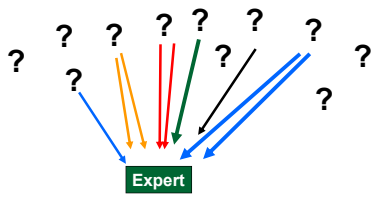
Clinical vaccinology : from general recommendations to individual patient problem solving

Prof. Claire-Anne Siegrist
Dr Alessandro Diana

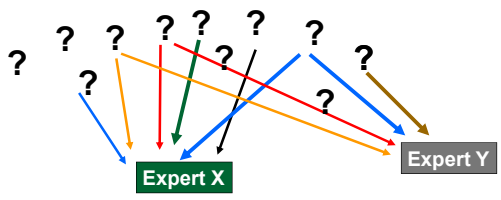
Decision-making for patients with vaccine-related questions



HCWs : Not so sure… Should I ask him/her for advice ? Do I dare bothering him/her again ? Let's not ask…

Expert : Again the beeper! Always the same questions!!! Is my answer correct ? Whom could I ask myself ?

Decision-making for patients with vaccine-related questions



HCWs : Should I ask for advice ? X never answers… Would X and Y answer similarly ? Whom may I bother ?

Experts : Again the beeper! Always the same questions!!! Is my answer correct? Whyt did Y answer differently ?!?

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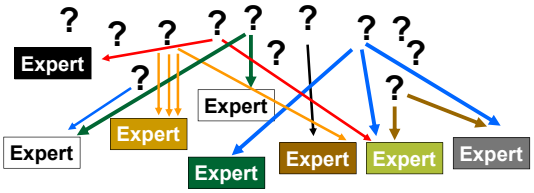
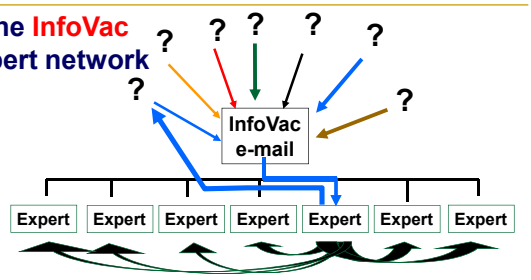
Decision-making for patients with vaccine-related questions



HCWs : So many experts – whom should I ask for advice ? Would X and Y answer similarly ? Who is available NOW ?

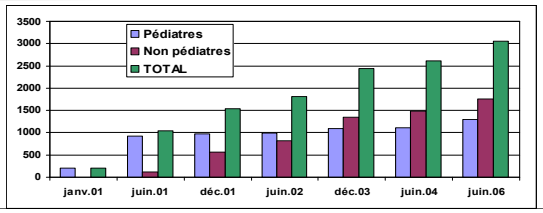
Experts : Again the same questions !!! Why did Y answer differently ? No time to ask myself… and I am THE expert !

The InfoVac expert network



- **Tasks sharing** with on/off duty periods (X experts / week) sharing questions / expertise / difficult decisions…
- **Protection of experts** : better time management, written questions / answers (liability), expert fees!
- **Continuous training of experts** – crossvalidation !

InfoVac-CH, a nation-wide network of 4216 HCWs - 1300 pediatricians, 1100 GPs, 900 internists, 200 Ob/Gyn, etc.



- Answer to any vaccine-related question within 24-48h
- Monthly newsletter (FAQs) + web site - reaching those who ever ask any question !
- Subvention of the Swiss Federal Office of Public Health for expert fees
- Annual subscription (1€ / mo) for administrative costs.

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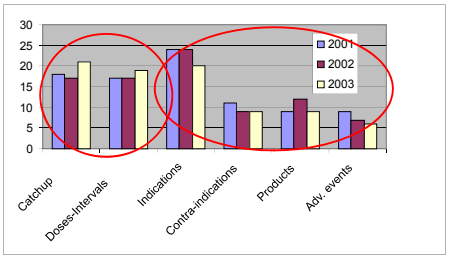
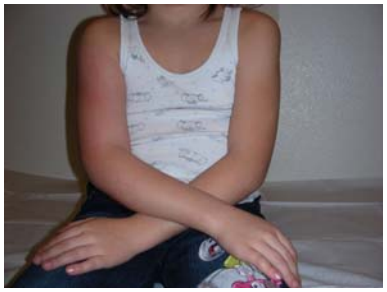
Questions sent to InfoVac by physicians



1) Indications, contra-indications, adverse events ?
2) Catch up immunization schedules !!

