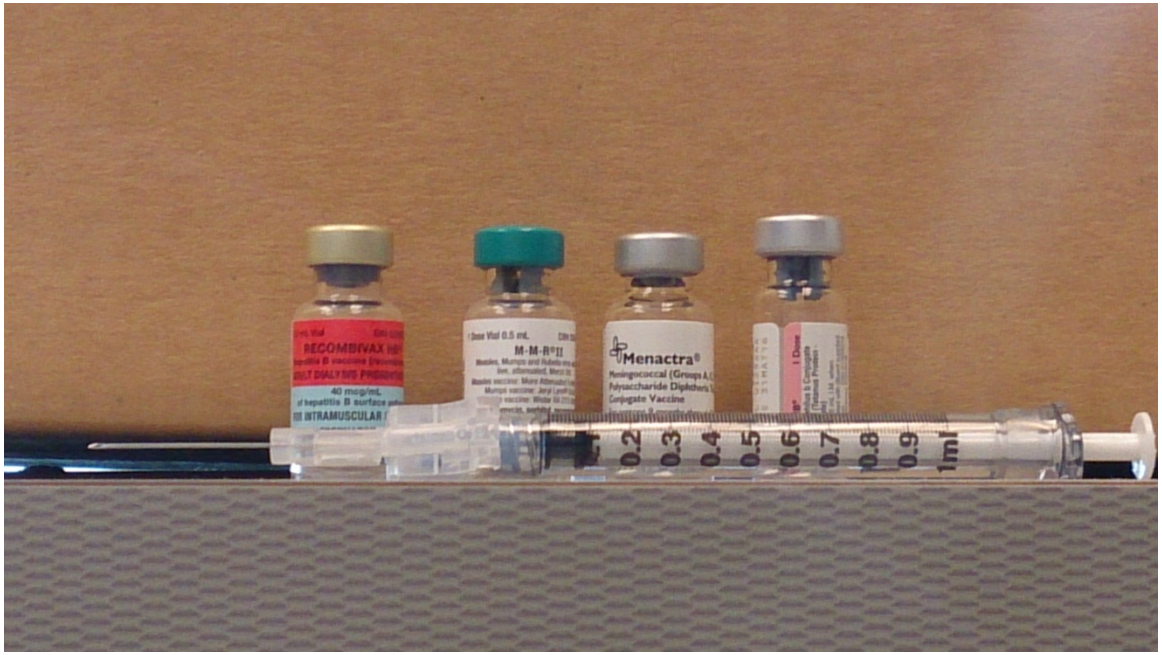
Immunizing Immunocompromised Adults



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Disclosure

- **Industry Funding: GSK, Roche**
- **Honoraria: Pfizer, Merck, Astellas**

Objectives

- Review the definition of ‘immunocompromised’ in context of vaccination
- Review the suggested vaccinations for various immunocompromised populations
- Be aware of updates to live vaccine recommendations for this population

Vaccine Classification

Live attenuated vaccines	*Inactivated vaccines*
Bacillus Calmette Guérin (BCG)	Diphtheria
Influenza - intranasal	Hemophilus influenza type B (protein conjugate)
Measles/mumps/rubella (MMR)	Hepatitis A
Polio - oral	Hepatitis B
Smallpox	Human Papilloma Virus (HPV)
Typhoid (oral)	Inactivated polio (IPV)
Varicella/ **Herpes Zoster**	Influenza
Yellow fever	Meningococcal
	Pertussis
	Pneumococcal (PCV13)
	Pneumococcal (PPV23)
	Rabies
	Tetanus*
	Typhoid - intramuscular

Vaccines for Adults (immune-competent)

Vaccine	Age 18-26 years	27-49 years	50-59 years	60 years	65 years and older
Td	1 dose every 10 years				
Tdap	1 dose				
Pneumo					1 dose
Zoster			1 dose	1 dose	
Influenza	Annually				Annually

*assuming immunized with HPV as children

Canada Immunization Guide, 2013

What makes up the Immune System?

- **Innate Immunity**
  - **Toll-like receptors**
  - **NK cells**
  - **Complement**
- **Adaptive Immunity (created by past experience with pathogens or vaccines)**
  - **Humoral**
    - **Immuneglobulins**
  - **Cellular**
    - **T-cells (CD4, CD8)**

•Needed to fight off a virus when re-exposed (natural infection or live virus by vaccine)
•Cellular immunity is most important for VZV

What is immune compromise?

- **Primary / Congenital**
  - **Several different types**
- **Acquired**
  - **HIV**
  - **Malignancy and chemotherapy (hematologic or solid)**
  - **Inflammatory disease treatment (Biologics for Rheumatologic disease; IBD)**
  - **Transplant (organ transplant, HSCT)**
  - **Corticosteroid use for various indications**

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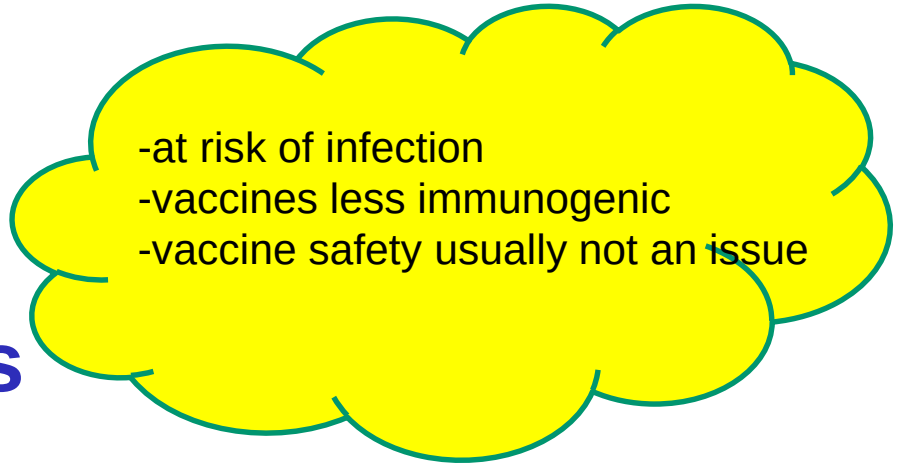
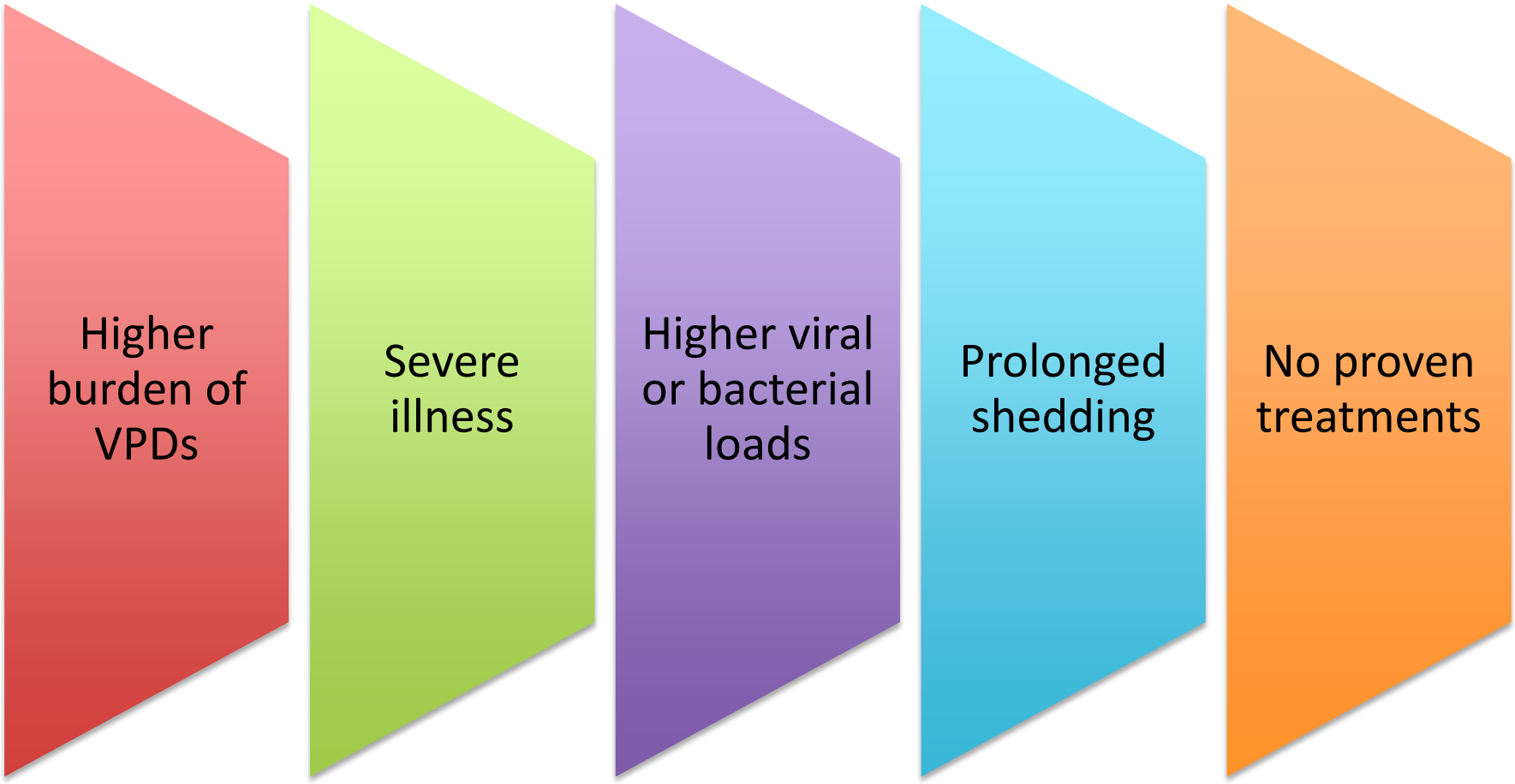
Immunodeficiency is a spectrum (things we don't always think of)

