Vaccination and Autoimmune Diseases
Paul-Henri Lambert
Centre of Vaccinology
University of Geneva

In relatively rare instances, vaccination has been associated with autoimmune diseases

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Associated Auto-ID</th>
<th>Attributable cases / 10^5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabies (phenolized sheep brain vaccine)</td>
<td>Encephalitis, anti-myelin T-cells &amp; Ab</td>
<td>30 - 300</td>
</tr>
<tr>
<td>Swine Influenza (1976-1977)</td>
<td>Guillain-Barre, anti-ganglioside Ab??, anti-myelin T-cells??</td>
<td>0.8-1.0</td>
</tr>
<tr>
<td>Pandemic Flu AS03-pH1N1</td>
<td>Narcolepsy, anti-hypocretin T-cells??</td>
<td>2-6</td>
</tr>
</tbody>
</table>

Vaccination and Autoimmunity

- Overwhelming number of individual case reports of autoimmune events following vaccination; usually only reflecting temporal association with vaccination
- Google: vaccination + autoimmunity = >2 million hits!

* A study has documented that, given enough vaccine injections, everyone will develop an autoimmune disorder*

www.the libertybeacon.com; allnurses.com; ref to Tsuniyama et al., PLoS 2009 % 2014
Every 5 days, 500 microgr DVA IP X 12mouse

What is the real risk of autoimmunity following vaccination?
Autoimmunity
- Antibodies or T-cells directed against self-antigens
- Autoantibodies are quite frequent (e.g. in older adults); most often, not associated with pathologic consequences (low avidity, anti-intracellular ag)

Autoimmune disease
- Pathology directly or indirectly caused by auto-reacting antibodies or effector T-cells
- e.g.
  - Autoimmune Haemolytic Anemia: red cell destruction due to auto-antibodies.
  - Multiple Sclerosis: anti-myelin T-cell mediated pathology

Autoimmune diseases are often poorly defined
- 81 diseases classified as autoimmune
- only a few of these have a defined pathogenic process
S.M. Hayter, Autoimmunity Reviews 2012

Level of evidence for auto-immune pathology
- Direct evidence of pathogenic autoantibody e.g. AHA, SLE, Goodpasture, Myasthenia, Grave's (materno-foetal transfer)
- Indirect evidence of autoimmune pathogenesis e.g. thyroiditis, multiple sclerosis, type1 diabetes (autoreactive T-cells within lesion)
Evidence of auto-immune process

- Suggestive evidence
  - Disease associated with presence of tissue specific auto-reactive antibodies or T cells
  - Strong association with a particular HLA haplotype (class II)

- Questionable evidence
  - Idiopathic inflammation in presence of some auto-antibodies
  - E.g. ASIA syndrome

Many diseases are called “autoimmune” without much evidence for an autoimmune pathogenesis

What is the risk of vaccination-induced autoimmune disease?

1- Lessons from intentional induction of autoimmune responses in human subjects

Human anti-self Amyloid β peptide vaccines (Alzheimer’s disease)

Inducing auto-antibody responses

Requirements:
1- Self B-cell epitope (preferably from antigen with a low level of expression; no B-cell tolerance)
2- Linked with dominant foreign CD4 T cell epitope(s) e.g. of microbial origin
3- In presence of appropriate co-stimulation
What is the risk of vaccination-induced autoimmune disease?

2- Risk of vaccine-induced auto-antibody response?

**Risk of vaccine-induced auto-antibody response?**

*Increased risk if:*
1. cross-reacting B cell epitope on vaccine antigen, particularly if:
   - area of extensive *sequence homology* with a host antigen (e.g. >35% identity on >50-80 aa sequences)
   - low level of expression of the homologous host antigen (e.g. myelin, gangliosides)
2. the cross-reacting epitope is linked with a dominant CD4 helper T cell epitope(s) of microbial origin
3. formulated with strong activator of Antigen Presenting Cells

Such risks are usually identified at pre- or early clinical stages; May be of little clinical relevance
Extensive homology of Group A Streptococcal protein peptide B2 and human cardiac myosin

Similar cross-reactive antibodies have been seen in clinical trials of some bacterial vaccines (Pn)- No Go!

