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Vaccination, allergy and autoimmunity : what are the risks ?

Part B : Autoimmunity

26th Infectious Disease Symposium
Zürich, March 25, 2004

Prof. Claire-Anne Siegrist
Center for Vaccinology and Neonatal Immunology, University of Geneva

The helpful contribution of Prof. Paul-Henri Lambert is gratefully acknowledged.

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IMMUNOLOGICAL SAFETY OF VACCINATION ALLEGATIONS

• MEASLES :	INFLAMMATORY BOWEL DISEASE AND AUTISM
• HEPATITIS B :	MULTIPLE SCLEROSIS
• ALUMINIUM :	MACROPHAGIC MYOFASCITIS
• HIB :	TYPE I DIABETES
• ANY VACCINE :	TRIGGERING OF AUTOIMMUNE CONDITIONS

C.A. Siegrist, March 2004

IMMUNOLOGICAL SAFETY OF VACCINATION
The risks of increasing autoimmunity

2 POTENTIAL RISKS :

VACCINES :

1. **May cause autoimmune diseases, through molecular mimicry…**
2. **May trigger autoimmune diseases through non-specific activation of preexisting autoreactive cells…**

C.A. Siegrist, March 2004

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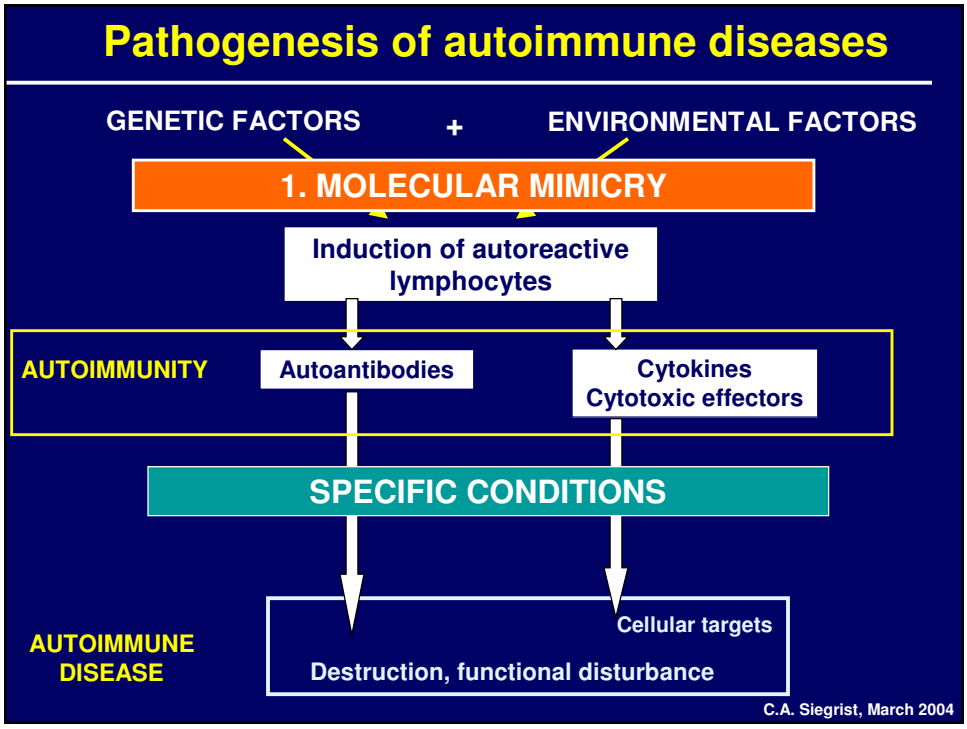

