



UNIVERSITÉ  
DE GENÈVE

FACULTÉ DE MÉDECINE

HUG    
Hôpitaux Universitaires de Genève

# Maternal immunization: which impact on infant immunity ? *(which immunological safety ?)*



The greatest challenge is to provide enough reassurance for maternal immunization to be accepted despite the common perception that pregnancy should be “vaccine free”



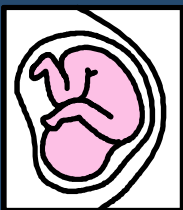
# THE *Complete* *Organic Pregnancy*



# *Organic Pregnancy Bible*™

The #1 Bestselling Holistic Pregnancy Program





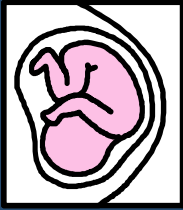
# Maternal immunization and risks of miscarriage ?

No increase of spontaneous abortion reported following

- tetanus immunization (...)
- trivalent inactivated influenza vaccine. (*Irving SA, Obst Gynecol 2013; Nordin JD Obst Gynecol 2013; Tama PD Am J Obst Gyn 2009*)
- adjuvanted pandemic influenza vaccine (*Tavares F Vaccine 2011; Rubinstein F BMJ 2013*)
- Tdap vaccine (*Shakib JH J Pediatr 2013; Zheteyeva YA Am J Obst Gyn 2013*)
- rubella vaccine (*Badilla X, PIDJ 2007, Castillo JID 2011, da Silva JID 2011*)
- yellow fever vaccine (*Suzano CE Vaccine 2006*)
- Etc

**Vaccine-triggered reactogenicity (including fever) does not result into pregnancy loss**



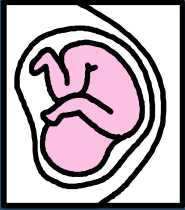


# Maternal innate responses may be deleterious for the developing fetal brain

- Infections during pregnancy (influenza, etc)  $\leftrightarrow$   $\uparrow$  risks of **schizophrenia** (up to 30% cases ?) and **autism** (2-3x ?)  
*(Brown Am J Psychiatry 2010, etc.) (Atladottir HI J Autism Dev Disord 2010, etc.)*
- Is reproduced in preclinical models (mice and non-human primates)
- **Can be elicited in the absence of pathogens**
  - by mimics of viral (poly (I:C)) or bacterial (LPS) pathogens
  - **by injection of IL6**

$\leftrightarrow$  **potential deleterious effects of maternal innate responses on the developing brain** (*mice, NHP, human - epi*)

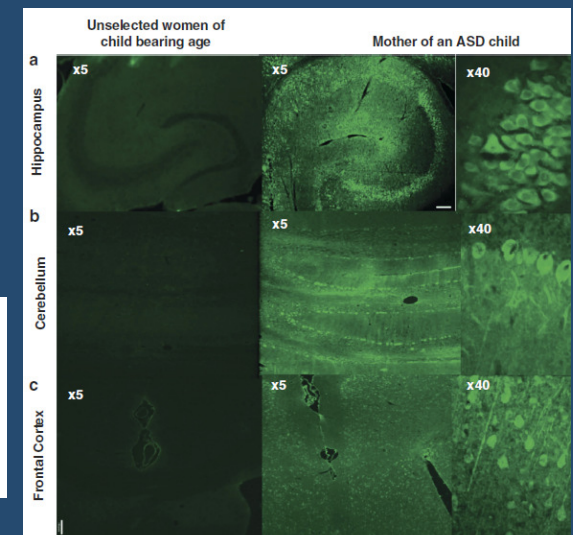
**Selection of vaccines with low inflammatory profiles**  
(*ex: dTaP rather than DTPw*) to prevent disease-induced brain alterations