Lilly*, 7 years, presented with swelling and red arm 48 hours after her 5th dose of DTPa-IPV. No pain nor fever were reported.



?

Courtesy of Prof. U. Heininger- Basel University

AD

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Lilly*, 7 years, presented with swelling and red arm 48 hours after her 5th dose of DTPa-IPV. No pain nor fever were reported.

What would you recommend for next diTe boosters…

- No further doses
- To postpone the next diTe booster empirically or based on vaccine antibodies
- Nothing special, « next boosters as usual ».
- Another strategy

AD

The individual risk – benefit balance

Risks of recurrence following immunization ?

- Causal or temporal relationship ?
- Risk of recurrence ?

Risks of disease without immunization ?

- Risk of exposure ?
- Acquired immunity : sufficient or not ?

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Table 3
The causality assessment checklist.

	Y	N	U	K	NA
I. Is there strong evidence for other causes?					
Does a clinical examination or laboratory tests on the patient confirm another cause?	□	□	□	□	□
II. Is there a known causal association with the vaccine or vaccination?					
Vaccine product(s)					
Is there evidence in the literature that this vaccine(s) may cause the reported event even if administered correctly?	□	□	□	□	□
Did a specific test demonstrate the causal role of the vaccine or any of the ingredients?	□	□	□	□	□
Immunization error					
Was there an error in prescribing or non-adherence to recommendations for use of the vaccine (e.g. use beyond the expiry date, wrong recipient etc.)?	□	□	□	□	□
Was the vaccine (or any of its ingredients) administered unsterile?	□	□	□	□	□
Was the vaccine's physical condition (e.g. color, turbidity, presence of foreign substances etc.) abnormal at the time of administration?	□	□	□	□	□
Was there an error in vaccine constitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?	□	□	□	□	□
Was there an error in vaccine handling (e.g. a break in the cold chain during transport, storage and/or immunization session etc.)?	□	□	□	□	□
Was the vaccine administered incorrectly (e.g. wrong dose, site or route of administration; wrong needle size etc.)?	□	□	□	□	□
Immunization anxiety					
Could the event have been caused by anxiety about the immunization (e.g. vasovagal, hyperventilation or stress-related disorder)?	□	□	□	□	□
II (time). If "yes" to any question in II, was the event within the time window of increased risk?					
Did the event occur within an appropriate time window after vaccine administration?	□	□	□	□	□
III. Is there strong evidence against a causal association?					
Is there strong evidence against a causal association?	□	□	□	□	□
IV. Other qualifying factors for classification					
Could the event occur independently of vaccination (background rate)?					
Could the event be a manifestation of another health condition?					
Did a comparable event occur after a previous dose of a similar vaccine?					
Was there exposure to a potential risk factor or toxin prior to the event?					
Was there acute illness prior to the event?	□	□	□	□	□
Did the event occur in the past independently of vaccination?	□	□	□	□	□
Was the patient taking any medication prior to vaccination?	□	□	□	□	□
Is there a biological plausibility that the vaccine could cause the event?	□	□	□	□	□

Note: Y, Yes; N, No; UK, Unknown; NA, Not applicable.

#1: look for a diagnosis !

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Lilly*, 7 years, presented with swelling and red arm 48 hours after her 5th dose of DTPa-IPV. No pain nor fever were reported.

This reaction is most likely…

- An allergic reaction requiring antihistaminics
- A hyperimmunization (Arthus), probably to tetanus, requiring an anti-inflammatory drug
- An extensive swelling of unknown etiology, no treatment required
- An injection-induced bacterial infection requiring antibiotics

AD

Lilly*, 7 years, presented with swelling and red arm 48 hours after her 5th dose of DTPa-IPV. No pain nor fever were reported.

