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Your Infovac experts

## **Vaccination, allergy and autoimmunity : what are the risks ?**

### **Part A : Allergy**

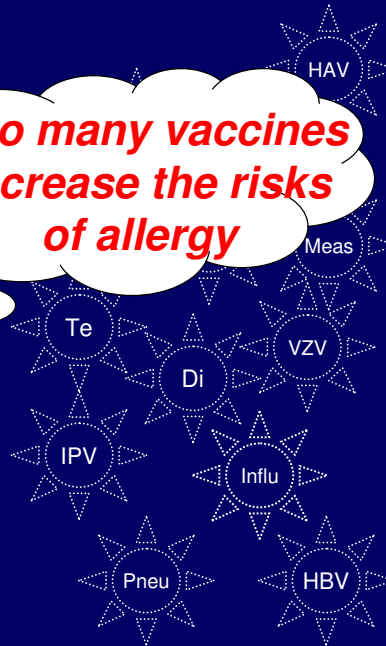
**26th Infectious Disease Symposium  
Zürich, March 25, 2004**

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

**A concern frequently  
expressed by  
parents...**

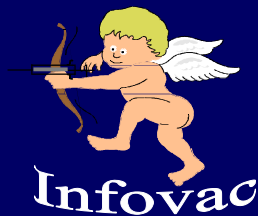


**Too many vaccines  
increase the risks  
of allergy**



C.A. Siegrist, March 2004

**Also a concern for physicians...**



**18.03.2004**

*Chers Collègues,*

*Y a-t-il un lien entre vaccination  
anti-pertussis et toux prolongée  
ou hyperréactivité bronchique  
chez un nourrisson ?*

*Je n'ai pas connaissance de cette  
association, mais un  
pneumologue de Berne aurait  
parlé de cela à des parents dont  
je suis l'enfant...*

C.A. Siegrist, March 2004

## IMMUNOLOGICAL SAFETY OF VACCINATION

### The risks of enhancing allergy

#### 2 THEORIES :

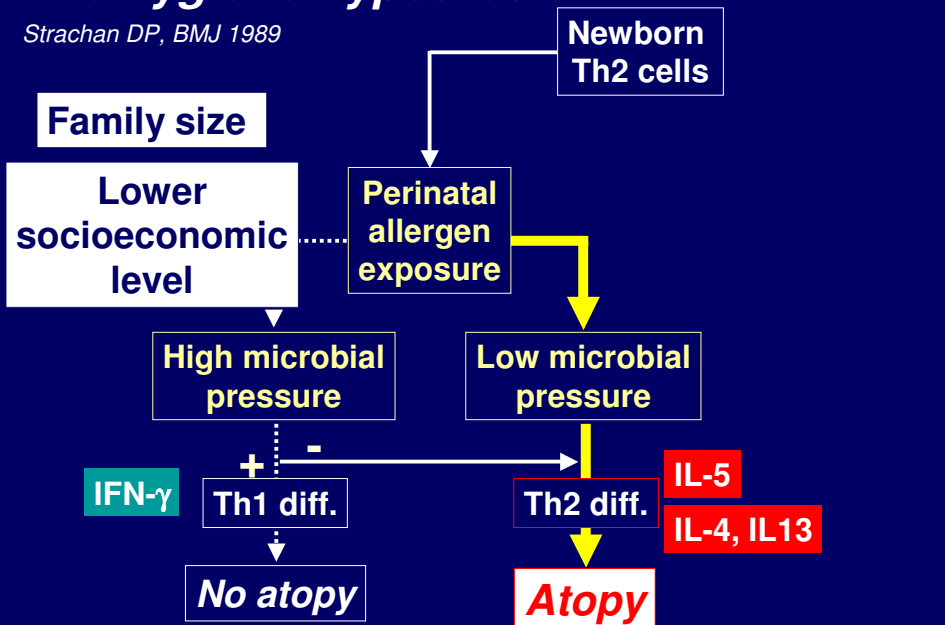
#### TOO MANY VACCINES :

1. **indirectly promote allergy by deprivation of "natural" infections**
2. contain aluminium salts promoting Th2-responses – which directly increase the risks of allergy