# The active transfer of maternal antibodies may also transfer autoreactive antibodies...

- Active receptor mediated (FcRn) transport of IgG antibodies
- **No distinction between protective / pathogenic antibodies : effective transfer of autoreactive antibodies ↔ autoimmunity !**
- **Neonatal hemolytic anemia, thrombopenia, lupus, etc.**
- **Autism** : brain-reactive IgG in 10% of mothers of a child with an autism spectrum disorder *(Brimberg L Molecular Psychiatry 2013)*
  - 2431 mothers of ASD child - 653 controls
  - Anti-brain antibodies: 10.5 vs 2.6%
  - More frequent in mothers with AID

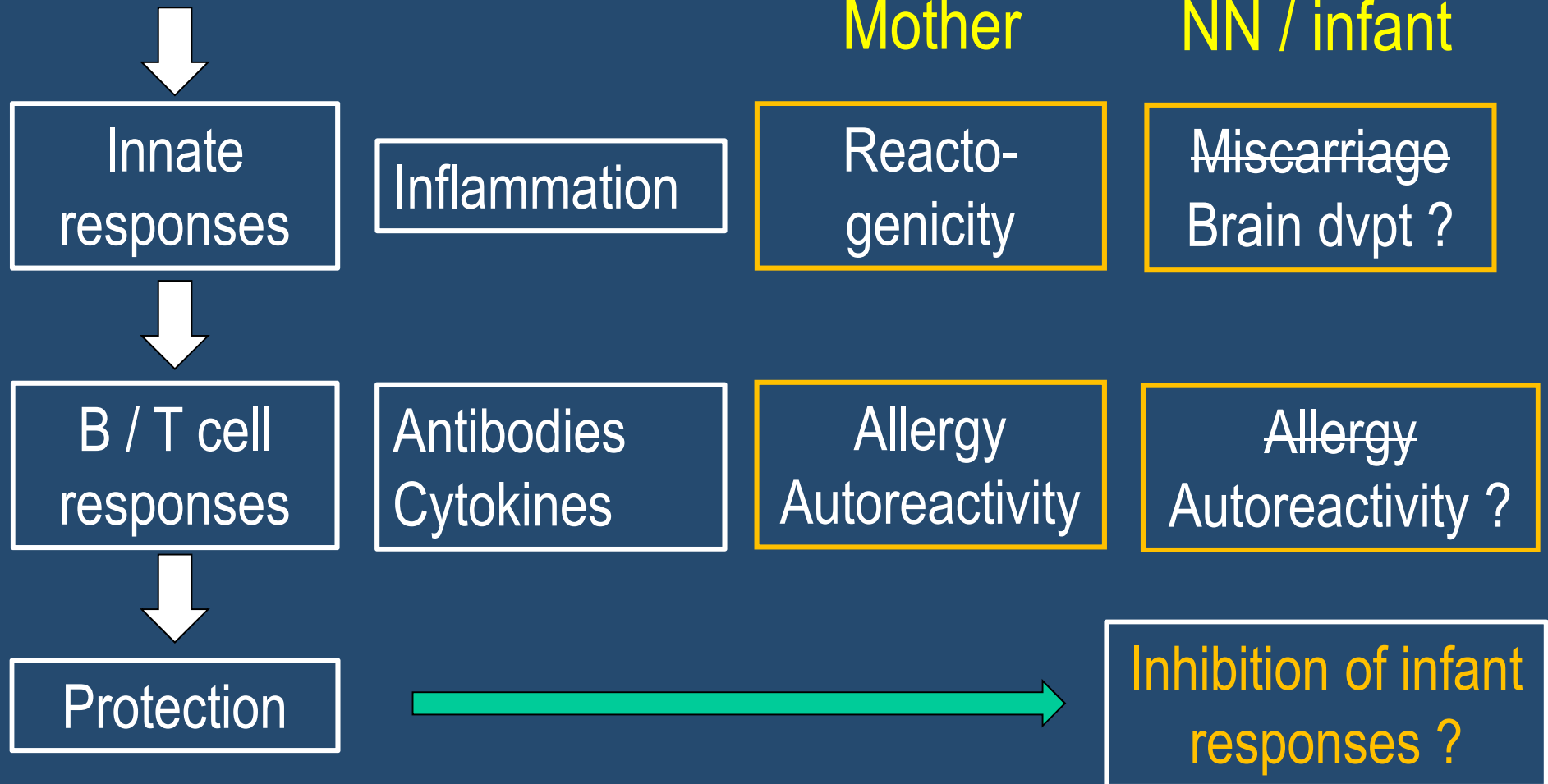
**Exclude autoreactivity  
for novel vaccine antigens**

