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Immunisations in the immunocompromised

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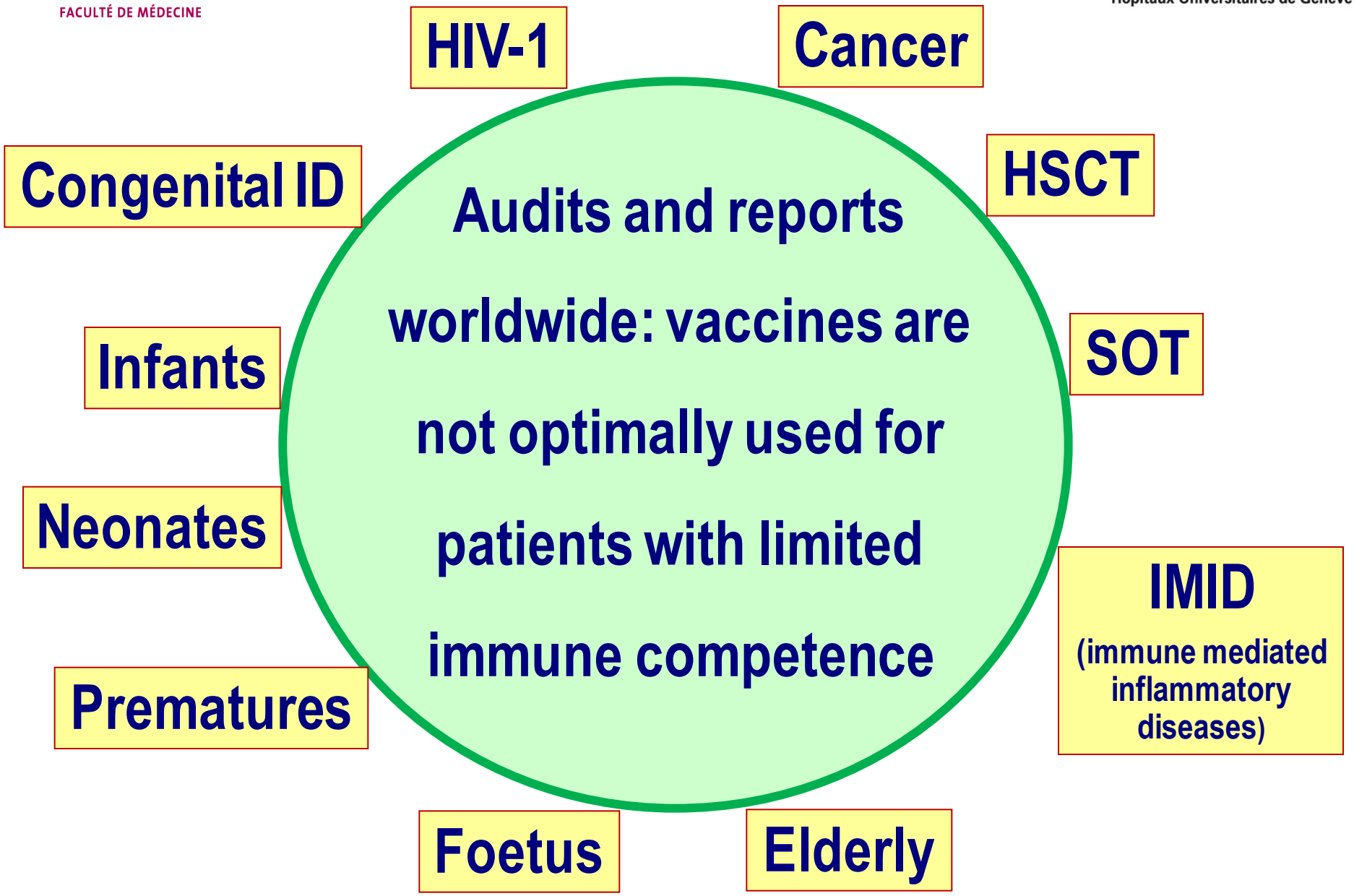
Medical Faculty and University Hospitals of Geneva

Switzerland


HIV-1
Cancer
Congenital ID
HSCT
Audits and reports worldwide: vaccines are not optimally used for patients with limited immune competence
Infants
SOT
Neonates
IMID
(immune mediated inflammatory diseases)
Prematures
Foetus
Elderly

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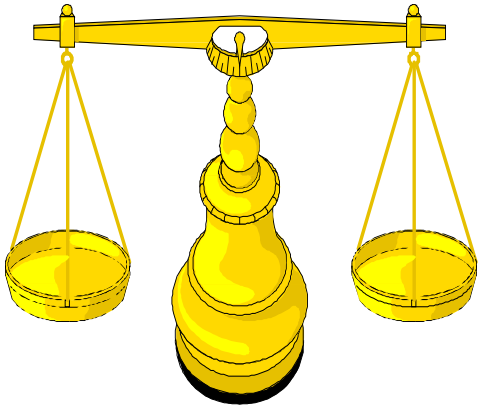
Vaccinations in the immunocompromised

Underestimated benefits



- **Lack of demonstration of vaccine efficacy** *(← sample size)*
- **Delayed / limited demonstration of immunogenicity**

← exclusion from licensing trials *(higher risks, small market)*
→ mostly investigator-based clinical trials
↔ off-label indications !

- **Perception that immunosuppression will prevent the induction of effective vaccine-induced responses…**

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Vaccinations in the immunocompromised

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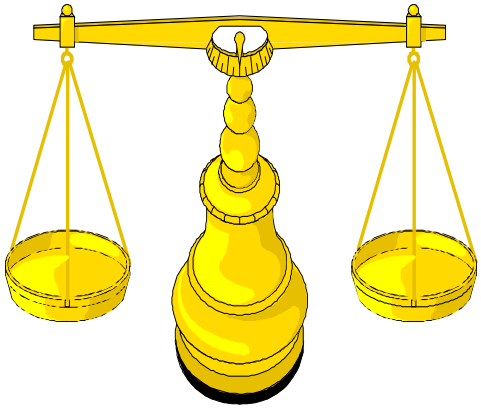

Fears of severe adverse events!

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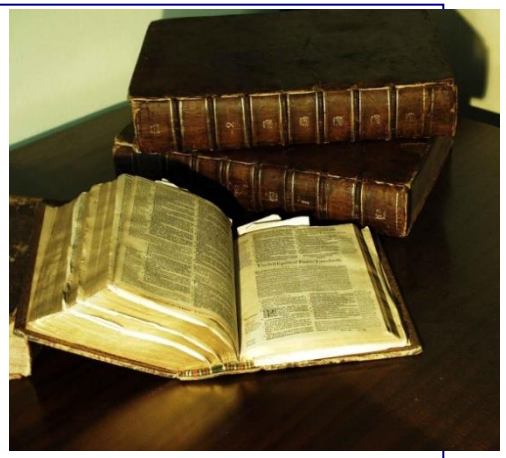
Vaccine-associated risks in immunocompromised patients

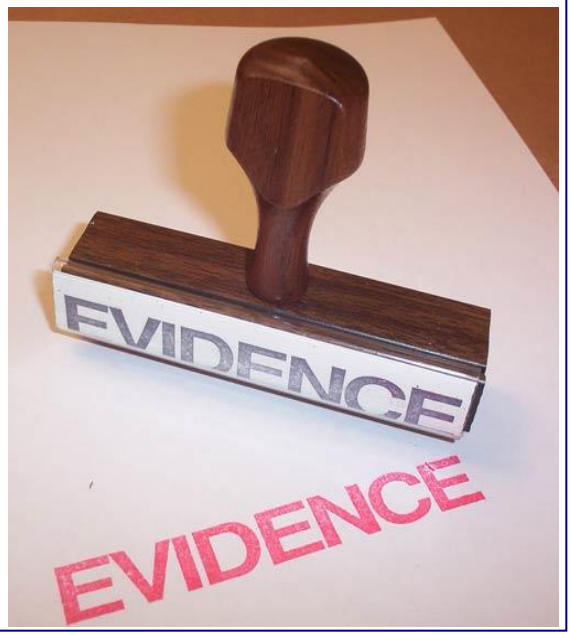
Official guidelines: NO LIVE VACCINE as soon as immunodeficiency is suspected !

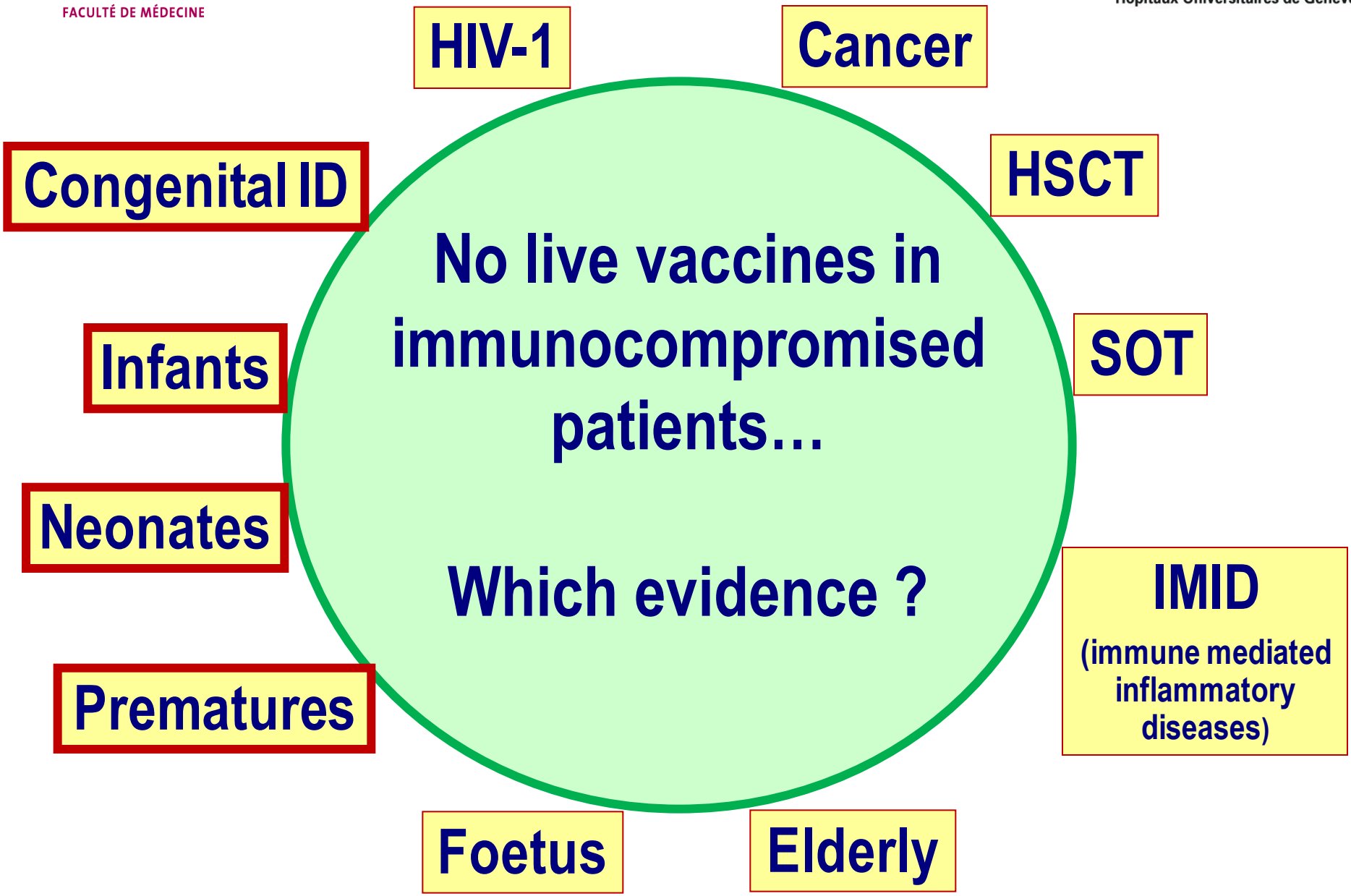


2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host

Clinical Infectious Diseases 2014;58(3):309–18

???