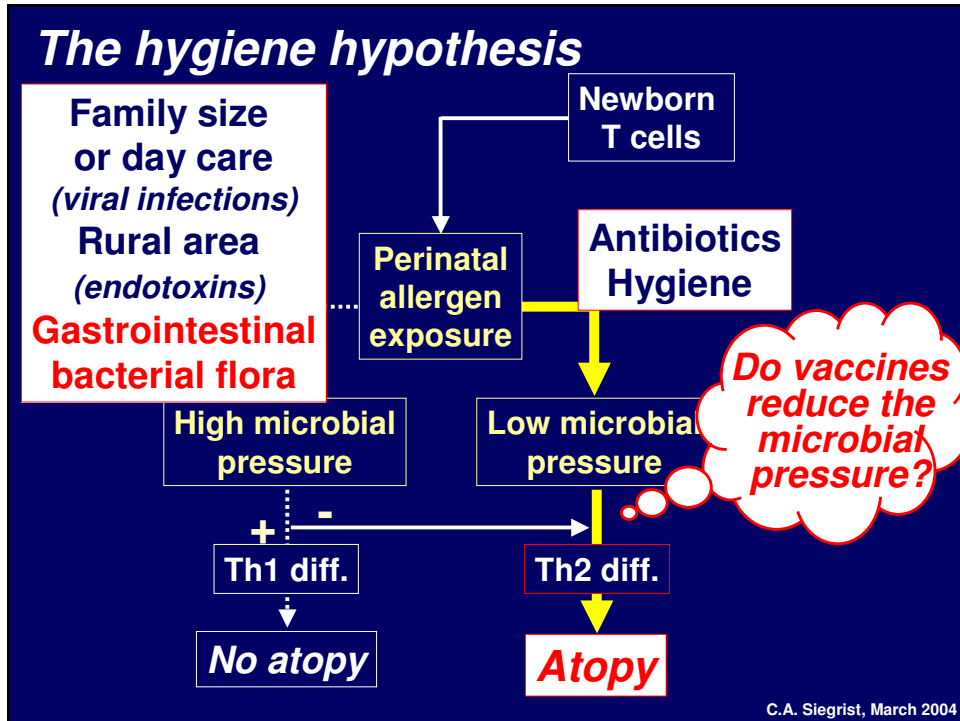
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## The hygiene hypothesis

Strachan DP, BMJ 1989



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### Indirect promotion of allergy by deprivation of natural infections ?

**Waldorf, Sweden :** Alm JS, Lancet 1999

Anthroposophic (AS) vs regular schools (RS), n = 2x300

	AS	RS
<b>Atopy prevalence</b>		
	<b>OR 0.62</b> [95% CI 0.43-0.91]	
<b>MMR coverage</b>	18%	93%
<b>Measles infection</b>	61%	1%

**Does measles protect against atopy ?**  
**A frequently quoted study...**

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## Main influence of the gastrointestinal flora on atopy prevalence !

**Waldorf, Sweden :** Alm JS, Lancet 1999, Pediatr Allerg. Immunol. 2002

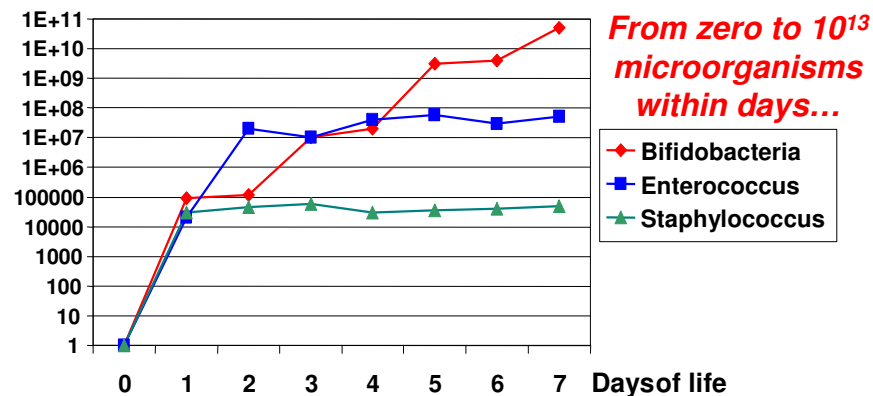
Anthroposophic (AS) vs regular schools (RS), n = 2x300

	AS	RS
<b>Atopy prevalence</b>	<b>OR 0.62</b> [95% CI 0.43-0.91]	
MMR coverage	18%	93%
Measles infection	61%	1%
<b>Antibiotics &gt;1x</b>	<b>52%</b>	<b>90%</b>
<b>Live lactobacilli</b>	<b>63%</b>	<b>4.5%</b>
<b>Enterococci / g</b>	<b>55Mi</b>	<b>21Mi</b>

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## The main microbial pressure in early life...

