

BC Cancer's Family Practice Oncology Network

Immunization of Pediatric Oncology Patients

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Speaker Disclosures

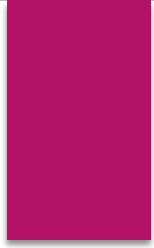
Advisory Board, Novartis (2020) – unrelated to current presentation

Objectives



- Apply guidelines for immunization after therapy
- Cite resources for vaccination information
- Relate the optimal timing for immunization in immune-compromised patients

Immune Response



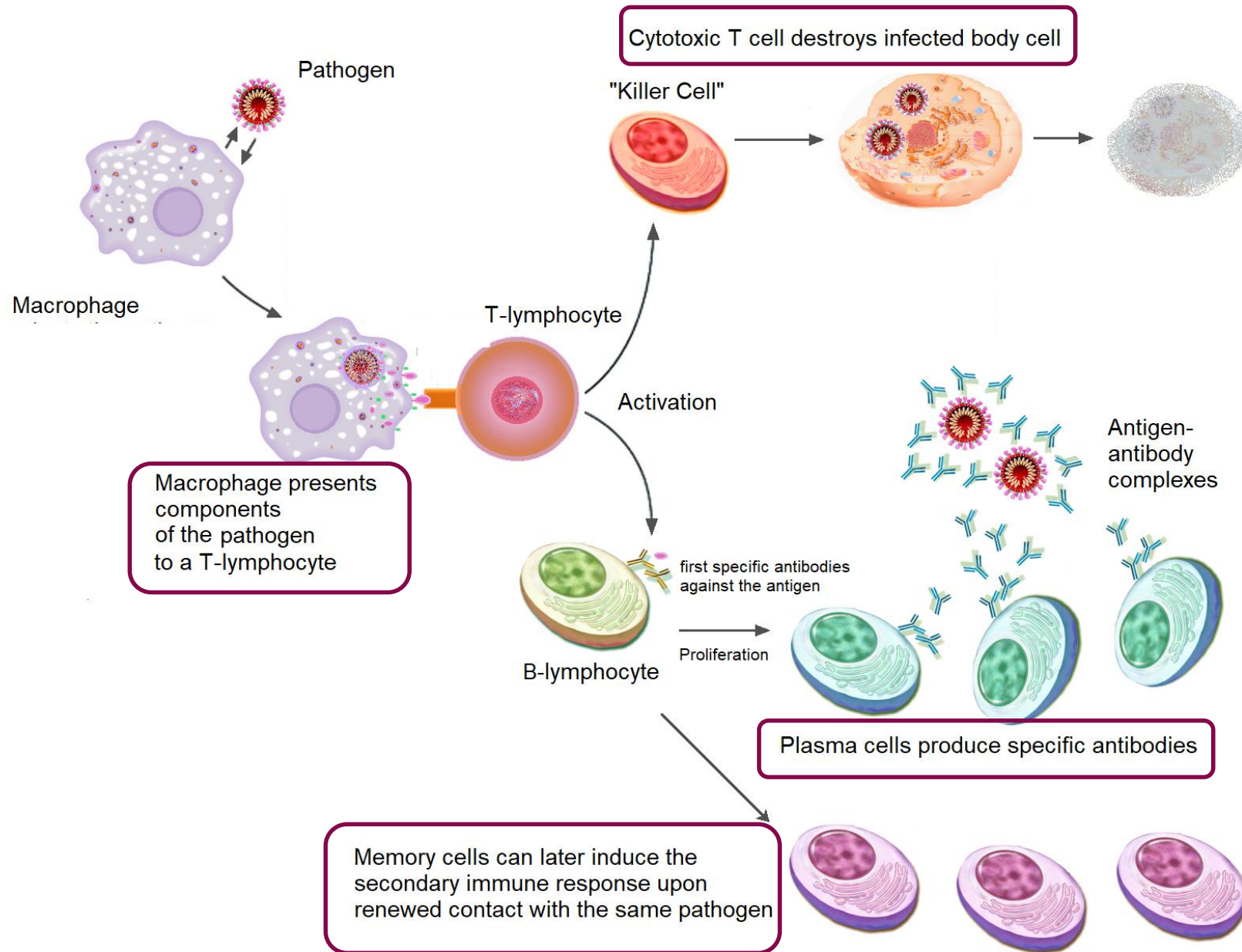
Immune Response

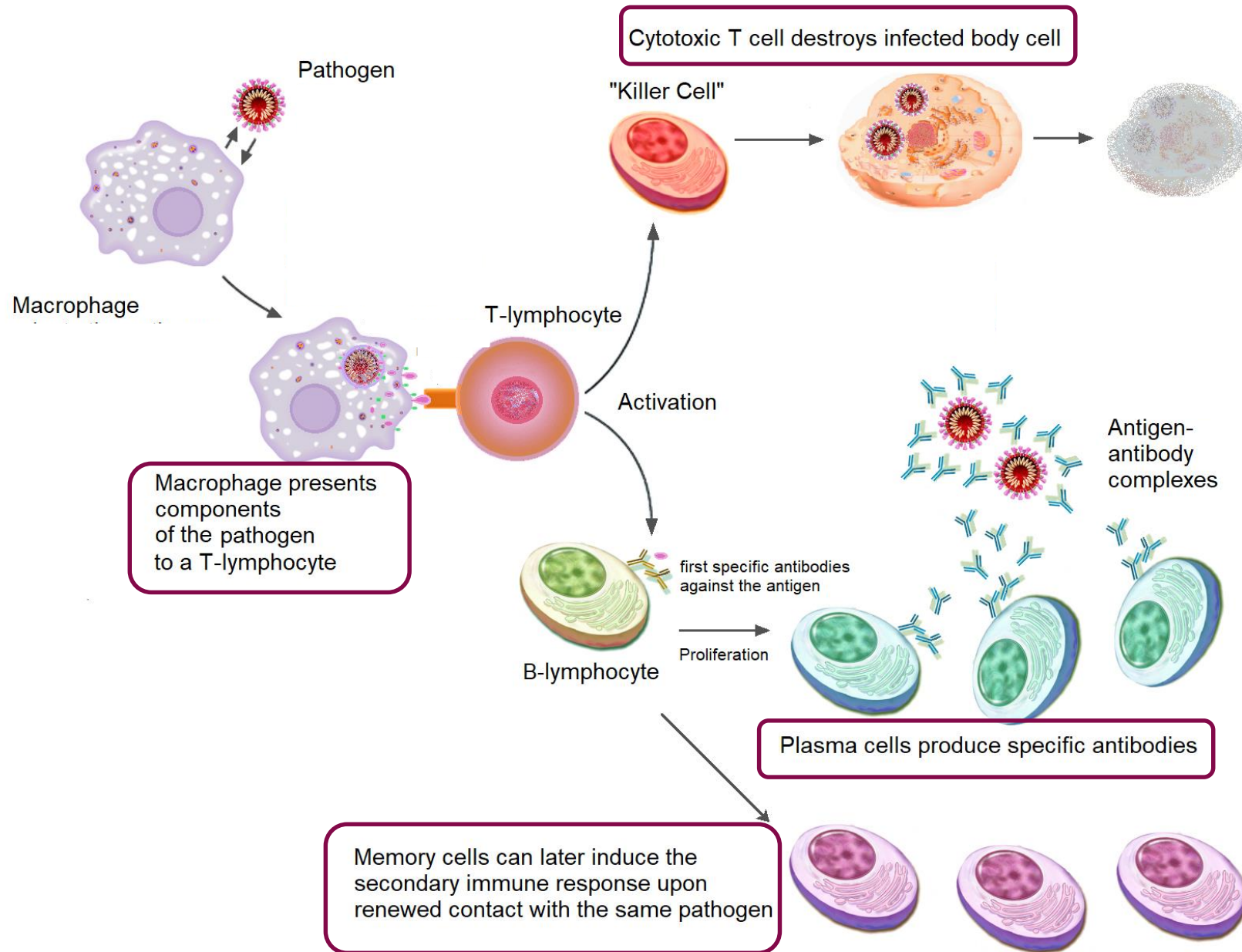
❑ Innate

- ❑ Hours
- ❑ Granulocytes (neutrophils, basophils, eosinophils), macrophages, dendritic cells, natural killer cells