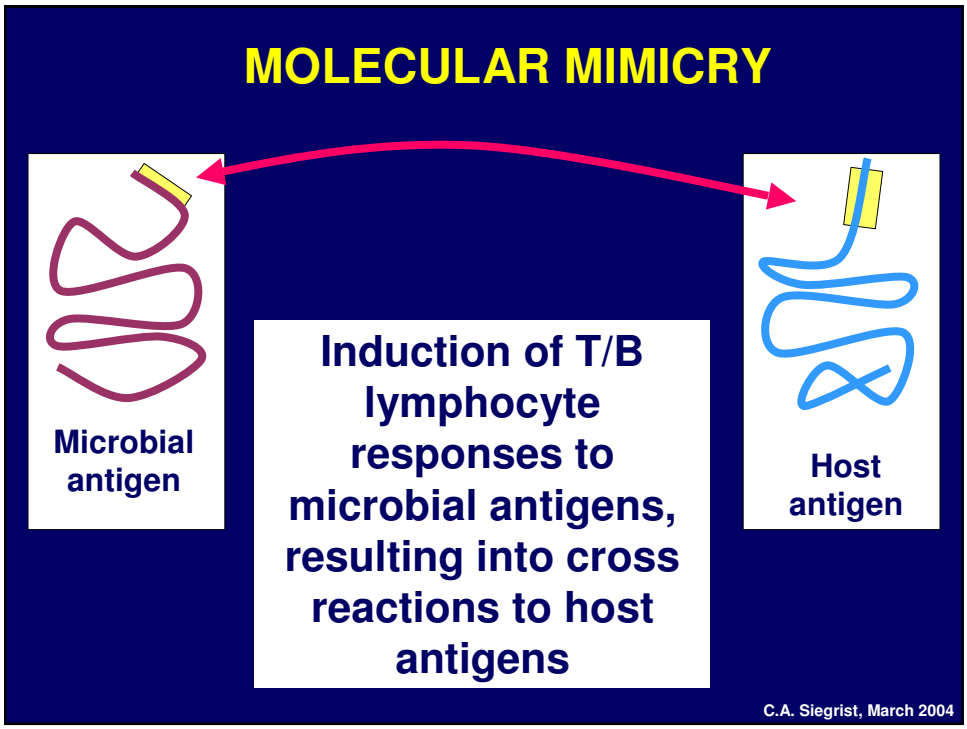

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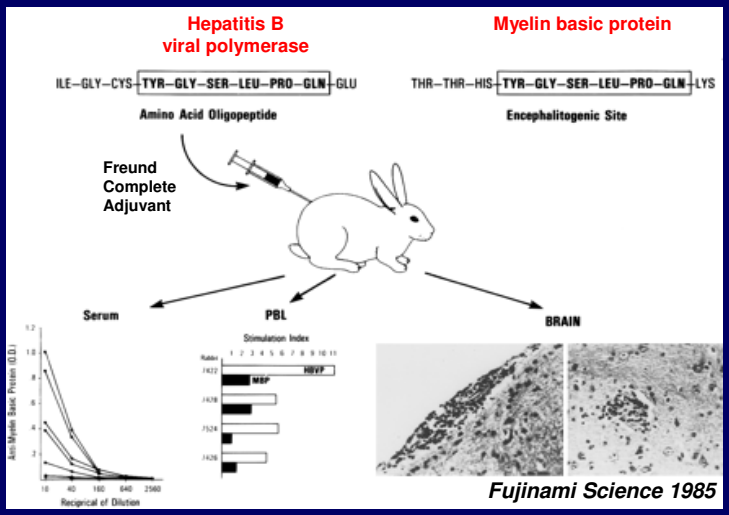
Demonstration of molecular mimicry



Fujinami Science 1985

A frequently evoked mechanism…

C.A. Siegrist, March 2004

MOLECULAR MIMICRY

1. The frequency of **homologous sequences** among the microbial and human genomes is very high :
   Tetanus toxin : 200 peptides with 6 aa, 95 with 7/8 aa

Peptide size	Matching level (common aa)	Hu. proteins with pept. similarity
6-mer	6/6	209
	5/6	>11,000
7-mer	7/7	9
	6/7	758
8-mer	8/8	0
	7/8	95
9-mer	8/9	8
	7/9	434

J. Thonnard and PH Lambert, pers. communic.

C.A. Siegrist, March 2004

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MOLECULAR MIMICRY

1. The frequency of homologous sequences among the microbial and human genomes is very high :
   Tetanus toxin : 200 peptides with 6 aa, 95 with 7/8 aa

2. B lymphocytes and antibodies may bind to peptides with totally distinct sequences :
   5% of antiviral antibodies may bind to a human protein !

3. Binding of T lymphocytes to antigenic peptides is very permissive :
   each T lymphocyte could recognize up to a million of different peptides !

Oldstone, Faseb 1998

C.A. Siegrist, March 2004

MOLECULAR MIMICRY

If molecular mimicry and induction of autoreactive lymphocytes are so frequent…

why are autoimmune manifestations not more frequent ?

C.A. Siegrist, March 2004

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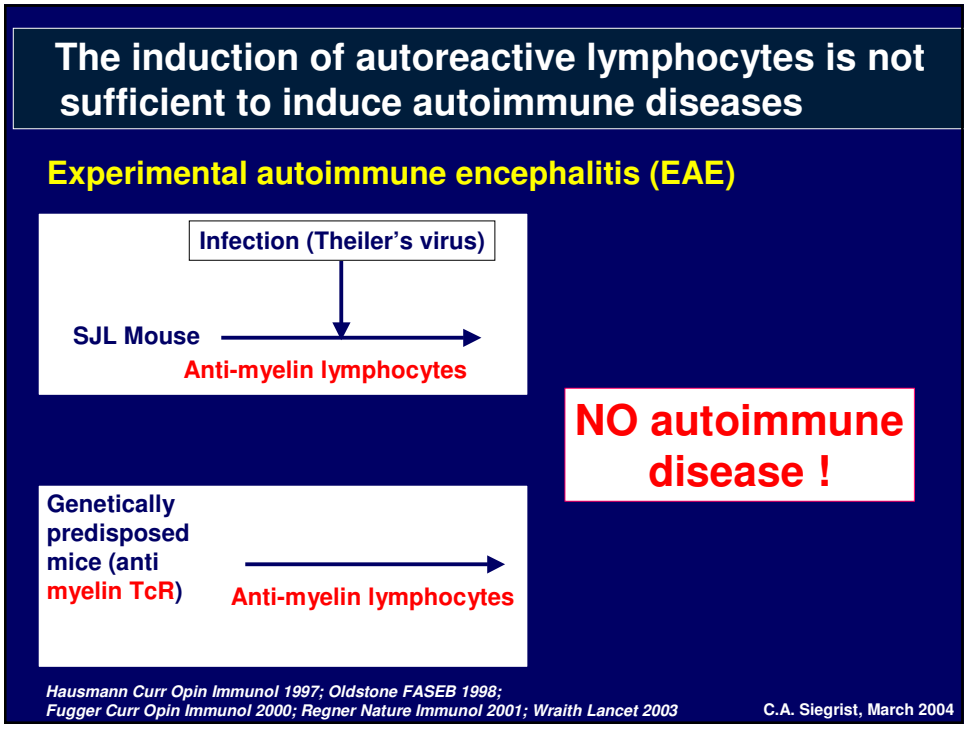