### Neonatal colonisation of the intestinal tract

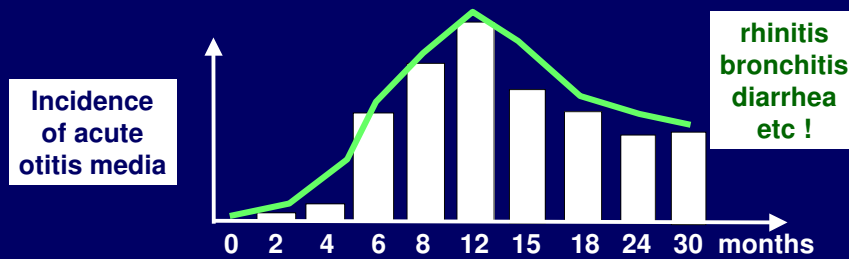


Pediatrics 1983: 72:319

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## Epidemiology of infectious diseases in the first year of life : mainly respiratory viruses

- Rhinoviruses, influenza, para-influenza viruses
- RSV
- ...



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## Current vaccines exert no influence on the microbial pressure !

**Common viral infections**  
**Bacterial flora**

	Birth	1	2	4	6 m	12	15	18 - 24m
Di-Te-Per								
Polio				↓↓↓				↓
MMR							↓	↓
H I B				↓↓↓			↓	
Hepatitis B				↓↓↓				↓

High microbial pressure

Low microbial pressure

Th1 diff.

Th2 diff.

No atopy

**Atopy**

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## Vaccination and allergy :

### what is the evidence ?

1. Vaccines do NOT deprive from « beneficial » infections... **but they protect against severe diseases**

Diseases < 5y	Cases USA	2000	Decline (%)
Measles	894'134 (1941)	37	-99.99
Pertussis	265'269 (1934)	2'878	-98.91
Diphtheria	206'939 (1921)	0	-100
Mumps	152'209 (1921)	57	-99.96
Cong. rubella	20'000 (1964)	10	-99.95
Poliomyelitis	21'259 (1952)	0	-100
Tetanus	601 (1948)	34	-94.34

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## IMMUNOLOGICAL SAFETY OF VACCINATION