What would you recommend for next diTe boosters…

- No further doses
- To postpone the next diTe booster empirically or based on vaccine antibodies
- Nothing special, « next boosters as usual ».
- Another strategy

Clinical case

- Mathias received a first dose of Men C vaccine at 9 months of age.
- Two days later, his parents noticed a skin lesion, which became numerous over 2 days and led to a medical visit. The pediatrician suspected an **idiopathic thrombopenic purpura** (ITP), which was confirmed by a platelet count of 4'000/mm^3.
- The clinical outcome was positive under intravenous immunoglobulins, with a progressive increase of the platelet count within 2 weeks.

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Questions

Mathias is now 12 months old.

Can he receive now his « normal » dose of meningococcal C vaccine and his first dose of MMR ?

- He can now receive both vaccines
- He can receive a dose of MMR but not of MenC
- He can receive a dose of MenC but not of MMR
- He should not yet receive any of these vaccines

The individual risk – benefit balance

Risks of recurrence following immunization ?

- Causal or temporal relationship ?
- Risk of recurrence ?

Men C vaccine

- ITP appeared within 2 days of 1st vaccine dose ↔ causal relationship biologically excluded !

Risks of disease without immunization ?

- Risk of exposure ?
- Acquired immunity : sufficient or not ?

- Epidemiology-dependent
- Insufficient *(1 dose ≥ 12 months)*

→ **YES !**

The individual risk – benefit balance

Risks of recurrence following immunization ?

- Causal or temporal relationship ?
- Risk of recurrence ?

MMR vaccine

- No relationship with ITP episode

Risks of disease without immunization ?

- Risk of exposure ?
- Acquired immunity : sufficient or not ?

- Significant (Switzerland !!!)
- None yet

→ **YES !**

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CAVE :
minimal interval after Ig administration !

Suggested intervals between administration of **immune globulin preparations** and **measles-** or **varicella-containing vaccine**

Product / Indication	Dose, including mg immunoglobulin G (IgG)/kg body weight	Recommended interval before measles or varicella-containing[1] vaccine administration
RSV monoclonal antibody (Synagis®)[2]	15 mg/kg intramuscularly (IM)	None
Tetanus IG (TIG)	250 units (10 mg IgG/kg) IM	3 months
Hepatitis A IG		
Contact prophylaxis	0.02 mL/kg (3.3 mg IgG/kg) IM	3 months
International travel	0.06 mL/kg (10 mg IgG/kg) IM	3 months
Hepatitis B IG (HBIG)	0.06 mL/kg (10 mg IgG/kg) IM	3 months
Rabies IG (RIG)	20 IU/kg (22 mg IgG/kg) IM	4 months
Measles prophylaxis IG		
Standard (i.e., nonimmunocompromised) contact	0.25 mL/kg (40 mg IgG/kg) IM	5 months
Immunocompromised contact	0.5 mL/kg (80 mg IgG/kg) IM	6 months
Blood transfusion		
Red blood cells (RBCs), washed	10 mL/kg negligible IgG/kg intravenously (IV)	None
RBCs, adenine-saline added	10 mL/kg (10 mg IgG/kg) IV	3 months
Packed RBCs (Hct 65%)	10 mL/kg (60 mg IgG/kg) IV	6 months
Whole blood (Hct 35%–50%)[3]	10 mL/kg (80–100 mg IgG/kg) IV	6 months
Plasma/platelet products	10 mL/kg (150 mg IgG/kg) IV	7 months
Cytomegalovirus intravenous immune globulin (IGIV)	150 mg/kg maximum	6 months
IGIV		
Replacement therapy for immune deficiencies[4]	300–400 mg/kg IV[5]	8 months
Immune thrombocytopenic purpura	400 mg/kg IV	8 months
Immune thrombocytopenic purpura	1,000 mg/kg IV	10 months
Immune thrombocytopenic purpura / Kawasaki disease	1.6–2 g/kg IV	11 months
Postexposure varicella prophylaxis[6]	400 mg/kg IV	8 months

CDC, Pink Book, Appendix A, April 2010

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Lucas, 4 months, experienced an episode of extreme pallor and unresponsiveness 20 minutes after his 2nd dose of DTPa-IPV/Hib. His parents thought he was dying!

This is most likely to be :

- An Apparent Life Threatening Event (ALTE)
- A vaccine-induced Hypotonic Hyporesponsive Episode.
- A type I anaphylactic reaction
- A vaccine-potentiated AE with atonic seizures.

