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How the vaccines work in the immunocompromised population

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Why vaccinate immunocompromised hosts

- Risk of **exposure** ~ **similar**, especially in pediatrics
- For most vaccine-preventable diseases
  - Risk of **severity of disease higher** in immunocompromised hosts
    - Flu, pneumococcus, Zoster, HPV, …
- But, risk may be **different** between types of immunosuppression

Feldman AG JPeds 2017

Vaccination in immunocompromised hosts

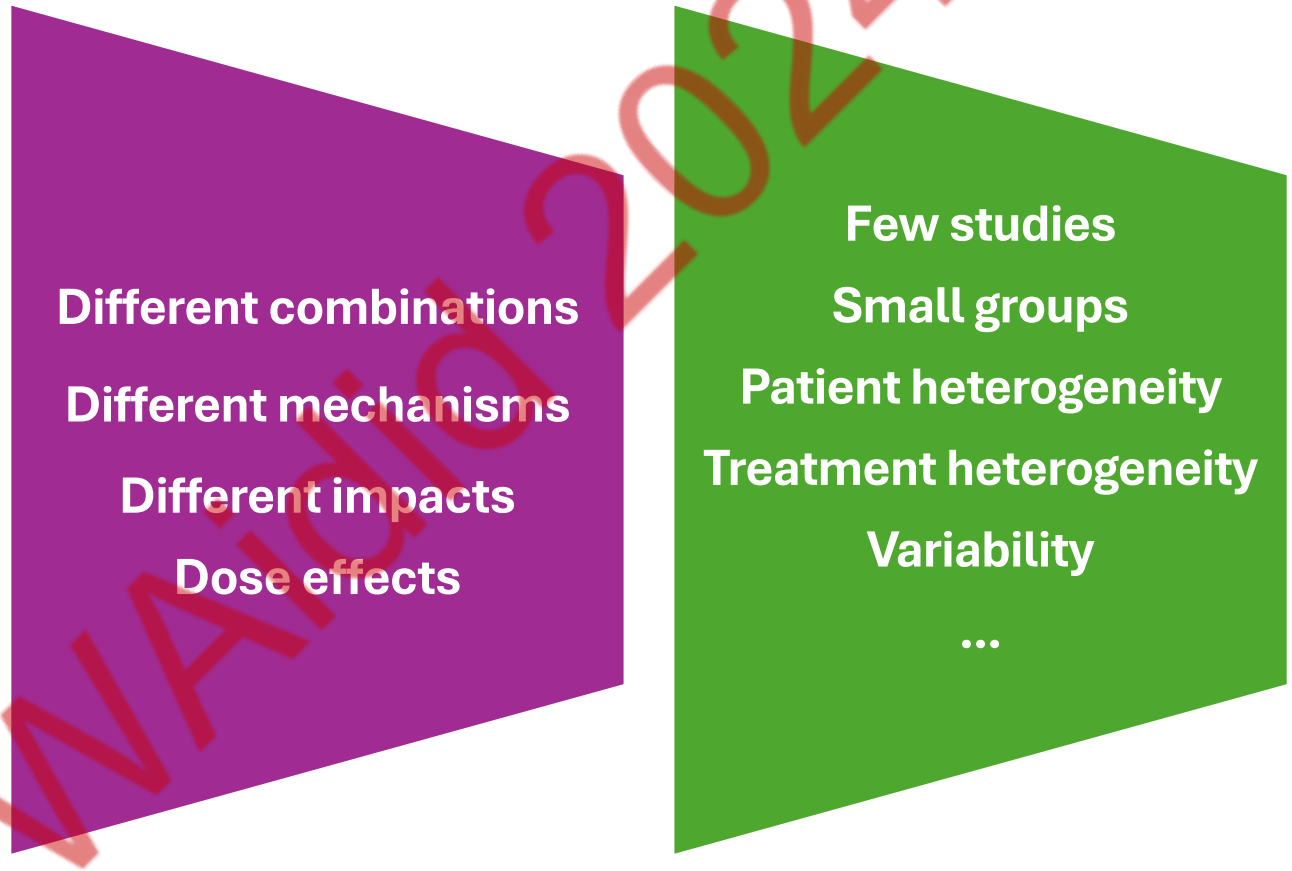
- Need to start immunosuppressive treatment quickly, and usually keep it for a very long time (sometimes lifelong): often no time for vaccination before start

- Very few recommendations and most based on small studies: however, more and more data is published ("COVID boost")

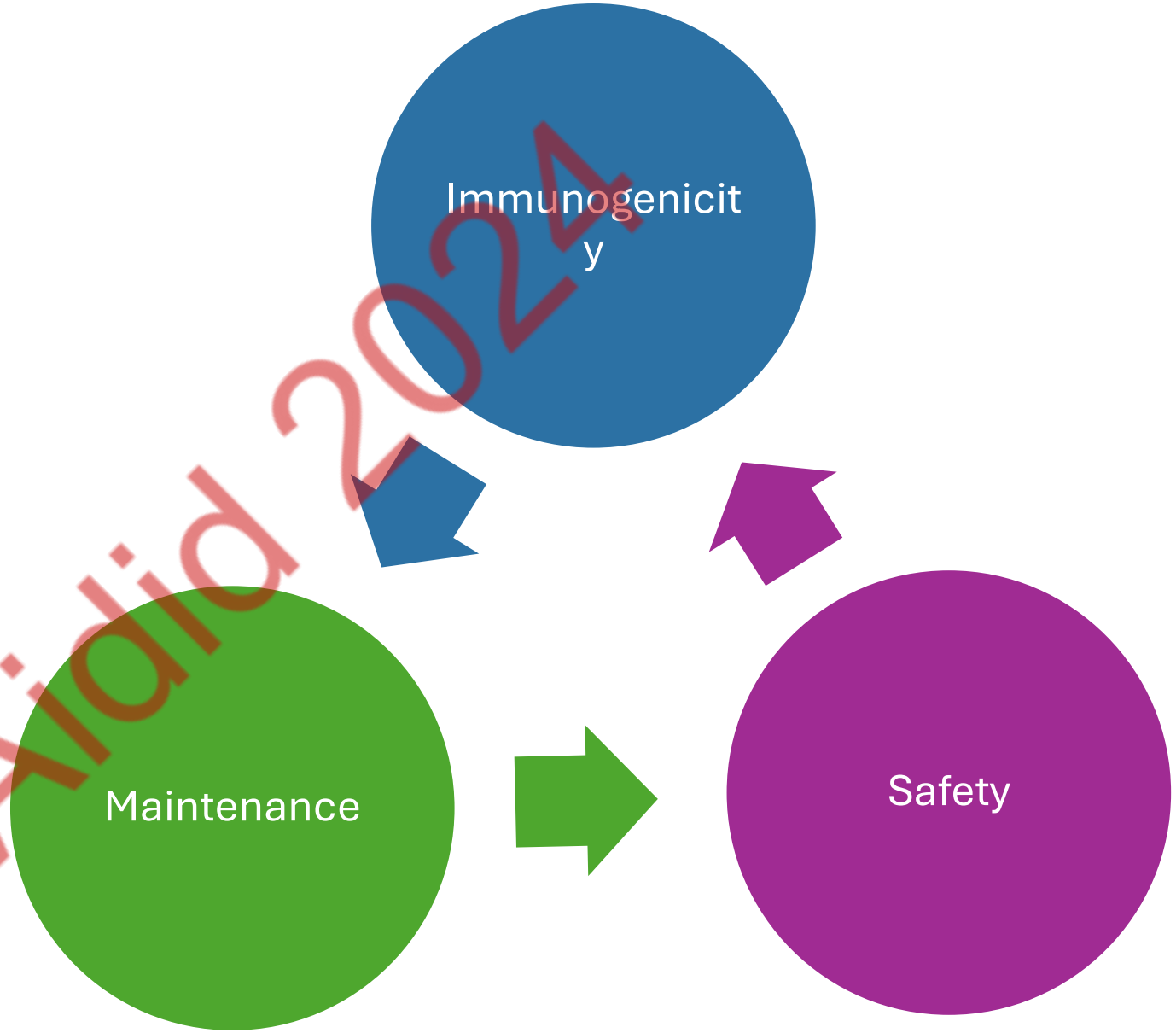
- Patients are more at risk for disease and are often insufficiently vaccinated