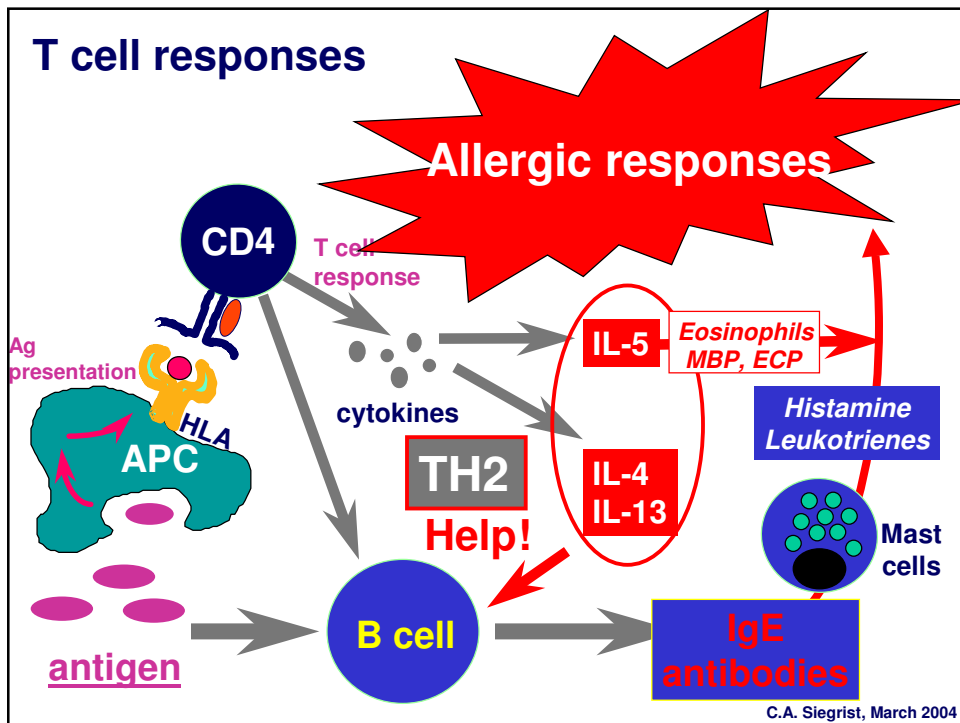
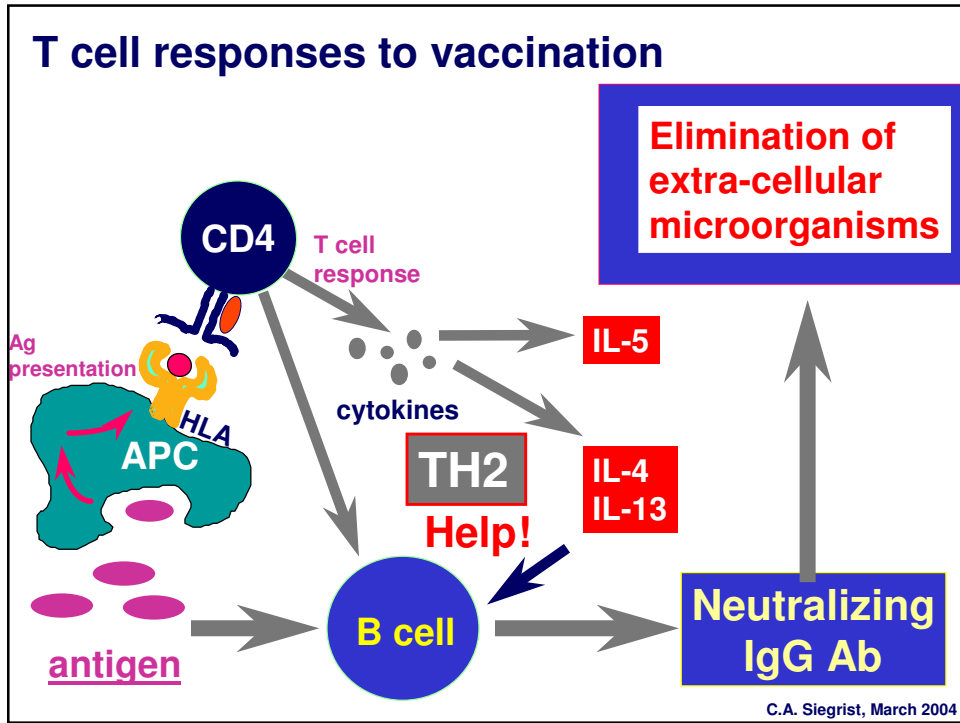
### The risks of enhancing allergy