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Hypotonic-Hyporesponsive Episode

2. Case definition for Hypotonic-Hyporesponsive Episode (HHE) as an adverse event following immunization

- Level 1 of diagnostic certainty
  The sudden onset of
  - Limpness (i.e. muscular hypotonia) *AND*
  - Reduced responsiveness (i.e. hyporesponsiveness) or unresponsiveness *AND*
  - Pallor or cyanosis.
- Level 2 of diagnostic certainty
  The sudden onset of
  - Two of the three inclusion criteria defining Level 1
- Level 3 of diagnostic certainty
  The sudden onset of
  - Two of the three inclusion criteria defining Level 1 and
  - The third criterion noticed to be absent.

Brighton definition ***Bonhoeffer J et al, Vaccine. 2004 Jan 26;22(5-6):563-8.***

PEDIATRICS

Hypotonic-Hyporesponsive Episodes Reported to the Vaccine Adverse Event Reporting System (VAERS), 1996-1998

Tracy S. DuVernoy, M. Miles Braun and the VAERS Working Group

Pediatrics 2000;106;52-

DOI: 10.1542/peds.106.4.e52

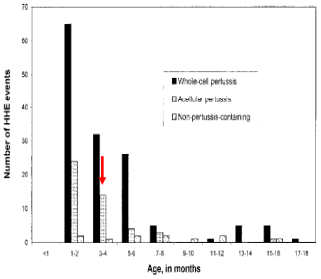


Fig 2. HHE events among children 18 months old and younger by age and vaccine type (n = 197).

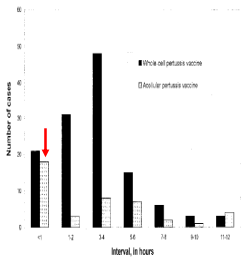
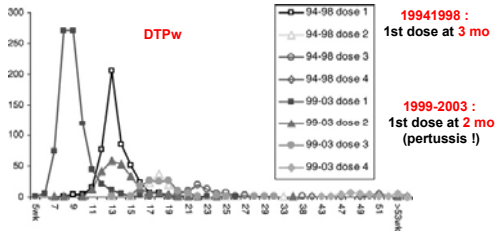


Fig 4. Time from vaccine administration to HHE onset for cases occurring within 12 hours after administration of a pertussis-containing vaccine.

THE EFFECT OF AGE AND DOSE NUMBER ON THE RISK OF COLLAPSE (HYPOTONIC-HYPORESPONSIVE-EPISODE) AFTER PERTUSSIS VACCINATION

Patricia E. Vermeer-de Bondt, MD, and Nicoline A. T. van der Maas, MD

The Pediatric Infectious Disease Journal • Volume 27, Number 4, April 2008 **355**



19941998 :
1st dose at 3 mo

1999-2003 :
1st dose at 2 mo
(pertussis !)

"Having heard over a thousand eye-witness reports, we believe that HHE is a vasomotor episode. Which factors are responsible for inducing HHE is unknown. Neither endotoxins, nor any other specific vaccine component has been proven to be responsible."

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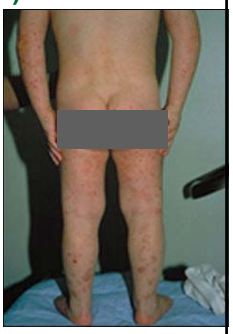
..

This is most likely to be :

- *An Apparent Life Threatening Event (ALTE) unrelated to immunization. Further doses may be given.*
- A vaccine-induced Hypotonic Hyporesponsive Episode. Further doses may be given with specific precautions.
- *A type I anaphylactic reaction to the 2nd vaccine dose: allergy evaluation required before further immunization.*
- *A vaccine-potentiated AE with atonic seizures. Neurological evaluation required.*

David*, 6 years, received a 1st dose of HBV vaccine (Engerix B10).

- 48 h later, he was brought in for abdominal and joint pain with a palpable purpura of the lower limbs.
- A diagnostic of rheumatoid purpura (Henoch- Schönlein) was made.
- Parents obviously accuse the immunization to have caused this worrying disease…



How does this event influence further immunizations with HBV and with DTPa-IPV (booster due) ?

