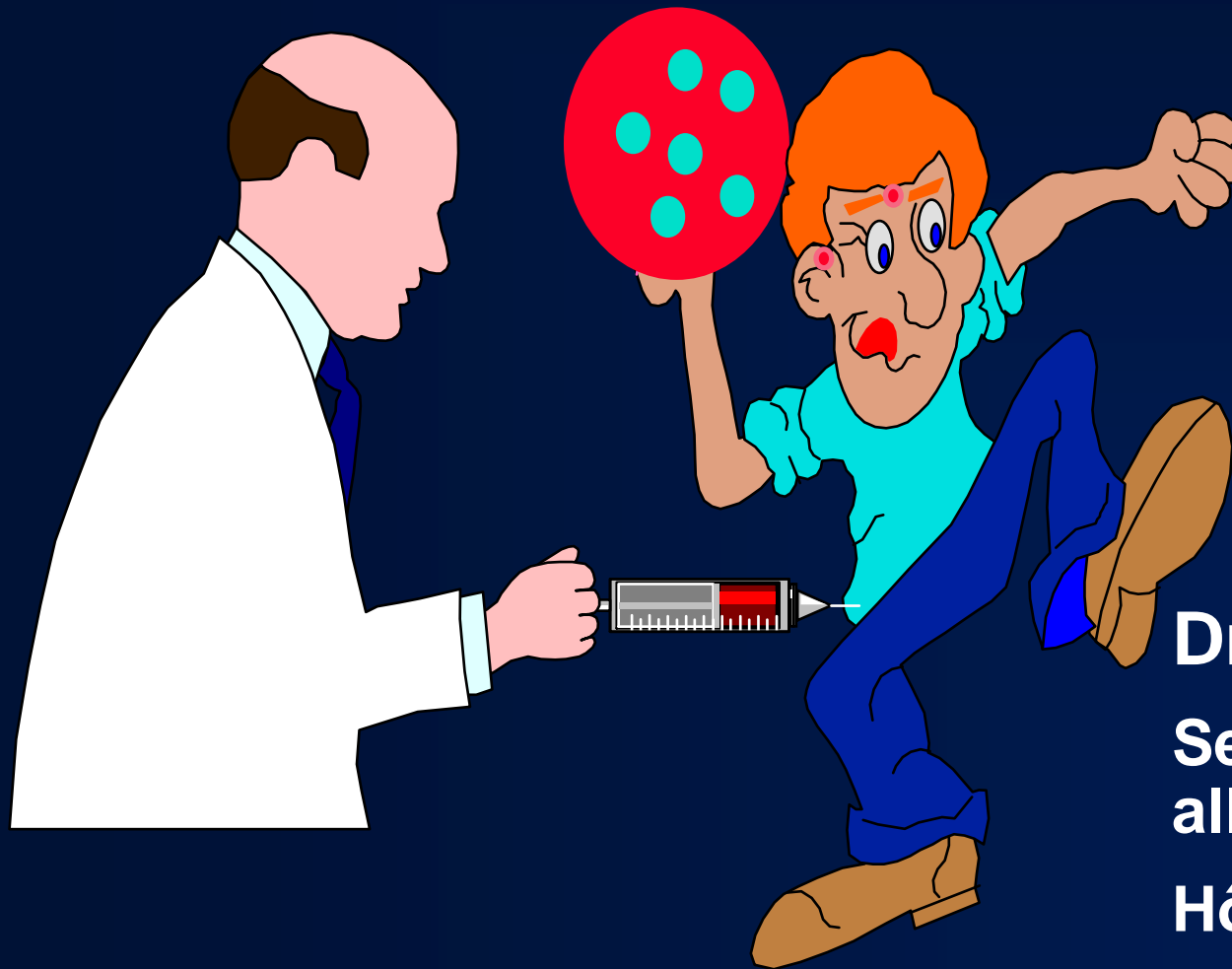


Réactions allergiques et pseudo-allergiques aux vaccins contenant des anatoxines chez l'enfant



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Pourquoi les vaccins associés contenant des anatoxines ???