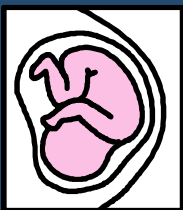




# Immunological safety of maternal immunization

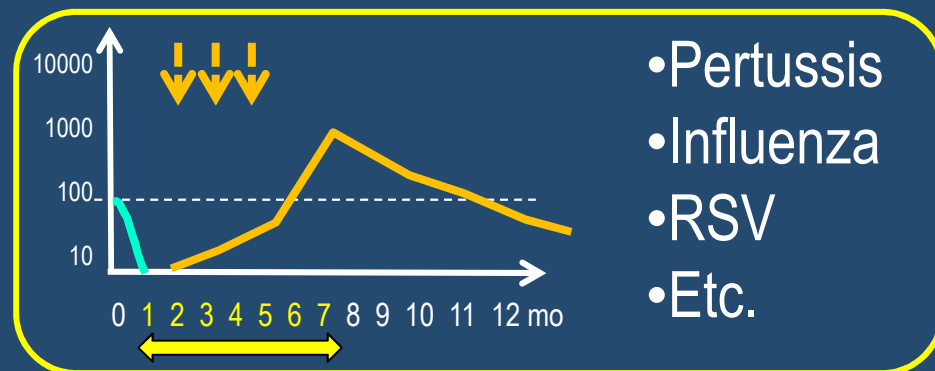
## Immunization

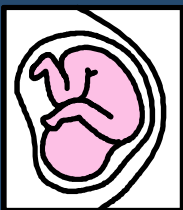




# Maternal immunization and the immunity gap

An immunity gap is created by the rapid waning of low-titers maternal Abs and the delayed infant responses.



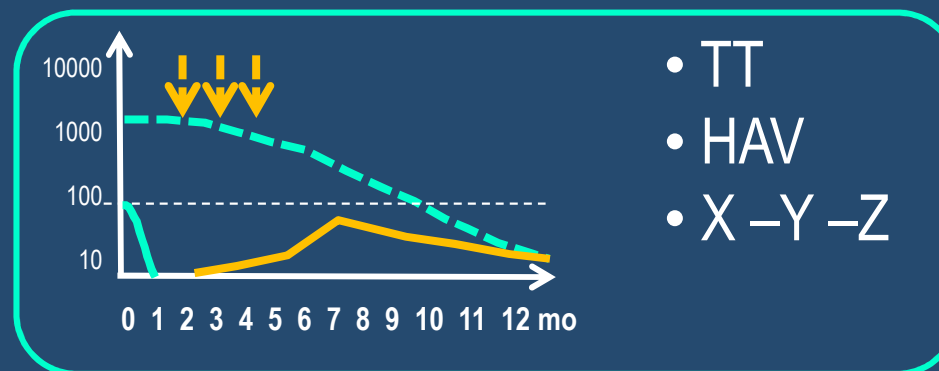
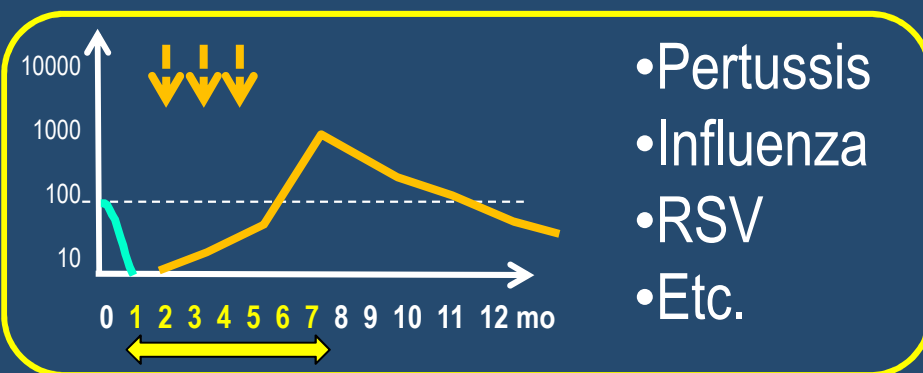