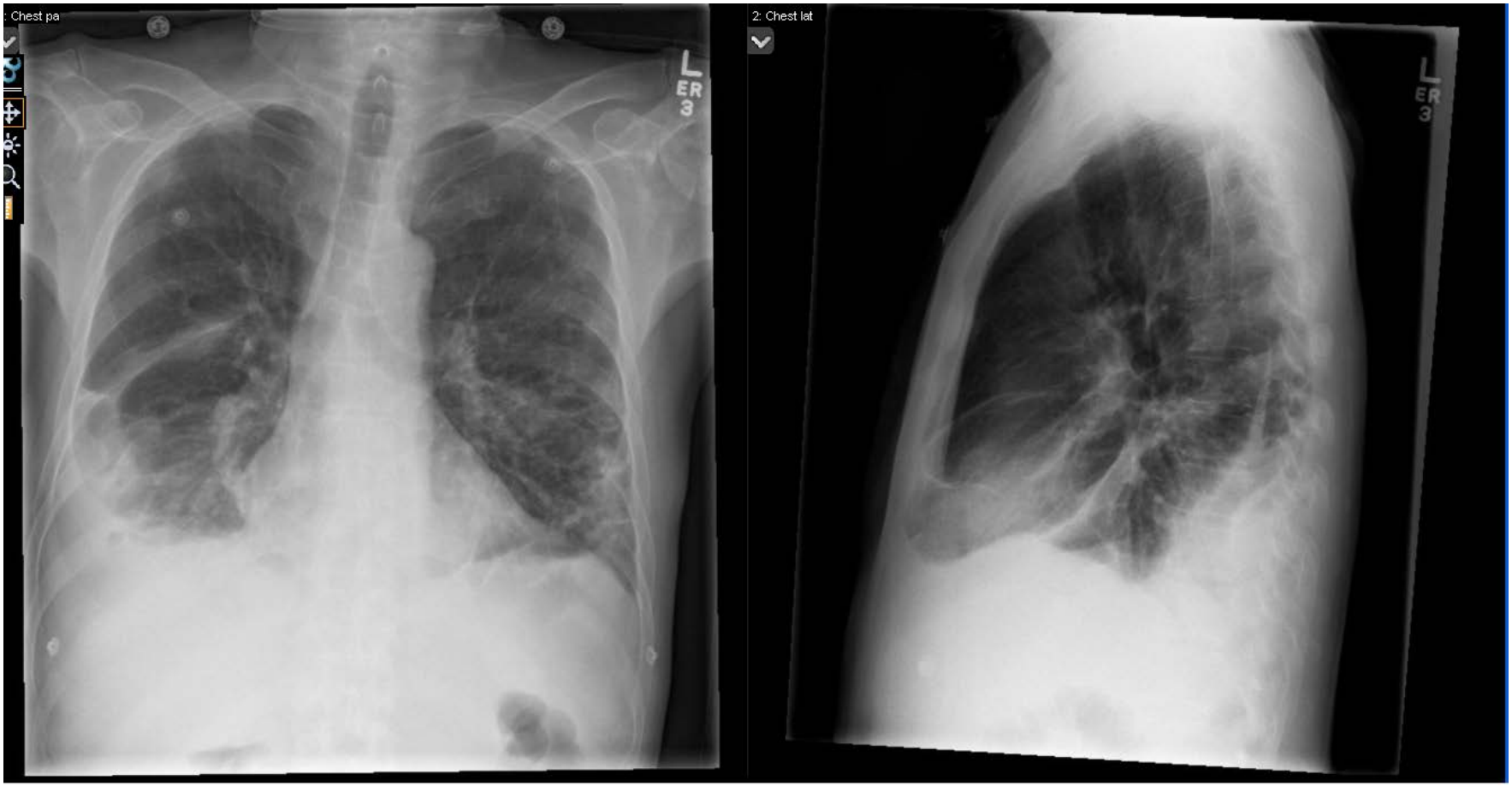
- **Malnutrition**
- **Aging/Elderly**
- **Chronic Diseases**
  - **Diabetes**
  - **Renal disease (CKI, dialysis, nephrotic syndrome)**
  - **Liver disease (cirrhosis)**
  - **Chronic heart disease (CHF)**
  - **Chronic Lung disease (COPD)**