.... ce sont les plus fréquemment accusés !!!

Nakayama et al. Incidence of (suspected) allergic reactions (cases/10⁶ doses) after vaccination (with gelatin-free) vaccines in Japan, 1994-2004. Vaccine 2007 ; 25 : 570-6.

Reactions/vaccines	JEV	DTP	Influenza
Anaphylaxis	1	1	3 (egg ?)
Urticaria/oedema	1	1	1
Non urticarial rash	1	11	9
Large local	1	19	14

Abbreviations : JEV (Japanese encephalitis vaccine), DTP (diphtheria-tetanus-pertussis vaccine)

Réactions allergiques et pseudo-allergiques aux vaccins contenant des anatoxines chez l'enfant

Réactions locales

- ❖ fréquentes
- ❖ sans gravité

On s'est fiche (presque) complètement !!!

Local reactions to vaccines

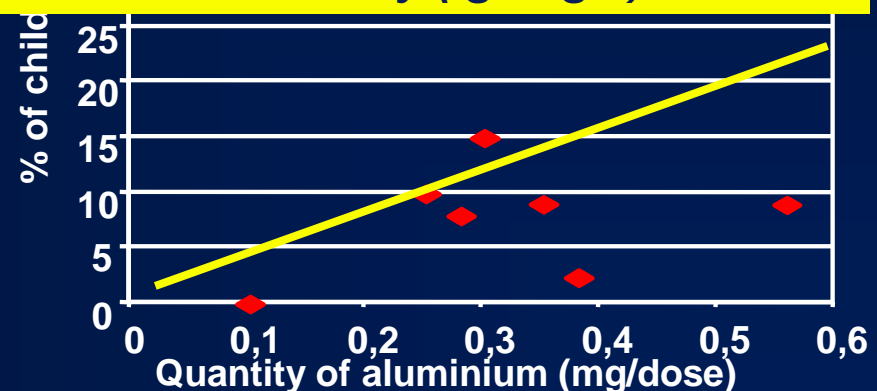
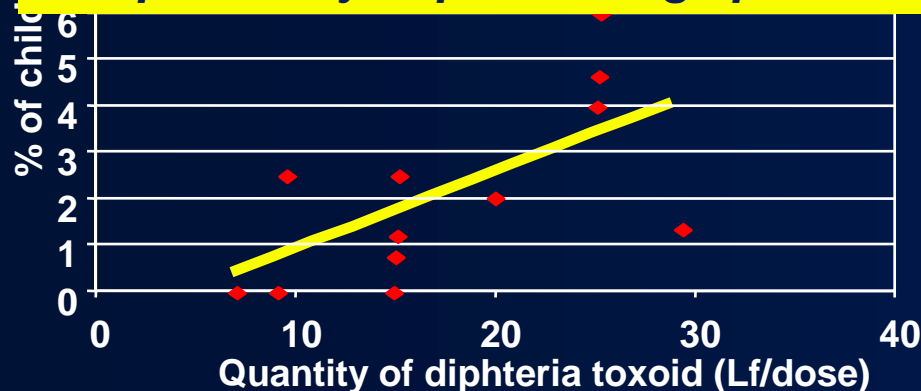
❖ **Local reactions** : the most frequent, but usually mild to moderate

Reaction (nature)	Patients	Frequency	Responsible substances	Mechanisms
Inflammation	Children Adults	≤ 15-25 %	Toxoids Al. hydroxyde	non sp./Arthus non specific



❖ Relationship between the quantity of diphtheria toxoid and AlOH in DTaP vaccines and rates of swelling after the fourth dose of DTaP (Rennels et al, Pediatrics 2000, Vaccine 2002)

independently of preexisting specific anti-toxoid antibody (IgM/IgG) levels !!!