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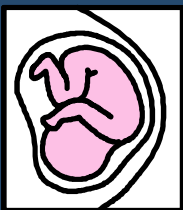
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Maternal immunization eliciting high MatAb titers :

- ↔ inhibition of infant responses
- ↔ closure of the immunity gap by protective MatAb







# Maternal immunization and the immunity gap

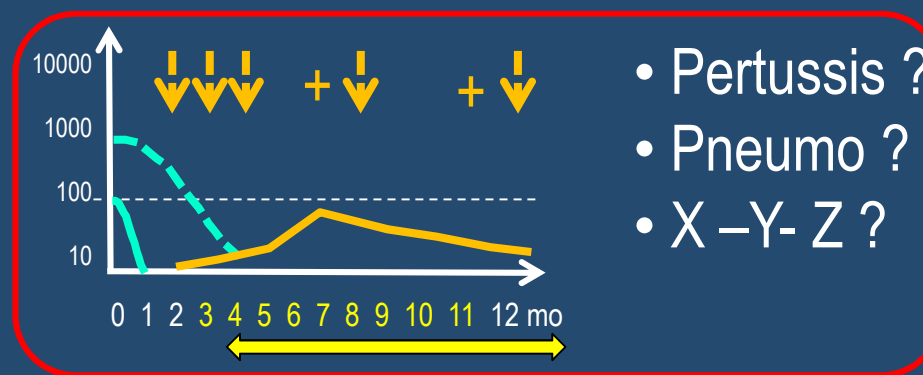
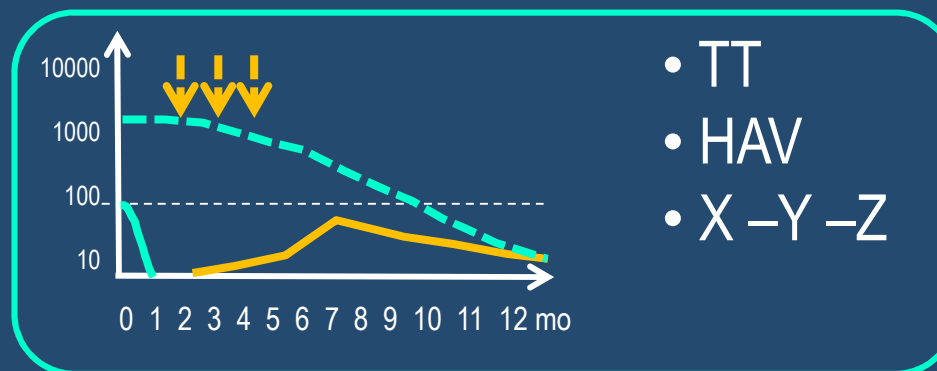
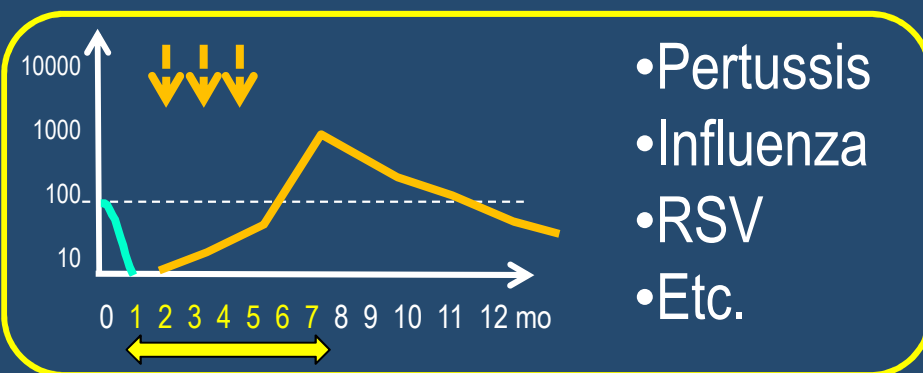
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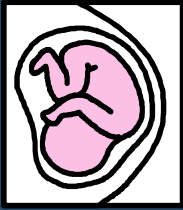
**Maternal immunization eliciting high MatAb titers :**