❑ Adaptive

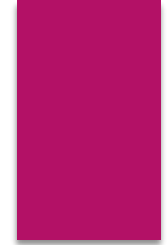
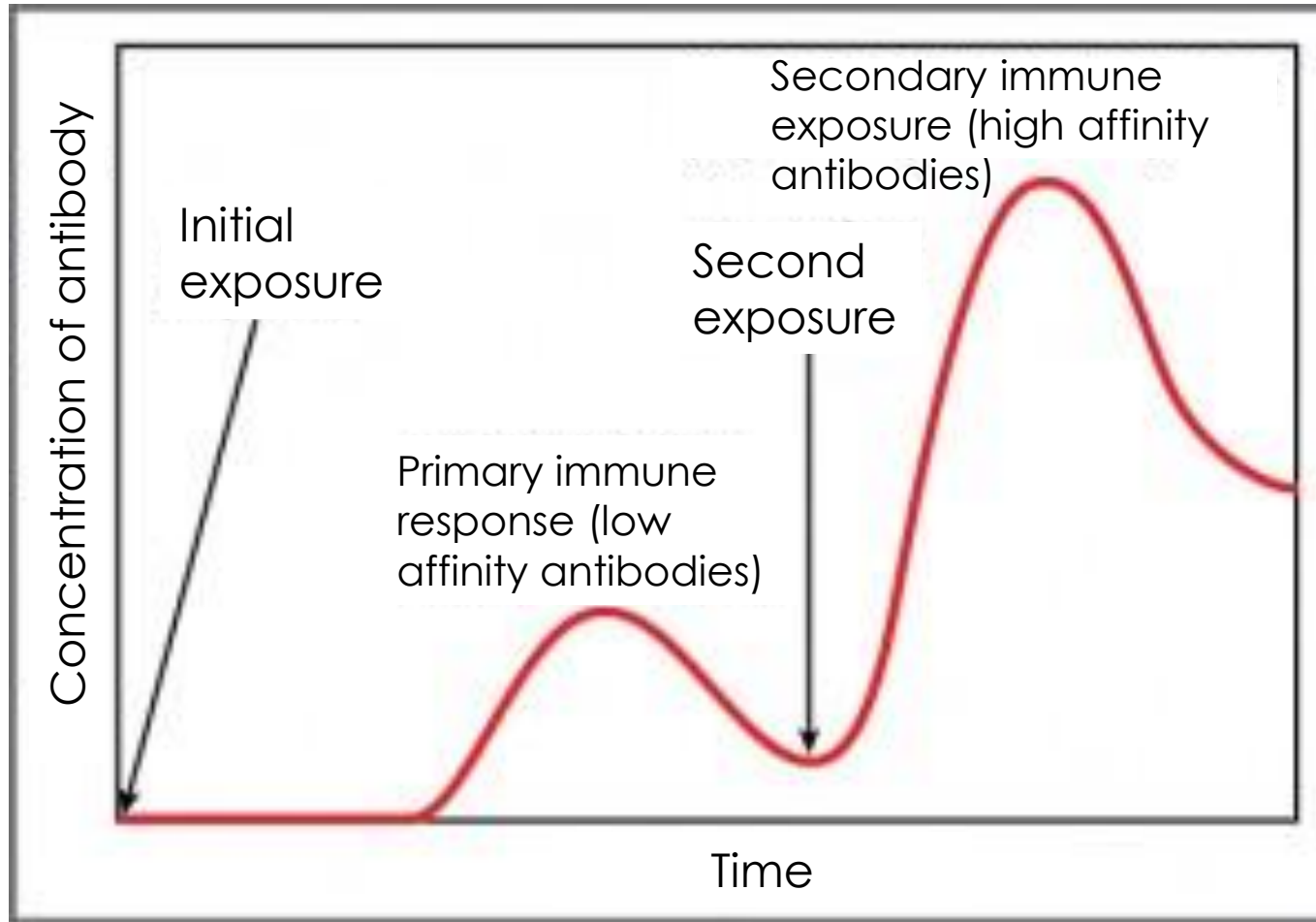
- ❑ Days (primary exposure), hours (secondary exposure)
- ❑ Lymphocytes
 - ❑ **Cellular** – helper and **cytotoxic T cells**
 - ❑ **Humoral** – helper T cells, **B-cells, antibodies**