- Hepatitis B vaccine may be a trigger such that hepatitis B immunization should be discontinued.
- Aluminium salts may contribute to this vasculitis reaction such that any immunization with aluminium vaccines should be contra-indicated.
- The hepatitis B vaccine is not the causal agent – any immunization may be continued as soon as the clinical condition is stable (1-2 months).
- It is impossible to tell. As a precaution, no vaccine should be given during 1 year.

Henoch Schönlein…

- **IgA-mediated necrotizing vasculitis**
- Palpable purpura, arthralgia / athritis, abdominal pain +/- bleeding, nephritis
- Incidence 14 / 100'000, mostly btwn 2 and 14 years
- 50% with identified infectious trigger 1-3 weeks earlier
- Pathophysiology : IgA-containing immune complexes (after mucosal infections !), deposition in small vessels, complement activation, leucocyte attraction, inflammation and vascular necrosis / thrombosis, extravasation of red blood cells…

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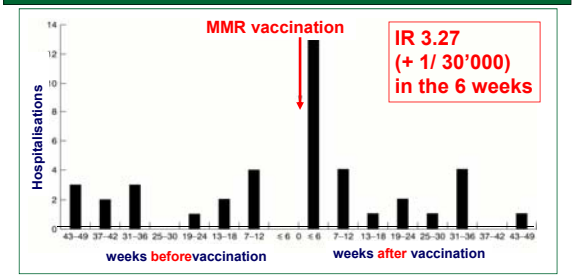
- *It is impossible to tell. As a precaution, no vaccine should be given during 1 year.*

Linda, 24 months, was hospitalized for an idiopathic thrombocytopenic purpura 12 days after a 1st MMR vaccination at 16 months. Evolution was positive with IVIG.
What should I do for her 2nd MMR ?

MMR is known to possibly cause ITP…

- A 2nd dose of MMR is formally contraindicated
- Risks of diseases are higher, a 2nd dose remains indicated if serologies are negative
- Risks of diseases are higher, a 2nd dose may be given without further delay
- Risks of diseases are higher, a 2nd dose may be given but should be postponed by 6-12 months.

- Measles & ITP : ≈ 1 / 6'000
- Rubella & ITP : ≈ 1 / 3'000
- **MMR vaccine & ITP ≈ 1/ 30'000**



E Miller, et al, Arch Dis Child

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- Risks of diseases are higher, a 2nd dose may be given but should be postponed by 6 to 12 months (immunoglobulins !).

Sabrina, 14 yrs old, suffering from severe cystic fibrosis (CF) developped a Guillain Barré syndrome 8 days after an inactivated influenza vaccine. What does that imply for subsequent immunizations ?

Influenza is known to trigger GBS…

- The risk of recurrence is high and the expected benefit too small to advise repeat immunization.
- The risk of recurrence is negligible, i.e. I would advise a 2nd dose without hesitation for this high-risk patient
- The risk of recurrence would be lower with live influenza vaccine, which I would suggest to use (if available)
- The risk of recurrence, if any, is lower than for flu-induced GBS, i.e. I would advise repeat immunization.

Relative Incidence of GBS After Influenza Vaccination

Table 2. Relative Incidence of GBS After Influenza Vaccination

Analysis	Risk Interval, wk*	GBS Cases During Risk Interval, No.	Control Interval, wk*	GBS Cases During Control Interval, No.	Relative Incidence (95% CI)
Primary	2-7	51	26-43	141	1.45 (1.05-1.99)
Secondary	2-7†	51	32-43	97	1.58 (1.12-2.21)
	2-7†	51	20-43	174	1.47 (1.07-2.00)
	2-9	65	18-41	144	1.35 (1.01-1.81)

Abbreviations: CI, confidence interval; GBS, Guillain-Barré syndrome.
*Risk and control intervals are expressed as the number of weeks after influenza vaccination.
†The control interval changed.

From 1 per 100'000 to 1.5 per 100'000…

Juurlink, D. N. et al. Arch Intern Med 2006;166:2217-2221.

ARCHIVES OF INTERNAL MEDICINE

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CAS

Chickenpox or not ?