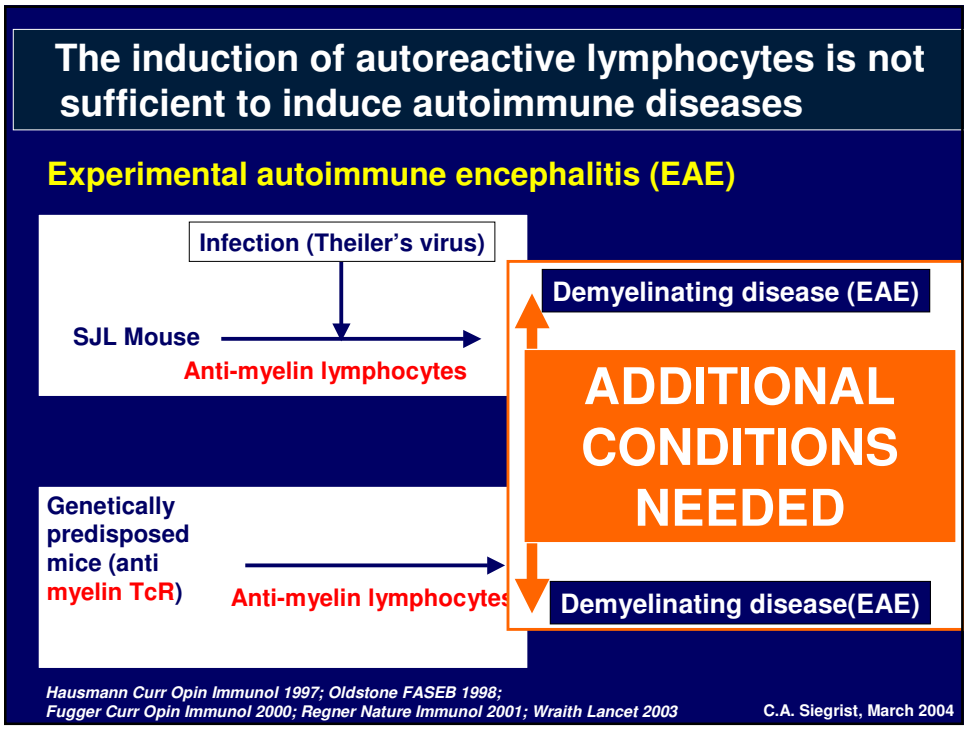

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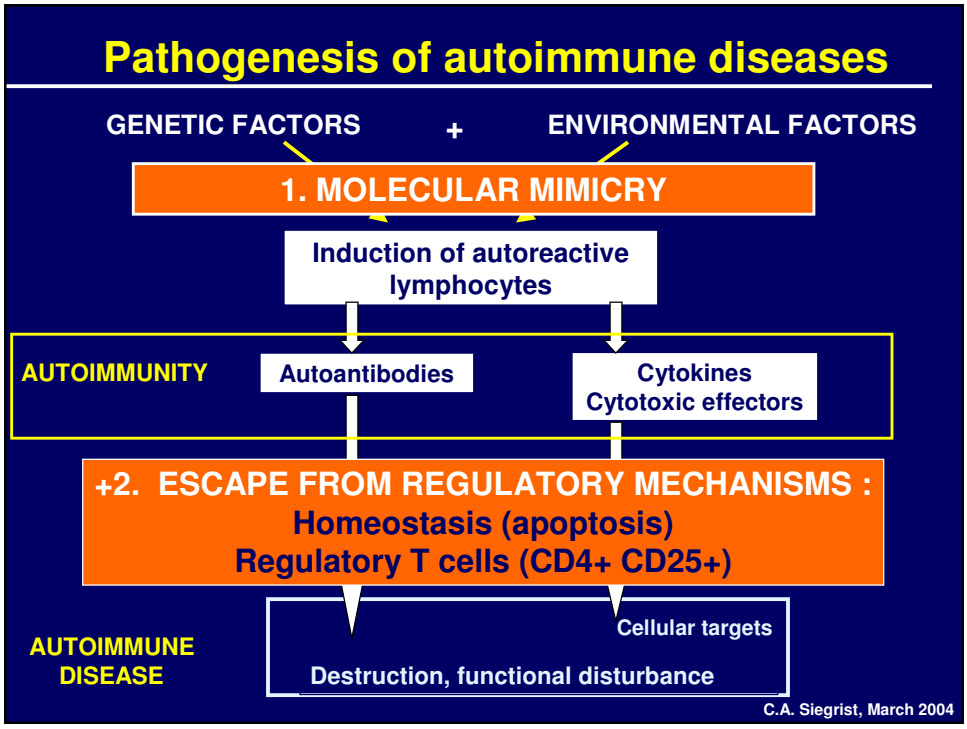