#### 2 THEORIES :

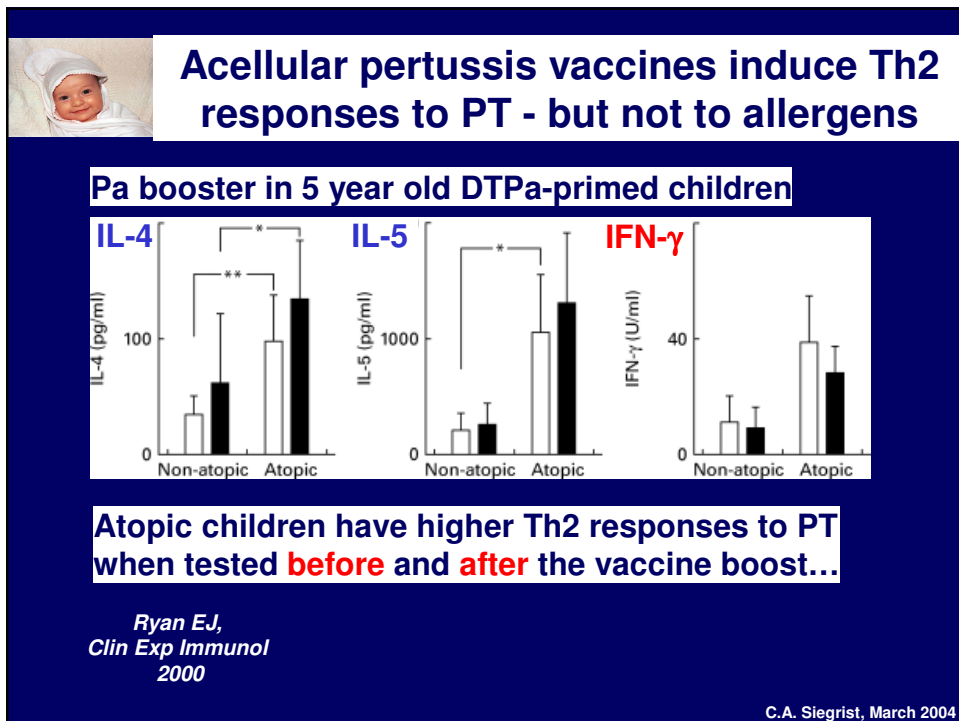
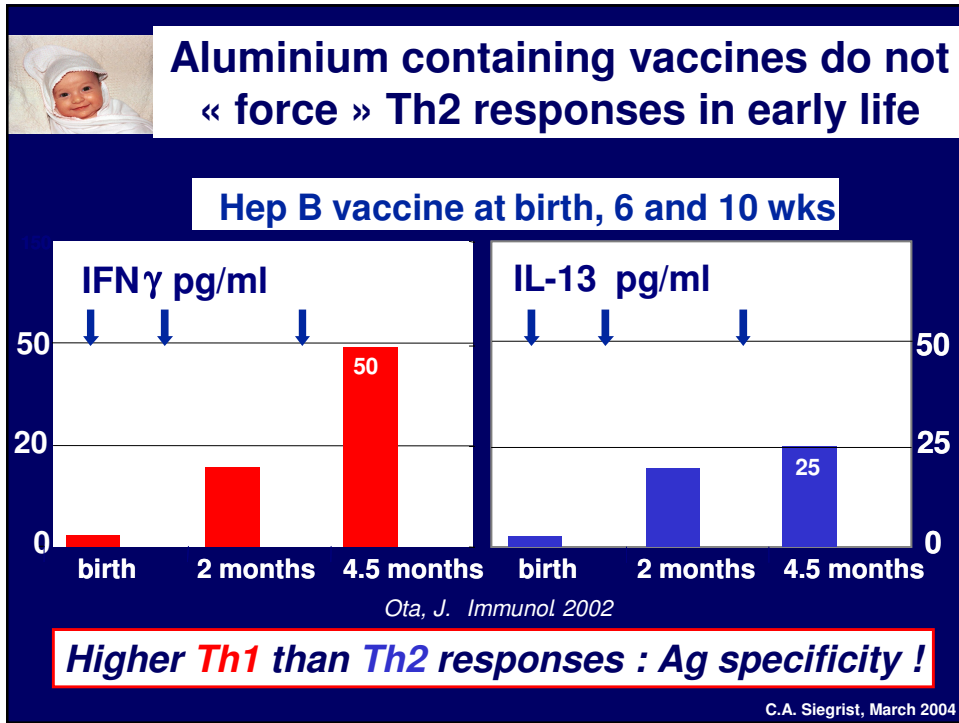
#### TOO MANY VACCINES :