Why are vaccines especially important for immune-compromised

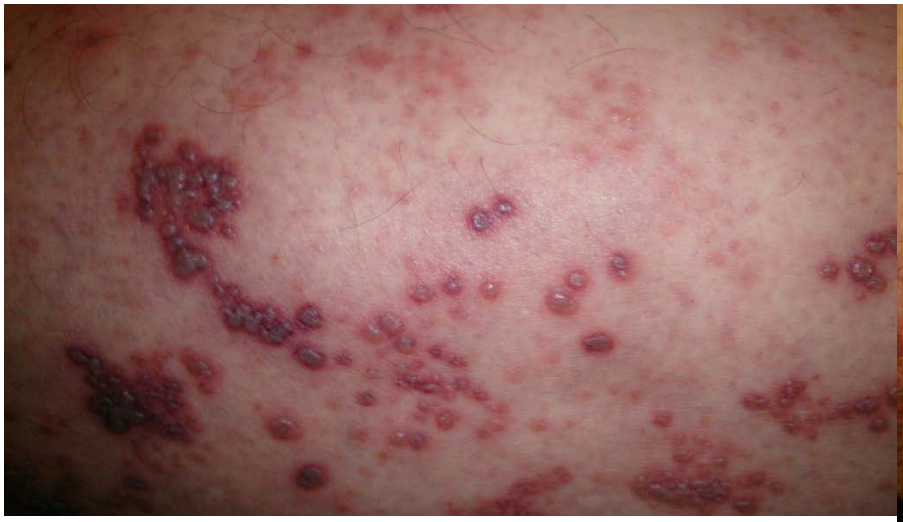


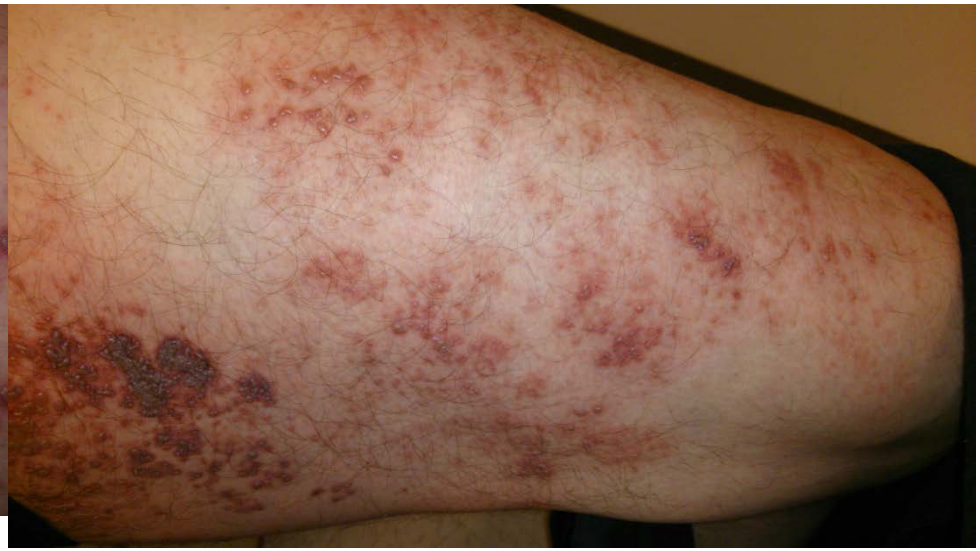
Pneumococcal pneumonia



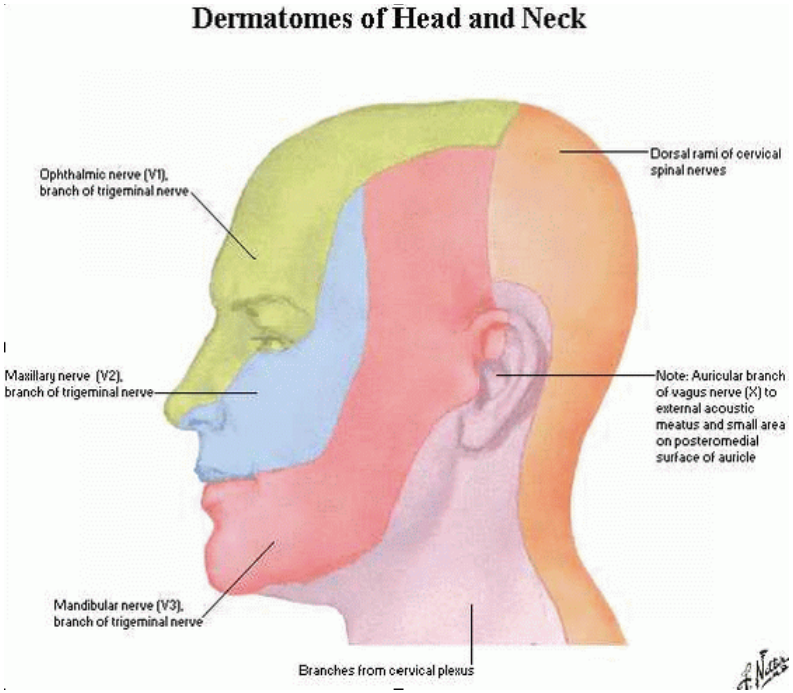
Herpes Zoster: Clinical Features

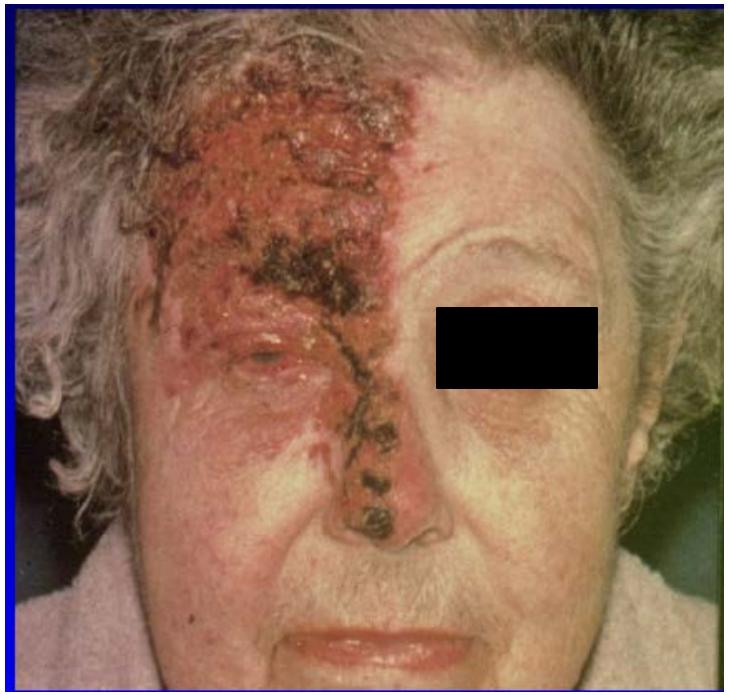
- Vesicles on erythematous base, usually in various stages (pustules, crusts)