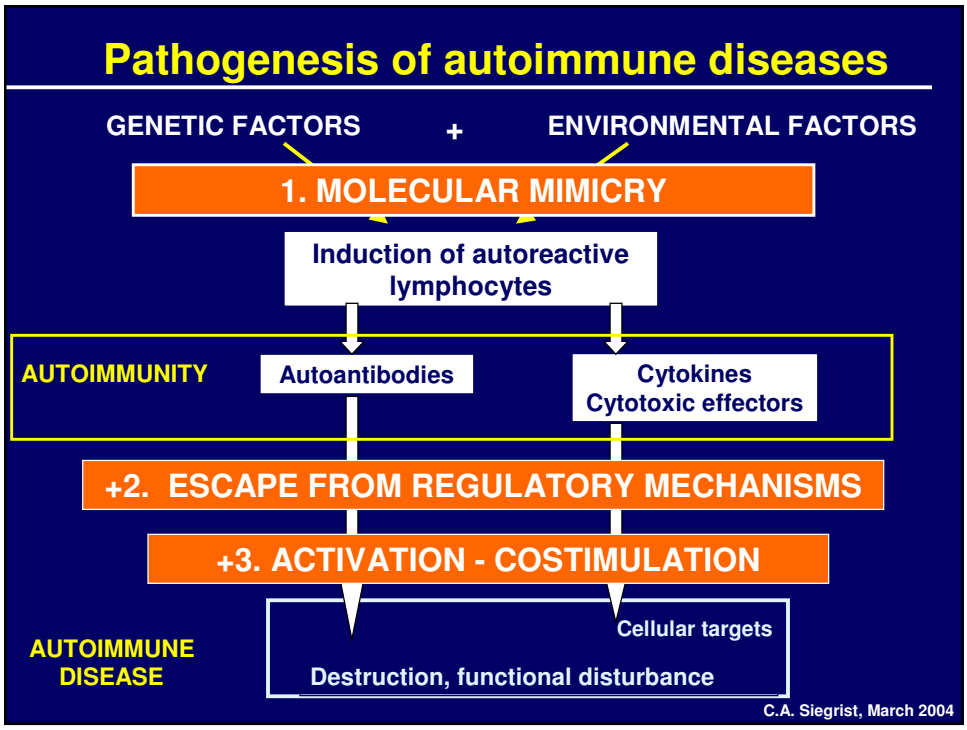

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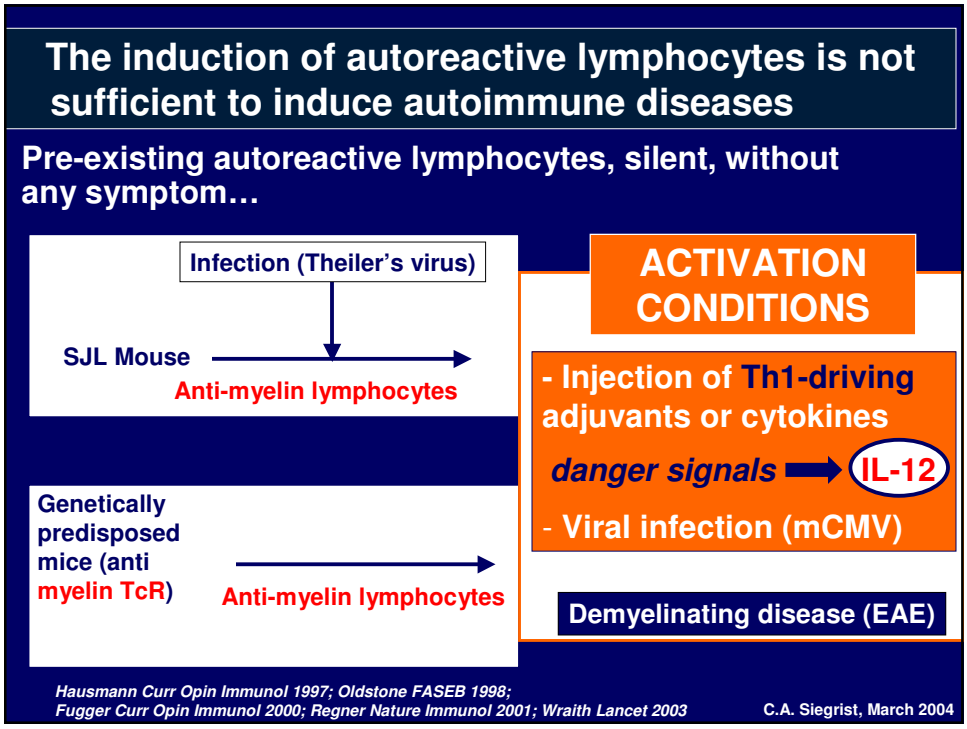

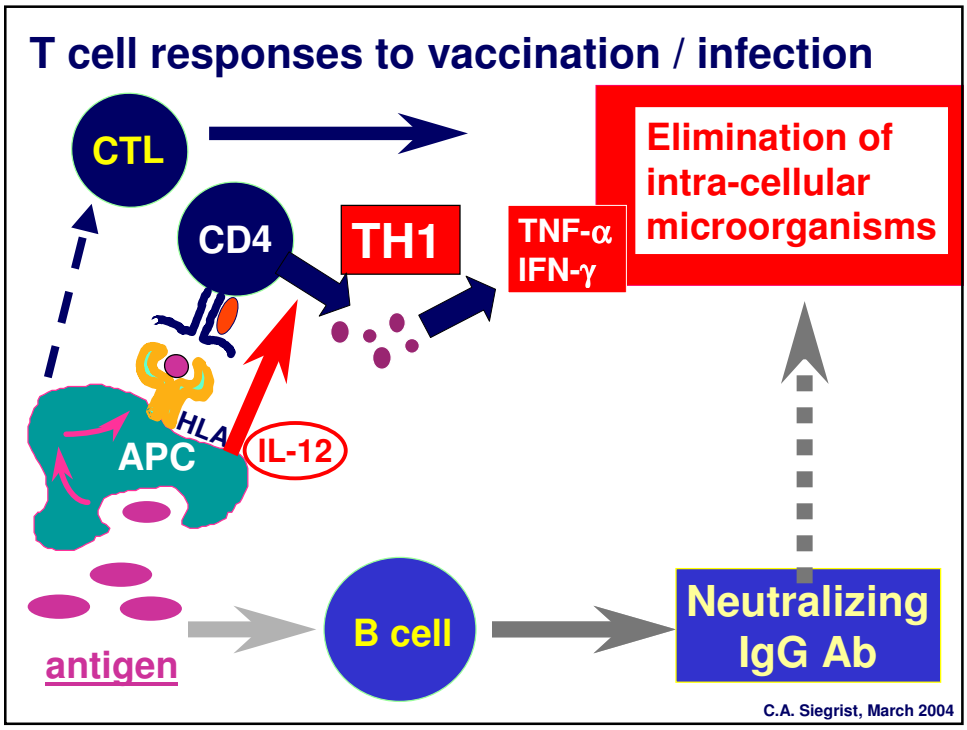

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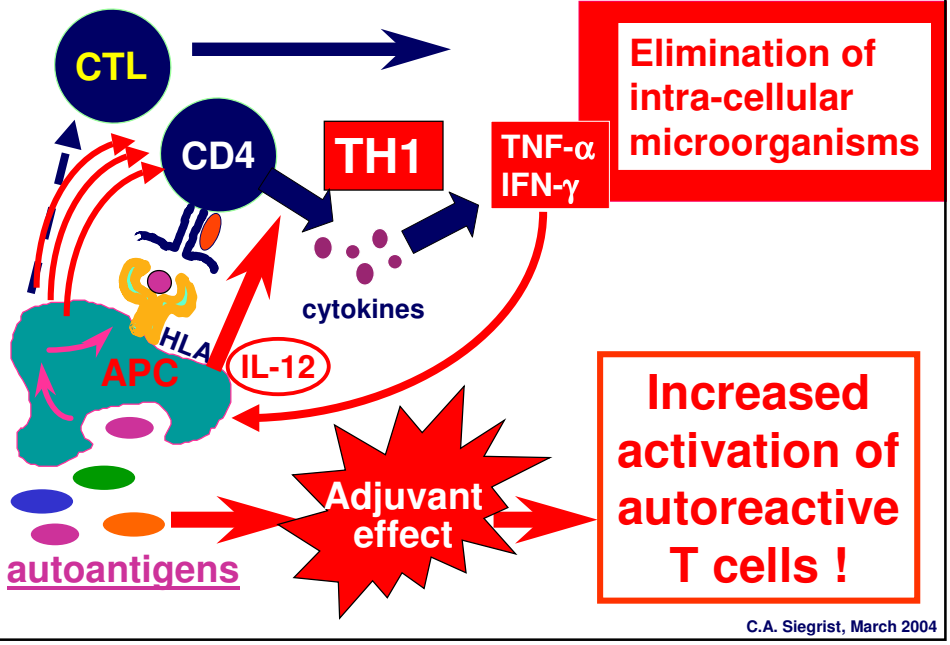
T cell responses to vaccination / infection