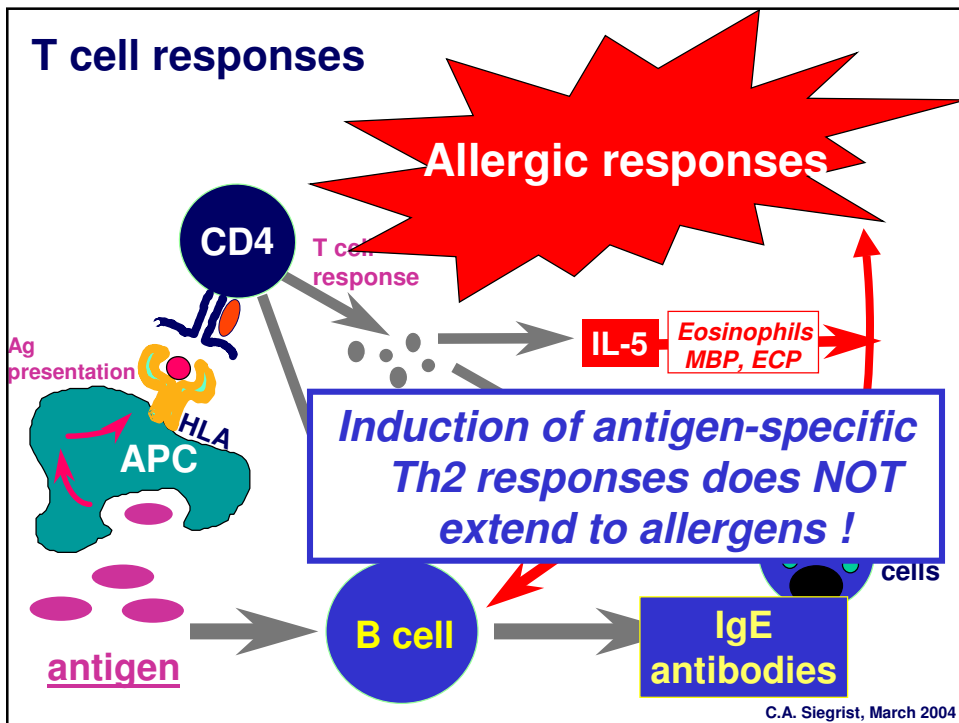
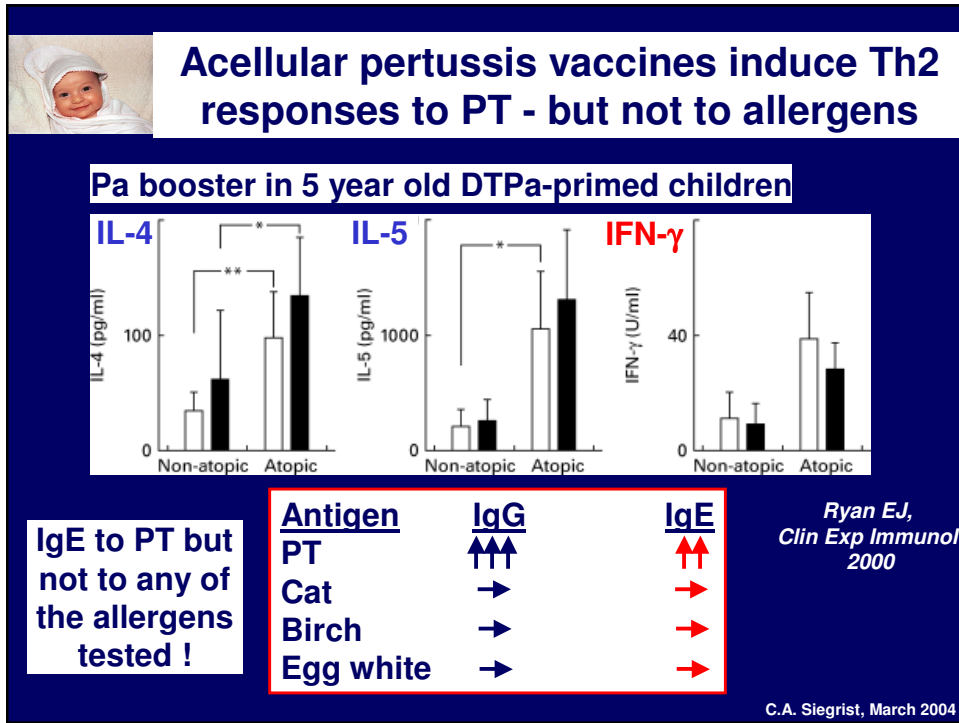
- ~~1. deprive of natural infections and indirectly promote allergy~~
2. **contain aluminium salts promoting Th2-responses - which directly increase the risks of allergy**

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## IMMUNOLOGICAL SAFETY OF VACCINATION

### The risks of enhancing allergy

#### 2 THEORIES :

#### MANY VACCINES :

1. may reduce the number of...  
during... cy... a...  
ns... es...  
...ing... allergy-  
... m2-responses

**Simple, but flawed !**

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## Effects of vaccines on atopy : which epidemiological evidence ?

