Immunisations in the immunocompromised

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Switzerland
Audits and reports worldwide: vaccines are not optimally used for patients with limited immune competence
Vaccinations in the immunocompromised

- 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...
Vaccinations in the immunocompromised

Underestimated benefits

Fears of severe adverse events!
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
No live vaccines in immunocompromised patients…

Which evidence?
Risks of VAPP in patients with B cell deficiency

- estimated risks: 1/700’000 (healthy subjects) ↔ 1/7’000 (B cell deficiency)
- Main risk = persistent viral excretion: immunodeficiency-related vaccine-derived polioviruses (iVDPVs)

- 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), 68 cases in 2015 (systematic review, Guo J, Vaccine 2015), mostly from industrialized countries, thus likely underestimation
  - Included in the polio endgame strategies...
BCG in patients with congenital ID: mendelian susceptibility to mycobacterial disease

- BCG vaccine in patients with severe congenital immune deficiency:
  - 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.


LOOK FOR SPECIFIC IMMUNODEFICIENCY!

- 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)
Risks of rotavirus vaccines in infants with severe combined immune deficiency


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)
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; Monk H Pediatrics 2014; Roue JM, Clin Vaccine Immunol 2014)

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
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
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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 transmission risk higher than the expected benefit?
Which evidence?

- OPV: ↑ relative risk if B-
- BCG: high risks if SCID!
- Rotavirus: ↑ risks if SCID

→ Search for underlying immune deficiency if complications!

HIV-1
Cancer
HSCT
SOT
IMID (immune mediated inflammatory diseases)

Congenital ID
Infants
Neonates
Prematures
Foetus
Elderly

HIV
HIV-1
Cancer
HSCT
SOT
IMID (immune mediated inflammatory diseases)

Prematures
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Neonates
Congenital ID
Foetus
Elderly

Search for underlying immune deficiency if complications!
## Risks of 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)

<table>
<thead>
<tr>
<th>Author (year of publication)</th>
<th>Country</th>
<th>Study population</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blanche (1986)</td>
<td>France</td>
<td>18 HIV-infected</td>
<td>Disseminated BCG infection in 3 (17%)</td>
</tr>
<tr>
<td>Carswell (1987)</td>
<td>Uganda</td>
<td>54 children born to HIV-infected women</td>
<td>No complications</td>
</tr>
<tr>
<td>Bregere (1988)</td>
<td>France</td>
<td>67 HIV-infected</td>
<td>BCG lymphadenitis in 7 (10%)</td>
</tr>
<tr>
<td>Houde (1988)</td>
<td>Canada</td>
<td>1 HIV-infected</td>
<td>Disseminated BCG infection in a 2-month-old girl</td>
</tr>
<tr>
<td>Ninane (1988)</td>
<td>Belgium</td>
<td>1 HIV-infected</td>
<td>Disseminated BCG infection in a 4-month-old boy from Zaire</td>
</tr>
<tr>
<td>Hlaa (1989)</td>
<td>Zambia</td>
<td>42 HIV-infected children</td>
<td>BCG lymphadenitis in 1 (3%)</td>
</tr>
<tr>
<td>ten Dam (1990)</td>
<td>Switzerland</td>
<td>1 HIV-infected</td>
<td>Disseminated BCG infection in an 8-month-old girl from Argentina</td>
</tr>
<tr>
<td>MMWR (1991)</td>
<td>Rwanda</td>
<td>37 HIV-infected</td>
<td>BCG lymphadenitis in 2 (5%)</td>
</tr>
<tr>
<td>Green (1992)</td>
<td>Zaire</td>
<td>21 HIV-infected</td>
<td>No complications</td>
</tr>
<tr>
<td>Ryder (1993)</td>
<td>Zaire</td>
<td>48 HIV-infected</td>
<td>Lymphadenitis in 5% HIV-infected and 3.5% HIV-uninfected Fistula in 5% HIV-infected and 6 to 8% HIV-uninfected</td>
</tr>
<tr>
<td>Besnard (1993)</td>
<td>France</td>
<td>68 HIV-infected</td>
<td>4 with BCG lymphadenitis, 3 with fistula, 2 with disseminated BCG (13%)</td>
</tr>
<tr>
<td>Edwards (1996)</td>
<td>USA</td>
<td>1 HIV-infected</td>
<td>BCG bacteraemia in a 3-year-old HIV-infected Brazilian girl</td>
</tr>
<tr>
<td>Sharp (1999)</td>
<td>Australia</td>
<td>1 HIV-infected</td>
<td>BCG lymphadenitis</td>
</tr>
<tr>
<td>Thailumyanoon (2000)</td>
<td>Thailand</td>
<td>26 HIV-infected</td>
<td>No complications</td>
</tr>
</tbody>
</table>