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IMMUNOLOGICAL SAFETY OF VACCINATION
The risks of increasing autoimmunity

2 POTENTIAL RISKS :

1. **May vaccination cause autoimmune diseases ?**
2. **May vaccination trigger autoimmune diseases through non-specific activation of autoreactive cells ?**

C.A. Siegrist, March 2004

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May vaccination play a causal role in the induction of autoimmune diseases ?

+

1. MOLECULAR MIMICRY — 1.

+2. ESCAPE FROM REGULATORY MECHANISMS — +2.

+3. ACTIVATION - COSTIMULATION — +3.

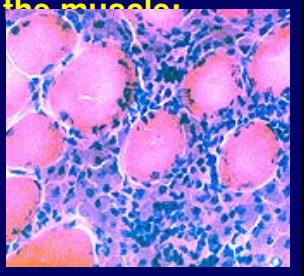
1. Novel type of autoimmune disease ?
2. Modification of known autoimmune diseases ?
   (genetic predisposition, markers, severity)
3. Retain some of the risks of pathogen-specific associated autoimmunity ?

C.A. Siegrist, March 2004

Do aluminium adjuvants cause a new autoimmune disease ?

1998 : new histological lesion described in France inpatients investigated (muscular biopsy) for diffuse myalgias

- Cellular infiltration in the periphery of the muscle:
  - Macrophages +++
  - Associated with lymphocytes
- Size 2-4 mm, in deltoid muscle
- Distinct from other myopathies



Gherardi, Lancet 1998
Gherardi, Brain 2001

= MMF (Macrophagic MyoFasciitis)

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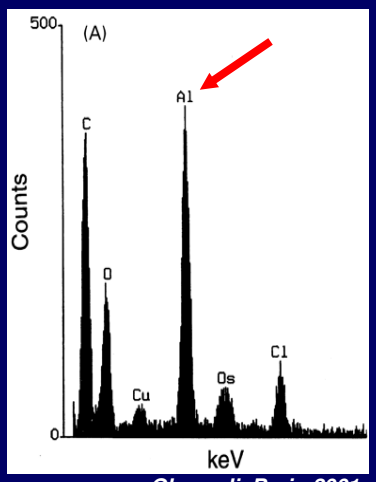
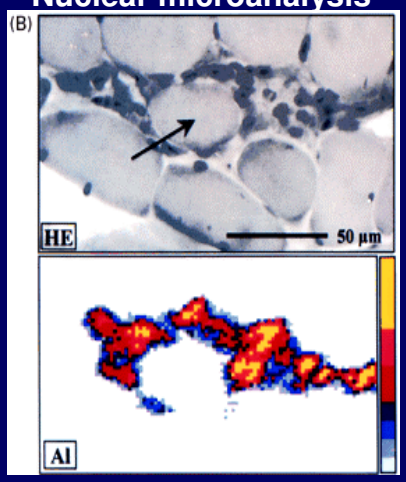
Microanalytical studies : aluminium hydroxide loaded macrophages

X-ray microanalysis



Gherardi, Brain 2001

Nuclear microanalysis



Gherardi, Brain 2001

Normal aluminium contents outside of the lesion

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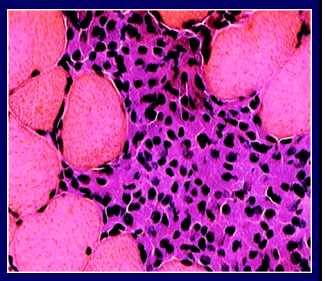
MMF : a limited inflammatory reaction to aluminium containing vaccines

- **Lesions similar to physiological responses observed in rodents after immunization**
- **Only at site of immunization** (deltoid, quadriceps…)
- Positive history of immunization with aluminium containing vaccines in "all" patients
- **Case-control study :**
  similar symptoms (myalgias) as in controls *(Chronic Fatigue Syndrome)…*



Rat lesion day 21
Gherardi, Brain 2001

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Aluminium and autoimmune diseases ?

1. A microscopic inflammatory lesion may persist after immunization *(vaccine tatoo).*
2. It does not reflect a diffuse muscular disease.
3. It is not associated to specific symptoms.
4. The most plausible explanation is that of a sampling bias in a mostly vaccinated adult population – among which myalgias and fatigue are frequent and non specific symptoms.

5. There is NO evidence questioning the safety of aluminium vaccines.

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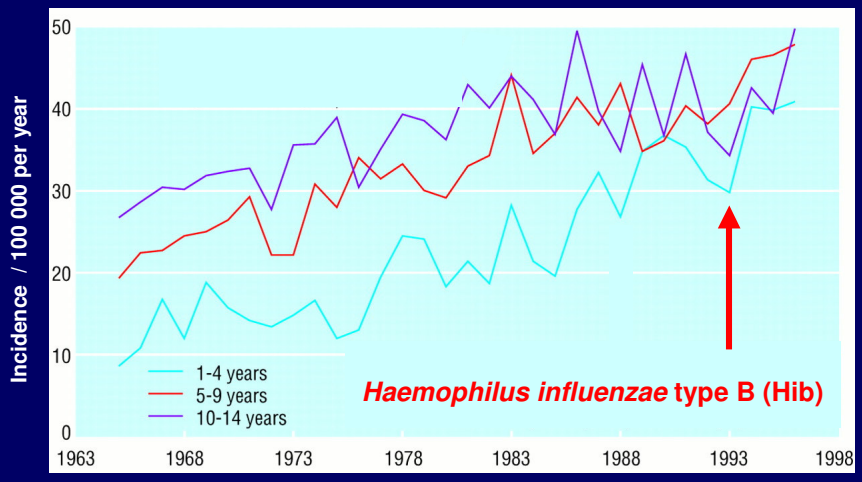
Is the incidence of type 1 diabetes increased by immunization ?