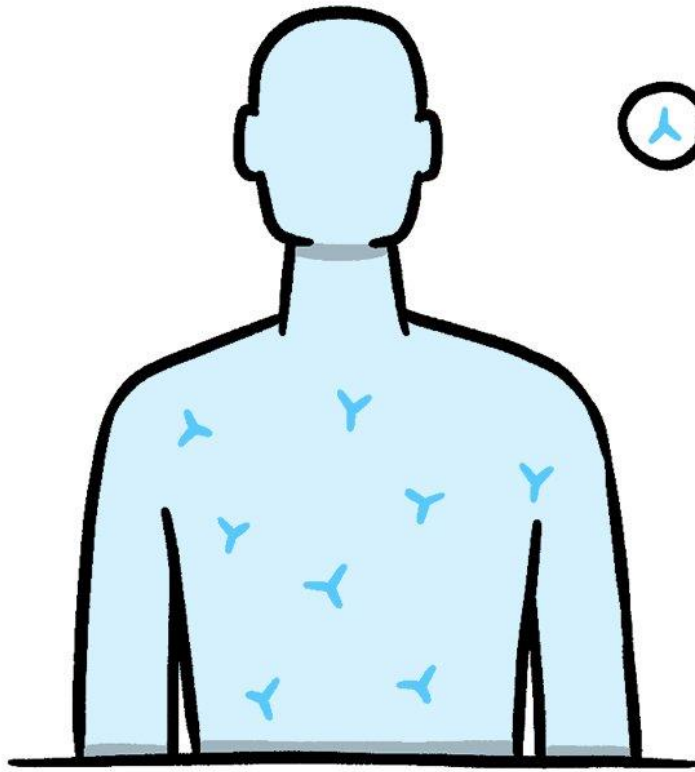


- **Viral**

- **Bacteria**
- **Viral**
- **Parasites**



Do people who've already had the virus still need to be vaccinated?

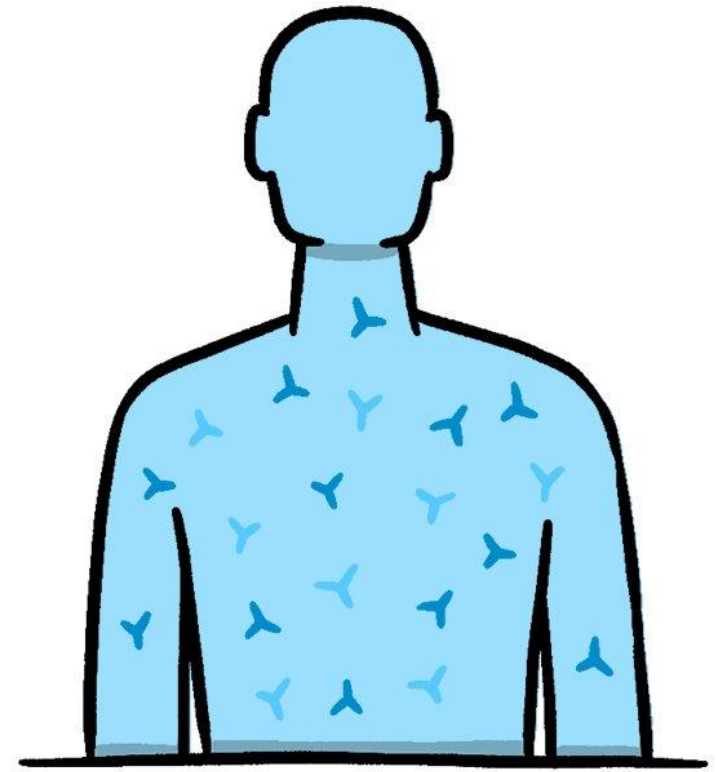


Natural Immunity



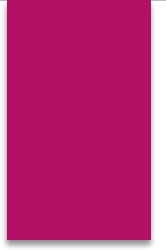
Immunity can weaken over time and be strengthened with vaccinations.

Even if a person has contracted and recovered from COVID-19, their immunity can be boosted by a vaccine.



Natural Immunity + Vaccine

BC Childhood Vaccinations



Other

- ❑ Rotavirus – 2, 4 months
- ❑ Hepatitis A – Indigenous children – age 6 and 18 months
- ❑ Influenza – annually, from 6 months of age
- ❑ SARS-CoV-2 – age 12 and above, 2 doses (as of Oct 2021)

Childhood Vaccinations - Organisms

- **Bacterial:** diphtheria, tetanus, pertussis, meningococcus, pneumococcus, haemophilus influenza type b
- **Viral:** polio, hepatitis B, measles, mumps, rubella, varicella, human papilloma virus, rotavirus, influenza, SARS-CoV-2

Live Attenuated Vaccines

- Derived from native viruses or bacteria
- Virulence is attenuated by repeated culturing
- Given to the patient in small doses

- After inoculation, pathogen replicates in vivo
 - Mild “infection” but risk of causing disease is very low*
 - Generates an immune response that is very similar to that of a natural infection, strong and often durable



<https://www.gadgetreview.com/how-to-jump-start-car-with-or-without-cables-another-car>

*** Except in when host immunity is weakened – disseminated vaccine strain infection**

Live Attenuated Vaccine - Examples

- MMR
 - Varicella
- } Relatively contraindicated during therapy, but have been given in select circumstances (ie. outbreaks/exposures)

- Rotavirus
 - BCG (Bacille Calmette-Guerin TB vaccine)
 - Typhoid
 - Yellow Fever
 - Live formulations of polio (oral), influenza (intranasal)
- } Absolutely contraindicated in those receiving chemo or immune suppression