Influence of immunosuppressive drugs on vaccine responses

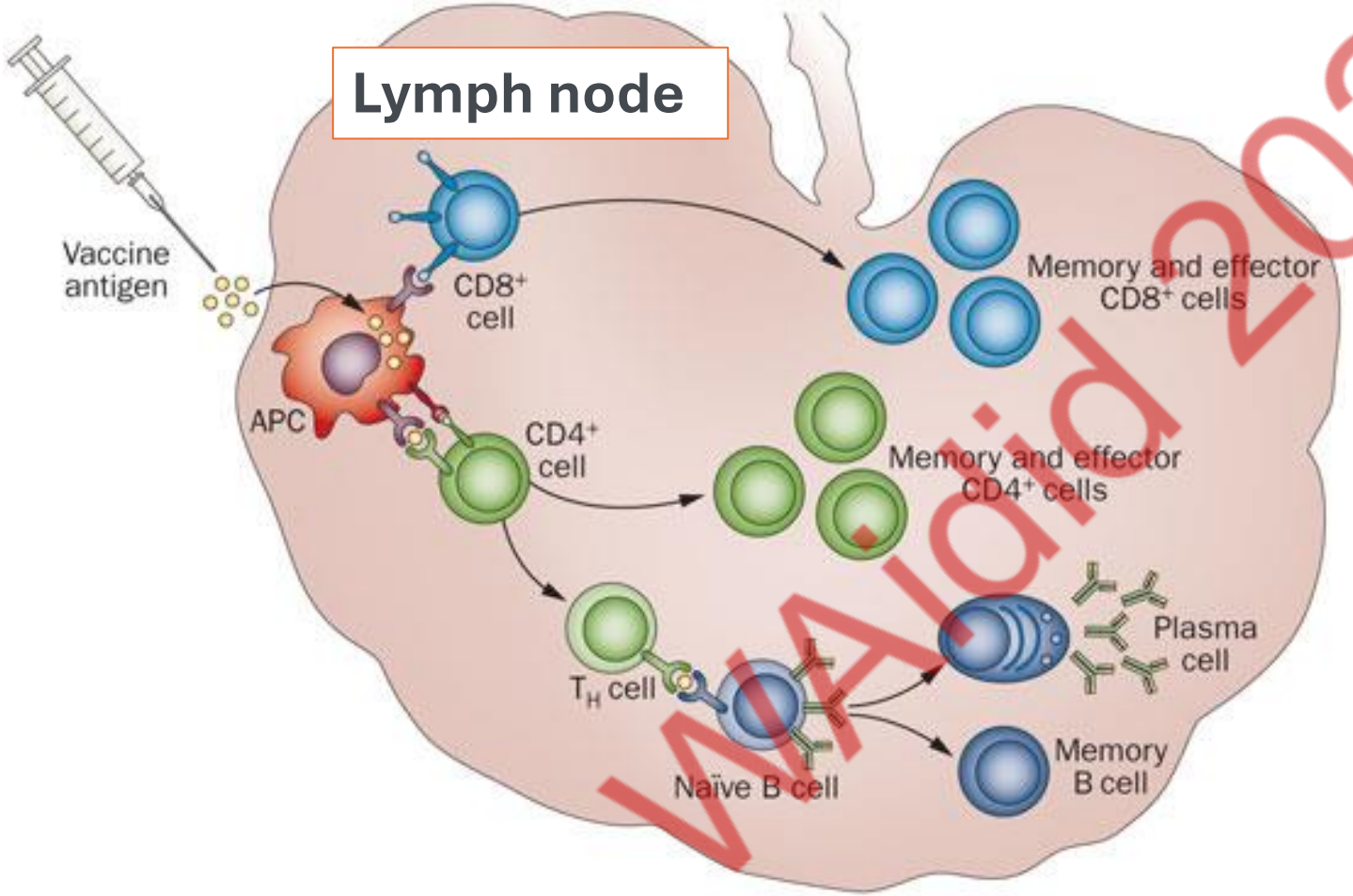
- Corticosteroids
- Adalimumab
- Azathioprine
- Ciclosporine
- Etanercept
- Fingolimod
- Infliximab
- Leflunomide
- Mesalazin
- Methotrexate
- Mycophenenolyte
- Natalizumab
- Rituximab
- Sirolimus / tacrolimus
- Sulfazalazin
- Tacrolimus
- …