From: Karvonen M, Cepaitis Z, Tuomilehto J., BMJ, 1999; 318:1169-72

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Childhood vaccination, vaccination timing and risk of type 1 diabetes mellitus

Finnish Birth Cohort Study : no correlation between age at HIB immunization and risk of diabetes

Karvonen M, et al. BMJ, 1999

Case-control study within 4 HMOs (1988-1997)
(tested vaccines: DTP, DTaP, HepB, Hib, MMR, varicella)

No significant association between any of the recommended childhood vaccines and an increased risk of type 1 diabetes.

DeStefano F, et al. *Pediatrics 2001*

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Hepatitis B and Multiple Sclerosis

France, 1993-99

25 millions Hepatitis B vaccinations including 18 millions adults

NO INCREASE IN THE INCIDENCE OF MULTIPLE SCLEROSIS

- **General population : 1-3 / 100'000 ***
- **Hepatitis B vaccinees : 0.6 / 100'000 ***

**** estimations***

C.A. Siegrist, March 2004

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May vaccination play a causal role in the induction of autoimmune diseases ?

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1. MOLECULAR MIMICRY — 1.

+2. ESCAPE FROM REGULATORY MECHANISMS — +2.

+3. ACTIVATION - COSTIMULATION — +3.

1. Novel type of autoimmune disease ? NO
2. Modification of known autoimmune diseases ? (incidence, genetic predisposition, markers, severity) NO
3. Retain some of the risks of pathogen-induced autoimmunity ?

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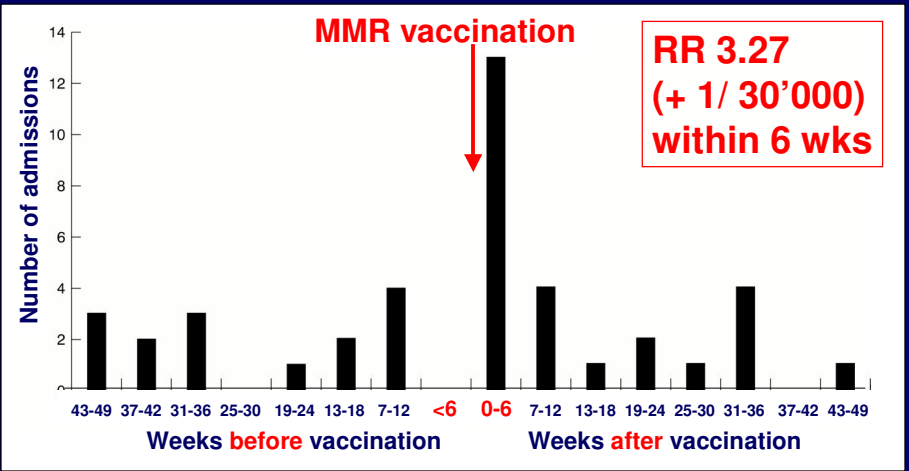
Idiopathic Thrombocytopenic Purpura and MMR vaccine



E Miller, et al, Arch Dis Child 2001;84:227-229

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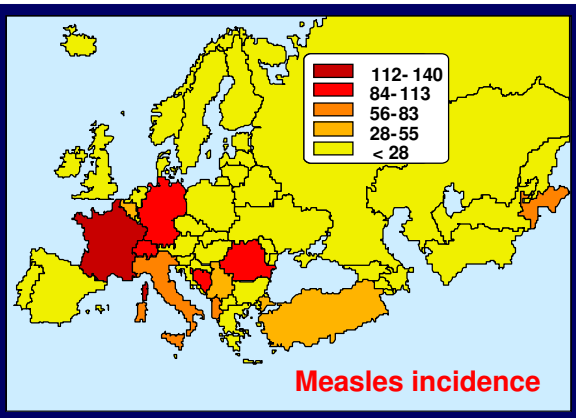
- ITP after MMR vaccine : ≈ 1 / 30'000
- ITP after measles : ≈ 1 / 6'000
- ITP after rubella : ≈ 1 / 3'000

Antibodies to platelets

Live attenuated vaccines retain some pathogen-associated features



The risk of measles remains high in CH…

MMR reduces the risks of viral induced ITP !

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INFECTION-TRIGGERED AUTOIMMUNE RELAPSES

Influenza infections induce exacerbations within the following 6 weeks in 33% of patients with relapsing form of multiple sclerosis

De Keyser J, et al J Neurol Sci 1998;159:51-3

Influenza immunization protects MS patients against infection-driven relapses

C.A. Siegrist, March 2004

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Vaccination and autoimmunity :

what is the evidence ?

1. Vaccines do NOT cause autoimmune diseases… and may prevent infection-induced diseases !

Group A strep	-	*Rheumatic fever*
Campylobacter	-	*Guillain-Barre*
Borr. Burgdorferi	-	*Lyme arthritis*

C.A. Siegrist, March 2004

IMMUNOLOGICAL SAFETY OF VACCINATION

The risks of increasing autoimmunity

2 THEORIES :

VACCINES :

~~1. May cause autoimmune diseases through molecular mimicry…~~

2. May trigger autoimmune diseases through non-specific activation…

C.A. Siegrist, March 2004

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May vaccination play a triggering role of preexisting autoimmune diseases ?

+

1. MOLECULAR MIMICRY

+2. ESCAPE FROM REGULATORY MECHANISMS

+3. ACTIVATION - COSTIMULATION

1.