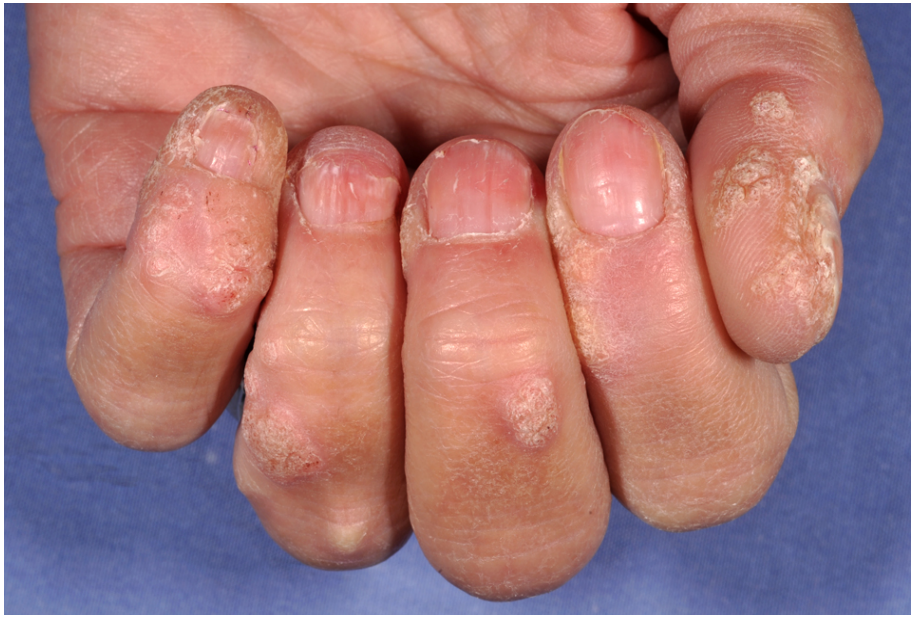


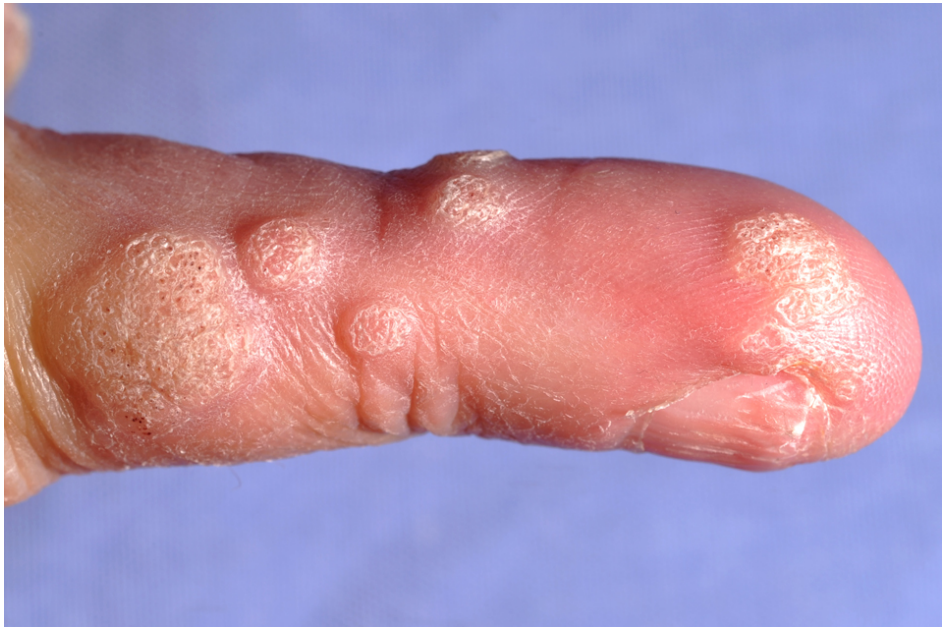
Herpes Zoster Ophthalmicus





Cutaneous HPV

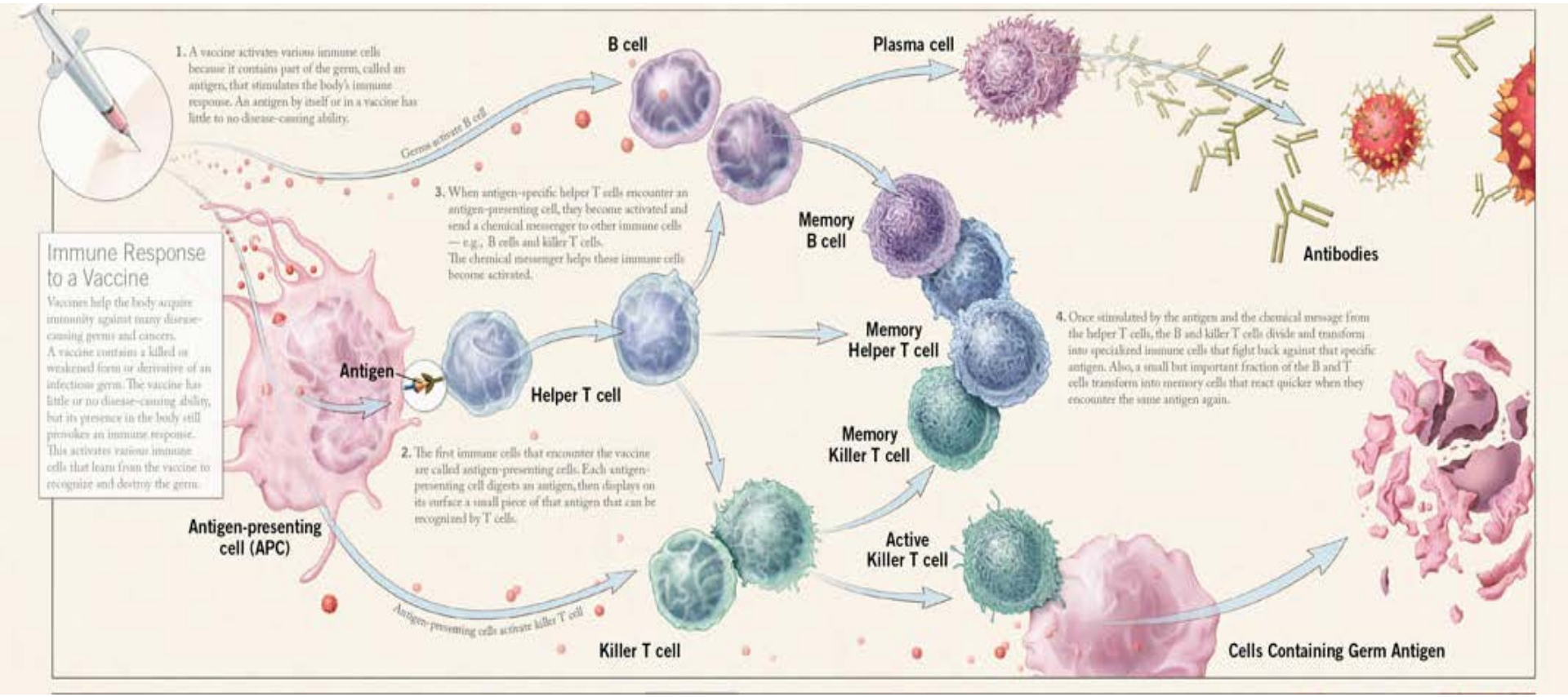




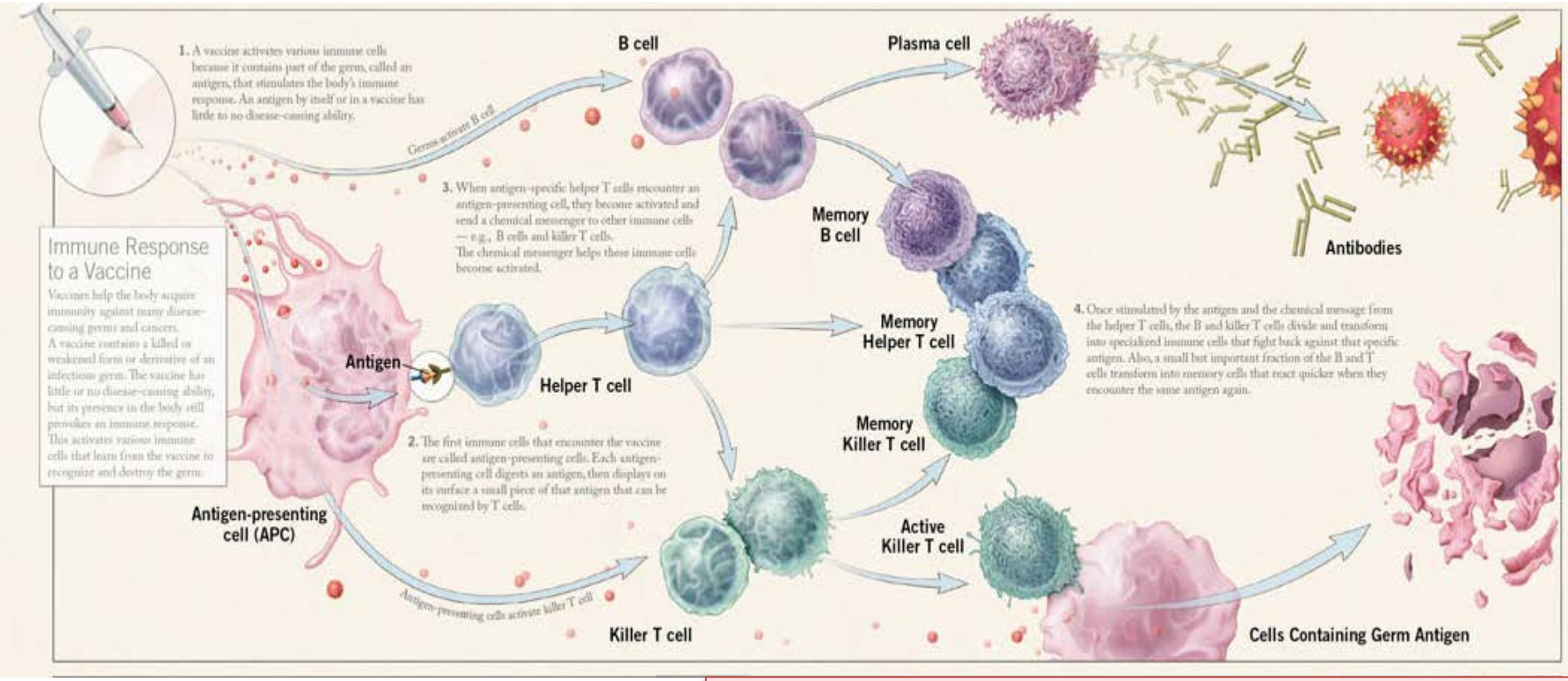
General Principles

- Immunosuppressed are at increased risk of vaccine preventable disease
- But...vaccines are not as immunogenic
- Timing is key!
  - Immunize prior to starting IS OR
  - At the point where IS will be the lowest
- Eg, before starting high dose steroids, when CD4>200 etc.

