT pos
  - ID-testing
    - 0.02 ml 1:100 (1:10) diluted vaccine
    - controle: saline 0.9%
    - neg
      - administer vaccine
    - pos
      - administer 0.1 ml SC
  - cancel administration

Adapted from Red book 2006
Desensitisation protocol

- Controlled setting
- interval of 30 min between doses
- next dose only when no signs of AR

<table>
<thead>
<tr>
<th>Option</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td>0.05ml of 1:10 solution</td>
</tr>
<tr>
<td>b.</td>
<td>0.05 ml of full strength</td>
</tr>
<tr>
<td>c.</td>
<td>0.10 ml of full strength</td>
</tr>
<tr>
<td>d.</td>
<td>0.15 ml of full strength</td>
</tr>
<tr>
<td>e.</td>
<td>0.20 ml of full strength</td>
</tr>
<tr>
<td>f.</td>
<td>0.50 ml of full strength (for 1.0 ml vaccines only)</td>
</tr>
</tbody>
</table>

- note: use of antihistamines or oral corticosteroids prior to vaccination has never been studied or proved effective for vaccine allergy; effectiveness? immunogenicity?

Red Book 2006, American Academy of Pediatrics
Gelatine allergy

- Often no prior known allergy to gelatine containing foods
- associated with immediate HS reactions after:
  - JE-vaccine (not Ixiaro)
  - YF-vaccine
  - MMR
  - varicella vaccines
  - ...

Plotkin 2008
Latex allergy: ACIP recommendations

- **Severe (anaphylaxis) allergy to latex**
  - No administration of vaccines supplied in vials or syringes that contain natural rubber
    (unless benefit of vaccination outweighs the risk)

- **Other allergic reactions than anaphylaxis** (ex. contact allergy latex gloves)
  - Vaccines supplied in vials or syringes that contain natural rubber can be administered

Yeast allergy and HBV-vaccine

- Saccharomyces cerevisiae-derived vaccines
- Few patients with immediate HS-reactions \(^1,^2\)
- Bakonde et al.\(^3\)
  - 4 children with urticaria, angio-edema, asthma after HBV-vaccine
    - all skin-test negative
    - all but 1 tolerated booster vaccination

\(^1\) André FE. Vaccine 1990; 8(S): 74-8
\(^3\) Bakonde VB et al. Rev Fr Allergol 1998; 38: 315-8
Contact allergy to formaldehyde or antibiotics present in vaccines

- Allergy diagnosed by patchtests
- If no history of systemic reaction
  ⇒ No contra-indication for vaccination
- possible adverse event:
  → exacerbation of eczema
  → Delayed type local reaction (48-96h): erythematous pruritic nodule
Thiomersal

- **Mercuric derivate** – common preservative in (multi-dose) vaccines, topical medicines and cosmetics

- **1990’s: association of Thiomersal and autisme spectrum disorders?**
  - no evidence for this association
  - 1999: US public health service + AAP
    - Recommendation to eliminate or reduce to trace amounts Thiomersal from vaccines for use in children < 24 months
    - 2002 implementation of recommendations for all childh vaccines in EU and USA

---

Thiomersal allergy

- **Mostly delayed type** - Patch-tests: not clinically relevant
  - Patch-test positive adults:
    - adverse events other than occasional injection site reactions are exceedingly rare
  - IM Challenge of allergic adults with increasing strengths of thiomersal
    - 100 μgr/ml solution induced only mild local reaction in 9% of pts
  - Comparison of inactivated influenza vaccine thiomersal containing and not containing in children < 2y
    - no difference in rash, injection site reactions and infections

- **Immediate hypersensitivity reaction**
  - Few adult case reports after influenza vaccine containing thiomersal

---

5 Hessel L. Bull Acad Nattl Med 2003; 187 (8): 1501-10  
7 Karsen H et al. J infect Devel countries 2007; 1 (3): 348-349
Conclusions

- SAE following vaccination are rare
- Most allergic patients can be safely vaccinated
- careful evaluation of the cause of a previous SAE is necessary to:
  - prevent another SAE
  - allow future vaccination of the patient