### WHO GACVS 2007: No BCG if known HIV-1 infection! *(WER 3,2007,82)*
Safety of rotavirus vaccines in HIV infected infants

Rotavirus vaccines safe and effective 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)
- No vaccine-associated SAE, similar all/grade 3 symptoms, prolonged shedding in 1/100
  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
- No vaccine-associated SAE
  Laserson KF, Vaccine 2012 A61-A70

No safety signal from South Africa:
- Rotarix®, case control study
Safety of VZV vaccine in HIV infected patients?

VZV appears safe in HIV patients with CD4 ≥ 15% or 200/μL 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
    • 60 children (only 34 seronegative)
  (Levin MJ, JID 2006) (Taweesith W, PIDJ 2011)

- VZV vaccine appears effective: chart review ← VE 82% (24-99)
  (Son M, JID 2010)

- One case report of disseminated VZV vaccine disease in an HIV adult
  (Maves RC J Clin Virol, 2014)

Varicella vaccine may be used / should be recommended in children with HIV
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
Yellow fever vaccine in HIV+ patients
- safe in asymptomatic young children (WHO)
- 1 case of meningoencephalitis in an adult patient (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)
- Cochrane review (Barth H, Cochrane Database Syst Rev. 2014)

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

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Check immunity and consider VZV vaccine if exposure likely!
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!
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 (?)**
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 immunocompromised children!
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)
Live vaccines in organ transplant patients?

<table>
<thead>
<tr>
<th>VACCINE</th>
<th>Before T</th>
<th>After T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varicella</td>
<td>YES</td>
<td>NO !</td>
</tr>
<tr>
<td>MMR</td>
<td>YES</td>
<td>NO !</td>
</tr>
<tr>
<td>Oral polio</td>
<td>YES</td>
<td>NO !</td>
</tr>
<tr>
<td>Typhoid fever</td>
<td>YES</td>
<td>NO !</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>YES</td>
<td>NO !</td>
</tr>
<tr>
<td>LAIV</td>
<td>YES</td>
<td>NO !</td>
</tr>
</tbody>
</table>

Recommendations ← presumptions of 1) sustained efficacy of pre-T immunity and 2) risks of post-T immunization
Live vaccines in organ transplant patients?

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)

- **Switzerland**: 36 seronegative transplant children > 12 mo:
  - Mild and transient adverse events, Ø acyclovir
  - 100% seroprotection (2-3 doses), † VZV-specific T cells
  - No breakthrough disease (> 4 yrs) Posfay-Barbe, Am J Transplant 2012

- **Japan**: 39 children: safe and immunogenic Kawano Y, Vaccine 2015
- **Japan**: 35 children: safe and immunogenic Shinjo M, Vaccine 2015
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...

<table>
<thead>
<tr>
<th>General patient data at the time of yellow fever vaccination (YFV)</th>
<th>Mean ± SD</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at the YFV (years)</td>
<td>45.6 ± 13.6</td>
<td>46</td>
<td>11–69</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.46 ± 0.62</td>
<td>1.25</td>
<td>0.8–3.4</td>
</tr>
<tr>
<td>Post-transplant time at YFV (months)</td>
<td>65 ± 83.9</td>
<td>36</td>
<td>3–340</td>
</tr>
<tr>
<td>Months from YFV at the time of the survey</td>
<td>45 ± 51</td>
<td>30</td>
<td>3–241</td>
</tr>
</tbody>
</table>

Azevedo LS, Transplant Inf Diseases 2011
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

No trigger of graft rejection!!

Vaccine safety? - Risks of triggering flares in IMID patients?