How Vaccines Work



Why vaccines don't work well in immunocompromised



Drugs that affect Antigen Presentation:
- Prednisone

Drugs that affect T-cells:
- Most chemotherapies for leukemia and lymphoma
- Anti-rejection / Anti-GVHD drugs for transplant

eg Thymoglobulin, MMF/Aza, cyclosporin/tac

Drugs that affect B-cells:
- Rituximab
- MMF / Azathiaprine

Conditions that affect T-cells:
- HIV/AIDS
- Leukemia / Lymphoma
- Transplant

HIV+ Persons

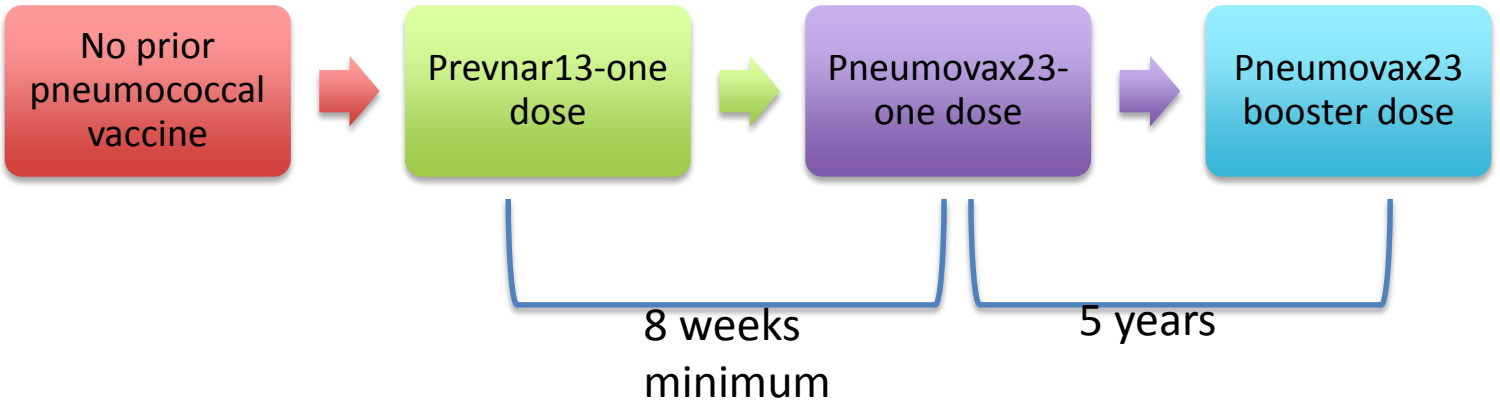
Vaccines for HIV+ Adults (as early in disease process as possible)	Influenza
	Hep A (MSM, drug use)
	HepB
	HPV (if not received in childhood)
	Pneumococcal
	Meningococcal (consider quadrivalent)
	TdaP booster

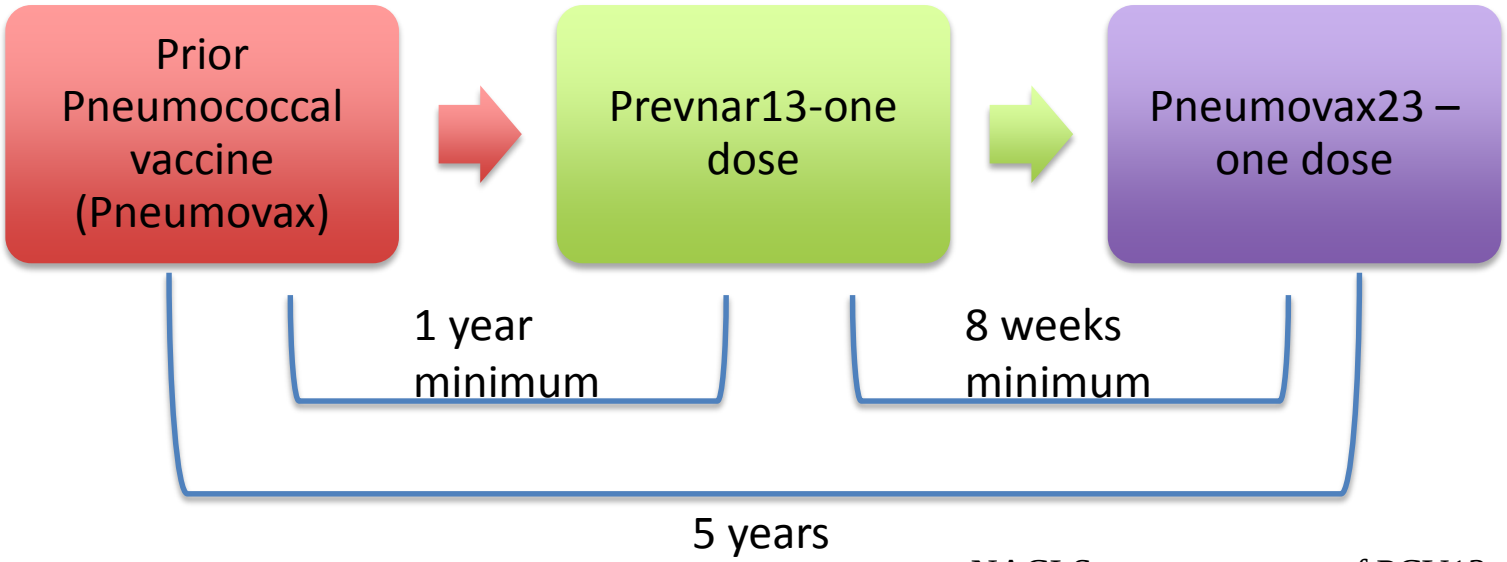
- **T-cell disorder; CD4<200 is immunocompromised**
- **Live vaccines: could be given if CD4≥200 but limited literature on safety if CD4<200**

Pneumococcal Vaccines

Polysaccharide (PPV23) Pneumovax	Conjugated (PCV13) Prevnar13
Available since 1980s	Available since 2000s
Covers 23 serotypes of pneumococcus (90%)	Covers 13 most common serotypes
T-cell independent – short lived antibody response, no memory	T-cell dependent – memory B cells and high avidity antibodies
No efficacy trials	Efficacy RCT (CaPITA) shows vaccine reduces IPD

Pneumococcal Vaccine Recommendations





NACI Statement on use of PCV13, CCDR, 2013

Persons with solid tumours

- A heterogeneous population
  - Patients in remission
  - Patients with active disease just pre- or post-chemotherapy
  - Patients with active disease that are on no chemotherapy (or palliative chemotx)

Is a patient with solid tumour immunocompromised?

Immunocompromised	Gray-zone	Immunocompetent
• Chemotherapy in the past 3 months	• Extensive active disease but no systemic therapy in the past 3 months • Consider life expectancy • Discuss risks/benefits with oncologist	• In remission • Limited disease • Limited radiotherapy

Breast, colon, lung, pancreas, liver, prostate etc

Solid Tumours

Vaccines for Adults with Solid Tumours	Influenza
	HepB
	HPV (if not received in childhood and in indicated age group)
	Pneumococcal
	TdaP booster
	Shingles (live) if not immunocompromised and in indicated age group

Is a patient with hematologic malignancy immunocompromised?