- ↔ inhibition of infant responses
- ↔ closure of the immunity gap by protective MatAb

**Maternal immunization eliciting modest MatAb titers :**

- ↔ inhibition of infant responses
- ↔ closure of early immunity gap but onset of new immunity gap ??





# Inhibitory influence of maternal antibodies: controversial findings !

## Significant inhibitory effects on infant IgG responses:

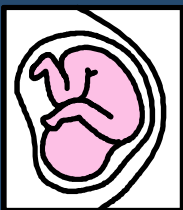
- Measles, OPV, VZV, rotavirus (live vaccines, incl. mucosal)
- Tetanus toxoid, diphtheria toxoid
- Pertussis toxin (Pw)
- Hib vaccines
- Hepatitis A
- Etc...

*Statistical significance ?  
Clinical significance ?*

## Unsignificant effects :

- The same vaccines... in other clinical trials !!!
- Hepatitis B in infected mothers
- Etc...





## Influence of maternal antibodies to PT on infant vaccine responses to DTwP and DTaP

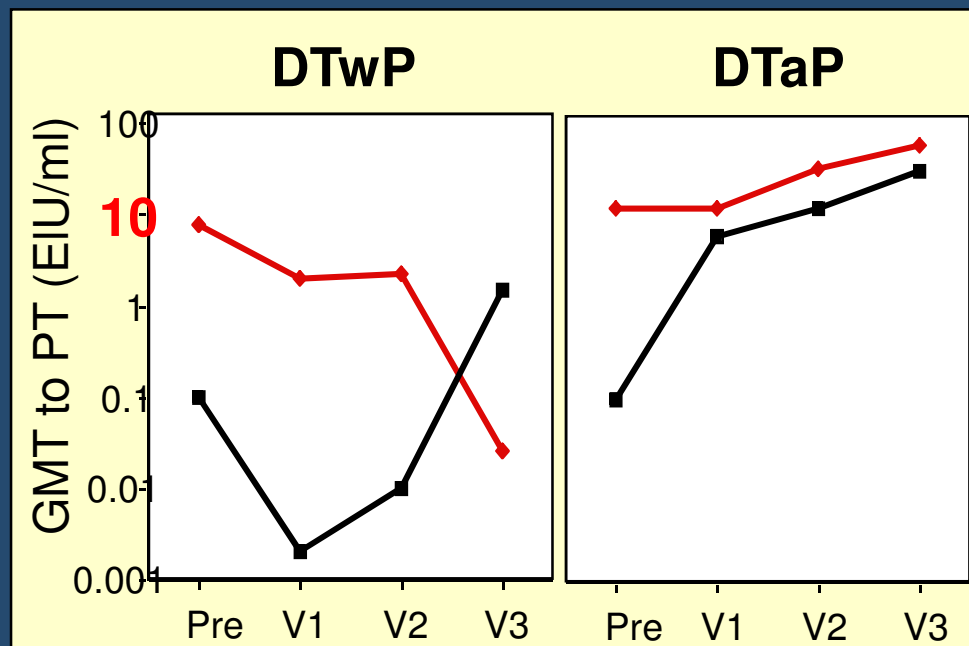
•DTaP or DTP vaccines at 2, 4, and 6 months of age : correlation between pre- and post-immunization titers:

• **infant DTwP**

- ↓ **28% - 56% anti-PT**
- ↓ 8-18% for other Ag

• **Infant DTaP:**

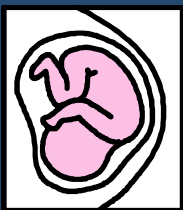
- **no ↓ of anti-PT**
- ↓ 8-18% for other Ag



Englund et al, Pediatrics 1995

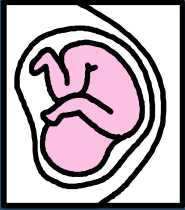
**1995 conclusion :** “The PT antibody response to DTaP, unlike DTP, is not adversely affected by preexisting antibody to PT.”