❖ **Ponvert et al (RFAIC 1998, 2001) : most local reactions are non specific**

- skin tests (immediate, semi-late and late-reading) negative in all the children
- (sequential) booster injections of mono/paucivalent vaccines tolerated in all the children

Large local reactions to vaccines

Réactions locales aux vaccins anti-coquelucheux

- Skowronski DM et al. Injection-site reactions to booster doses of acellular pertussis vaccine : rate, severity and anticipated impact. *Pediatrics* 2003; 112: e453-e459. : étude rétrospective de 800 enfants (questionnaires aux parents)

Résultats: taux de réactions	Erythème	Oedème
Vaccin classique (5 ^e injection)	10 %	9 %
Vaccin acellulaire (5 ^e injection)	24 %	16 %

- Gold MS et al. Local reactions after the fourth dose of acellular pertussis vaccine in South Australia. *Med J Aust* 2003; 179: 191-4.

- ✓ Analyse des bases de données des centres de pharmacovigilance australiens
- ✓ Taux de réactions locales importantes 30/10 000 injections de rappel (tous vaccins)
- ✓ liées au vaccin anti-coquelucheux classique 18 %
- ✓ liées au vaccin anti-coquelucheux acellulaire 48 %
- ✓ facteur de risque = primo-vaccination par le vaccin acellulaire (RR = 6,7)

➤ Physiothologie ?

- ✓ réactions inflammatoire non spécifique ?
- ✓ réactions à type de phénomène d'Arthus (patients hyperimmunisés) ?

Large local reactions to toxoid-containing vaccines

3) In practice : *specific IgM/IgG determination a few weeks/months after the reaction*

- high specific antibody titers

- highly suggestive of Arthus-type reaction
- withhold booster injections of vaccine

- low specific antibody titers

- non-specific inflammatory reaction
- sequential booster injections of the vaccines

Local reactions to toxoid-containing vaccines in children

❖ **Local reactions** : the most frequent, but usually mild to moderate

Reaction (nature)	Patients	Frequency	Responsible substances	Mechanisms	Diagnosis : value good/low
Persistent SC nodules	Children	≤ 19 % (3 mth) ≈ 0 % (6 mth)	Al. hydroxide	non specific DTH ?	CH ± patch-tests

❖ **Diagnostic tests in persistent nodules**

- patch-tests with aluminium salts : **usually negative**
- correlation with in situ concentrations of aluminium hydroxide (animals, humans)

⇒ *non specific inflammatory reaction to foreign body*

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Bergfors E et al (2003). Unexpetedly high incidence of persistent itching nodules and delayed hypersensitivity to aluminium in children after the use of adsorbed vaccine

- Trial of new aluminium-adsorbed vaccines (DT, DTaP, aP) in 76 000 children
- Development of itching nodules (persistence ≥ 4 years) in 645 children (0,8 %)
- Results of patch tests with aluminium salts

Children	Positive patch-tests
With nodules	77 %
Without nodules	8 %

- **Conclusion** : in children

↓ persistent nodules induced by vaccines may result from DTH to aluminium salts

↓ but, sensitization to aluminium salts may also result from persistence of aluminium in the nodules

Local reactions to toxoid-containing vaccines in children

❖ **Local reactions** : the most frequent, but usually mild to moderate

Reaction (nature)	Patients	Frequency	Responsible substances	Mechanisms	Diagnosis : value good/low
Inflammation	Children Adults	≥ 15-25 %	Toxoids Al. hydroxyde	non sp./Arthus non specific	CH ± sp. IgM/IgG
Persistent SC nodules	Children	≤ 19 % (3 mth) ≈ 0 % (6 mth)	Al. hydroxide	non specific DTH ?	CH ± patch-tests
Eczemas	Adults	Rare	Al. hydroxide Formaldehyde Mercurothiolate	DTH DTH DTH	patch-tests patch-tests (?) patch-tests
Sterile abscesses	Children	Rare	Toxoids Al. hydroxide ?	DTH ? DTH	CH + neg. microbiol. ± ID/patch-tests

Réactions allergiques et pseudo-allergiques aux vaccins contenant des anatoxines chez l'enfant

Generalized reactions

- ❖ rare, but worrying
- ❖ types
 - suggesting immediate-type HS
 - suggesting non immediate-type HS