HIV-1
Cancer
Congenital ID
HSCT
No live vaccines in immunocompromised patients…
Which evidence ?
Infants
SOT
Neonates
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(immune mediated inflammatory diseases)
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Safety of oral polio vaccine in SCID patients

Risks of VAPP in patients with agammaglobulinemia

- Relative risk difficult to estimate, mostly based on case reports and estimations *(↑ risks from 1/700'000 to 1/7'000 ?)*
- Main risk = persistent viral excretion in stools
  - no complications in 6/116 SCID patients *Stephan J. Pediatr. 1993 :*
  - persistent (up to 22 years) but asymptomatic excretion

McLennan C., Lancet 2004

- Search for poliovirus carriers among people with primary immune deficiency diseases (United States, Mexico, Brazil, UK): none found in 2004 (Halsey N, Bull WHO 2004), now ≈ 40 cases
  - Not a major threat for polio eradication…

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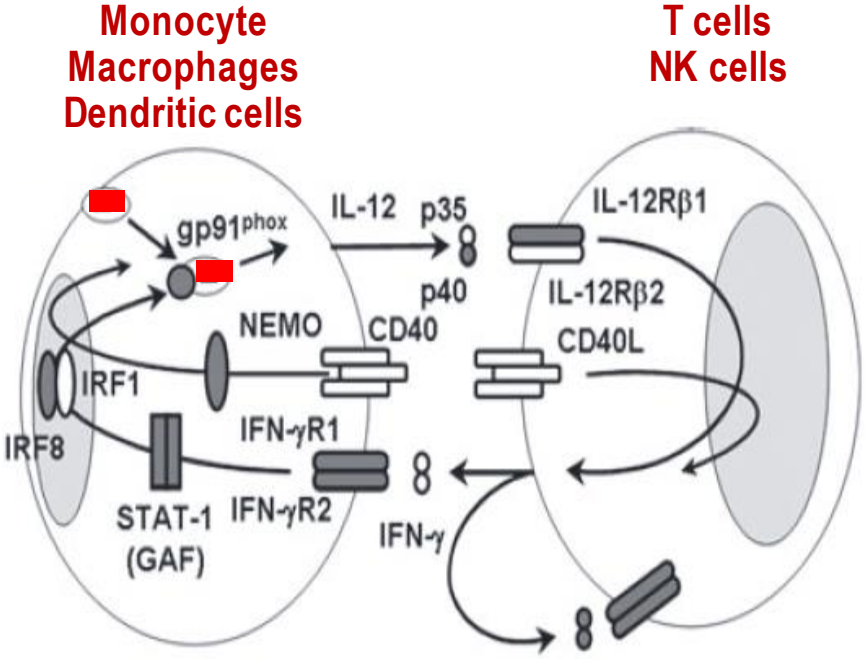
BCG in patients with congenital ID: mendelian susceptibility to mycobacterial disease

BCG vaccine in patients with severe congenital immune deficiency (SCID):

- 1993: 33% (10/28) BCG infection, 80% disseminated disease, 3 †
  (*Stephan et al., J. Pediatr. 1993*)
- Numerous similar reports → identification of mutations in autosomal genes involved in IL-12/23–dependent, IFN-γ–mediated immunity.

  (review: Bustamante J, Ann N Y Acad Sci. 2011)



- impaired IL-12 secretion by infected APCs *(IRF8, Cybb, NEMO, IL12b)*
- impaired T cell response to IL12 ↔ impaired IFNγ production *(ILR2β1)*
- impaired responses to IFN-γ by APCs / T cells *(IFNγR1/R2, STAT-1)*

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Risks of rotavirus vaccines in infants with severe combined immune deficiency

N Engl J Med 2010;362:314-9.

Vaccine-Acquired Rotavirus in Infants with Severe Combined Immunodeficiency

Niraj C. Patel, M.D., Paula M. Hertel, M.D., Mary K. Estes, Ph.D., Maite de la Morena, M.D., Ann M. Petru, M.D., Lenora M. Noroski, M.D., Paula A. Revell, Ph.D., I. Celine Hanson, M.D., Mary E. Paul, M.D., Howard M. Rosenblatt, M.D., and Stuart L. Abramson, M.D., Ph.D.

- 3 infants with severe and chronic gastroenteritis after Rotateq®
  - rotavirus vaccine strain (PCR on stool samples)
  - → diagnostic of congenital immune deficiency (ADA deficiency, IL2Rγ, RAG1)

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Rotavirus are safe in preterm infants… but rarely administered !

- **Preterm infants at higher risks of hospitalization for rotavirus**
- **RV vaccines are safe and recommended in preterm infants**
  (Rotateq: Goveia MG, PIDJ 2007; Rotarix: Omenaca F, PIDJ 2012)

But rotavirus vaccines are rarely given to preterm infants!

- **63% (135 of 213) of VLBW infants did not receive RVV before NICU discharge** *Stumpf KA Pediatrics 2013*

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Rotavirus are safe in preterm infants… but rarely administered !

- Preterm infants at higher risks of hospitalization for rotavirus
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But rotavirus vaccines are rarely given to preterm infants!

- 63% (135 of 213) of VLBW infants did not receive RVV before NICU discharge *Stumpf KA Pediatrics 2013*

↔ guidelines recommend to only immunize after hospital discharge, by fear of nosocomial transmission *(ACIP 2009)*

- some infants are too young (<42 days), others are too old !
- documented viral excretion (Rotateq® 5%, Rotarix® 25%) and a few case reports of asymptomatic transmission to siblings

Is the potential vaccine risk worth the risk of disease?

HIV-1

Cancer

Congenital ID

HSCT

Which evidence ?

- **OPV:** only risky if B cell def.
- **BCG :** high risks if SCID !
- **Rotavirus :** only risky if SCID

→ *Search for underlying immune deficiency if complications!*

Infants

SOT

Neonates

IMID

(immune mediated inflammatory diseases)

Prematures

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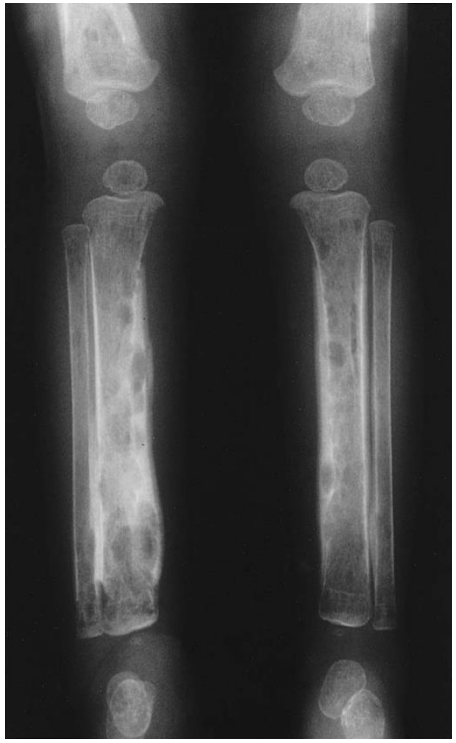
Risks of BCG vaccine in HIV infected patients

BCG vaccine in HIV-infected patients:
Enhanced risks of disseminated disease - at time of CD4 depletion and AIDS

Moss WJ,
WHO Bulletin 2003;81:61

Table 5. **Adverse events associated with BCG vaccination in children infected with human immunodeficiency virus (HIV)**

Author (year of publication)[a]	Country	Study population	Adverse events[b]
Blanche (1986)	France	18 HIV-infected	Disseminated BCG infection in 3 (17%)
Carswell (1987)	Uganda	54 children born to HIV-infected women	No complications
Bregere (1988)	France	67 HIV-infected	BCG lymphadenitis in 7 (10%)
Houde (1988)	Canada	1 HIV-infected	Disseminated BCG infection in a 2-month-old girl
Ninane (1988)	Belgium	1 HIV-infected	Disseminated BCG infection in a 4-month-old boy from Zaire
Hira (1989)	Zambia	42 HIV-infected children	BCG lymphadenitis in 1 (3%)
ten Dam (1990)	Switzerland	1 HIV-infected	Disseminated BCG infection in an 8-month-old girl from Argentina
Lallemant (1991)	Congo	21 HIV-infected	BCG lymphadenitis in 5 (24%)
MMWR (1991)	Rwanda	37 HIV-infected	BCG lymphadenitis in 2 (5%)
Green (1992)	Zaire	21 HIV-infected	No complications
Ryder (1993)	Zaire	48 HIV-infected 640 HIV-uninfected	Lymphadenitis in 5% HIV-infected and 3.5% HIV-uninfected Fistulae in 5% HIV-infected and 6 to 8% HIV-uninfected
Besnard (1993)	France	68 HIV-infected	4 with BCG lymphadenitis, 3 with fistula, 2 with disseminated BCG (13%)
O'Brien (1995)	Haiti	13 HIV-infected	BCG lymphadenitis, ulceration or abscess in 4 (31%); double dose of BCG
Edwards (1996)	USA	1 HIV-infected	BCG bacteraemia in a 3-year-old HIV-infected Brazilian girl
Sharp (1999)	Australia	1 HIV-infected	BCG lymphadenitis
Thaithumyanon (2000)	Thailand	26 HIV-infected	No complications



WHO GACVS 2007: No BCG if known HIV-1 infection ! *(WER 3,2007,82)*

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Safety of rotavirus vaccines in HIV infected infants

Rotavirus vaccines appear safe in asymptomatic or midly symptomatic HIV-infected infants

RCT of rotavirus vaccine in HIV-infected infants (South Africa):

Rotarix® (3 doses at 6, 10, 14 wks) vs placebo, 100 HIV-infected (WHO stage I or II) south African infants, without HAART at enrolment

- No vaccine-associated SAE, similar all/grade 3 symptoms
- Prolonged shedding in 1 of 100 *Steele DA, PIDJ 2011, 30:125*

RCT of rotavirus vaccine in HIV-infected infants (Kenya):

Rotateq® (3 doses at 6, 10, 14 wks) vs placebo, 21 HIV-infected infants, without HAART at enrolment

- No vaccine-associated SAE *Laserson KF, Vaccine 2012 A61-A70*

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Safety of VZV vaccine in HIV infected patients ?

VZV appears safe in HIV patients with CD4 ≥ 15% or 200/μL, whether before or after immune reconstitution

- **VZV vaccine is safe in children with CD4 T cells > 25%**
  (Levin MJ, J Pediatr 2001; Armenian SH PIDJ 2006)
- **VZV vaccine appears safe if CD4 T cells > 15% or ≥ 200/μL**
  - **Few and small series only:**
    - **54 seronegative children** *(Levin MJ, JID 2006)*
    - **60 children (only 34 seronegative)** *(Taweesith W, PIDJ 2011)*
- **VZV vaccine appears effective: chart review ↔VE 82% (24-99)**
  (Son M, JID 2010)

⇨ **Varicella vaccine may be used / should be recommended in children with HIV**

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Safety of measles vaccine in HIV infected patients ?