The 3 questions for any vaccine and any person



Vaccine = antigen and adjuvant.... at least



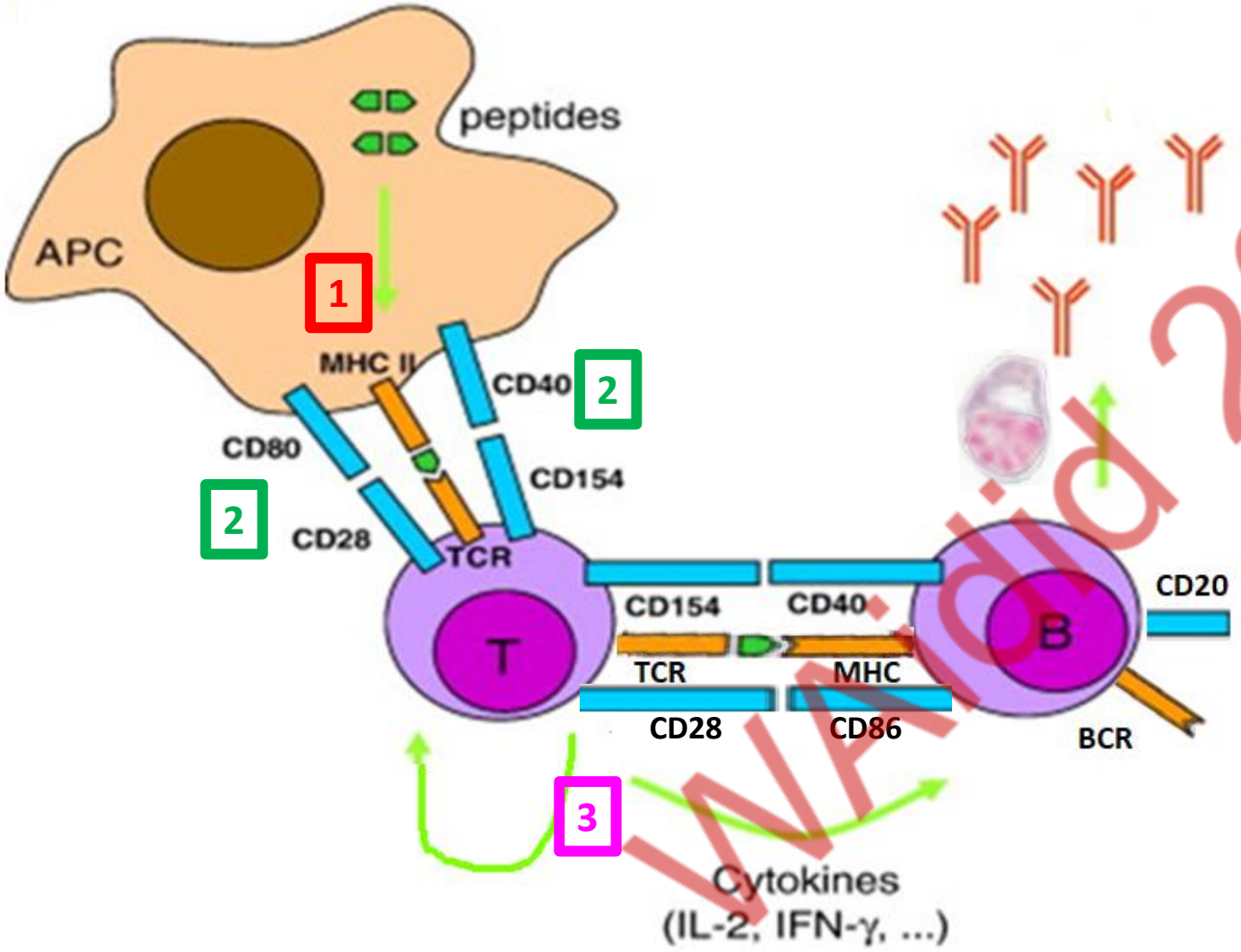
Production of antibodies by B cells requires

1) Binding of antigen (surface receptors)

2) Co-stimulatory signal by T cells activated by dendritic cells

Silva CA 2013 Nat Rev Rheumatol

Cellular activation



Activation of T lymphocytes

Signal 1: recognition of Ag presented by Antigen-presenting cells (APC) in Major Histocompatibility Complex (MHC) to a T-cell receptor (TCR)
→ pro-inflammatory transcription factors

Signal 2: linking of co-stimulatory molecules CD28/CD80 and CD40/CD40L (also called CD154)

Signal 3: fixation of IL2 on receptor, inducing proliferation

Activation of B lymphocytes

Collaboration of T and B cells through co-stimulatory molecules → activation and differentiation of plasmocytes →antibodies

Blanchard-Rohner G, Frontiers Immunol 2022

Molecular targets of the immunosuppressive treatments

1. **Inhibition of intracellular signal transduction and cellular proliferation**
   - ***Inhibition of DNA synthesis (ex: analogue of purine, pyrimidines)***
     - Azathioprine, 6-Mercaptopurine, Mycophenolate Mofetil, Methotrexate
   - ***Calcineurine inhibitors, mToR inhibitors***
     - Cyclosporine, Tacrolimus, Sirolimus
   - ***JAK inhibitors***
     - Baricitinib, Tofacitinib
2. **Interference with co-stimulatory signals**
   - ***Analogue of CTLA-4*** Abatacept
3. **Modulation of the effect of the response of the B or T cells through monoclonal anti-cytokines antibodies**
     - anti-TNFα, anti-IL1, anti-IL6
4. **Depletion of specific cells**
     - anti-CD20: Rituximab, Ocrelizumab

Halloran NEJM 2004

Effects of immunosuppressive drugs

- **Non-specific drugs**

→Suppress both innate and adaptive immunity

- **Monoclonal antibodies**

- to various cytokines or cell receptors -

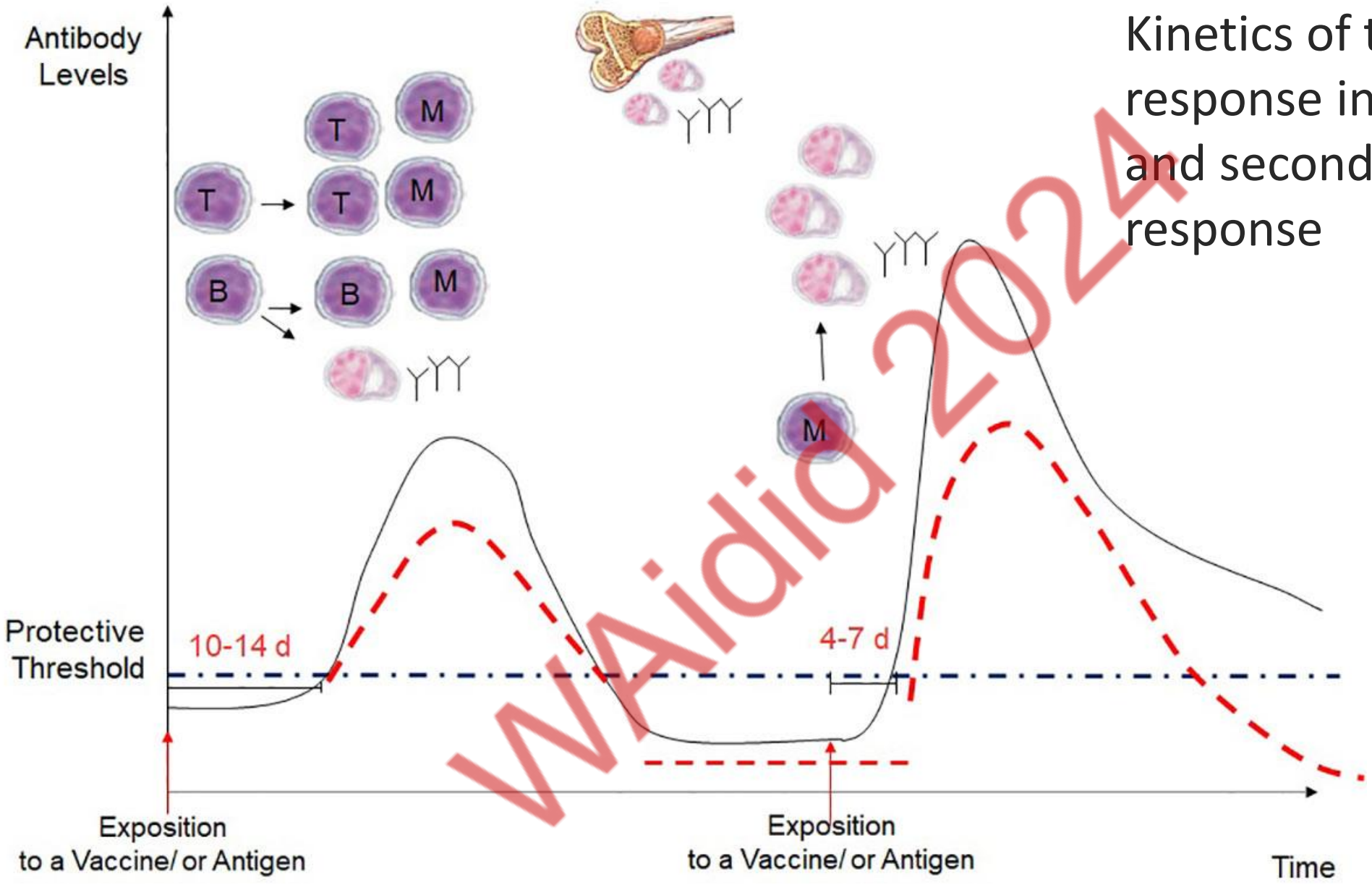
→ May have different suppressive effects on cell-mediated and humoral immunity based on the downstream targets