### Retrospective studies

- 5x increased risk for asthma in DTPw vaccinated children  
*Odent MR JAMA 1994*
- 23% asthmatic children among 1'265 DTPw vaccinated children - none of 23 (!) controls  
*Kemp T, Epidemiology 1997*
- 1.8 relative risk of atopic manifestations in Pw vaccinated U.K. children  
*Farooqi IS, Thorax 1998*

**Small numbers of non-vaccinated control children, no match, many confounding factors...**

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## Effects of vaccines on atopy : which epidemiological evidence ?

### Prospective study

German cohort of 1'314 atopy risk- enhanced infants,  
 many unvaccinated (pertussis, MMR) ! , assessed at 5 y

*Grüber C, Pediatrics 2003*

Prevalence	Non vaccinated	Vaccinated	p value
<u>Pertussis</u>			
Asthma	12.1%	9.3%	0.180
<b>Atopic dermatitis</b>	<b>14.8%</b>	<b>9.3%</b>	<b>0.014</b>
Atopic rhinoconj.	5.5%	4.9%	0.816
<u>MMR</u>			
Asthma	16.5%	10.5%	0.135
<b>Atopic dermatitis</b>	<b>22.4%</b>	<b>11.5%</b>	<b>0.007</b>
<b>Atopic rhinoconj.</b>	<b>11.8%</b>	<b>4.4%</b>	<b>0.007</b>

**Protection against atopic dermatitis / rhinitis ?!**

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## Effects of vaccines on atopy : the best epidemiological evidence

### Well-controlled studies :

1. Relative risk of **asthma** in 18'407 vaccinated versus non vaccinated children  
*De Stefano F, PIDJ 2002*

**DTPw 0.92    OPV 1.09    MMR 0.97    HepB 1.0**

2. 667 children, **randomized to 1 of 4 vaccine groups** and **prospectively followed** (1, 3 and 7 years) for the relative risk of asthma, atopic dermatitis, allergic rhinoconjunctivitis, urticaria, food allergies  
*Nilsson L, Arch Ped Adol Med 1998 - 2003*

DT  
 DTPw  
 DTPa 2 components  
 DTPa 5 components

**35%**

**Incidence of atopic disease similar in each vaccine group !**

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## Vaccination and allergy :

### what is the evidence ?

1. Vaccines do NOT reduce the microbial pressure... but they protect against severe diseases

2. Vaccines do NOT increase the risk of atopy manifestations...

... and protect against infection-driven asthmatic exacerbations  
*(influenza, pertussis)*

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## Vaccination may trigger anaphylaxis

<u>Vaccine</u>	<u>Risk of anaphylaxis</u>	<u>Reference</u>
- DTP	8.6 / Mi doses	VSDL <i>Bohlke K, Pediatrics 2003</i>
- MMR	1.8 / Mi doses	VAERS <i>Pool V, Pediatrics 2002</i>
- MMR	5.0 / Mi doses	Finland, <i>Patja A, PIDJ 2000</i>
- MMR	3.5 -14.4 / Mi doses	VSDL <i>Bohlke K, Pediatrics 2003</i>
- Hep B	7.8 / Mi doses	Canada, <i>Dobson S, JAMA 1995</i>
- Hep B	1.7 / Mi doses	VAERS, <i>ACIP, MMWR 1996</i>
- Hep B	1.1 / Mi doses	VSDL <i>Bohlke K, Pediatrics 2003</i>

**Overall vaccine risk :**

**0.65 cases / million doses (CI95 0.21-1.53)**

*Bohlke K, Pediatrics 2003*

**Allergens : gelatin – neomycin**

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## Vaccination may trigger allergic reactions

### Frequency of vaccine-associated allergic reactions among 50'000 pediatric allergy consultations ?

– urticaria, erythema multiforma :

• MMR OR 3.3 (CI95% 1.2 - 8.9)

– various skin rash, wheezing :

• MMR OR 2.4 (CI95% 1.4 - 3.2)

• Hepatitis B OR 2.0 (CI95% 1.4 - 2.8)

• HIB OR 1.7 (CI95% 1.1 - 2.6)

– allergens : gelatin, neomycin >> vaccine antigens !