**2014:** Increasing evidence that higher titers of maternal antibodies, elicited by Tdap boosting, may interfere with infant vaccine responses.



## Inhibitory influence of maternal antibodies on infant responses: which immunological mechanisms ?

- **Neutralization of live viral vaccines by neutralizing MatAb?**
  - *Inhibition of responses to live vaccines even at low titers*
- **Fc-receptor mediated anergy of infant B cells?**
  - *Shown for measles in cotton rats ↔ sustained inhibition*
- **Formation of MatAb:antigen immune complexes captured by dendritic cells ?**
  - *Preservation of CD4 T cell responses; influence on conjugates*
- **Masking of specific B cell epitopes by MatAb ?**
  - *Epitope-specific inhibition ?*
- **Modulation of antigen delivery to B cells, FDCs, etc. ?**
  - *Influence on GC responses ? On T follicular cells ?*
- **Impact on effector rather than memory responses ?**



# Inhibitory influence of maternal antibodies: many potential determinants !

## Vaccine immunogenicity :

- Influence of vaccine antigens (epitopes) ?
- Influence of vaccine antigen content (dose) ?
- Influence of vaccine type / delivery systems ?
- Influence of immunization routes, including mucosal ?
- Influence of infant immunization schedules (age, # doses) ?

## Maternal antibodies :

- Distribution of antibody titers ?
- Persistence of antibody titers ?
- Influence on B and T cell effector responses ?
- Influence on B and T cell memory responses ?

A white thought bubble with a black outline, containing the text 'What ? When ? How ? What if ?' in blue. The bubble is connected to the text above by three small circles of decreasing size.

*What ? When ?  
How ? What if ?*



Freedom Bar

Rasta Art Bar 137

เชียงใหม่

PAI

City of lover

Chiang Mai

K.F.C

Starbucks

MacDonalds

PIZZA HUT

District office

Moe Hong Son

Police Station

Hospital

Pai town

AirPort

Longneck

Be bop

Chanon Bar

Beauty

Nature

HAP...PII

Land of action

HOLLYWOOD

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Jeans

fake

Parang cuckoo

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Belive

GOD

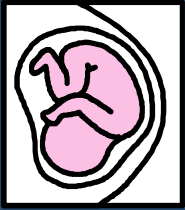
Mr. Crocodile

Mrs. Lacoste

Jazy day - crazy night

ต้อนรับ  
TingTong

WELCOME



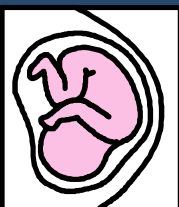
# Benefit-risks balance of maternal immunization: the TdaP example