VACINATION & B-CELL EPITOPE MIMICRY

Particular relevance for some polysaccharide vaccines
Structural homologies involving oligosaccharide (repetitive epitopes) have been sufficient to select out some vaccine antigens: No Go!

e.g.
- *Campylobacter* crossreaction of LPS with human gangliosides (risk of Guillain-Bare Syndrome!)
- *Group B mening.* crossreaction of capsular PS with human Neural Cell Adhesion Molecule (NCAM)

What is the risk of vaccination-induced autoimmune disease?

3- Risk of vaccine-induced autoimmune T-cell response? Importance of small peptide mimicry?
Similarity profile of influenza A H5N1 polyprotein vs the human proteome

Sequence homologies between microbial proteins and human proteins are extremely frequent (6-9 mer peptides)

Thymus main site of T-cell maturation, education and selection.

Mimicry is everywhere …

The development of the T-cell repertoire depends on self-recognition!

Development of T-cell repertoire depends on self-recognition

1. T-cell precursors migrating from BM to the thymus recognize a nearly infinite number of antigens.

2. Positive selection: only T-cells with sufficient affinity for endogenous self peptides remain

("presented on self HLA by cortical Thymus Epithelial Cells")
Medullary epithelial cells (mTEC) express a diverse set of genes (AIRE) representing essentially all tissues of the body.

Emigrant naïve T cells are all self-peptide reactive.

The immune system has developed several strategies to prevent the activation of autoreactive T-cells in the periphery.

These include:
- Inhibition by regulatory T-cells (Treg).
- Restriction of the expression of co-stimulatory molecules
- Expression of inhibitory receptors (e.g. CIta-4, PD-1),
- Limiting the availability of growth factors (such as IL-2)
- Production of inhibitory cytokines (e.g. TGF-β)

Autoimmune T-cell responses largely reflect missing tolerogenic signals or Treg dysregulation: relatively rare events.

Narcolepsy & T-cell epitope mimicry

Sci Transl Med 5, 216ra176 (2013);

- anti-HCRT peptides T-cells do exist in healthy controls; additional specificities in NP
- modest increase of anti-HCRT56-68 & HCR787-99 T-cell reactivity after H1N1 seasonal immunization
- HLA-DQB1*06:02 is not expressed on neurons
- “Our results do not explain the particular association of narcolepsy with the Pandemrix vaccine. “Other factors are likely to be involved”
What is the risk of vaccination-induced autoimmune disease?

4. Can vaccines exacerbate a pre-existing autoimmune disease?
   Importance of bystander activation?

Human TT boosting can expand unrelated memory T-cells

Vaccines: activation of innate immunity
Genetically susceptible and identical individuals (B1 and B2) might progress (or might not progress) into autoimmune disease depending on the environmental factors they are exposed to.

Wahren-Herlenius, M, Lancet 2013

Narcolepsy-Cataplexy
- likely to be slowly progressive, over several years
- unknown immunological mechanism
- Pandemrix as an accelerator of disease?

Unchanged disease activity scores in patients with autoimmune rheumatic diseases after pH1N1-AS03 adjuvanted vaccine (2 doses)

Gabay C et al., Arthritis and Rheum. 2011
1. Diagnosis of autoimmune events should be evidence-based and essential criteria should be respected.

2. Temporal association of autoimmunity with vaccination is not sufficient to support a causal relationship. Most case reports are irrelevant if not confirmed by good epidemiological studies.

3. The risk of inducing pathogenic autoantibodies through epitopic mimicry is relatively low and can often be identified at early stage of vaccine development.

4. The risk of inducing cell-mediated autoimmune pathology through epitope mimicry appears extremely limited in the context of highly regulated T-cell responses. A causal relationship is rarely demonstrated.

5. Such rare events may reflect the acceleration of an on-going process in a context of individual genetic susceptibility.

6. The absence of disease exacerbation following adjuvanted H1N1 vaccines in patients with known autoimmune diseases is reassuring. It does not suggest a high risk of triggering an underlying autoimmune disease after vaccination.