C.A. Siegrist, March 2004

Clinical studies of the association between Multiple Sclerosis or Demyelinating Diseases with Hepatitis B Vaccination

ANALYSIS	STUDY SITE	RR/OR (time intervall)	CI 95%	REF.
MS, 1st episode	USA	0.7 (24 months) 0.9 (any time)	0.3-1.8 0.5-1.6	Ascherio A 2001
MS, relapses	Europe	0.71 (2 months)	0.4-1.3	Confavreux C, 2001
Acute Demyelin.	France	1.7 (2 months) 1.5 (2-6 months)	0.5-6.3 0.5-5.3	Touzé E, 2000
MS, 1st episode	Canada	*5/ 288657 (pre- vacc. period, 1986-92.)* *9/ 289651(post- vacc. period., 1992-98)*		Sadovnick A, 2000
MS, 1st episode	USA	1.3 (6 months) 1.0 (12 months) 2.0 0.9 (36 months)	0.4-4.8 0.3-3.0 0.4-2.1	Zipp F, 1999
Acute Demyelin.	USA	1.09	0.7-1.7	Verstraeten T, 2001
MS, relapses	France	*0.6/yr (incid. before vaccin)* *0.5/yr (incid. after vaccin.)*		Coustans M, 2000
Acute Demyelin.	France	1.05 (2 months, expected 102.7 vs observed 108 / 7.18 million vaccinees)		Fourrier A, 2001
MS, 1st episode & Acute Demyelin.	UK	1.4 (2 months) 1.5 (12 months)	0.8-2.4 0.6-3.9	Sturkenboom M, 1999
Acute Demyelin.	USA	0.6 (2 months)	0.1-4.6	Weil J, 1998

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MS, rela				
Acute D				
MS, 1st e				
MS, 1st e				
Acute D				
MS, rela				
Acute D				
MS, 1st				
Acute D				
Acute D				

Immunization Panel of the Multiple Sclerosis Council for Clinical Practice Guidelines :

- No evidence that hepatitis B, varicella, tetanus or Bacille Calmette-Guerin vaccines increase the risk of MS exacerbations *Rutschmann OT; Neurology 2002*

French Ministry commissioned expert meeting (September 03) : the analysis of available evidence does NOT conclude to the existence of an increased risk of MS or MS exacerbations.

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Non-specific triggering by immunization ?

Vaccination and diabetes : lack of identified triggering role in studies with appropriate controls (vaccines, age).

Vaccination and MS : lack of identified triggering role in multiple studies performed.

Vaccination and rheumatoid arthritis : triggering role suggested by some series (n=15), but non identified in case-control study (GPRD), nor by vaccination of patients (VHB, pneumococcus, influenza)

Vaccination and lupus (LED) : triggering role non identified in case-control study (GPRD) nor by vaccination of patients (TT, VHB, pneumoc., influenza)

No evidence for non-specific triggering…

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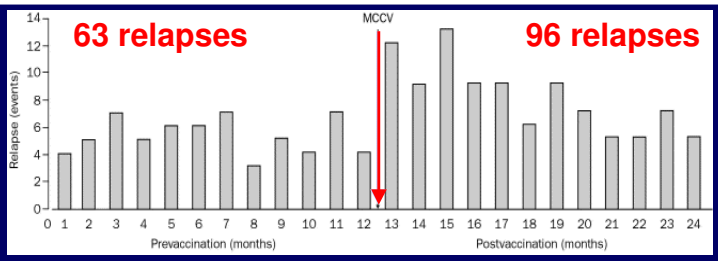
Exceptions to the rule ?

Vaccination and Guillain-Barré : triggering role identified after tetanus vaccine (6 wks). *Hyperimmunisation ?*

Men C vaccination and nephrotic syndrome :

- Young children immunized during national campaign
- 24 months study period



Slight increase of the relative risk of relapse within 6 months

1.84 (1.3-1.7) (0-6 mo) 1.21 (0.8 – 1.8) (7-12 mo)

Abeyagunawardena, Lancet 2003

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The risk of unbalancing an autoimmune condition by vaccination may not be zero, but it is very low…

C.A. Siegrist, March 2004

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Vaccination and autoimmunity :

what is the evidence ?

1. Vaccines do NOT cause autoimmune diseases… and may prevent infection-induced diseases !

2. Vaccines do NOT significantly increase the risks of exacerbations…

and prevent from infection-triggered autoimmune relapses

C.A. Siegrist, March 2004

INFECTION-TRIGGERED AUTOIMMUNE RELAPSES

Influenza infections induce exacerbations in 33% of patients with multiple sclerosis

De Keyser J, et al J Neurol Sci 1998;159:51-3

Influenza immunization protects MS patients against infection-driven relapses

Which is the best choice for the patient ?

Which is the easiest choice for the physician in charge ?

C.A. Siegrist, March 2004

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THE IMMUNOLOGICAL SAFETY OF VACCINATION IS HIGHER THAN EXPECTED !

Which mechanisms prevent

- **Th1 responses (e.g. to live vaccines)**

from triggering autoimmune diseases?

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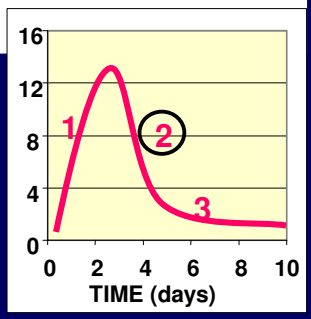
The non antigen-specific effects of vaccines are essentially :

- **time-limited (days)**
- **localised to regional draining lymph nodes *(exception : live vaccines)***
- **controlled by regulatory mechanisms (e.g. CD4⁺ CD25⁺ T cells)**

Example :

BCG vaccine in patients with MS : no relapses triggered !

Ristori G, et al. Neurology 1999



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Vaccination and autoimmunity…

What are the risks ?

The risks are those of COINCIDENTAL associations. This risk is high and it is increasing !