Alnaimat F Vaccine 2023

Immunogenicity

of vaccines in Immunosuppressed population

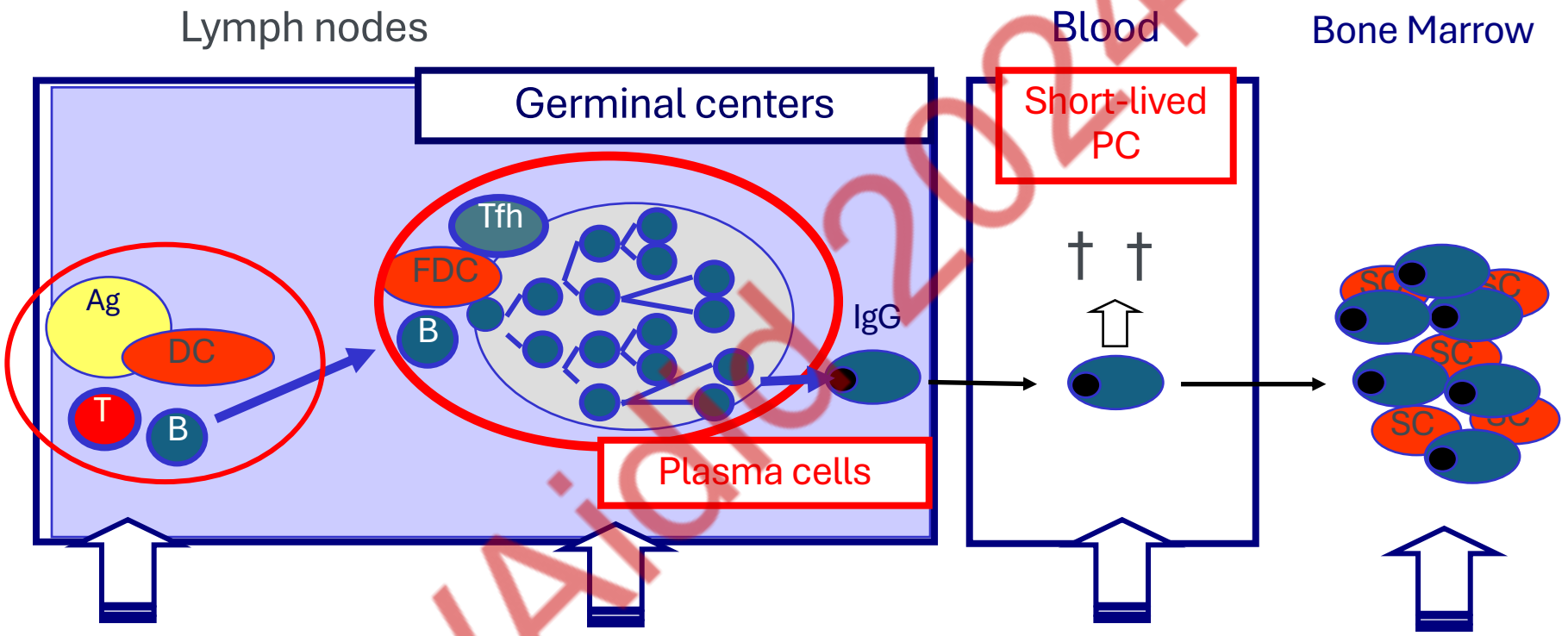
Kinetics of the antibody response in a primary and secondary immune response



——— = healthy; ------ = transplant

Blanchard-Rohner, Frontiers Immunol 2021

Lower & shorter antibody responses in immunocompromised patients



B cell activation (DC, T cells) ↓

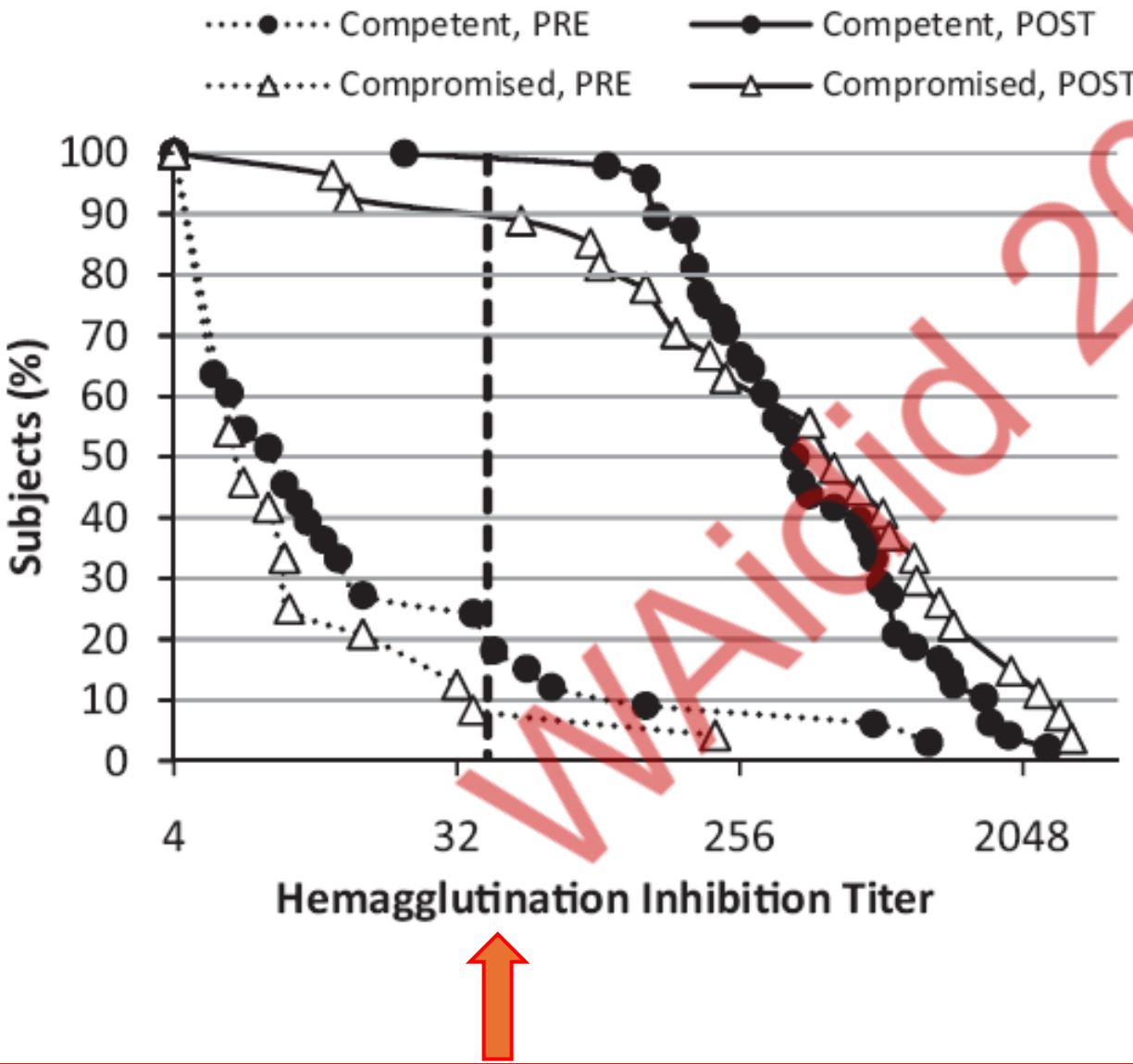
Germinal center responses (Tfh ↓↓ and GC B cells)