Measles vaccine:

- safe in children with CD4 > 15% *(Krasinski K, Pediatrics 1988)*
- safe in 6-mo-old HIV-infected infants *(Chandwani S JID 2011)*
- meta-analysis: numerous studies - safety of measles (MMR) in HIV-infected children ***(Scott P, S JID 2011)***
- a few cases (1 lethal) of measles vaccine-strain infection in HIV-infected adults with CD4 counts < 200/μL

(MMWR 1996;45:603; Goon P, Vaccine 2001; Permar SR, JID 2001)

↔ no safety data in patients with $CD4^+$ T cells < 200/μL

MMR appears safe in HIV patients with CD4 ≥ 15% or 200/μL, whether before or after immune reconstitution

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Yellow fever vaccine in HIV+ patients

- safe in asymptomatic young children *(WHO)*
- 1 case of vaccine meningoencephalitis in an adult patient with low CD4 *(Kengsakul J Med Assoc Thai. 2002)* ⟶ few studies
  - safe in 12 patients with CD4 > 300/µL *(Tattevin, AIDS 2004)*
  - safe in 102 patients with CD4 > 300µL (Swiss cohort study) *(Veit O, Clin Inf Dis 2009)*
  - safe in 115 patients with CD4 > 200mL (Mali campaign) *(Sidhibe M,Trop Med Hyg 2012)*
- YFV campaigns in HIV-endemic areas : NO safety signals *(WHO GACVS, Wkly Epidemiol Rec. 2011 Jan 28;86(5):38)*

Characteristic	Value (*n* = 102)
Age, median years (IQR)	34.7 (28.1–41.5)
Female sex	48 (47)
Region of origin	
Europe or North America	59 (58)
Sub-Saharan Africa	41 (40)
South America	1 (1)
Other	1 (1)
Mode of HIV transmission	
Heterosexual sexual contact	63 (62)
Male-male sexual contact	22 (22)
Injection drug use	8 (8)
Other or unknown	9 (9)
CDC HIV infection category	
A	71 (70)
B	24 (24)
C	7 (7)
CD4 cell count	
Median cells/mm³ (range)	512 (368–664)
Missing data	16 (16)
<200 cells/mm³	7 (7)
200–349 cells/mm³	13 (13)
350–499 cells/mm³	22 (22)
>500 cells/mm³	44 (43)
Nadir CD4 cell count	
Median cells/mm³ (IQR)	280 (163–469)
Missing data	15 (15)
HIV RNA level <50 copies/mL, *n/N* (%)	41/84 (48)
Missing data on HIV RNA level	18 (18)
Receipt of triple-drug ART	41 (40)
Chronic hepatitis B or C	19 (19)

Yellow fever vaccine appears safe in HIV-infected patients with CD4 > 15% or 200/µL !

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HIV-1

Cancer

Congenital ID

HSCT

Infants

SOT

Neonates

IMID
(immune mediated inflammatory diseases)

Prematures

Which evidence?

- OPV: safe
- BCG : high risks !
- Rotavirus : expected as safe
- VZV : safe *(if CD4 ≥ 15% / 200mm3)*
- MMR: safe *(if CD4 ≥ 15% / 200mm3)*
- YF : safe ? *(if CD4 ≥ 15% / 200mm3)*

No worsening of HIV disease !!

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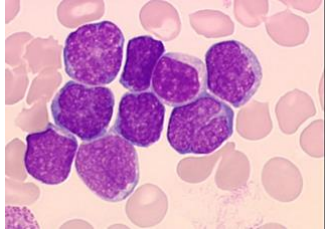
Safety of varicella vaccine in patients with cancer ?



VZV immunization in acute lymphoblastic leukemia:

- AAP 2006: VZV recommended for ALL children in remission ≥ 1 year, if lymphocytes > 700/µL and if chemotherapy withheld for 7 days before/after immunization
- VZV vaccination-induced † in one ALL child *(Schrauder A, Lancet 2007)* - who was immunized only 5 months after remission !
- AAP 2009: vaccination ONLY with expert guidance as
  - ↓ community prevalence of VZV *(← routine immunization)*
  - ↓ risks of serious complications (← antiviral therapies). 20† (0.057%) in review of 35'128 ALL *(Caniza MA Ped Blood Cancer 2012)*
- Loss of immunity after chemotherapy ! *(Bochennek K Vaccine 2014)*

Check immunity and consider VZV vaccine if exposure likely !

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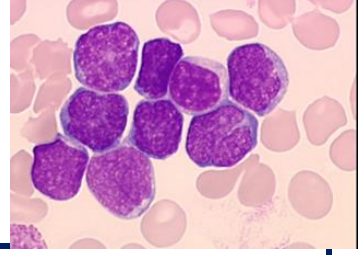
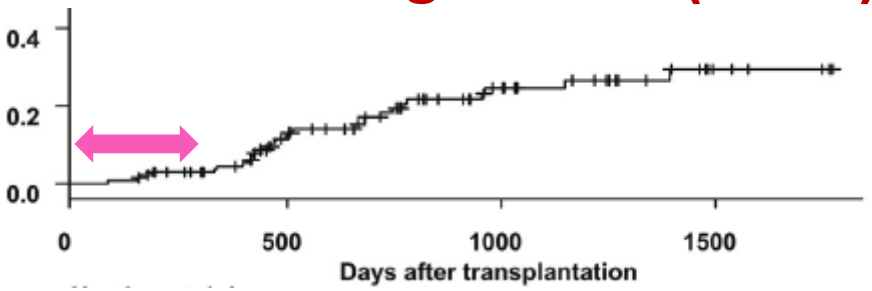
Safety of VZV vaccine in patients after HSCT ?



- **Risks of varicella following hematopoietic stem cell transplant (HSCT) ↔ acyclovir during 12 mo (or IS)**

Kawamura K Intl J Inf Dis 2014



- **VZV immunization recommended 24 mo after HSCT (if no GVHD = OFF immunosuppression):**
  - **46 VZV seronegative children with CD4 cell count ≥200/µL, median time since HSCT: 4 years.** *(Chou CF, Biol Blood Marrow Transplant. 2011)*
  - **68 HSCT recipients - with positive seroresponse and lymphocyte proliferation to tetanus vaccine** *(Kusmaul SC, Bone Marrow Transplant 2010)*
  - **110 HSCT adults 24 months after HSCT** *(Issa NC, Biol Blood Marrow Transplant 2014*

Why not immunize after acyclovir waning ? Study needed !

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Safety of live attenuated influenza vaccine in the immunocompromised?

Contraindication ← fear of impaired viral clearance

1. Which biological evidence ?

The influenza virus strains in FLUMIST are (a) *cold-adapted (ca)* (i.e., they replicate efficiently at 25°C, a temperature that is restrictive for replication of many wild-type influenza viruses); (b) *temperature-sensitive (ts)* (i.e., they are restricted in replication at 37°C (Type B strains) or 39°C (Type A strains), temperatures at which many wild-type influenza viruses grow efficiently); and (c) *attenuated (att)* (they do not produce classic influenza-like illness in the ferret model of human influenza infection). The cumulative effect of the antigenic properties and the *ca*, *ts*, and *att* phenotypes is that the attenuated vaccine viruses replicate in the nasopharynx and induce protective immunity.

- viral replication occurs only below 37°C
- prevention of viral dissemination is thus controlled by body temperature (nasopharynx) - and not by immunity !
- risks = prolonged upper respiratory tract symptoms (?)

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Safety of live attenuated influenza vaccine in the immunocompromised?

2. Which clinical evidence of ↑ viral shedding?

- **in children with HIV:**
  - **243 children with CD4 ≥ 15%** (mean 12 yrs), RCT of LAIV vs TIV
    - No adverse events, similar viral shedding *(Levin MJ, Vaccine 2008)*
- **in children with cancer :**
  - **20 children** (mean 12.2 yrs) : LAIV vs placebo *(Halasa N, Vaccine 2011)*
    - → more runny nose/nasal congestion; no related SAEs
    - → **4/10 LAIV recipients shed vaccine virus, none ≥ 7-10 days**
  - **55 children** (mean 10.2 yrs) : LAIV vs TIV *(Carr S, JID 2011)*
    - → rhinorrhea; no related SAEs
    - → **10/28 LAIV recipients shed vaccine virus, none ≥ 7 days**

LAIV expected as safe and the optimal strategy to prevent influenza in in immunocompromised children !

HIV-1

Cancer

Congenital ID

HSCT

Which evidence?

- BCG : no data – to avoid !
- Rotavirus : no data (age)
- LAIV : expected as safe !!!
- VZV : safe under conditions
- MMR: no data *(≥ 24 mo after HSCT)*
- YF : no data *(≥ 24 mo after HSCT)*

Infants

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Neonates

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(immune mediated inflammatory diseases)

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Live vaccines in organ transplant patients?

Official recommendations for the use of live vaccines in organ transplant recipients

VACCINE	Before T	After T
Varicella	YES	NO !
MMR	YES	NO !
Oral polio	YES	NO !
Typhoid fever	YES	NO !
Yellow fever	YES	NO !
LAIV	YES	NO !

Recommendations ← presumptions of 1) sustained efficacy of pre-T immunity and 2) risks of post-T immunization

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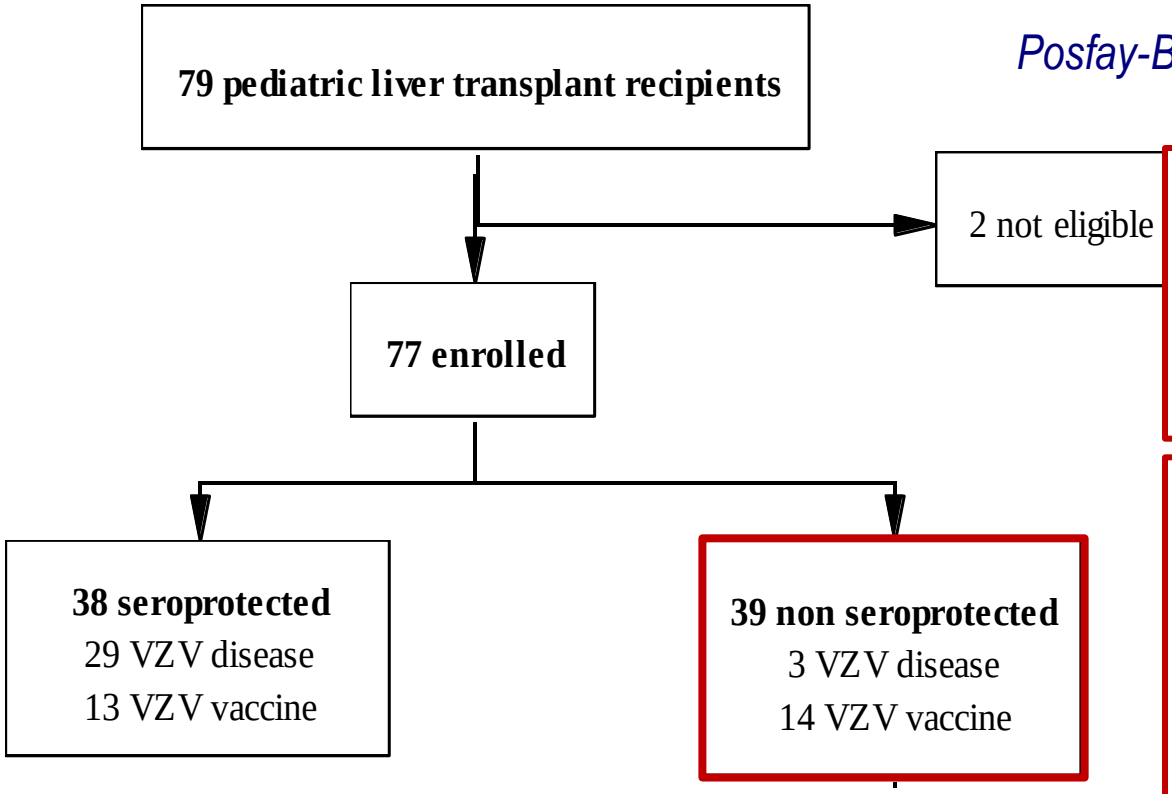
Live vaccines in organ transplant patients?