Immunocompromised	Gray-zone	Immunocompetent
• Active disease → all have cellular immune defects (B or T cell) • Chemotherapy for disease • Some disease may be active but not treated (eg low grade CLL)	• In remission < 5 years • Discuss risks/benefits with oncologist	• In remission for 5 years • No maintenance chemotherapy

Acute leukemia, Chronic leukemia, Myelodysplastic syndrome, Multiple Myeloma, Lymphoma

Hematologic Malignancy

Vaccines for Adults with Heme Malignancy	Influenza
	HepB
	Pneumococcal (PCV13-PPV23)
	TdaP booster
	Shingles (determine if immunecompetent and in indicated age group)

- Delay vaccination for patients undergoing intense chemotx (eg induction or consolidation for leukemia)
- For pts receiving Rituximab, defer vaccination till 6 months

Inflammatory Diseases

- IBD (Crohn's, Ulcerative colitis)
- Rheumatologic
  - SLE, Rheumatoid arthritis
- Therapies
  - TNF-α inhibitors (Etanercept, Infliximab) associated with viral reactivation
  - Non-TNF immunosuppression

Medications in Inflammatory conditions

TNF-α blockers (several)	Non-TNF immunosuppressives	Others
Adalimumab (Humira)	Azathioprine	Hydroxychloroquine (Plaquenil)
Etanercept (Enbrel)	Methotrexate	Sulfasalazine
Infliximab (Remicade)	Leflunomide	Auranofin (rarely used)
Golimumab (Simponi)	Abatacept	
Certolizumab (Cimzia)	Rituximab	

Vaccination

Summary of CRA Recommendations for Vaccination in Patients with RA (Recommendations 7-9)

	Inactivated/ Killed Vaccines			Live attenuated vaccines	
	Influenza *(annual)*	*Pneumococcal* *(booster after 3-5 years)*	*Hepatitis B*	*Herpes Zoster*	*Other*
Methotrexate*	✓	✓	✓ †	✓ ††	Caution
Leflunomide	✓	✓	✓ †	✓ ††	Caution
Sulfasalazine	✓	✓	✓ †	✓ ††	Caution
All biologics	✓	✓	✓ †	Avoid	Avoid

✓ Recommended; ideally administer prior to initiating therapy.

† Recommended in high-risk groups including residents, travelers or close contact with individuals from hepatitis B endemic areas, illicit drug users, persons engaging in risky sexual behaviors/history of STI, men who have sex with men, chronic liver disease, occupational exposures, frequent blood transfusions.

†† Recommended in RA patients > 60 years old.

* Methotrexate ≤ 25 mg per week.

Bombardier et al. The Journal of Rheumatology 2012; 39:8

Association Between Vaccination for Herpes Zoster and Risk of Herpes Zoster Infection Among Older Patients With Selected Immune-Mediated Diseases

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Fenglong Xie, MS
Elizabeth Delzell, ScD
Lang Chen, PhD
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James D. Lewis, MD, MSCE
Kenneth G. Saag, MD, MSc
John W. Baddley, MD, MSPH
Jeffrey R. Curtis, MD, MS, MPH

Context Based on limited data, the live attenuated herpes zoster (HZ) vaccine is contraindicated in patients taking anti–tumor necrosis factor (anti-TNF) therapies or other biologics commonly used to treat immune-mediated diseases. The safety and effectiveness of the vaccine are unclear for these patients.

Objective To examine the association between HZ vaccination and HZ incidence within and beyond 42 days after vaccination in patients with selected immune-mediated diseases and in relation to biologics and other therapies used to treat these conditions.

Design, Setting, and Patients Retrospective cohort study of 463 541 Medicare beneficiaries 60 years and older with rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, or inflammatory bowel disease using Medicare claims data from January 1, 2006, through December 31, 2009.

- >460,000 person retrospective Medicare cohort of patients >60 yrs with autoimmune conditions
- 4% received HZ vaccine and f/u 2 yrs
- 11.6 vs. 7.8 per 1000 py in unvaccinated vs. vaccinated

Zhang et al., JAMA 2012

Biologics and Zoster incidence

- 633 were on anti-TNF/biologics who were vaccinated (no cases of HZ in 6 wks post-vaccine)
- Those vaccinated (while receiving biologics +/- steroids) had a lower incidence of shingles

Table 3. Herpes Zoster Incidence Rate for Unvaccinated and After Vaccination[a]

	>42 Days Since Vaccination		Unvaccinated	
	HZ Cases, No.	HZ IR	HZ Cases, No.	HZ IR
Overall	138	6.7 (5.7-7.9)	9960	11.6 (11.4-11.9)
Medications, mutually exclusive groups[b]				
Biologics, regardless of concomitant DMARDs or oral glucocorticoids	14	8.5 (5.1-14.4)	1592	16.0 (15.2-16.8)
Anti-TNF therapies	12	8.5 (4.8-15.0)	1368	15.9 (15.1-16.8)
DMARDs, without biologics but regardless of oral glucocorticoids	25	7.0 (4.7-10.3)	2363	13.6 (13.1-14.2)
Oral glucocorticoids alone	21	10.3 (6.7-15.8)	2080	17.2 (16.5-17.9)

Abbreviation: DMARDs, disease-modifying antirheumatic drugs; HZ, herpes zoster; IR, incidence rate per 1,000 person-years; TNF, tumor necrosis factor.
[a] More than 42 days after vaccination.
[b] Classified using the following hierarchy: biologics with or without nonbiologic DMARDs or oral glucocorticoids; nonbiologic DMARDs with or without oral glucocorticoids; oral glucocorticoids only.

Zhang et al., JAMA 2012

Updated Canadian Recommendations (2014)

- **Herpes zoster vaccine is not indicated for persons with immune compromise including**
  - **Corticosteroids > 2mg/kg daily or >20mg/d**
  - **Chemotherapies**
  - **Transplantation**
  - **HIV**
- **HZ vaccine can be given to**
  - **Persons on low dose MTX / AZA / 6-MP for inflammatory conditions**
- **HZ vaccine can be considered for**
  - **Persons on biologics on a case-by-case basis**

Update on HZ vaccine, PHAC 2014

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy of an Adjuvanted Herpes Zoster Subunit Vaccine in Older Adults