Reactions suggestive of immediate-type HS to toxoid-containing vaccines in children

Symptoms	Estimated frequency (Bohlke et al, Pediatrics 2003)
Urticaria ± AO	≤ 15 p. 100 injections
Anaphylaxis	≤ 21.2 p. 1 Million injections (vs 0.65 for other vaccines)

❖ Diagnosis

➤ Immediate-reading skin tests with vaccines :

- good sensitivity and specificity
- but false-positive responses with some batches of vaccines
- but negativation with time

➤ Specific IgE-determination

- confirmation of positive responses in skin tests
- but negativation with time
- but available for tetanus toxoid and formaldehyde only

➤ Specific IgM/IgG determination

- differential diagnosis/very accelerated IgM-IgG-dependent reactions (urticaria ± angioedema, serum sickness) in hyperimmunized children
- indication for booster injections

Reactions suggestive of immediate-type HS to toxoid-containing vaccines in children

Symptoms	Estimated frequency (Bohlke et al, Pediatrics 2003)
Urticaria ± AO	≤ 15 p. 100 injections
Anaphylaxis	≤ 21.2 p. 1 Million injections (vs 0.65 for other vaccines)

Diagnostic value of skin tests and specific IgE determination in 30 children with suspected allergic reactions to D.T-containing vaccines (Ponvert et al. Rev Fr Allergol Immunol Clin 2001)

Reaction (type)	Immediate responses in skin tests ± specific IgE
Severe anaphylaxis	4/6 (66.6 %)
Immediate urticaria ± AO	4/6 (66.6 %)
Very accelerated urticaria ± AO	2/8 (25 %)
Delayed urticaria ± AO	0/2
Non urticarial rashes	0/3
Large local reactions	0/5 (0 %)

Reactions suggestive of immediate-type HS to toxoids in children (diagnostic value of immediate-reading ST and RASTs)

Results of a study based on skin tests and specific IgE determination in 30 children with suspected allergic reactions to D.T-containing vaccines (Ponvert et al. Rev Fr Allergol Immunol Clin 2001)

Reaction to	ST ± RAST positive	ST ± RAST negative
1st injection	0/11	11/11
Booster	10/19	9/19

Results of booster injections in 9 children with (suspected) IgE-dependent allergy to D.T-containing vaccines (Ponvert et al. Rev Fr Allergol Immunol Clin 2001)

Children	Protocol of injections	Reactions to injections
1 child with anaphylaxis and positive ST and RAST	« Desensitization » with D.T vaccine	Large local (accelerated)
8 children with negative ST and RASTs, and low specific IgM/IgG titers	Sequential injections of D.T, P & Polio vaccines	No reaction

Exploration des réactions immédiates aux vaccins courants

Méthodologie/risque de faux-positifs



Enfant	Alain V	Céline M	Claude J	Joelle M	Bernard W	Lucie R
Réaction	Anaphyl.	Urtic + AO	Urticaire	Urtic + AO	Urtic + AO	Rash
Vaccin	DTP	DTCP	DTCP	DTCP	DTP	DTCP
Inj. n°	5	1	1	2	5	1
TC						
- DTCP	ND	0	0	0	ND	0
- DTP	+++	0	++	++	0	++
- DTC	ND	0	0	0	ND	0
- DT	+++	0	0	0	0	0
- T	+++	0	0	0	0	0
- Polio	0	0	0	0	0	0
Cap-RAST						
- T	++	Neg	Neg	Neg	Neg	Neg
- D	Neg	Neg	Neg	Neg	Neg	Neg
- formol	Neg	Neg	Neg	Neg	Neg	Neg
Ac. sériques	0	0	0	0	++	0
Rappels dissociés	Tolérés (DT/acc.)	Tolérés	Tolérés	Tolérés	ND	Tolérés



Exploration des réactions immédiates aux vaccins courants

Réactions anaphylactiques sévères (cas n°2)