- **A 4-months-old infant has had a very mild chickenpox (a few crops, no fever). Does this confer immunity or should he be immunized against chickenpox ?**

- Chickenpox is chickenpox – no vaccine needed !
- Infant chickenpox does not confer sustained immunity against chickenpox : immunize against chickenpox !
- Infant chickenpox does not confer sustained immunity against zoster : immunize against chickenpox !
- I have no idea !

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- I have no idea !

Sara, 19 years old, presents with arthralgia (knees & wrists) and arthritis (both knees) 15 days after she received a first MMR vaccine.

This polyarthritis :

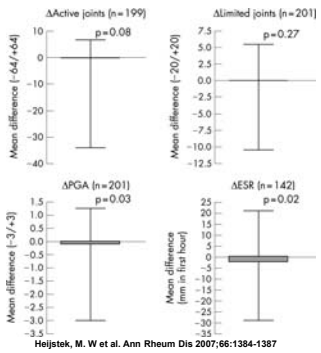
- is likely a coincidental event unrelated to immunization, i.e. a 2nd vaccine dose is recommended.
- is likely a rubella vaccine-induced arthritis, i.e. a 2nd dose of rubella-containing vaccine is contraindicated.
- may be either vaccine-related or not, and serology will be useful to define how to proceed.
- may be either vaccine-related or not, but serology will not be useful and a 2nd dose of MMR may be given.

CAS

Safety of measles, mumps and rubella vaccination in juvenile idiopathic arthritis

Marloes W Heijstek et al

Ann Rheum Dis 2007;66:1384-87



Heijstek, M. W et al. Ann Rheum Dis 2007;66:1384-1387

Figure 1 Differences (open triangles) in disease activity criteria before and after the MMR vaccination in the whole group. Mean values in 6 months before the MMR were subtracted from the mean values after. ESR, erythrocyte sedimentation rate; PGA, physician's global assessment.

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Assessing potential vaccine-induced adverse events in a given patient

Official rules :

« *Causal association can not be determined from passive reports of individual cases without identification of vaccine agent.* »

Official example :

« *Although these data suggest a small increased risk for GBS after MCV4 vaccination, the inherent limitations of VAERS and the uncertainty regarding background incidence rates for GBS require that these findings be viewed with caution.* »
CDC, 2006

- **Scientifically and politically correct, but…**
  - **What do I answer to the parents ?**
  - **What should I recommend for future immunizations?**

Evaluation of the probability of causal associations

1. Concordance of results : reproducibilities of studies ?
2. Strength of relationship : increase of relative risk ?
3. Specificity : characteristical association or association of two frequent events ?

Has this event been reported as a SAE ?

4. Temporal relationship : neither too early, nor too late…
5. Biological plausibility : most useful for live vaccines (comparisons with wild type virus); essentially useful if positive; should not lead to discard something simply because it is not understood !

WHO Global Advisory Committee on Vaccine Safety
Wkly Epidemiol Rec. 2001 Mar 23;76(12):85-9.

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Evaluation of the probability of causal associations – at the individual patient level

Criteria that may be useful to « exclude » causality :

- Unappropriate temporal association
  - Vasovagal : before – at time of injection
  - Anaphylaxis : 5 min – few hours
  - Non anaphylactic allergy : < 24h - 48h
  - Inflammatory reaction : < 48 h
  - Delayed hypersensitivity : 48-96 h
  - Vasculitis, autoimmune reactions : >2 wks < 6 wks
- Absence of biological plausibility
  - Ex : sudden death after immunization (except through anaphylaxis)…

Assessing potential vaccine-induced adverse events in a given patient

Suggested way forward:

1. Establish a diagnosis *(clinical diagnosis +- laboratory, imaging, etc.)* without presuming for or against a vaccine-inducing role…
2. Consider the biological plausibility of a vaccine-inducing role
   - Known vaccine-associated adverse event ?
   - Potential mechanisms at play ?
   - Intervals between immunization and onset ?
3. Estimate the relative risks of recurrence of the AE (likelihood, severity)
4. Estimate the relative benefits of continuing the immunization process.

InfoVac : a direct expert networks for vaccine-related questions

2001	2003	2008	2011
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In preparation:
India (?) Portugal (?) Others ?

If interested : contact us for help !