## Demonstrated high protective vaccine efficacy:

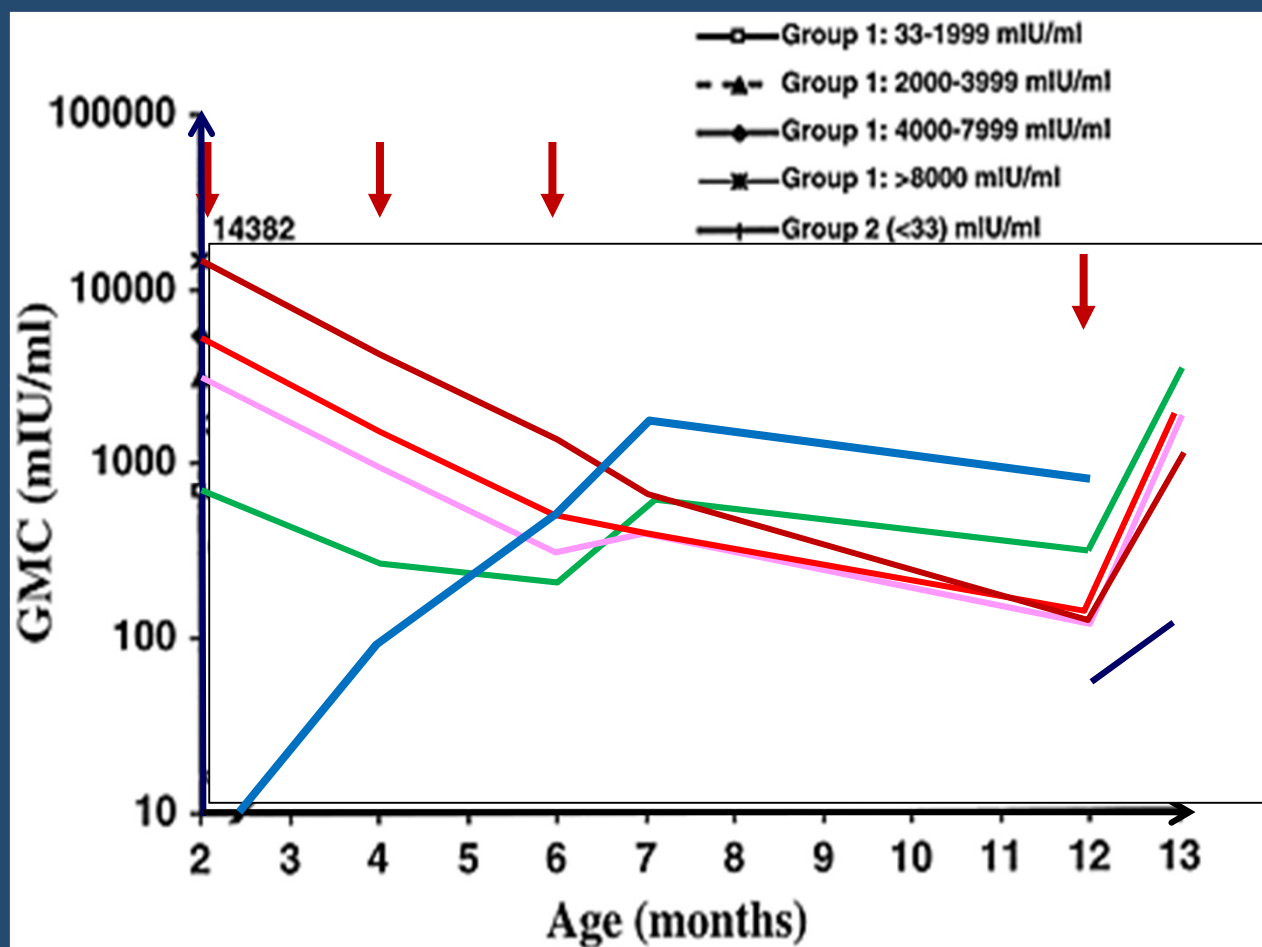
- Pertussis, UK TdaP program (*L. Miller et al, submitted*)

## Potential risks:

- No obstetrical risks identified (*submitted*)
- Developmental risks ? (*none identified - ongoing studies*)
- Statistical reduction of infant antibody responses : which clinical significance ?
  - Limited impact on seroprotective rates !
  - TRANSIENT potential impact on infant disease , as responses to subsequent boosting are usually maintained.



# Influence of maternal antibodies on infant responses to hepatitis A: a case story



Israeli infants, HAV 720, 3 doses at 2-4-6 months

Titer-dependent inhibition of infant responses...

But preserved booster responses !