**Vaccines may reveal preexisting sensitization to food or drugs !**

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## Vaccination and allergy :

### what is the evidence ?

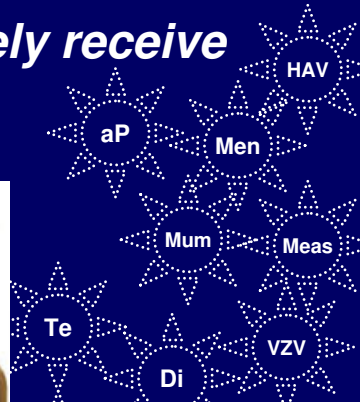
1. Vaccines do NOT reduce the microbial pressure

2. Vaccines do NOT increase the risk of atopic diseases

3. Vaccination MAY induce allergic reactions to vaccine components  
- rarely severe – mostly self limited -

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## *Atopic patients can safely receive all existing vaccines*



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### Vaccination and allergy :

#### few contra-indications

1. Anaphylaxis to a previous vaccine dose : **→** allergology evaluation

2. Anaphylaxis to egg : **NO** influenza, yellow-fever vaccines (OK : MMR, FSME)

3. Patients with non-anaphylactic reactions can be immunized safely (antihistaminics)

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## THE IMMUNOLOGICAL SAFETY OF VACCINATION IS HIGHER THAN EXPECTED !

Which mechanisms prevent

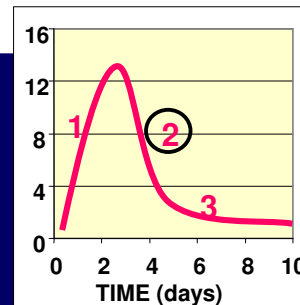
- **Th2 responses** to vaccine antigens from spreading **to allergens ?**

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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<sup>+</sup> CD25<sup>+</sup> T cells)

These control mechanisms allow the immune system to react simultaneously to hundreds of antigens without losing antigen-specificity !



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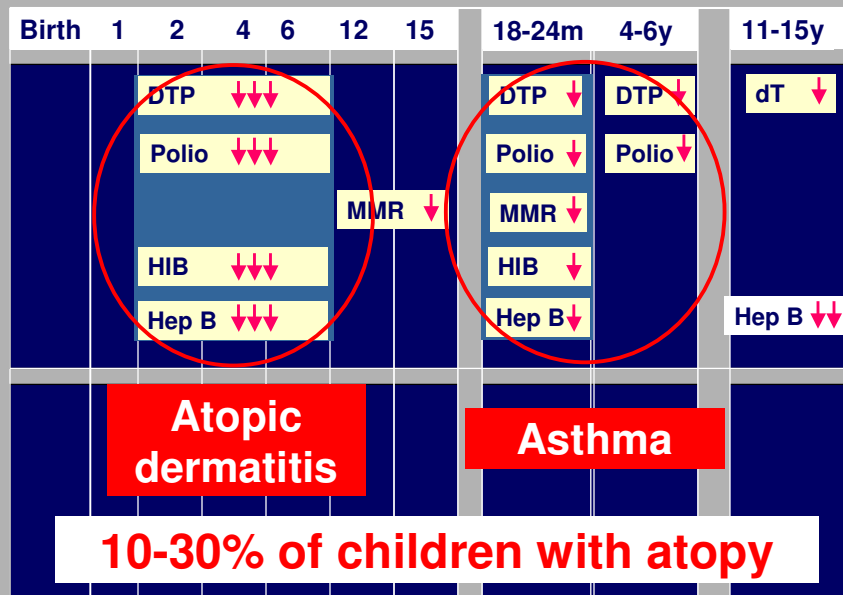
## Vaccination and allergy...

### What are the risks ?

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

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### The risks of coincidence



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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
• <b>Pertussis :</b>	Incidence < 1/100'000	<b>NO !</b>
• <b>Measles :</b>	No death	<b>NO !</b>
	Incidence < 1/100'000	<b>NO !</b>
• <b>Rubella :</b>	No cases during pregnancy	<b>NO !</b>
	No congenital rubella	<b>NO !</b>
• <b>Mumps :</b>	Incidence < 1/100'000	<b>NO !</b>
• <b>Hepatitis B :</b>	No new carriers (-80%)	<b>NO !</b>

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**Vaccination and allergy :  
what are the risks ?**

**The risk of COINCIDENTAL  
associations is increasing !**

**COINCIDENTAL associations  
challenge the future  
of vaccination**

**The future is up to us...**

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