Bone marrow plasma cells ↓↓

Slide courtesy of CA Siegrist

DC: dendritic cells; FDC: follicular DC; Tfh: T follicular helper cells; GC: germinal cells; PC plasma cells; Ag: antigens

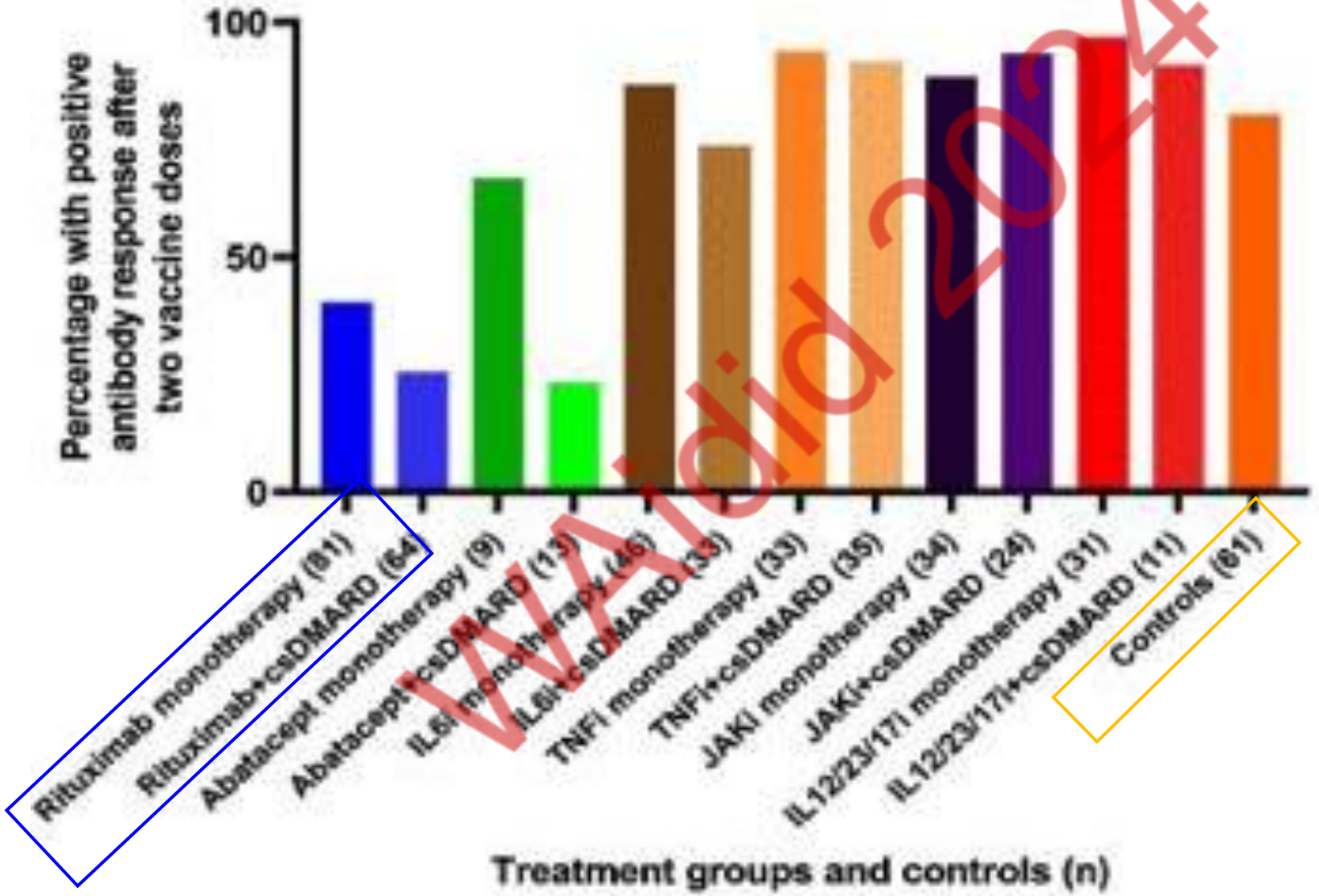
H1N1 pediatric solid organ transplant



98% controls
Vs.
89%
immunocompromised

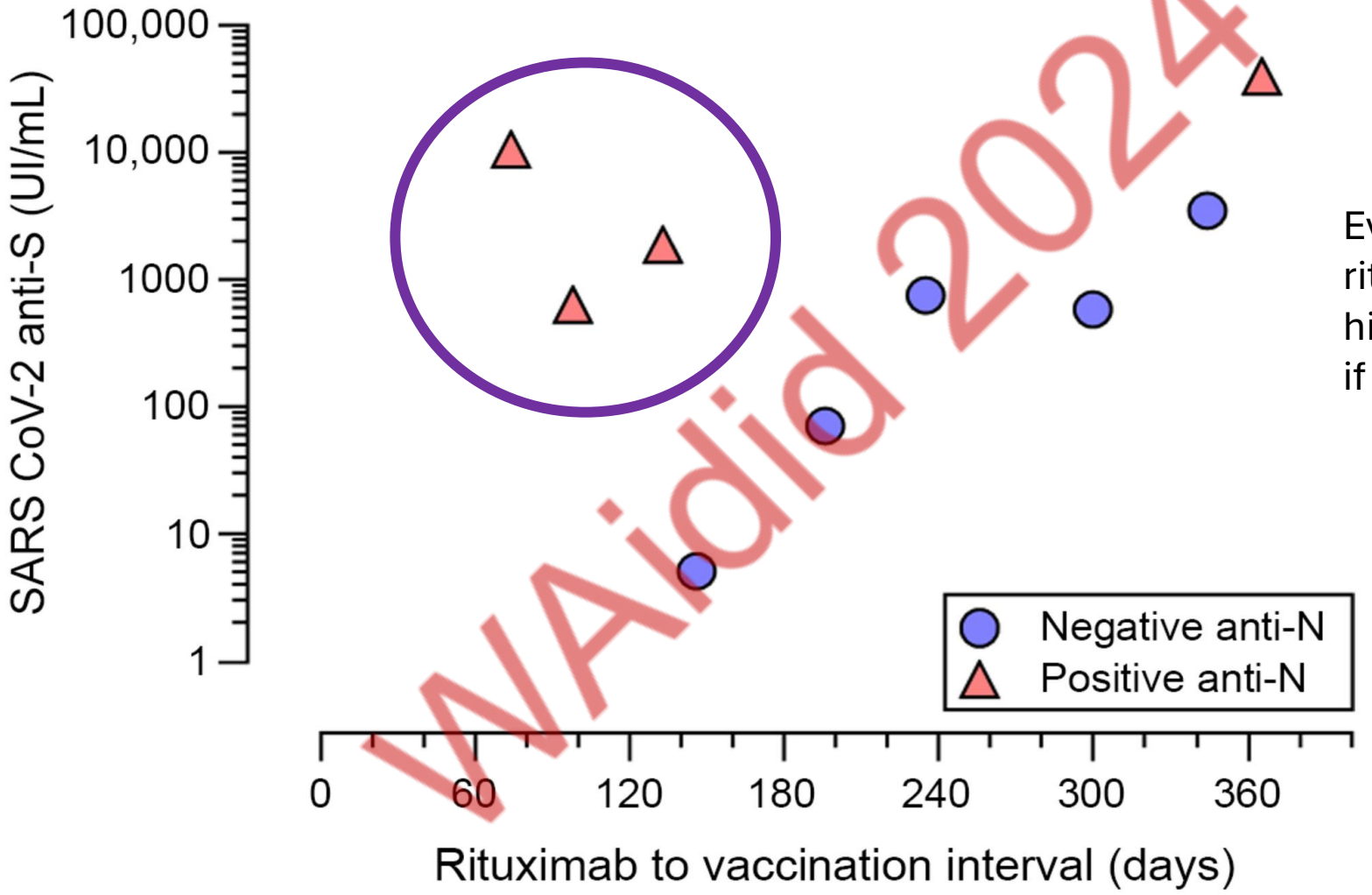