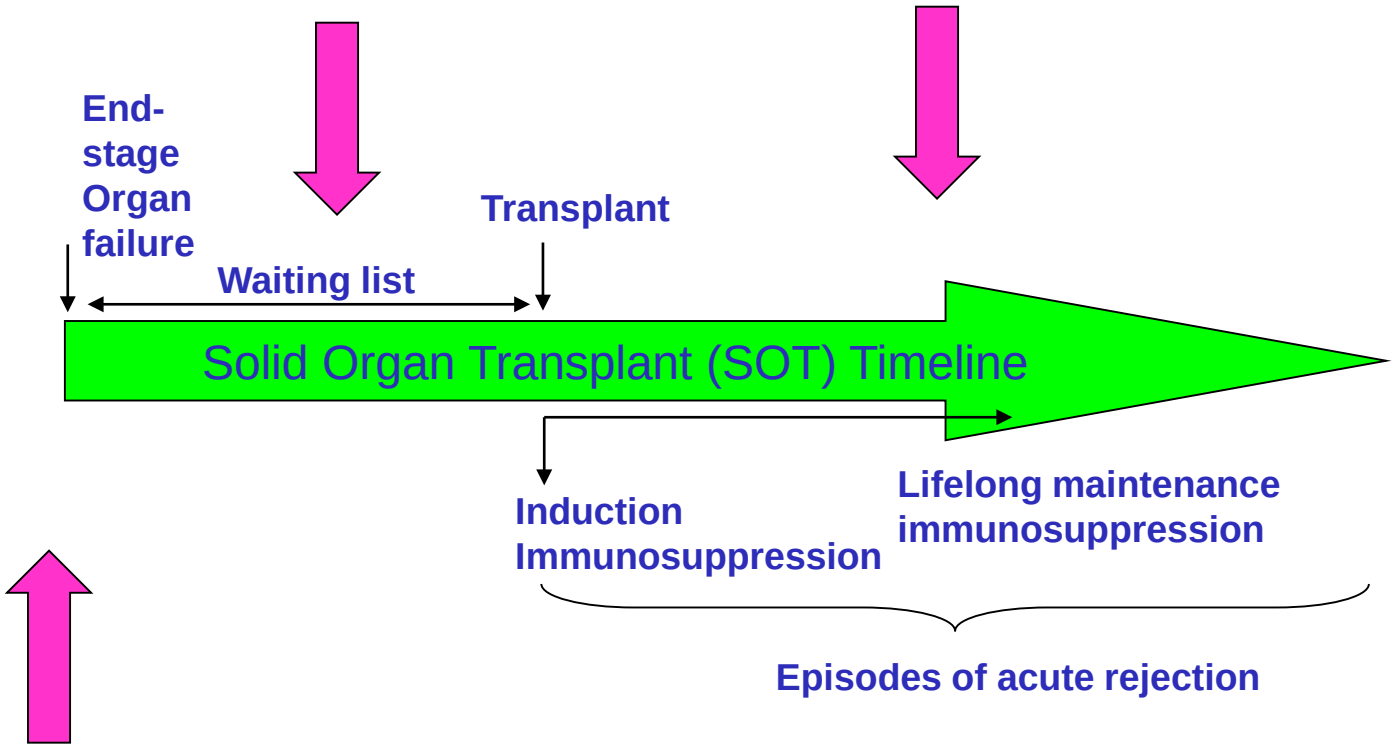
Himal Lal, M.D., Anthony L. Cunningham, M.B., B.S., M.D., Olivier Godeaux, M.D., Roman Chlibek, M.D., Ph.D., Javier Diez-Domingo, M.D., Ph.D., Shinn-Jang Hwang, M.D., Myron J. Levin, M.D., Janet E. McElhaney, M.D., Airi Poder, M.D., Joan Puig-Barberà, M.D., M.P.H., Ph.D., Timo Vesikari, M.D., Ph.D., Daisuke Watanabe, M.D., Ph.D., Lily Weckx, M.D., Ph.D., Toufik Zahaf, Ph.D., and Thomas C. Heineman, M.D., Ph.D., for the ZOE-50 Study Group*

- **Subunit inactivated vaccine based on gE glycoprotein of VZV**
- **>16,000 patients (age>50) in RCT (prior shingles excluded)**
- **Endpoint of confirmed herpes zoster**
- **VE = 97.2%**

Subunit gE-Adjuvanted Vaccine (inactivated)

Population	
Autologous HSCT (phase 1/2) Stadtmauer et al., Blood 2014	N=121 3-doses vaccine given at 0,1,3 months 50-70 days post-transplant
HIV (phase 1/2) Berkowitz et al., JID 2015	N=94 with CD4>=200 on ART N=14 with CD4 50-199 on ART N=15 with CD4>=500 with no ART 3-doses of vaccine at 0,2,6 months
Kidney Transplant (Phase 3) www.clinicaltrials.gov	2 doses at 0,1-2 months Safety and Immunogenicity
Leukemia/Lymphoma (Phase 3) www.clinicaltrials.gov	2 doses at 0,1-2 months Safety and Immunogenicity
Solid tumour pre-chemo and on chemo (Phase 3) www.clinicaltrials.gov	2 doses at 0,1-2 months Safety and Immunogenicity

Solid Organ Transplant Timeline (Kidney, Liver, Heart, Lung)



Immunization principles in SOT

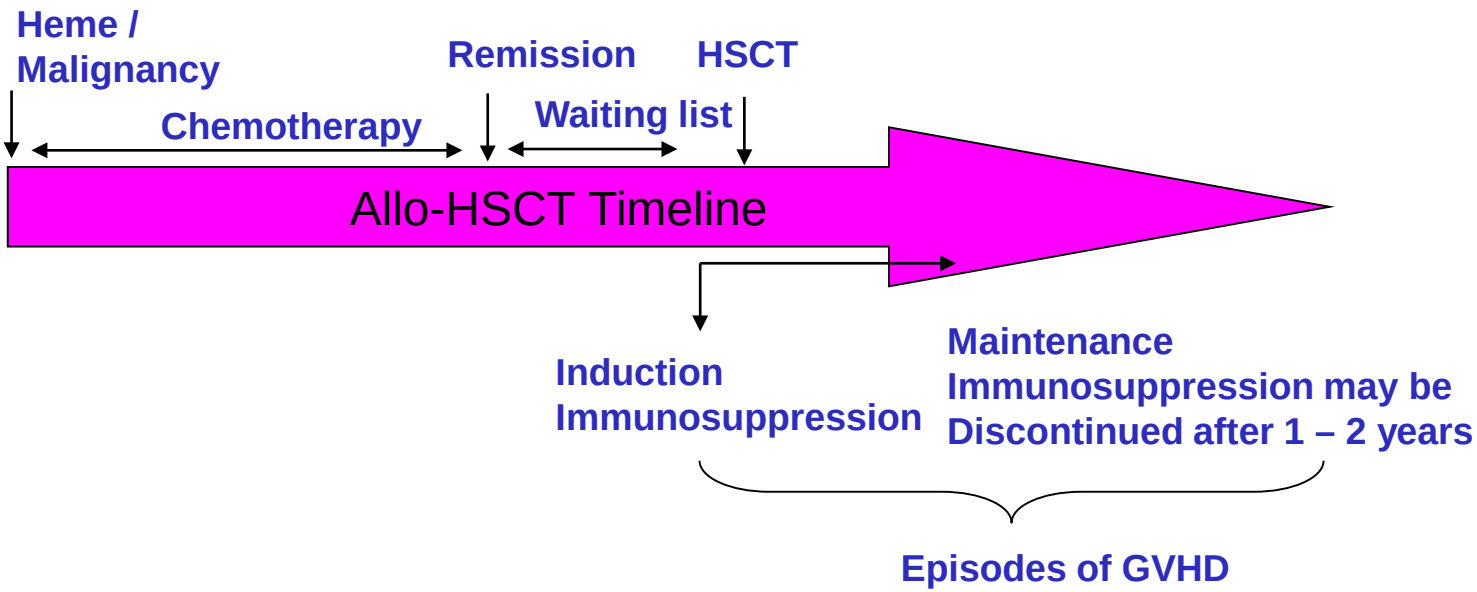
- When possible, vaccinate pre-transplant
- When giving live vaccines pre-tx (eg MMR, varicella, zoster), wait 4 wks to do translant
- Wait at least 3-6 months post-transplant to start immunization series (stable immunosuppression)
- Wait at least 1 month after rejection therapy (3 months after rituximab)
- Generally, no live vaccines post-transplant

SOT Guidelines for Routine Vaccination(2013)