*Dagan et al, PIDJ 2000*

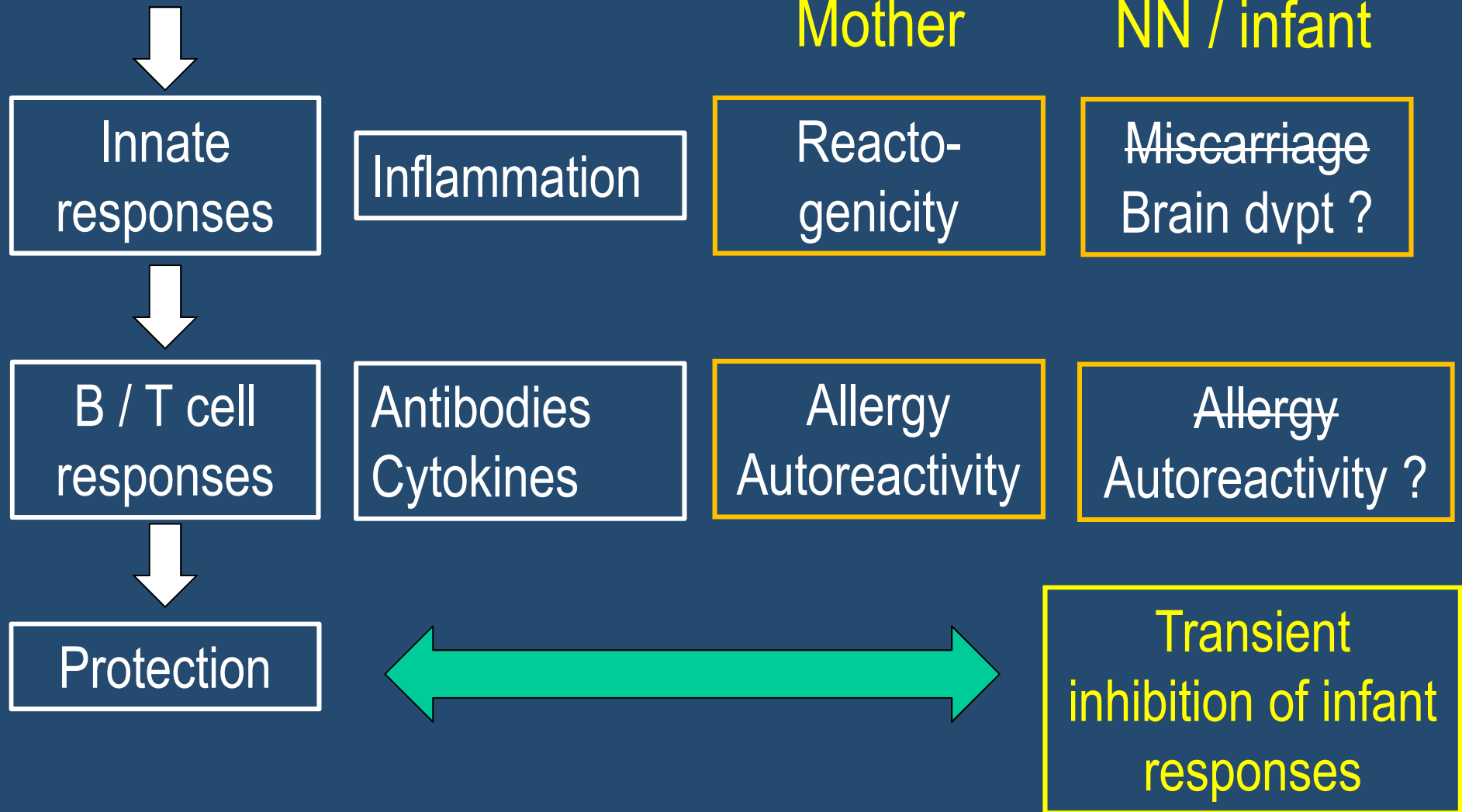
**Even high titers of MatAb appear not to prevent the induction of immune memory ↔ transient impact !**





# Immunological safety of maternal immunization

## Immunization





# The right way is FORWARD !!

## Clinical studies in various settings

- Magnitude and clinical implications of interference on infant responses ?
- Immunological safety (reactogenicity, autoreactivity)

## Vaccine immunology studies

**Mechanisms** ↔ impact on memory B and T cells (Tfh, etc.) ↔ long-term impact of interference ?

The greenest pregnancy is disease-free... and this may best be achieved through immunization.



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