~~Presumption 1~~: persistence of pre-transplant immunity ??

- **Waning of vaccine- or infection-induced VZV B and T cell immunity in liver transplanted children**

Posfay-Barbe K, Amer J Transplant 2012



Loss of anti-VZV IgG Ab despite sensitive assay:

- 3/32 (10%) post infection

-14/27 (52%) post immunization

Loss of detectable anti-VZV-specific T cells in 28/73 patients (38%):

- 5/32 (15%) post infection

-8/16 (50%) post immunization

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Live vaccines in organ transplant patients?

~~Presumption 2~~: High risks of post-transplant immunization ??

VZV immunization after liver / intestine transplantation:

- **US : 16 transplant children > 12 mo;** > 6-12 mo after T; receiving tacrolismus (14/16, through level < 10ng/ml), cyclosporine A (2/16), prednisone (9/16, max 0.3mg/kg on alternate day).
  - **Vaccine rash (3-4 vesicles) in 4/16 (→ oral acyclovir)**
  - Immunogenicity : 87%

  Weinberg A, Am J Transpl 2006

- **Switzerland: 36 seronegative transplant children > 12 mo** :
  - **Mild and transient local/systemic adverse events, Ø acyclovir**
  - **No clinical / biological graft rejection**
  - **100% seroprotection (2-3 doses), † VZV-specific T cells**
  - **No breakthrough disease (> 4 yrs)**

Posfay-Barbe, Am J Transplant 2012

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Live vaccines in organ transplant patients?

Yellow fever immunization to solid organ recipients ???

- **Brazil**: YFV campaigns, questionnaire to all transplant centers
- **Retrospective** identification of **19 SOT patients** inadvertently immunized with YF vaccine despite their immunosuppression

No severe adverse event identified, but…

General patient data at the time of yellow fever vaccination (YFV)

	Mean ± SD	Median	Range
Age at the YFV (years)	45.6 ± 13.6	46	11–69
Creatinine (mg/dL)	1.46 ± 0.62	1.25	0.8–3.4
Post-transplant time at YFV (months)	65 ± 83.9	36	3–340
Months from YFV at the time of the survey	45 ± 51	30	3–241

Azevedo LS, Transplant Inf Diseases 2011

HIV-1

Cancer

Congenital ID

HSCT

Which evidence?

- BCG : no data – to avoid !
- Rotavirus : no data (age)
- LAIV : expected as safe !!!
- VZV : safe under conditions
- MMR: yet limited data (ongoing)
- YF : limited data – to avoid

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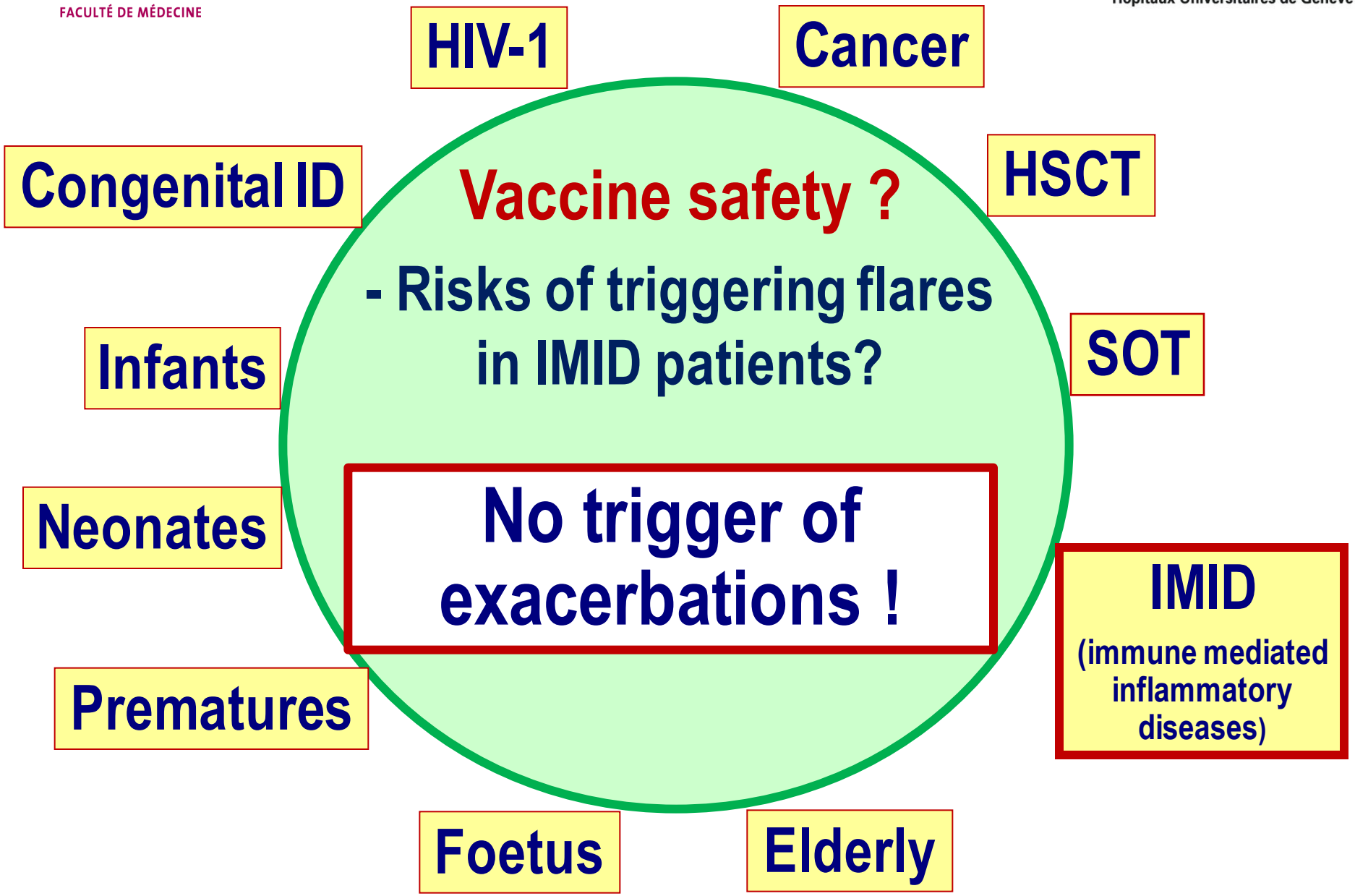
IMID

(immune mediated inflammatory diseases)

Prematures

No trigger of graft rejection !!


HIV-1
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Vaccine safety ?
- Risks of triggering flares in IMID patients?
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No trigger of exacerbations !
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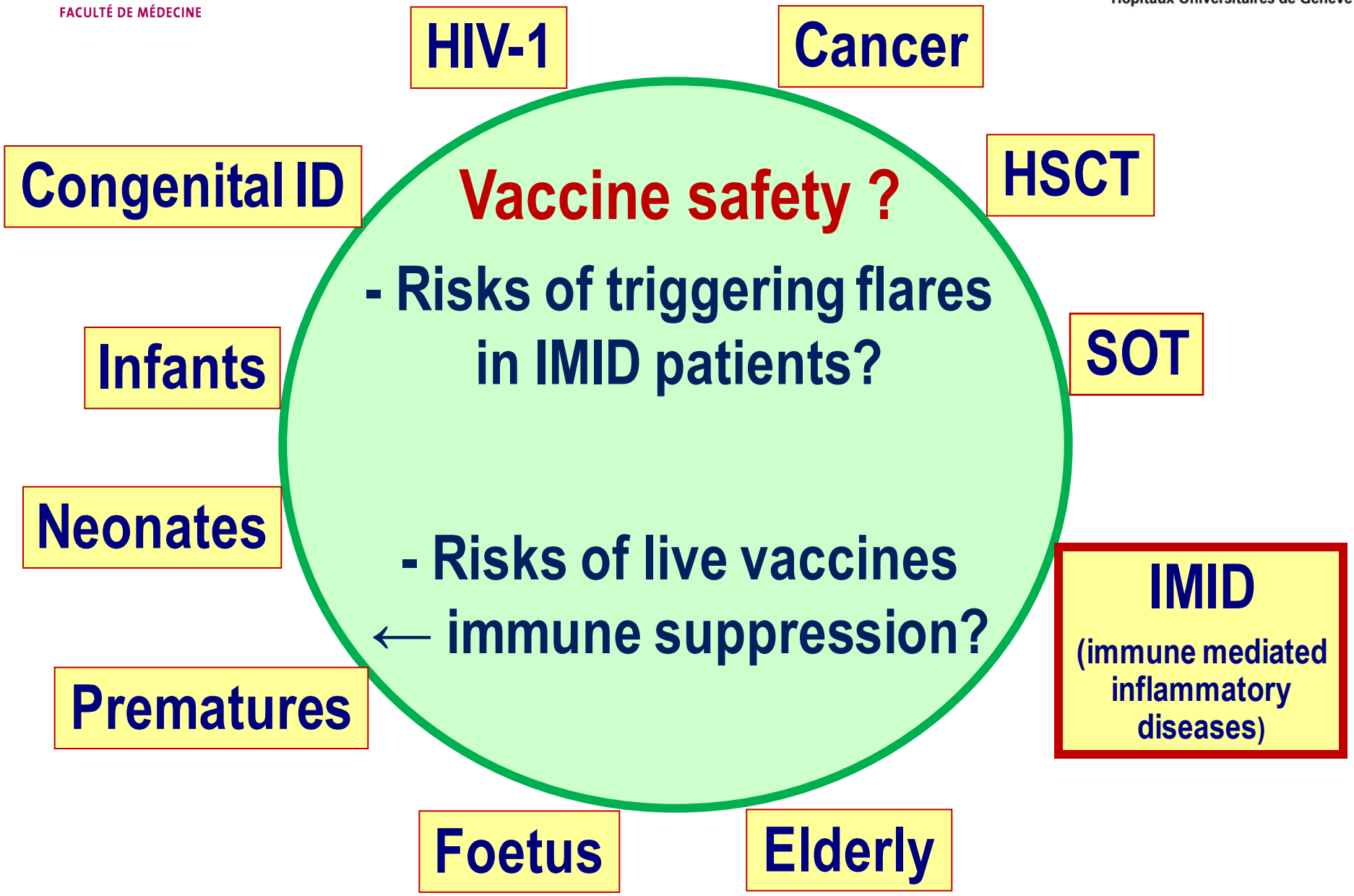
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Live vaccines in immunosuppressed IMID patients

Varicella immunization in juvenile rheumatic diseases ?

One single prospective study (Brazil) !

- 25 patients (20 seronegative)
  - MTX: 25, prednisone:13, other:5
  - No severe adverse events
  - 20% with limited VZV rash, i.e. within normal range
  - No IMID exacerbation…

Pileggi GS, Arthritis Care Res 2010

MMR immunization in juvenile rheumatic diseases ?

- Retrospective study:
  - 314 patients (49 MTX) : no disease exacerbation nor complication
- Prospective study :
  - 15 patients (MTX +- ethanercept), revaccination after 2 MMR
  - No safety issue

Heijstek MW, Ann Rheum Dis 2007

Borte S, Rheumatology 2009

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Live vaccines in immunosuppressed IMID patients

Yellow fever immunization to IMID patients ???

- Brazil, retrospective identification of 70 IMID patients inadvertently immunized against YF:
  - mean age 46 years, 90% females
  - rheumatoid arthritis (54), systemic lupus erythematosus (11), spondyloarthropathy (5), systemic sclerosis (2)
  - methotrexate (42), corticosteroids (22), sulfasalazine (26), leflunomide (18), cyclophosphamide (3), immunobiological agents (9).
  - 16 (22.5%) with minor adverse effect.
- No safety issue identified…

Mota LM, Rev Soc Bras Med Trop. 2009

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Adjuvanted influenza vaccines in immunosuppressed IMID patients

Few studies, but similar results : no safety issue !