Meier S Vaccine 2011

Seroconversion to COVID vaccine in treated rheumatic diseases patients



Frodlund M Vaccine 2023

Rituximab-to-vaccine interval on SARS-CoV-2 immunogenicity in children



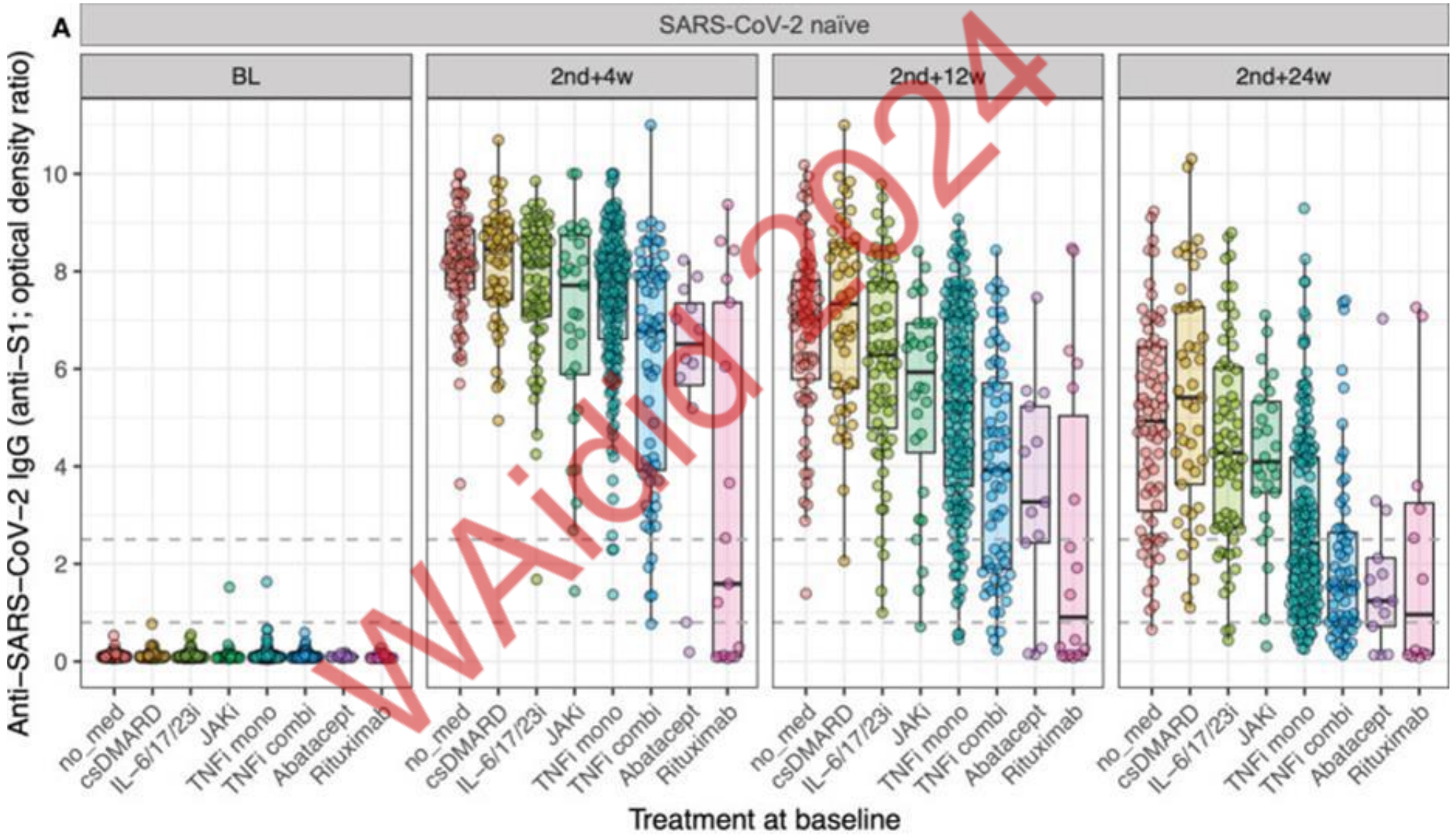
Even if shorter time between rituximab and vaccine, higher response if previously infected