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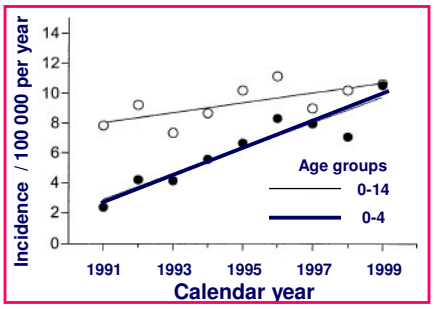
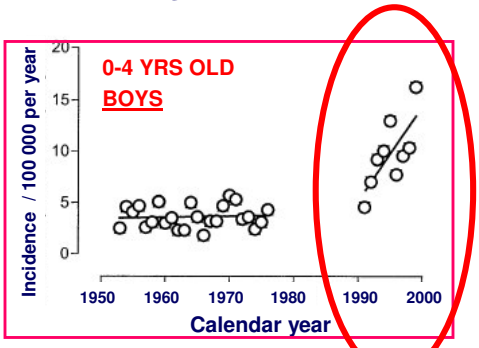
Incidenc in childhood diabetes in Switzerland : 4x increase within 10 years





From 4.5 to 16.4 / 100´000

Schoenle EJ et al., Diabetologia, 2001, 44:286-289

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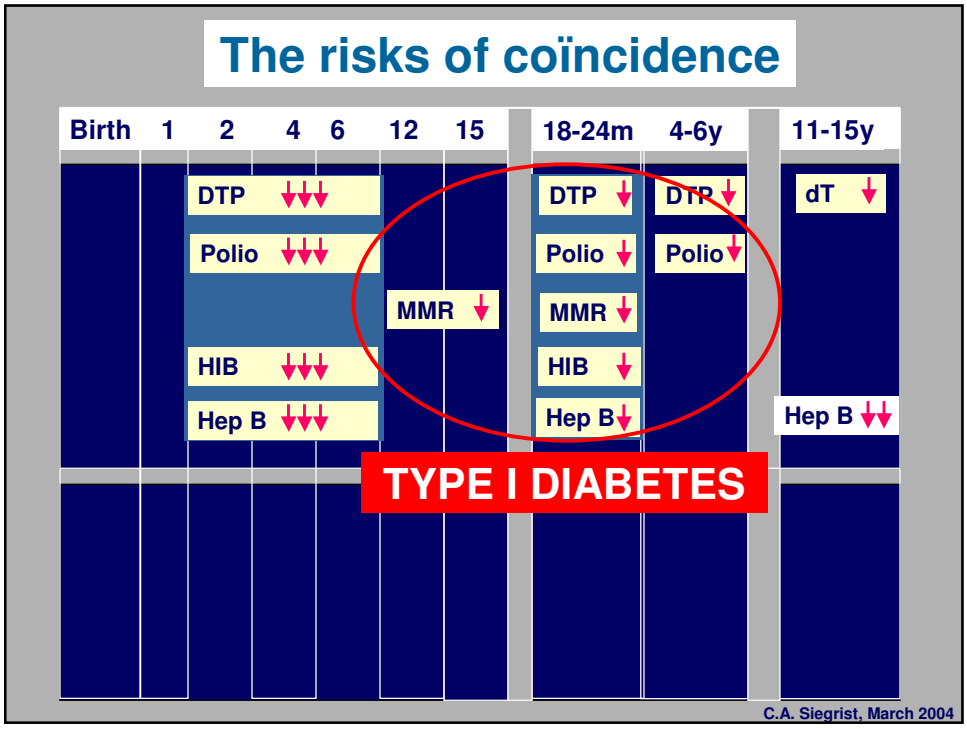

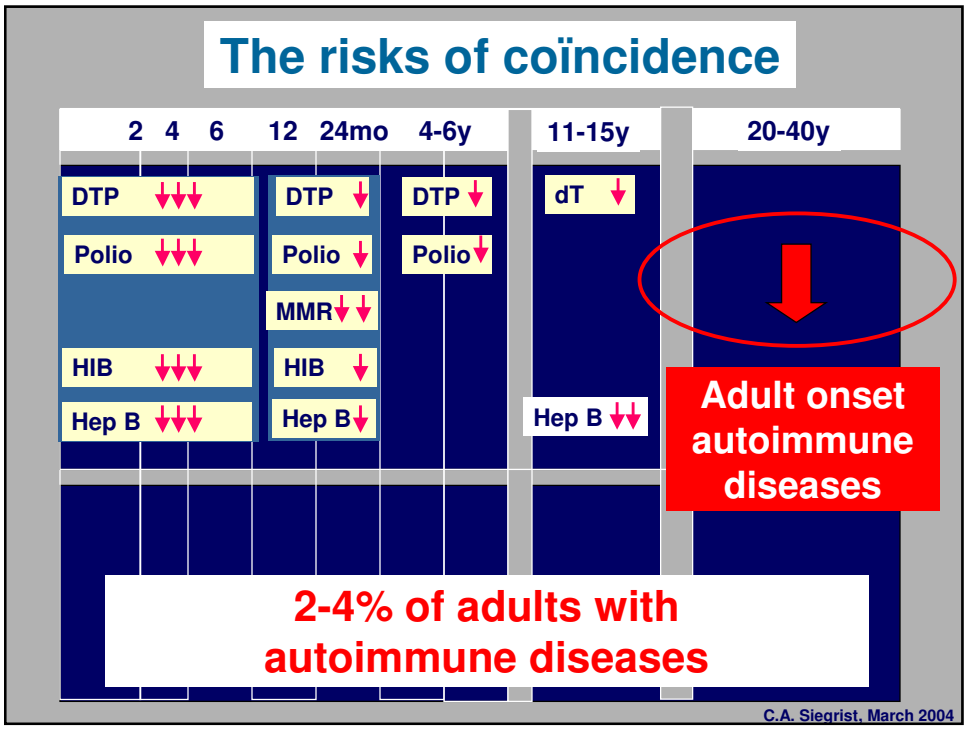

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Vaccine fears prevent Switzerland from reaching its public health objectives

• Diphtheria :	Elimination	YES
• Tetanus :	No neonatal tetanus	YES
• Poliomyelitis :	Elimination	YES
• Pertussis :	Incidence < 1/100'000	NO !
• Measles :	No death	NO !
	Incidence < 1/100'000	NO !
• Rubella :	No cases during pregnancy	NO !
	No congenital rubella	NO !
• Mumps :	Incidence < 1/100'000	NO !
• Hepatitis B :	No new carriers (-80%)	NO !

C.A. Siegrist, March 2004

Vaccination, allergy and autoimmunity : what is the evidence ?

The risk of COINCIDENTAL associations is increasing !

COINCIDENTAL associations challenge the future of vaccination

C.A. Siegrist, March 2004