- Gabay C, et al. Arthritis Rheum. 2011 Jun;63(6):1486-96.
  - n= 173 patients (mixed population), Geneva / Switzerland
  - 2 doses of AS03-adjuvanted H1N1v vaccines (Pandemrix®, GSK)
  - Unchanged disease activity scores + immune monitoring

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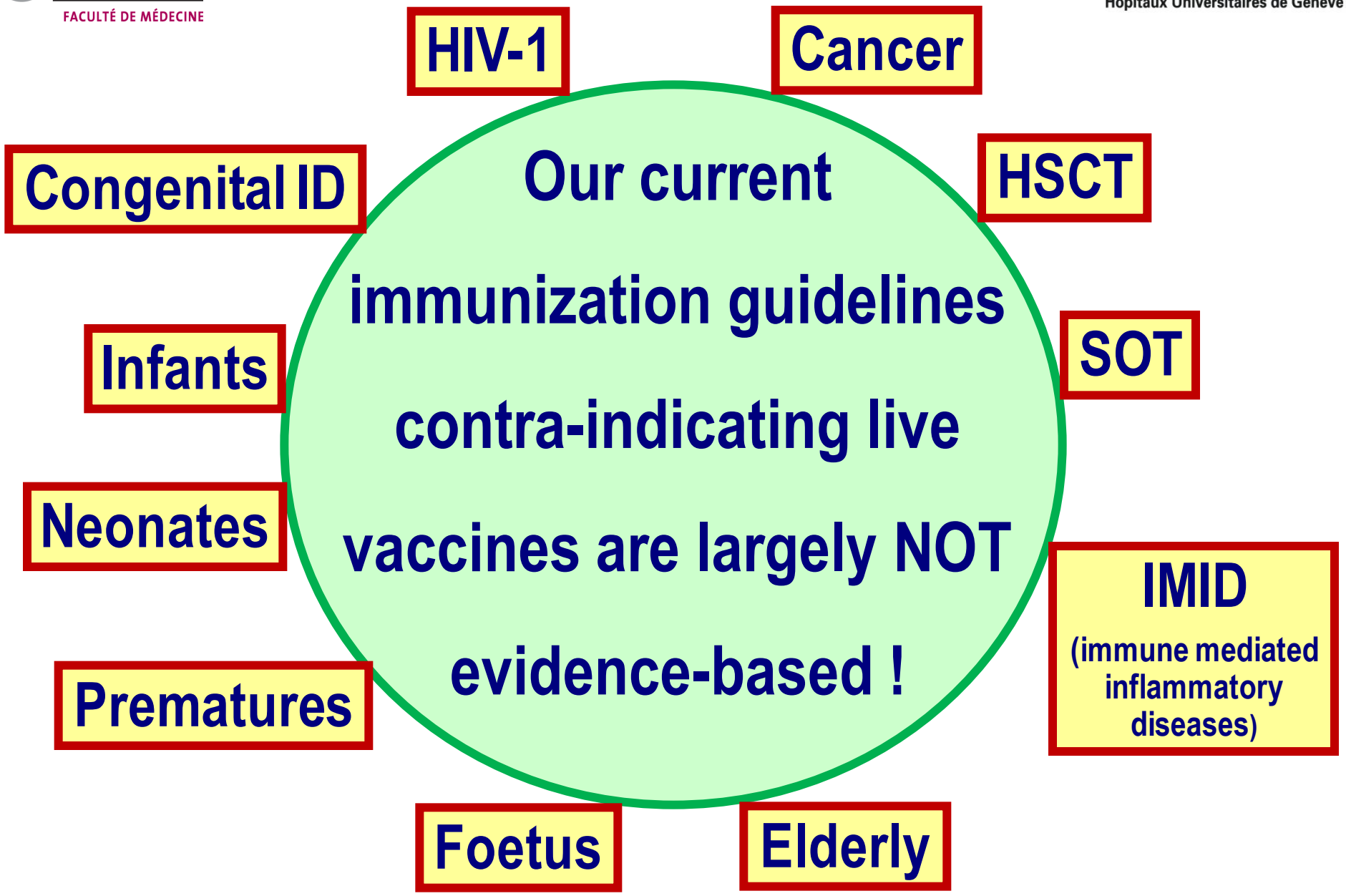
- Urowitz MB, Arthritis Care Res. Nov 2011;63(11):1517-20.
  - n = 103 SLE patients, Toronto /Canada
  - 1 dose of AS03-adjuvanted (n=52) or non-adjuvanted H1N1v vaccine (n=51)
  - Unchanged prevalence / titers of nine selected auto-antibodies
- Elkayam O, Arthritis Care Res. Jul 2011;63(7):1062-7
  - n= 94 patients (mixed population), Tel Aviv /Israel
  - 1 dose of MF59-adjuvanted H1N1v vaccine (Novartis Vaccine)
  - Unchanged disease activity scores


HIV-1
Cancer
Congenital ID
HSCT
Infants
SOT
Our current immunization guidelines contra-indicating live vaccines are largely NOT evidence-based !
Neonates
IMID
(immune mediated inflammatory diseases)
Prematures
Foetus
Elderly

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HIV-1

Cancer

Congenital ID

HSCT

Towards a coordinated off-label use of live viral vaccines in our IC patients:

1. LAIV
2. VZV
3. Measles
4. Yellow fever

Infants

SOT

Neonates

IMID

(immune mediated inflammatory diseases)

Prematures

Foetus

Elderly

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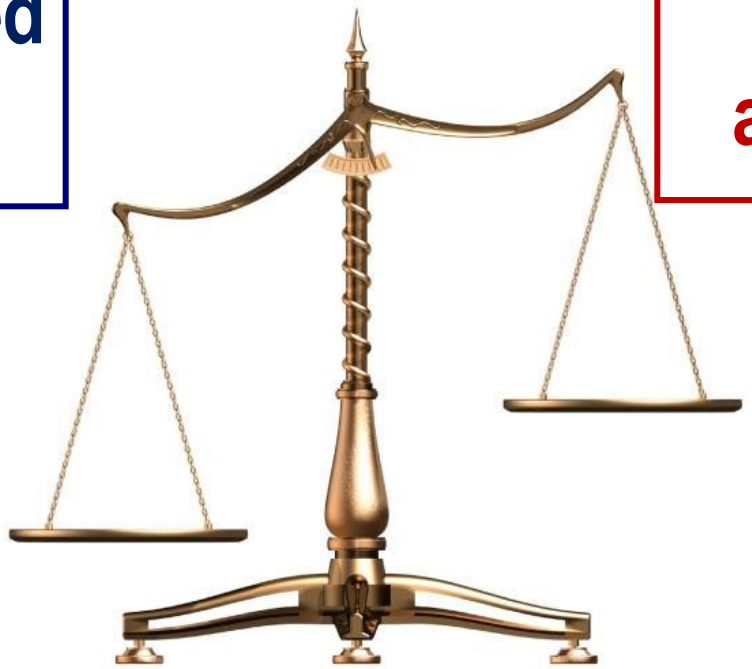
Vaccinations in the immunocompromised

Underestimated benefits



Fears of adverse events

If vaccines are safe…

Even partial efficacy is higher than the lack of efficacy which results from the lack of immunization…

May immunocompromised hosts raise protective vaccine responses ?

- CONGENITAL IMMUNODEFICIENCIES
- ACQUIRED IMMUNODEFICIENCIES
  - HIV INFECTION
  - CHRONIC DISEASES AND IMMUNOSUPPRESSION
    - TRANSPLANT PATIENTS
    - CANCER PATIENTS
    - IMMUNE MEDIATED DISEASED PATIENTS

Vaccine type, Ag, dose, adjuvant, schedule ⇨ *Vaccine immunogenicity* ⇧ *Ab-mediated protection*

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Vaccine type, Ag, dose, adjuvant, schedule ⇨ *Vaccine immunogenicity* ⇨ *Activation of dendritic cells*

Induction of follicular T cells

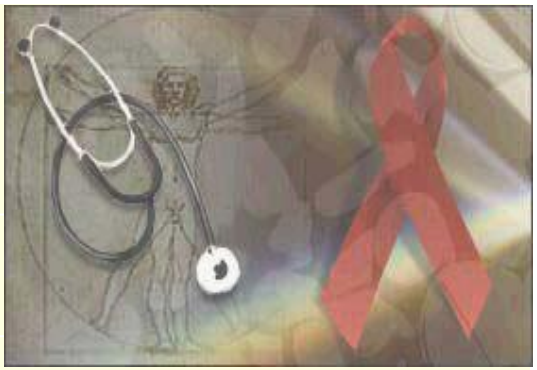
Induction of GC B cells

Induction + persistence of plasma cells

Ab-mediated protection

HIV infection and vaccine responses

Moss et al, Bull WHO 2003;
Obaro Lancet Inf Dis 2004



CD4: >300
USUALLY CONSERVED RESPONSES

Vaccine immuno-genicity

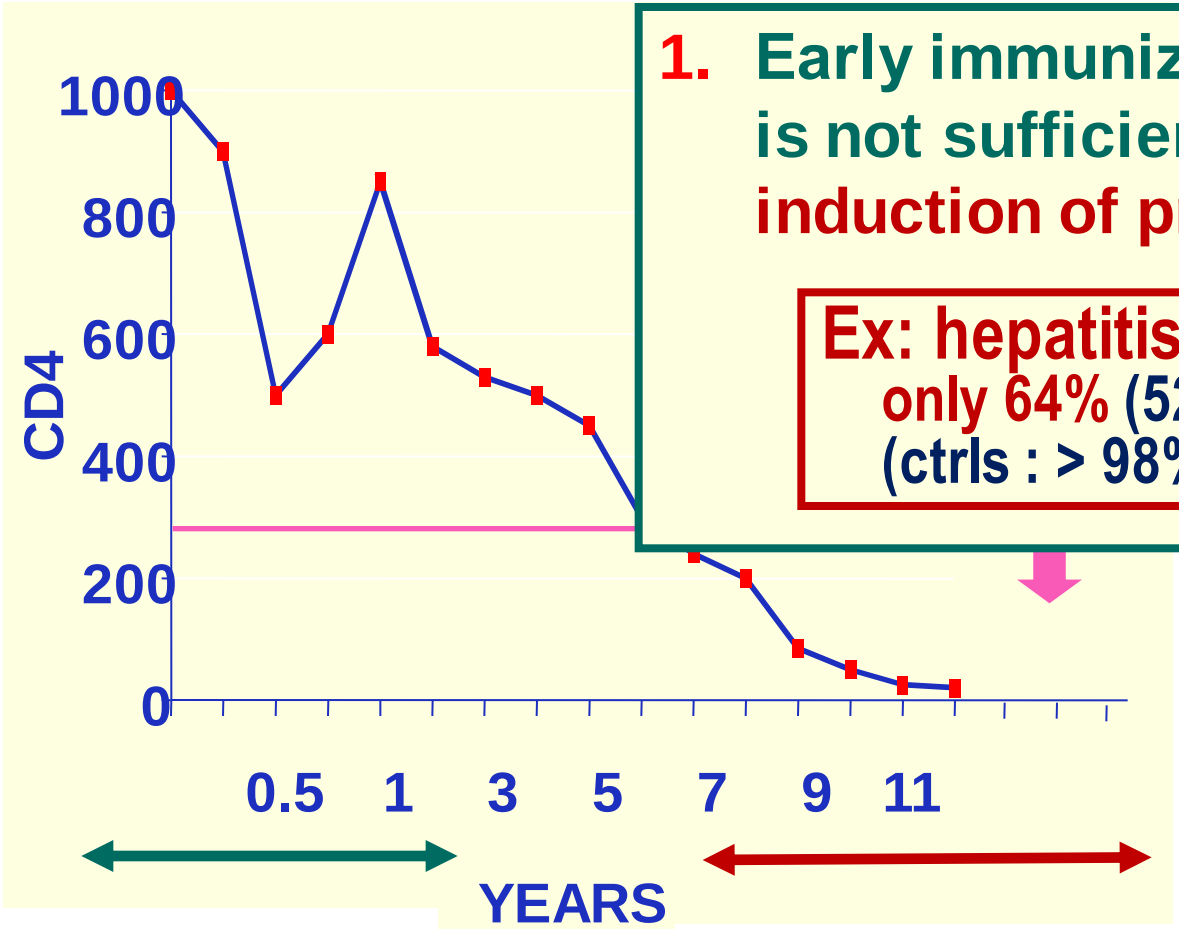
CD4: <200
REDUCED RESPONSES

Optimal period for immunization

Decreased immunogenicity
Risk of complications

HIV infection and vaccine responses

Moss et al, Bull WHO 2003;