No significant trigger of exacerbations!
Vaccine safety?
- Risks of triggering flares in IMID patients?
- Risks of live vaccines ← immune suppression?

- HIV-1
- Cancer
- HSCT
- SOT
- IMID (immune mediated inflammatory diseases)
- Congenital ID
- Prematures
- Neonates
- Infants
- Foetus
- Elderly
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...

MMR immunization in juvenile rheumatic diseases?

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

Pileggi GS, Arthritis Care Res 2010
Heijstek MW, Ann Rheum Dis 2007
Borte S, Rheumatology 2009
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… but…

Adjuvanted influenza vaccines in immunosuppressed IMID patients

Few studies, but similar results: no safety issue!

  - n = 173 patients (mixed population), Geneva / Switzerland
  - 2 doses of AS03-adjuvanted H1N1v vaccines (Pandemrix®, GSK)
  - Unchanged disease activity scores + immune monitoring

  - 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
Our current immunization guidelines contra-indicating live vaccines are largely NOT evidence-based!
Novel vaccines?

Novel adjuvanted zoster subunit candidate vaccine (GSK)
- Effective and safe in older adults (Lal H, NEJM 2015)
- Immunogenic and safe in 130 HIV adult patients (Berkowitz EM, JID 2015)
- Immunogenic and safe in 90 patients after autologous BMT (Statdtmauer EA, Blood 2014)
Towards a coordinated off-label use of live viral vaccines in IS patients:

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

Congenital ID
HSCT
IMID (immune mediated inflammatory diseases)
Foetus
Elderly
Prematures
Neonates
Infants
Cancer
HIV-1
SOT
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
Determinants of responses to protein-containing vaccines

Lymph nodes

- **Ag**
- **DC**
- **T**
- **B**

**Germinal centers**

- **Tfh**
- **FDC**
- **B**
- **IgG**

**Plasma cells**

Blood

- **Short-lived PC**

Bone Marrow

- **Bone marrow plasma cells**

B cell activation (DC, T cells)

Germinal center responses (Tfh and GC B cells)
Determinants of responses to protein-containing vaccines

Lymph nodes

- **Ag**
- **DC**
- **T**
- **B**

**Germinal centers**

- **Tfh**
- **FDC**
- **B**
- **IgG**

**Plasma cells**

- **B cell activation (DC, T cells)** ↓
- **Germinal center responses (Tfh ↓↓ and GC B cells)**

Blood

- **Short-lived PC**

Bone Marrow

- **Bone marrow plasma cells ↓↓**

Lower and shorter Ab responses in immunocompromised patients
HIV infection and vaccine responses

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

**CD4:** >300 USUALLY CONSERVED RESPONSES

**CD4:** <200 REDUCED RESPONSES

Optimal period for immunization

Decreased immunogenicity

Risk of complications
HIV infection and vaccine responses

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 immunogenicity

Risk of complications
HIV infection and vaccine responses

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 immunogenicity
Risk of complications

Moss et al, Bull WHO 2003;
May immunocompromised hosts raise protective vaccine responses?

HIV infection

- Ab-mediated protection
- Induction + persistence of plasma cells
- Induction of GC B cells
- Induction of follicular T cells
- Activation of dendritic cells

Expected efficacy:
- Hep A = HPV > Hep B
- PCV > PS23
- Tetanus > Diphtheria
- Measles > Mumps

Vaccine type, Ag, dose, adjuvant, schedule

Vaccine immunogenicity

Activation of dendritic cells
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

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

- Distinct mechanisms
- Distinct impacts
- Dose effects
- Combinations
H1N1/09 pandemic

916 adults

Immunocompromised patients (n=778)

1. HIV infection (n=129)
   - CD4 > 500: n=85
   - CD4 < 350: n=44

2. Rheumatic diseases (n=173)
   - Rheum. arthritis: n=82
   - Spond. arthropathies: n=45
   - SLE/vasculitis: n=46

3. Cancer (n=197)
   - Lymphoma: n=57
   - Glioma: n=26
   - Lung/head/neck: n=37
   - Digestive: n=41
   - Breast: n=36

4. Transplant (n=279)
   - Lung: n=25
   - Liver: n=45
   - Kidney: n=95
   - Heart: n=27
   - Pancreas: n=22
   - Allogenic HSCT: n=65