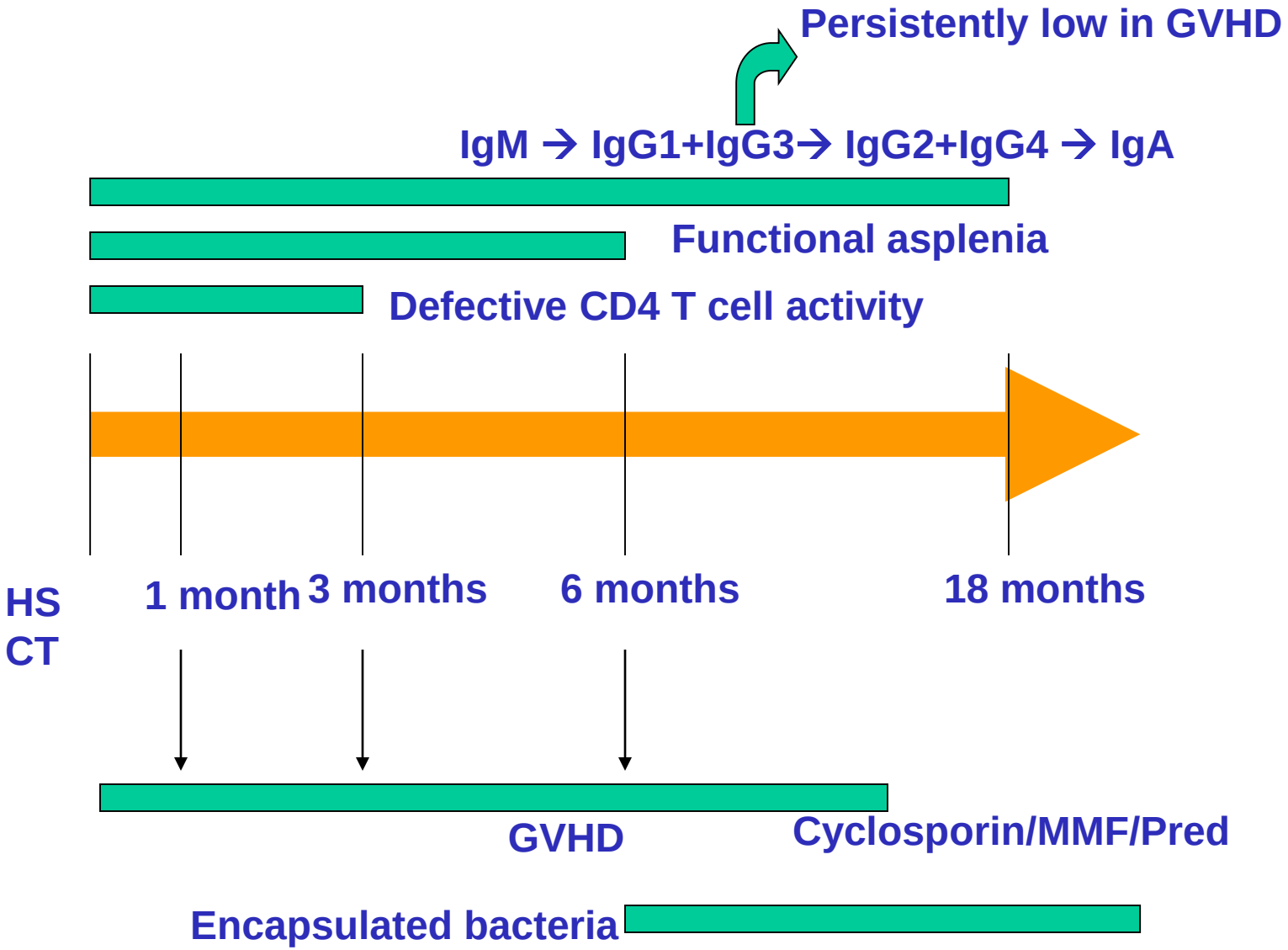
Vaccine	Pre-tx	Post-tx	
PCV13-PPV23	+	+	
HiB	+	+	
DTaP	+	+	
IPV	+	+	
HBV	+	+	
Influenza	+	+	≥ 3-6 mos
HPV	+	+	
Meningo-coccal	For special situations		
MMR	+	-	Wait 4 wks to tx
Varicella	+	-	Wait 4 wks to tx
Zostavax	+	-	

Danzinger-Isakov and Kumar, AJT 2013

Hematopoietic Stem Cell Transplant Timeline



HSCT Immune Reconstitution



Principles of Vaccination in HSCT

- Vaccination to begin no sooner than 3 months post-HSCT (pre-tx vaccination may help but can be logistically difficult)
- Multiple doses required
- No live vaccines early post-transplant
- Donor vaccination may help with certain vaccines (eg HiB, Td, HepB, PCV7)

Allo-HSCT vaccination

Vaccine	Recommendations
PCV13-PPV23	3-6 months post (3 doses PCV then PPV23 at 12 months)
HiB conjugate	6 months (3 doses)
Td	6 months
IPV	6 months
HBV	6 months (3 doses)
HPV	6 months (3 doses; age appropriate)
Meningococcal	6 months
Influenza	≥ 6 mos (as early as 4 months)

Live vaccine and Allo-HSCT

Live Vaccine	
MMR	24 months
Varicella	24 months

- Assess immunocompetence
- No GVHD
- Off immunosuppression
- IVIg can affect response to live vaccines

Auto-HSCT (PMH Expert Recs)

Vaccine	Allo	Auto
PCV-PPV23	3-6 months post (3 doses PCV then PPV23 at 12 months)	3 months 1 dose PCV then PPV23 at 6 months
HiB conjugate	6 months (3 doses)	3 months (1 dose)
Td	6 months	3 months
IPV	6 months	3 months
HBV	6 months (3 doses)	3 months (3 doses If serology negative)
HPV	6 months (3 doses; age appropriate)	3 months (3 doses)
Meningococcal	6 months (2 doses)	3 months (1 dose)
Influenza	≥ 6 mos (as early as 4 months)	3 months

- **Immunity is retained better after transplant**
- **No immunosuppression or GVHD**
- **Vaccines can start at 3 months post-transplant**
- **Live vaccines can be given at 1 year post-transplant**

Household Contacts of Immunocompromised patients

- HH contacts can receive all age appropriate vaccines
- MMR, varicella, zostavax, rotavirus can be administered to HH contacts (but not smallpox or oral polio)
- Varicella transmission is rare and usually when rash is present
- Wash hands after changing infant diaper
- LAIV can be administered to HH contacts (unless the immunocompromised person requires care in a protective environment)

ACIP general recommendations MMWR. 2011; 60(RR02):1-60.

For any person with immune compromise…

- Try to immunize prior to onset of IC state (if possible)
- Wait for 2-4 wks before starting immunosuppression
- Effectiveness of inactive vaccine will likely be less after onset of IC
- The only exception is HSCT where vaccines are given after transplant
- If ongoing immunosuppressed state, can’t give live vaccine (with some exception [zoster vaccine in inflammatory diseases])
- Almost all live vaccines can be given to close contacts

QUIZ!

Timing of Immunization

- **What is the best time to immunize (inactivated vaccine)?**
  - **Patient who will get a stem cell transplant in 2 weeks**
  - **Patient who is on maintenance daily chemotherapy for AML**
  - **Patient who received an auto-stem cell transplant for lymphoma 1 month ago**
  - **Patient who is receiving local radiation for prostate cancer**

Is this patient immunocompromised enough (live vaccine contraindicated)?

- **A) Patient who is 6 months after auto-stem cell transplant for myeloma**
- **B) Patient receiving local radiotherapy for breast cancer**
- **C) Patient with Chronic Lymphocytic Leukemia (on no chemotherapy)**
- **D) Patient who is 2 years post-stem cell transplant and on no immunosuppression with no GVHD**

True or False

- **A) Transplant patients should receive “dialysis-dose” hepatitis B vaccine**
- **B) Pneumococcal conjugate vaccine (Prevnar13) is recommended only for children**
- **C) HPV vaccine induces antibody against 9 different HPV types that cause cervical cancer or anogenital warts**
- **D) Influenza vaccine should be withheld if a patient receives chemotherapy during influenza season**

True or False

- **A) The best time to immunize (live or inactive vaccine) a patient waiting for a stem cell transplant is before their transplant**
- **B) It is OK to give Varicella vaccine to the child of an IC person.**
- **C) Two doses of HPV vaccine at 0,6 months can be used for immunocompromised persons**
- **D) It is OK to give LAIV to a needle-phobic HCW looking after a stem cell transplant patient requiring isolation.**

Thank you!

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