1. **Early immunization is optimal… but is not sufficient to ensure the induction of protective efficacy**

Ex: hepatitis A meta-analysis:
only 64% (52-75) responders
(ctrls : > 98%)! (*Shire N, Vaccine 2006*)

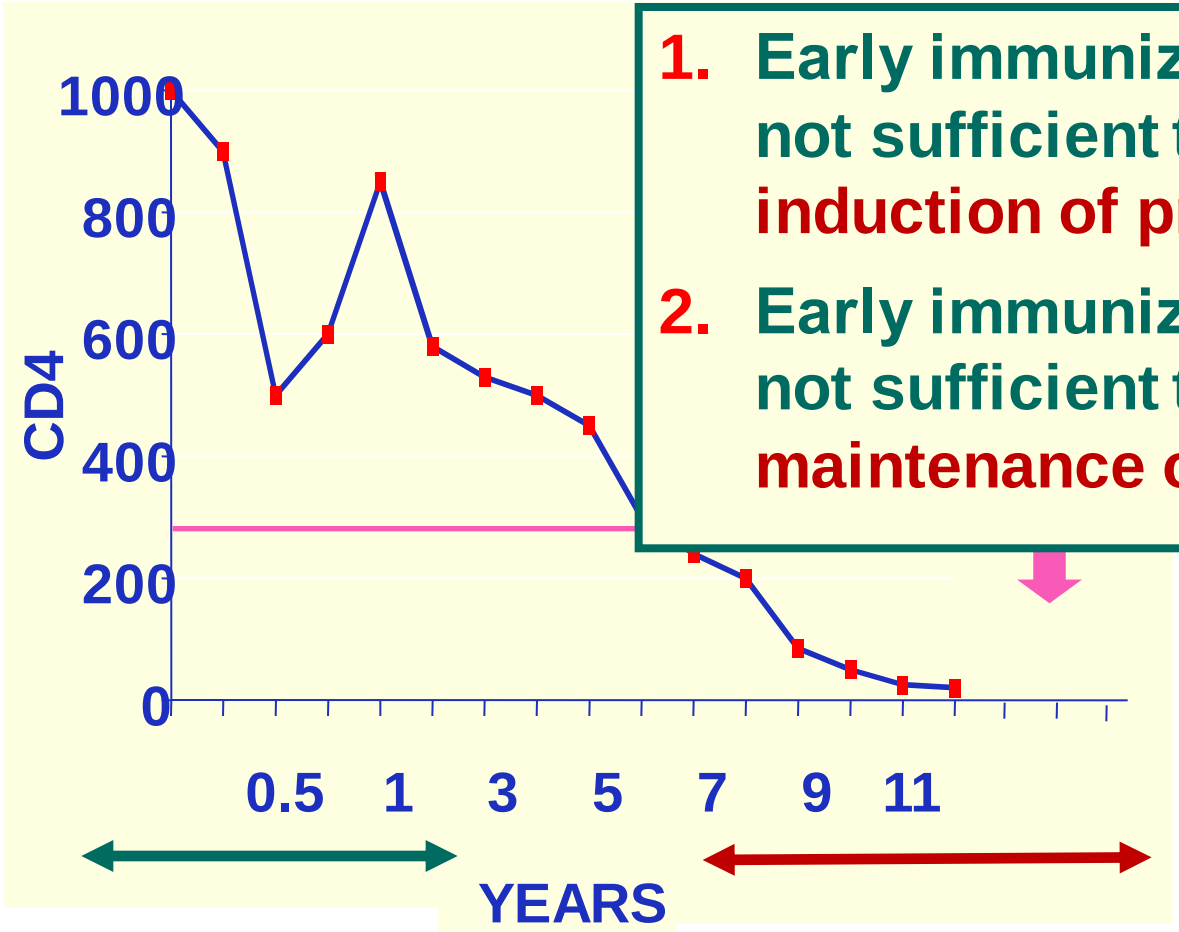
Numerous studies showing LOWER vaccine antibody responses !

Optimal period for immunization

Decreased immunogen
Risk of complications

HIV infection and vaccine responses

Moss et al, Bull WHO 2003;



1. **Early immunization is optimal… but not sufficient to ensure the induction of protective efficacy**
2. **Early immunization is optimal… but not sufficient to ensure the maintenance of immunity**

Numerous studies showing EARLY WANING of vaccine antibodies !

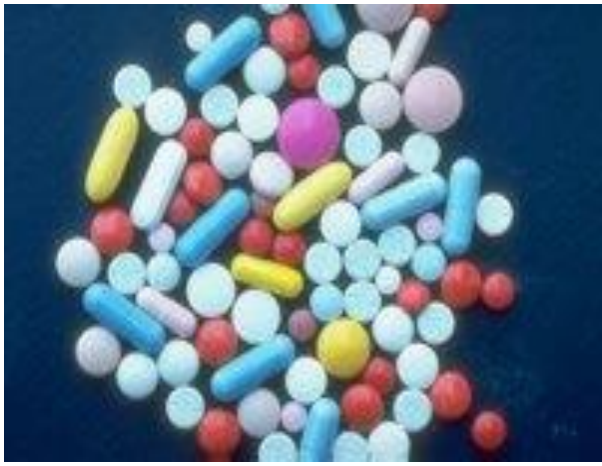
Optimal period for immunization

Decreased immunogen
Risk of complications

Influence of highly active anti-retroviral therapy on vaccine responses

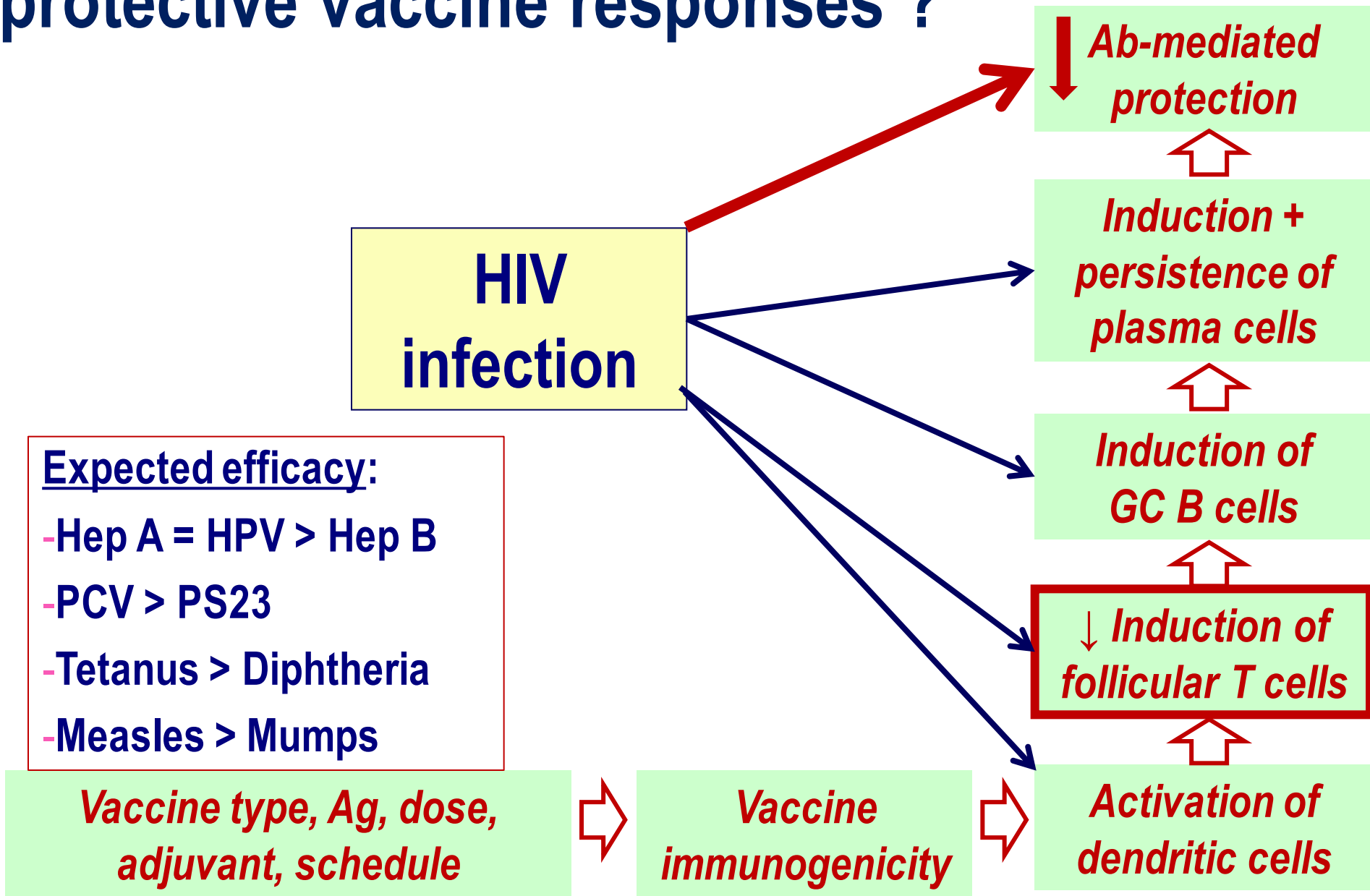
HAART is efficient at prolonging or restoring immune competence…

1. but is not sufficient to ensure the induction of immunity
2. … but is not sufficient to ensure the maintenance of immunity
3. …but is not sufficient to restore the diversity of the preexisting repertoire (clonal restriction of immune expansion).



Too few studies yet with potent multivariate analyses !

May immunocompromised hosts raise protective vaccine responses ?



Influence of new drugs on vaccine responses ???