Gualtieri R, Pediatr All Immunol 2024

Waning

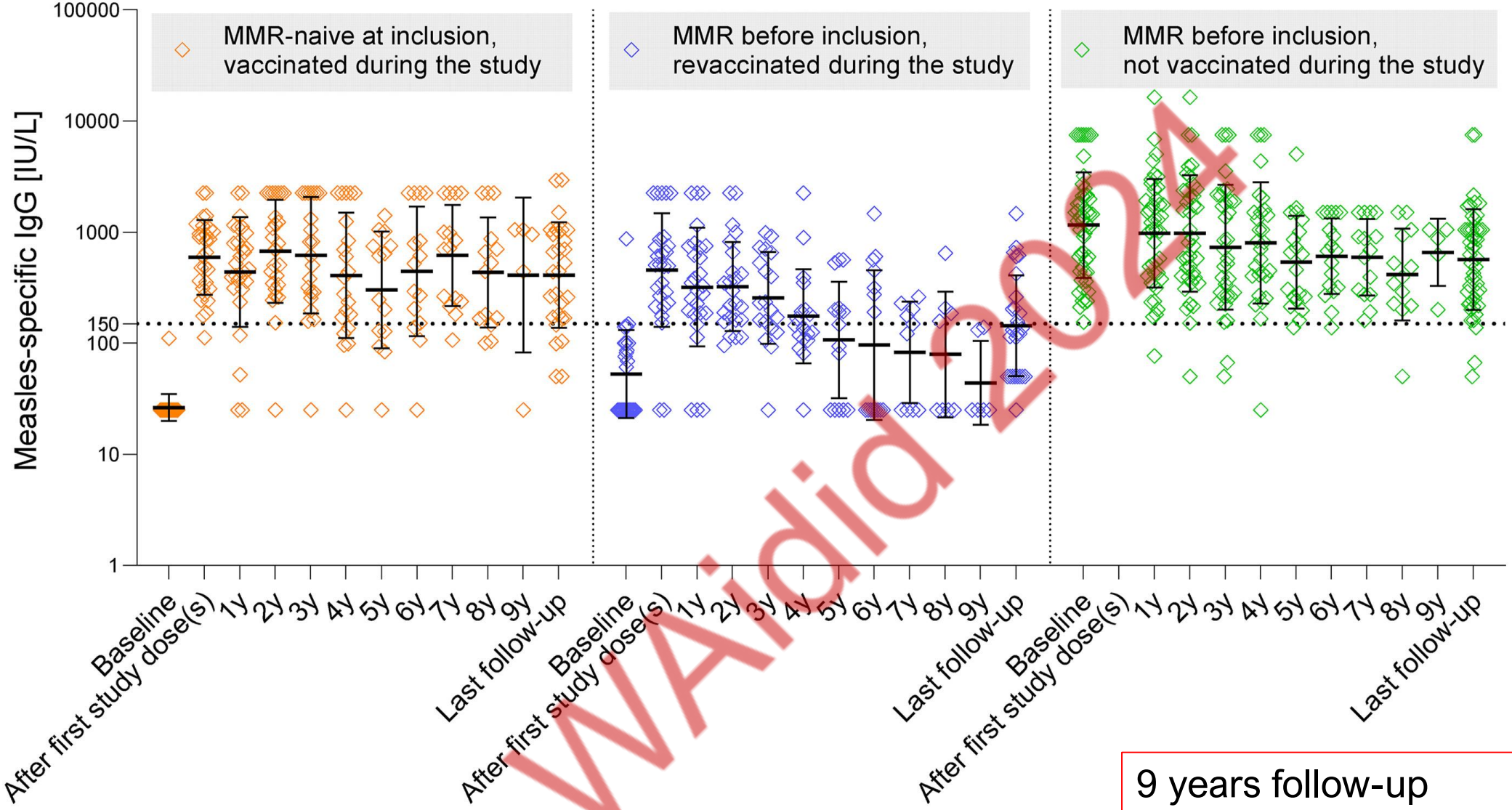
of antibody response in immunocompromised hosts

Effect of the treatment on the vaccine response



Rheumatic diseases patients, n= 565

Raptis CE Frontiers Immunol 2022



9 years follow-up
MMR vaccine to 56 children
95% seroprotection

N= 119 pediatric liver transplant recipients

Pittet LF AJT 2024

SAFETY

of vaccines in immunocompromised patients

Safety of vaccination in immunocompromised hosts- direct effect

Table II. Adverse events presented by vaccinated and unvaccinated systemic lupus erythematosus (SLE) patients and vaccinated controls, in the first 45 days after vaccination.

Adverse events	SLE		
	Vaccinated n=28 (%)	Unvaccinated n=26 (%)	Vaccinated controls n=28 (%)
n. (%)	12 (42.9) [§]	6 (23.1)	13 (46.4) [§]
Local reactions	2 (7.1)	0	6 (21.4)
Localised rash (less than 5 vesicles)	1 (3.6)	0	1 (3.6)
Fever (≥37.8° C)	3 (10.7)	0	4 (14.3)
Vomiting	0	1 (3.8)	1 (3.6)
Headache	10 (35.7)	5 (19.2)	6 (21.4)
Herpes zoster	0	1 (3.8)	0

[§]Chi-square test. p=0.1663 (between vaccinated SLE and vaccinated controls). Some individuals presented more than one adverse event.

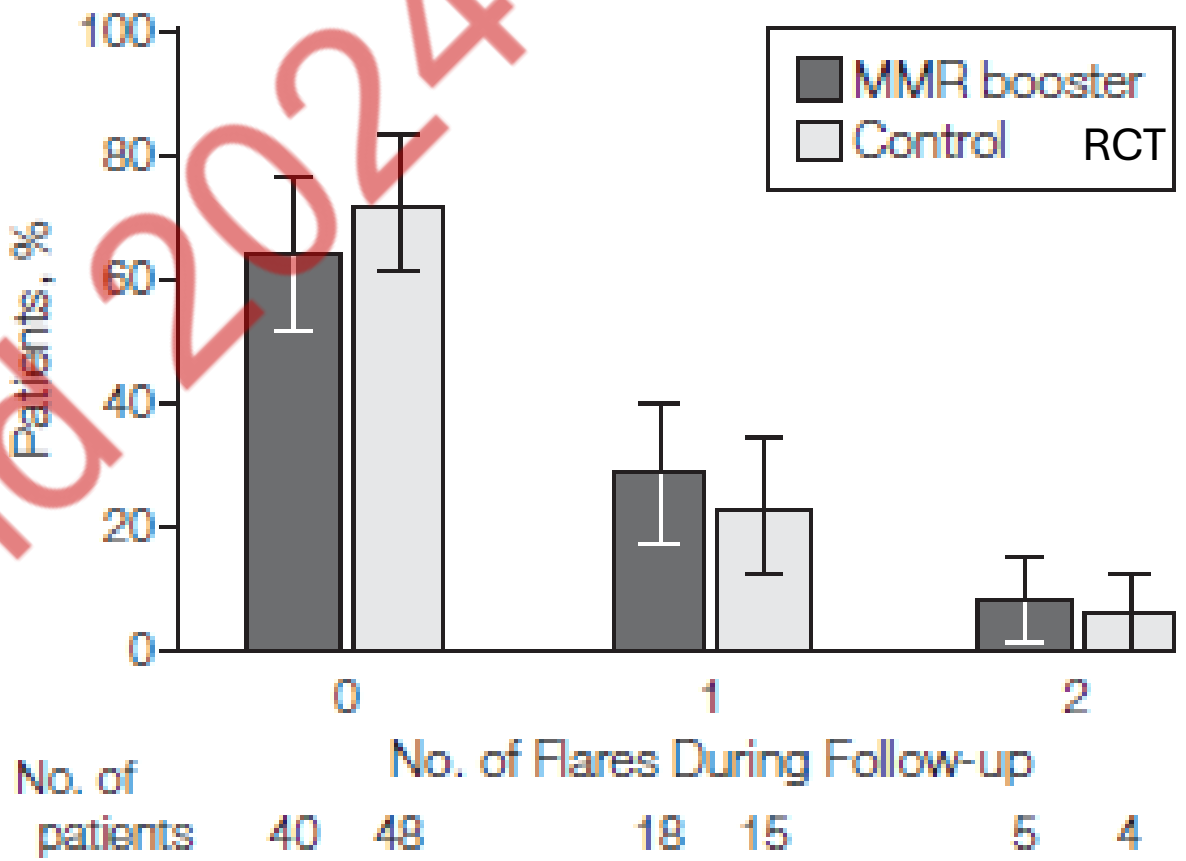
Prospective studies monitor the occurrence of possible direct side effects →
~ no ↑ between patients & controls