❖ Résultats des bilans immuno-allergologiques ❖ Alain V. : enfant non atopique

Tests/bilan	1995 (9 ans)	1999 (13 ans)
TC lect. Imm.		
- DTCP	ND	ND
- DTP	+++ 	++
- DT	+++	++
- T	+++	++
- Polio	0	ND
Cap-RAST		
- D	0	0
- T	20 KU/I 	0
- formol	0	0
Ac sériques		
- D	protecteurs	0
- T	pour	0
- Polio	5 ans	0

- » 1986-198 : 4 premières injections de D.T.C.Pol.HiB bien tolérées
- » 1993 (7 ans) : 5^e injection de D.T.Polio : **urticaire et angio-oedème généralisés immédiats avec gêne laryngée**
- » 1995 (9 ans) : 1^{er} bilan immuno-allergologique
- » 1999 (13 ans) : 2^e bilan immuno-allergologique

← injections de rappel

- » D.T (accoutumance) : réact. locale importante
- » Polio per os : tolérée

Reactions suggestive of immediate-type HS to toxoids

- **Conclusion : skin tests + RASTs**

- » **Positive work-up** : highly suggestive of immediate-type HS
- » **Negative work-up** : highly suggestive of non-specific reaction (high doses of Al-hydroxide or microbial antigens ?)

Réactions allergiques et pseudo-allergiques aux vaccins contenant des anatoxines chez l'enfant

Generalized reactions

- ❖ rare, but worrying
- ❖ types
 - suggesting immediate-type HS
 - suggesting non immediate-type HS

Reactions suggestive of non immediate-type HS to toxoid-containing vaccines in children

- ❖ **Epidemiology** : accelerated and delayed skin reactions (urticarias and/or angioedemas and non urticarial rashes) reported in $\leq 10-15$ % of children
- ❖ **Results of immuno-allergological studies (Ponvert et al : 1998, 2001) :**
 - » immediate, semi-late and late responses in skin tests with DT-containing vaccines : negative
 - » (sequential) booster injections of vaccines usually tolerated in children with low specific antibody titers
- ❖ **Pathophysiology :**
 - probable non-specific inflammatory reactions resulting from injection of high doses of bacterial components in most cases
 - IgM/IgG-dependent reaction in a few cases (hyperimmunized patients)

Conclusion (1) : etiopathogeny of HS reactions to toxoid-containing vaccines

- **Etiopathogeny** : allergic HS reactions to toxoid-containing vaccines occur only in children sensitized by previous injections of the vaccines

Allergic (like) reactions to toxoid-containing vaccines

In practice (1)

- **Vaccination/booster injection is not essential** (high levels of specific IgM/IgG antibodies) :
 - withhold injection
- **Vaccination or booster injection of the vaccine is necessary** :
 - choice of a vaccine that does not contain the responsible or suspected component (if possible)

Vaccines and excipients	T Pasteur	Imovax Polio	Revaxis (TP)	DT.Polio	Boostix-4	Infanrix-4	Repevac (DTCP)	Tetravac acellul.	Infanrix-5	Pentavac	Infanrix-6
Aluminium											
Formaldehyde											
Merthiolate											
2-phenoxyeth.											
Neomycine											
Polymyxine B											
Streptomycine											
Polysorbate											
Amino-acids											
Others (*)											