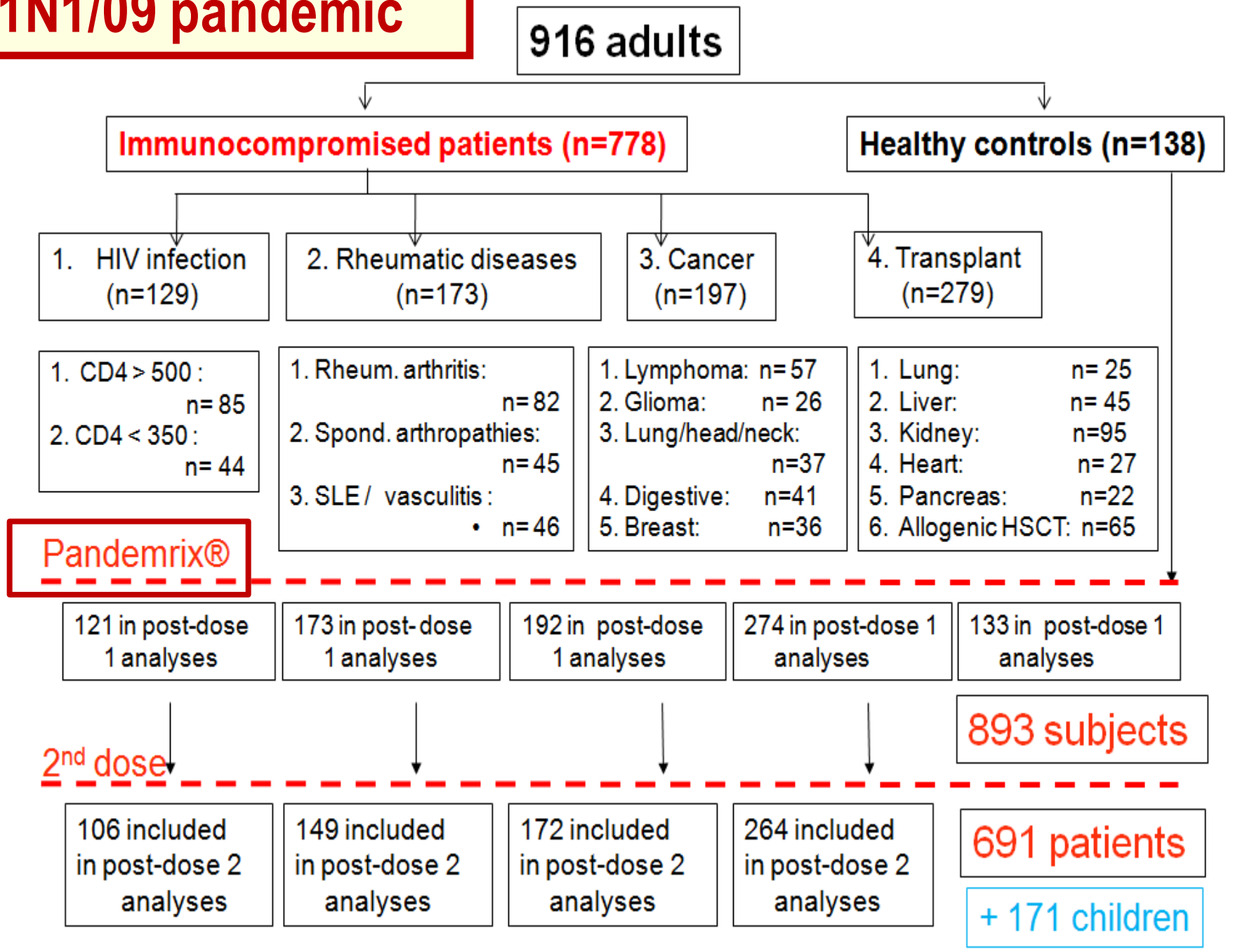
Patients with autoimmune disease are often maintained for years on various drugs:

- Corticosteroids *(unless ≤ 20mg/d for ≤ 2 wks or topical)*
- Adalimumab
- Azathioprine
- Ciclosporine
- Etanercept
- Fingolimod
- Infliximab
- Leflunomide
- Mesalazin
- Methotrexate
- Mycophenenolyte
- Natalizumab
- Rituximab
- Sirolimus / tacrolimus
- Sulfazalazin

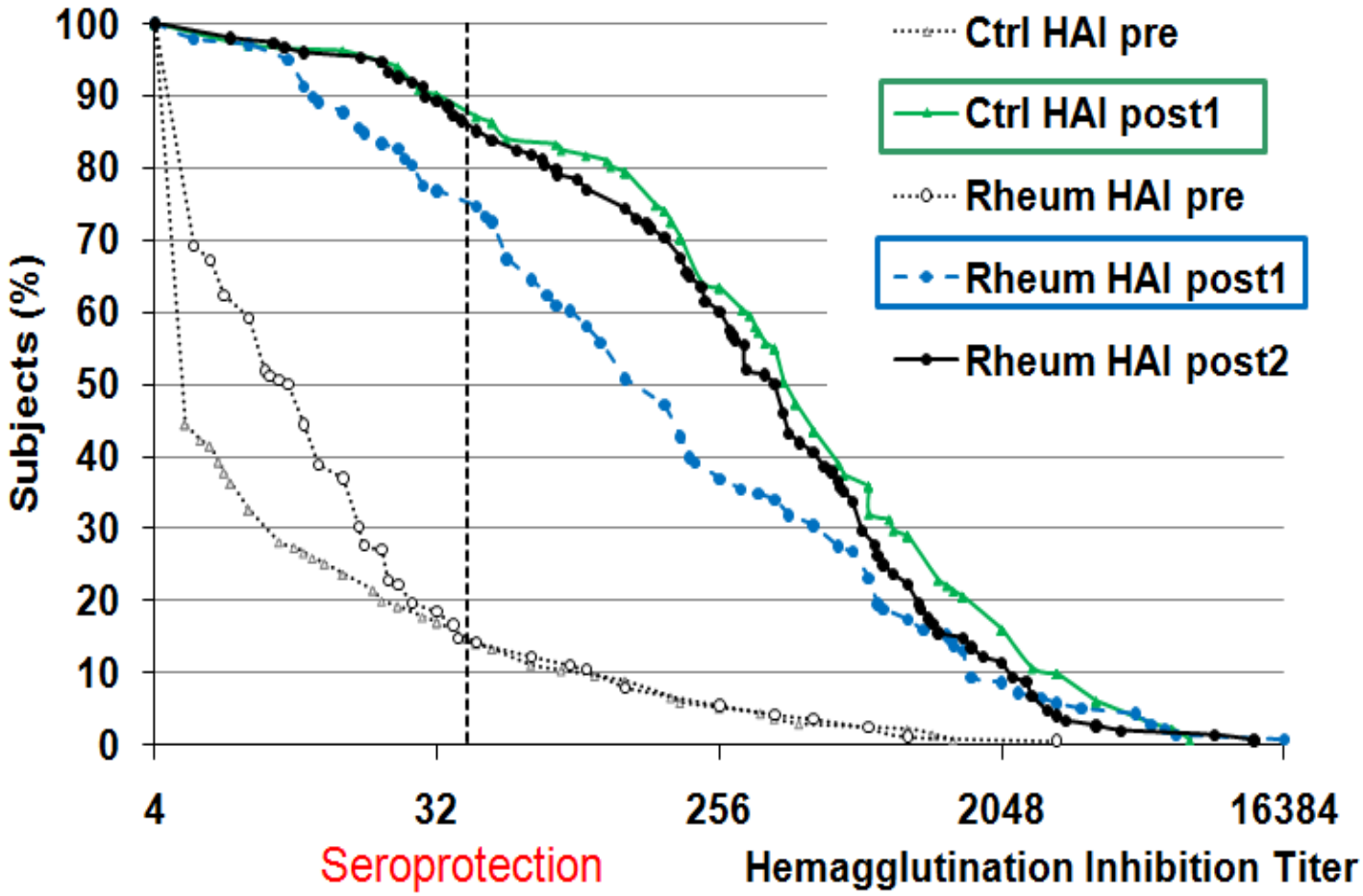
- Distinct mechanisms
- Distinct impacts
- Dose effects
- Combinations

Few studies – often with contradictory results : small groups, patient heterogeneity, treatment heterogeneity, variability, etc.

H1N1/09 pandemic



Influence of IS on H1N1/09 adjuvanted vaccine responses in patients with rheumatic diseases



Reduced seroprotection after 1 dose ↔ corrected after 2 doses

Gabay C, et al. Arthritis Rheum. 2011

Influence of IS on H1N1/09 adjuvanted vaccine responses in patients with rheumatic diseases

		Controls (POST 1) & Patients (POST 2)					
		POST1			POST2		
		Estimates (SE)	Effect	p-value	Estimates (SE)	Effect	p-value
Underlying disease	Controls						
	Patients w/o DMARDs				-0.04 (0.15)	-9%	0.78
	Patients with DMARDs				-0.39 (0.10)	-59%	<0.001
Disease groups	RA						
	SA	-0.05 (0.18)	-11%	0.76	-0.13 (0.16)	-26%	0.44
	Other	-0.18 (0.28)	-34%	0.53	-0.04 (0.20)	-9%	0.83
TNF-α antagonists	No						
	Yes	0.06 (0.16)	15%	0.72	-0.02 (0.15)	-5%	0.91
B cell depletion	No						
	Yes	-0.32 (0.23)	-52%	0.16	-0.50 (0.19)	-68%	0.01
Oral steroids	No						
	Yes	0.25 (0.15)	78%	0.10	-0.05 (0.13)	-11%	0.72
MTX	No						
	Yes	-0.46 (0.17)	-65%	0.01	-0.34 (0.15)	-54%	0.03
SSZ, HCQ	No						
	Yes	0.37 (0.16)	134%	0.03	0.11 (0.14)	29%	0.45
LEF	No						
	Yes	-0.64 (0.22)	-77%	0.004	-0.33 (0.19)	-53%	0.04
AZA, CYC, MMF	No						
	Yes	-0.66 (0.29)	-78%	0.03	-0.45 (0.20)	-65%	0.03

DMARDs: Disease modifying antirheumatic drugs; MTX : Methotrexate; SSZ: sulfasalazine; HCQ: hydroxychloroquine;

Gabay C et al

Arthritis Rheum. 2011

Marked inhibition by some – and not by other – IS treatments !

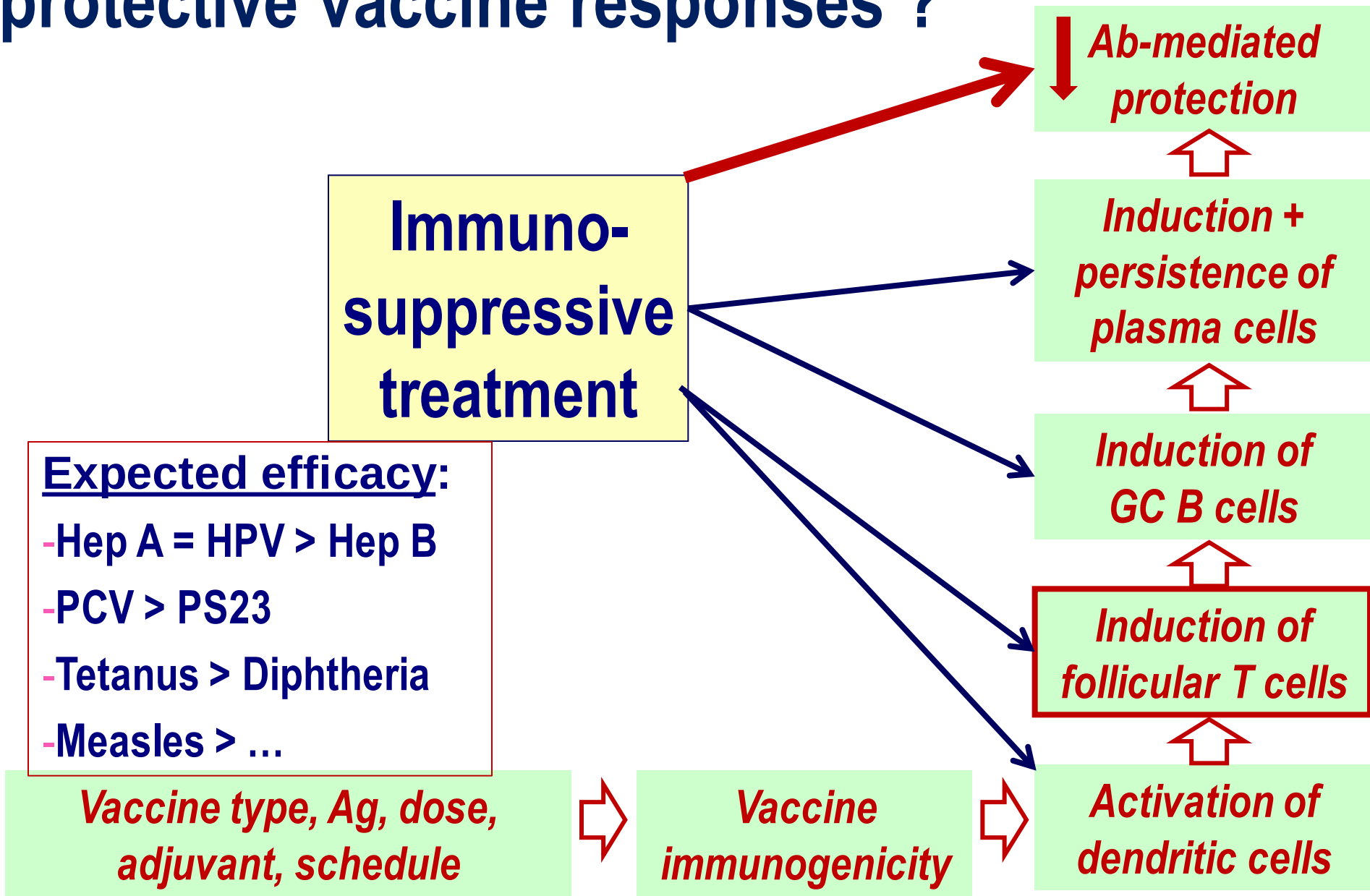
Influence of IS on H1N1/09 adjuvanted vaccine responses in solid organ transplant recipients