VZV vaccine

Alnaimat F, Vaccine 2023

Influence of vaccination on disease activity

- In general, **no** increase in disease activity or mild
  - SARS-CoV-2: flare risk after disease higher than after vaccine



Li X Ann Rheum Dis 2021; Heijstek Jama 2013

Strategies to give better protection to immunocompromised hosts

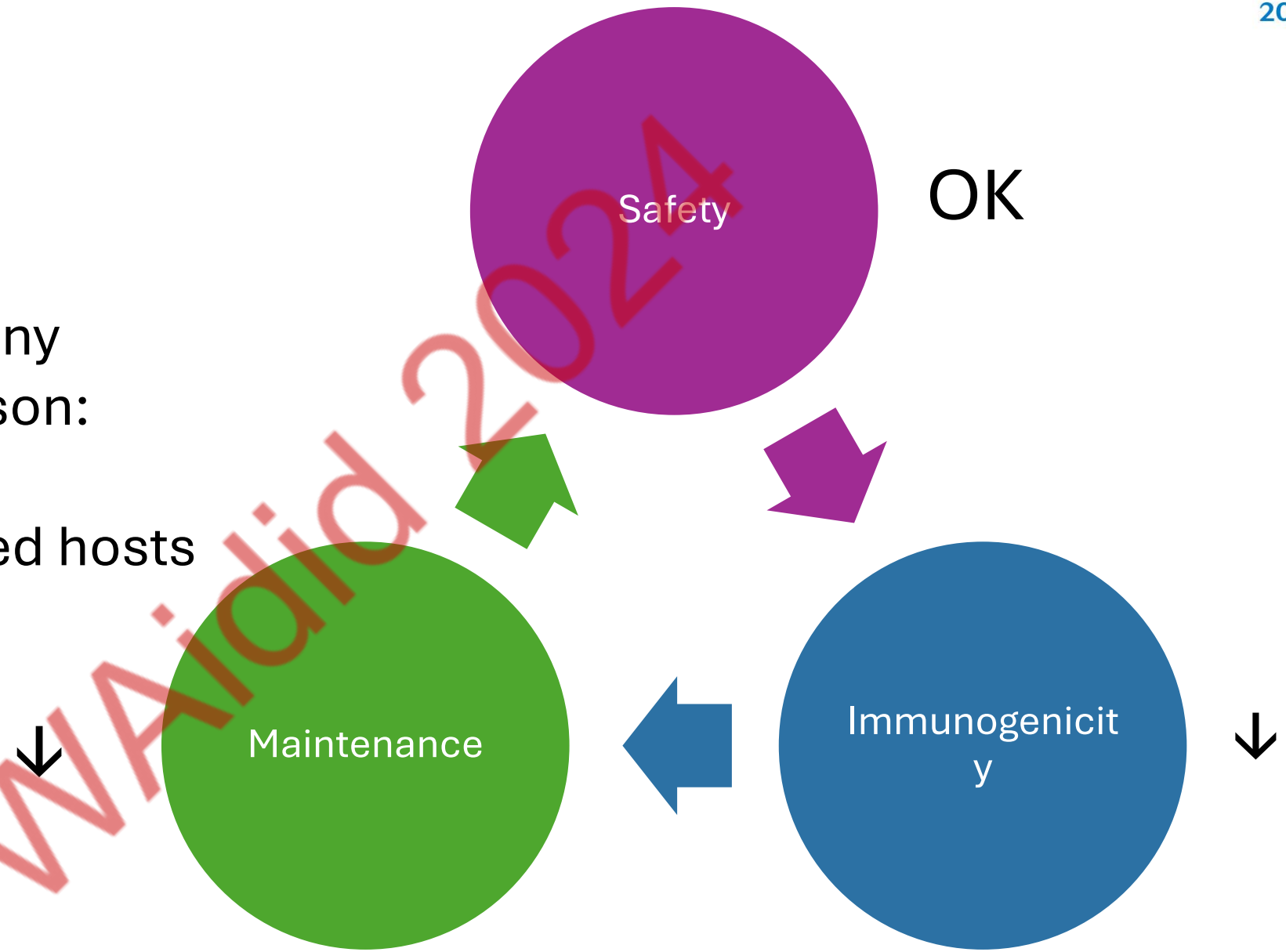
1. **Increase number of doses** for baseline vaccination:
   - HPV vaccine: 3 doses regardless of age
   - Additional COVID vaccines
   - Double dose pneumococcal vaccine (?)

2. **Increase dose of vaccine**: High-dose influenza vaccine

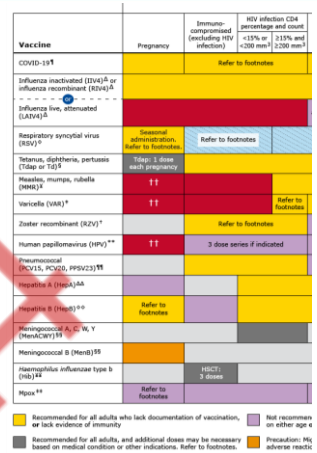
3. **Increase** numbe[illegible]oses by **giv**[illegible]**oosters** regularly: mostly [illegible]ines for wh[illegible]rotective levels are known & measurable

Rama N, NEJM 2021; Larsen L Vaccine 2022; Natori Y CID 2018

The 3 questions for any vaccine and any person: the answer for immunocompromised hosts



What can you do?



- Vaccinate whenever possible before immunosuppression is started
- Look for the latest guidelines for your population and the drugs used
- Ask for help from vaccine specialist
- Check seroresponses after vaccination and repeatedly afterwards

Bass AR Arthritis Care Res 2023; Danzinger-Isakov L AJT

Protective levels of Immunity

		No protection	Protection	Long-lasting protection
Tetanus	Anti-Te Toxoid (IU/l)	<100	≥100	≥1000
Haemophilus influenzae type b	Anti-PRP IgG (mg/l)	<0.15	>0.15	>1
Hepatitis B	Anti-HBs IgG (IU/l)	<10	≥10	≥100
Pneumococcus	Serotype specific IgG (mg/l)	<0.3	0.3-0.9	≥1
Measles	Measles IgG (EIA) (IU/l)	<50	50-149	≥150
Rubella	Rubella IgG (IU/ml)	<10	≥10	≥10
VZV	VZV IgG (gp-ELISA-test) (IU/l)	<50	≥50	≥150
Rabies	Rabies IgG (RFFIT-test) (IU/ml)	<0.5	≥0.5	≥0.5

Swiss Vaccination Recommendations 2024

Thank you very much!

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