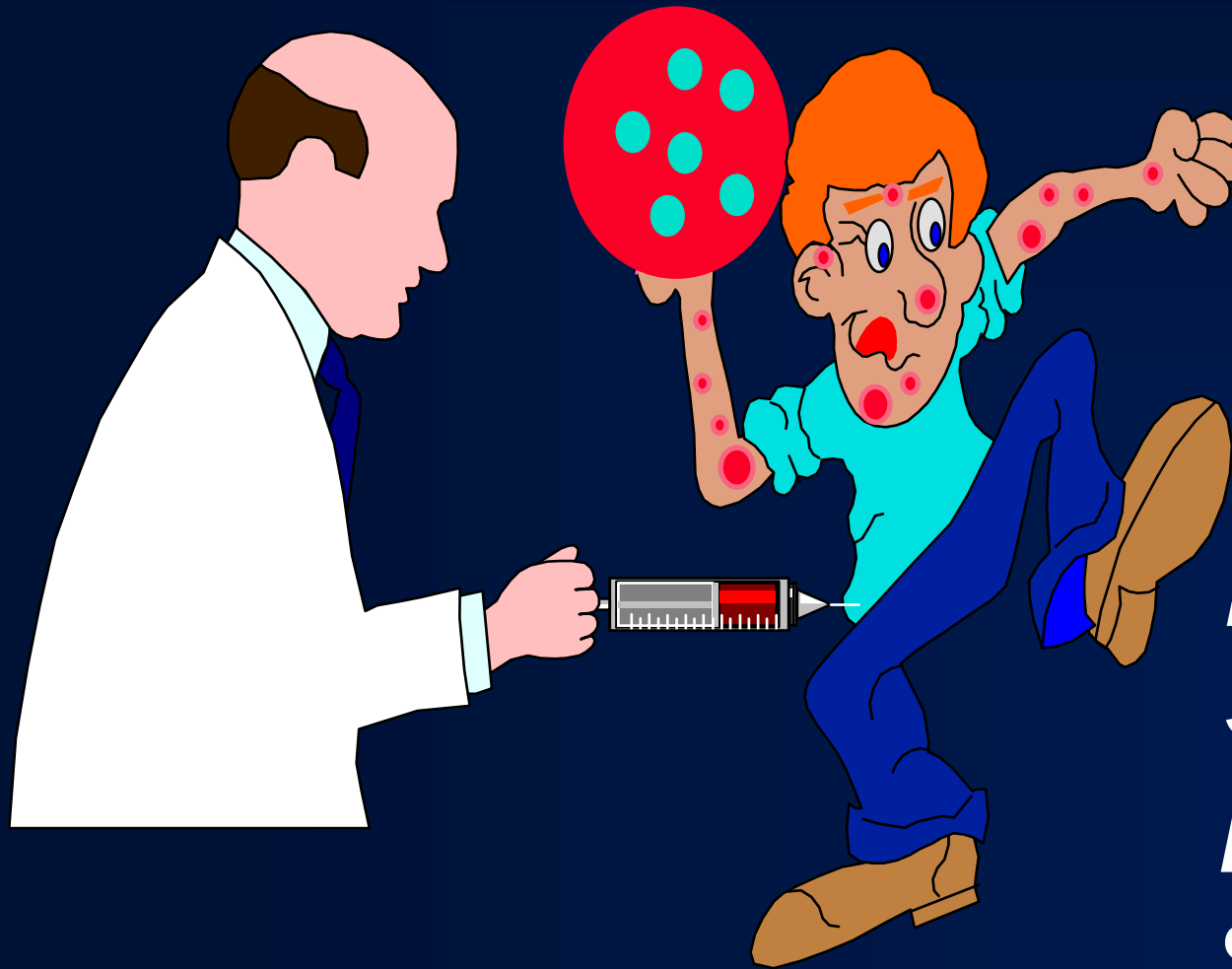
(*) acids, glutaraldehyde, mineral salts, phenylalanine, sugars (lactose, saccharose), trometamol, vitamins.

Allergic reactions to toxoid-containing vaccines

In practice (2)

- **Vaccination or booster injection of the vaccine is necessary :**
 - **when choice of a vaccine that does not contain the responsible component is not possible :**
 - **in large local inflammatory reactions & persistent nodules :**
 - choice of a mono/paucivalent vaccine (if possible)
 - IM injection (if possible)
 - choice of long and large needles (25/25)
 - **in immediate-type HS reactions :**
 - choice of a mono/paucivalent vaccine (if possible)
 - injection using a « desensitization » procedure in the hospital
 - **in other reactions (eczema, recurrent abscesses) : ???**

Réactions allergiques et pseudo-allergiques aux vaccins contenant des anatoxines chez l'enfant



***Merci
sincèrement
pour votre
attention***