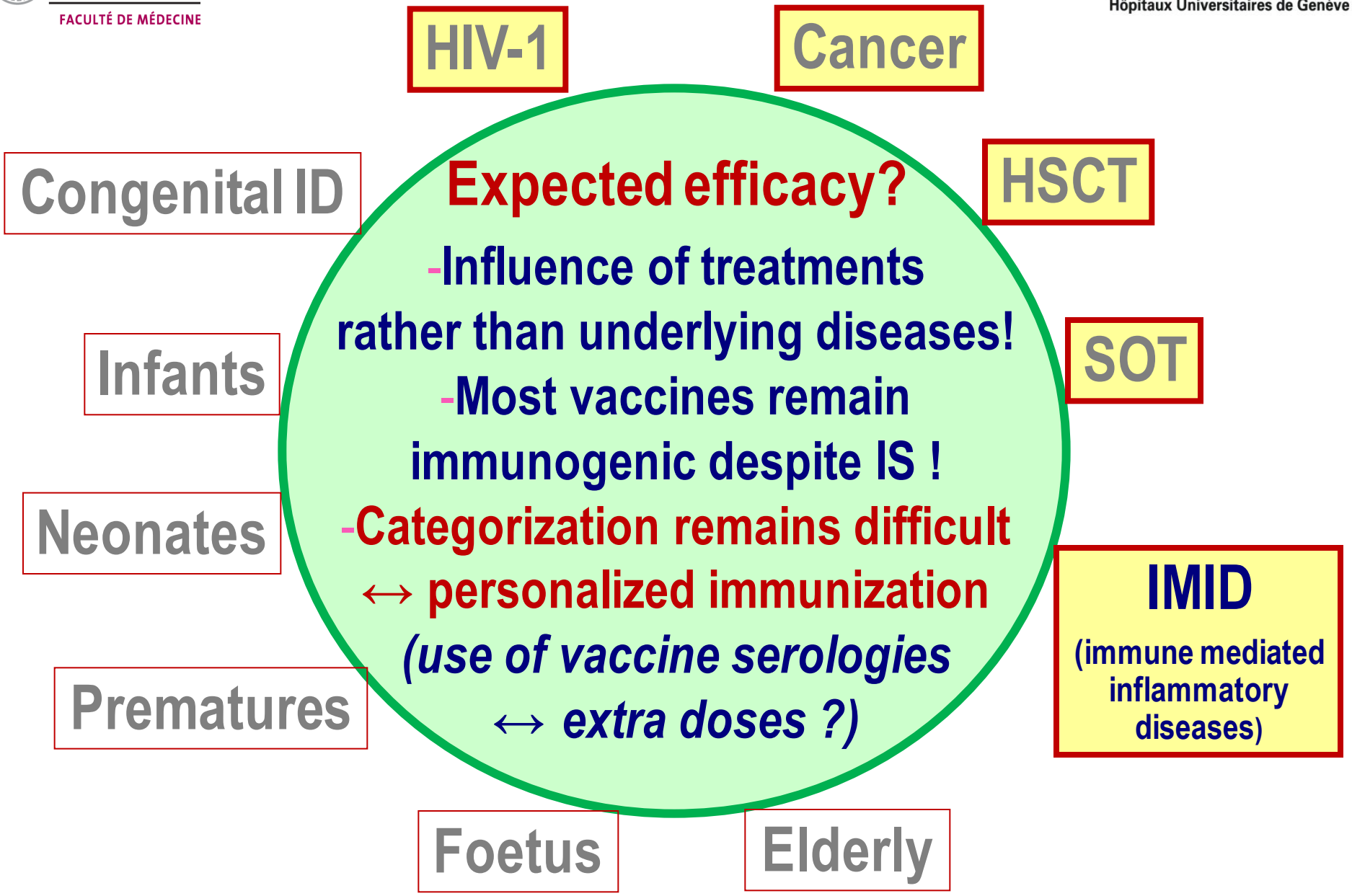
		Controls (POST1) - Patients (POST2)		
		Estimates (SE)	Effect	p-value
	Controls	0		
SOT transplant	Pancreas	-0.16 (0.18)	-31%	0.36
SOT transplant	Lung	-0.83 (0.16)	-85%	<0.001
	Liver	-0.14 (0.13)	-28%	0.29
	Kidney	-0.38 (0.10)	-58%	<0.001
	Heart	-0.17 (0.16)	-32%	0.30
Oral steroids	No	0		
	Yes	-0.04 (0.13)	-9%	0.75
MMF and/or ECMPA	No	0		0.0006
	< 2mg/mL	-0.18 (0.13)	-35%	0.17
	2-4 mg/mL	-0.42 (0.15)	-62%	0.004
	>4 mg/mL	-0.73 (0.19)	-82%	0.0001
Tacrolimus	No	0		
	Yes	0.09 (0.17)	23%	0.59
Cyclosporine	No	0		
	Yes	-0.05 (0.19)	-12%	0.77

Siegrist, et al. Antiviral Therapy, 2012

Marked inhibition by some – and not other – IS treatments !

May immunocompromised hosts raise protective vaccine responses ?




HIV-1
Cancer
Congenital ID
HSCT
Expected efficacy?
-Influence of treatments rather than underlying diseases!
-Most vaccines remain immunogenic despite IS !
-Categorization remains difficult
↔ personalized immunization
(use of vaccine serologies
↔ extra doses ?)
Infants
SOT
Neonates
IMID
(immune mediated inflammatory diseases)
Prematures
Foetus
Elderly

Friday afternoon with the vaccinologist's beeper in the middle of a measles outbreak !

4y, nephrotic syndrome, steroid treatment stopped 1week ago?

18y, rheumatoid arthri-tis, on methotrexate ?

15 y, Hodgkin, 1 month off chemottt ?

14 y, Crohn's disease, cyclosporine ?

??

22 mo, liver transplant at 4 mo of age ?

23y, rheumatoid arthritis, on anti-TNF ?

14y, 13 months post bone marrow T ?

Vaccinations in immunocompromised patients: 3 main challenges

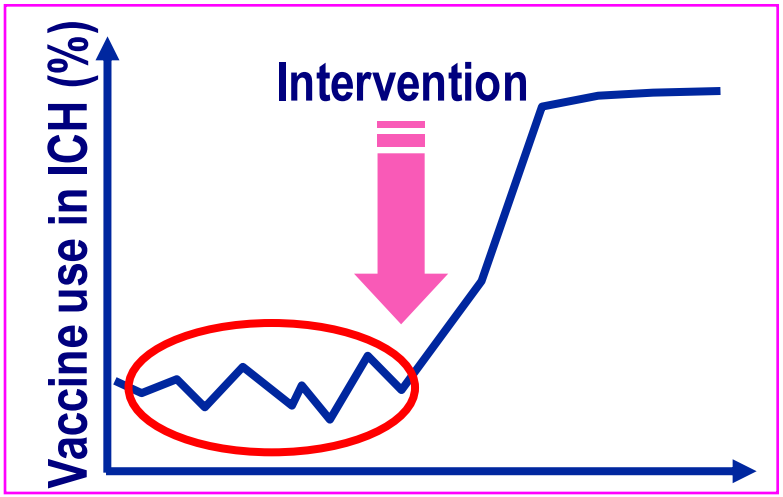
1. Maximize the expected benefits of vaccination for each individual immunocompromised patient

- Immunize as early as possible after diagnosis
- Assess vaccine seroresponses to evaluate immune competence / correlates of protection
- Give additional primary doses - as needed…
- Control the persistence of vaccine-induced immunity
- Give additional boosters as needed !

Individual patient - based strategies!

Vaccinations in immunocompromised patients: 3 main challenges

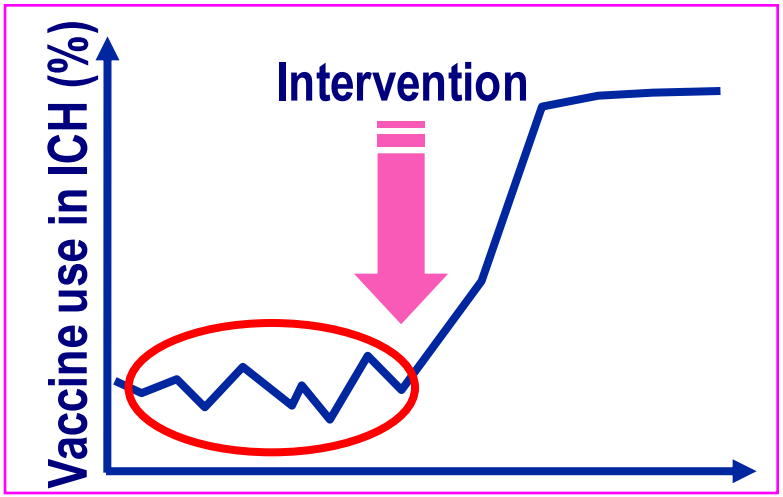
1. Maximize the expected benefits of vaccination for each individual immunocompromised patient
2. Implement the interventions required to increase the proportion of patients who benefit from vaccine-induced immunity !



Vaccinations in immunocompromised patients: 3 main challenges

1. Maximize the expected benefits of vaccination for each individual immunocompromised patient
2. Implement the interventions required to increase the proportion of patients who benefit from vaccine-induced immunity !
3. Contribute to update our missing or largely empirical policies !!

Studies wanted !



Improving the use of vaccinations in our immunocompromised patients

From empiric towards evidence-based guidelines :

Splenectomised patients

- Which vaccines (conjugate / PS) ? When ?
- Whether / when / how to use boosters ?

Cancer patients

- Delay after chemotherapy ? Live vaccines?

Transplant patients (HSC, organ)

- Delay after transplant ? Live vaccines ?

HIV patients with lower CD4 T cells

- Yellow fever vaccine ?

IMID patients

- All questions open !

If you have the vaccinologist's beeper…

- **Do not assume to be called in : reach out for the patients !**
- **Do not assume that immunization have been previously given : check vaccine status !**
- **Do not assume that immunization have been effective : check for vaccine-induced immunity !**

If you have the vaccinologist's beeper…

- **Recommend what would be needed…**

  …but do not assume your advice will be followed !

- **Keep on boosting :**

  this is how vaccinologists are most effective !