Pandemrix®

121 in post-dose 1 analyses
173 in post-dose 1 analyses
192 in post-dose 1 analyses
274 in post-dose 1 analyses
133 in post-dose 1 analyses

893 subjects

2nd dose

106 included in post-dose 2 analyses
149 included in post-dose 2 analyses
172 included in post-dose 2 analyses
264 included in post-dose 2 analyses

691 patients

+ 171 children
Influence of IS on H1N1/09 adjuvanted vaccine responses in patients with rheumatic diseases

Reduced seroprotection after 1 dose ↔ corrected after 2 doses

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

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

<table>
<thead>
<tr>
<th>Underlying disease</th>
<th>Controls (POST 1) &amp; Patients (POST 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>POST 1</td>
<td>POST 2</td>
</tr>
<tr>
<td>Estimates (SE)</td>
<td>Effect</td>
</tr>
<tr>
<td>RA</td>
<td>0.06 (0.16)</td>
</tr>
<tr>
<td>SA</td>
<td>-0.05 (0.18)</td>
</tr>
<tr>
<td>Other</td>
<td>-0.18 (0.28)</td>
</tr>
<tr>
<td>TNF-α antagonists</td>
<td>No</td>
</tr>
<tr>
<td>RA</td>
<td>0.06 (0.16)</td>
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<tr>
<td>B cell depletion</td>
<td>No</td>
</tr>
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<td>RA</td>
<td>0.06 (0.16)</td>
</tr>
<tr>
<td>SA</td>
<td>-0.05 (0.18)</td>
</tr>
<tr>
<td>Other</td>
<td>-0.18 (0.28)</td>
</tr>
<tr>
<td>Oral steroids</td>
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</tr>
<tr>
<td>RA</td>
<td>0.06 (0.16)</td>
</tr>
<tr>
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<tr>
<td>MTX</td>
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<tr>
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<tr>
<td>SSZ, HCQ</td>
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</tr>
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<tr>
<td>Other</td>
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</tbody>
</table>

DMARDs: Disease modifying antirheumatic drugs; MTX: Methotrexate; SSZ: sulfasalazine; HCQ: hydroxychloroquine;
Influence of IS on H1N1/09 adjuvanted vaccine responses in solid organ transplant recipients

<table>
<thead>
<tr>
<th></th>
<th>Controls (POST1) - Patients (POST2)</th>
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<td>Estimates (SE)</td>
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<td><strong>SOT transplant</strong></td>
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<td>Heart</td>
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<td><strong>MMF and/or ECMPA</strong></td>
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<td>&lt; 2mg/mL</td>
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<td>2-4 mg/mL</td>
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<td>&gt;4 mg/mL</td>
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<tr>
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<td>-0.05 (0.19)</td>
</tr>
</tbody>
</table>

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

May immunocompromised hosts raise protective vaccine responses?

**Immunosuppressive treatment**

- **Ab-mediated protection**
- **Induction + persistence of plasma cells**
- **Induction of GC B cells**
- **Induction of follicular T cells**
- **Activation of dendritic cells**

**Expected efficacy:**
- Hep A = HPV > Hep B
- PCV > PS23
- Tetanus > Diphtheria
- Measles > ...

**Vaccine type, Ag, dose, adjuvant, schedule**

**Vaccine immunogenicity**
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 ?)

Congenital ID
HIV-1
Cancer
HSCT
SOT
IMID
(immune mediated inflammatory diseases)

Infants
Prematures
Neonates
Foetus
Elderly

Pretamures
Elderly
Foetus
Neonates
Congenital ID
HIV-1
Cancer
HSCT
SOT
IMID
(immune mediated inflammatory diseases)
Friday afternoon with the vaccinologist’s beeper in the middle of a measles outbreak!

18 y, rheumatoid arthritis, on methotrexate?

14 y, Crohn’s disease, cyclosporine?

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

15 y, Hodgkin, 1 month off chemot?

22 mo, liver transplant at 4 mo of age?

23 y, rheumatoid arthritis, on anti-TNF?

14 y, 13 months post bone marrow T?
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!
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!
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!