Inactivated Vaccines



<https://www.hydro.com/en/aluminium/industries/automotive/body-in-white/>

- Do not replicate, cannot cause disease even in immunocompromised host
- Can safely be given to infants, immunocompromised, and immunosuppressed
- Immunity is not as robust or durable as live attenuated vaccinations
 - Sometimes first dose acts to prime, followed by boosters to generate immune response
 - Generates more humoral (antibody) than cellular immunity

Inactivated Vaccines - Examples

- Diphtheria, tetanus, H. flu, acellular pertussis, Hep B
- Meningococcal, Pneumococcal
- HPV
- Intramuscular versions of influenza, polio
- SARS-CoV-2

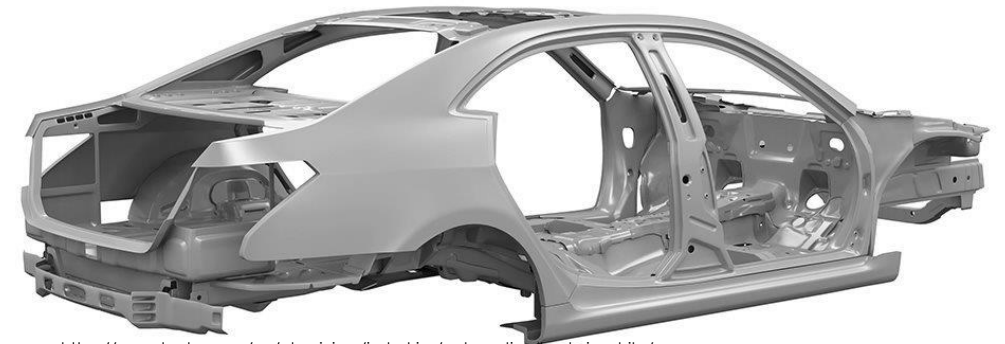
Immunizations during chemotherapy



<https://www.gadgetreview.com/how-to-jump-start-car-with-or-without-cables-another-car>

Live Attenuated Vaccine

- May generate immune response
- May not be safe!



<https://www.hydro.com/en/aluminium/industries/automotive/body-in-white/>

Inactive Vaccine

- Safe
- May not be very effective

Vaccinations in Oncology



Why is our Oncology population at risk?

Consequence of Therapy

- Chemotherapy – immunosuppressive, decreases durability of past vaccinations
- Hematopoietic Stem Cell Transplant (HSCT) – become immune naïve
- Radiation to the flank/spleen/marrow

Further at-risk populations

- Young children <5 years (ALL, neuroblastoma, Wilms tumour, hepatoblastoma, infant brain tumours, etc.)
 - Primary series often interrupted
 - Often very intensive myeloablative therapy
- Primary immunodeficiencies / Immune-dysregulated – immunosuppressive therapies or HSCT

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Waning Vaccine Immunity and Vaccination Responses in Children Treated for Acute Lymphoblastic Leukemia: A Canadian Immunization Research Network Study

Karina A. Top,¹ Wendy Vaudry,² Shaun K. Morris,³ Anne Pham-Huy,⁴ Jeffrey M. Pernica,⁵ Bruce Tapiéro,⁶ Soren Gantt,⁷ Victoria E. Price,⁸ S. Rod Rassekh,⁹ Lillian Sung,³ Athena McConnell,¹⁰ Earl Rubin,¹¹ Rupesh Chawla,¹² and Scott A. Halperin¹³

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i. Pediatric Acute Lymphoblastic Leukemia (ALL) versus Healthy Controls

- Non-protective or undetectable antibody levels in 1 or more antigens in nearly all ALL patients
 - Pertussis Toxin, Tetanus Toxin, varicella and *s. pneumoniae* immunity significantly lower in ALL patients ($P < .001$), regardless of vaccine history
 - 70% of ALL patients had seroprotective Tetanus antibody levels versus 100% of controls ($P < .001$)
- Suggestive of vulnerability to vaccine-preventable diseases following chemotherapy

ii. Pre and Post Chemotherapy, Waning Immunity

At diagnosis: 48 post-chemotherapy participants varicella seropositive at ALL diagnosis

Post Chemo:

- 11 (23%) remained varicella seropositive after chemotherapy
- 37 (77%) had indeterminate or negative serology

iii. Response to post-chemotherapy vaccination

Patient were vaccinated 4-12 months post-chemotherapy

- PCV13 and DTaP-IPV-Hib
- PPV23 two months later

- Response to all antigens increased at 2 months post-vaccination

- Remained significantly above baseline at 12 months ($p < 0.001$ for all antigens)

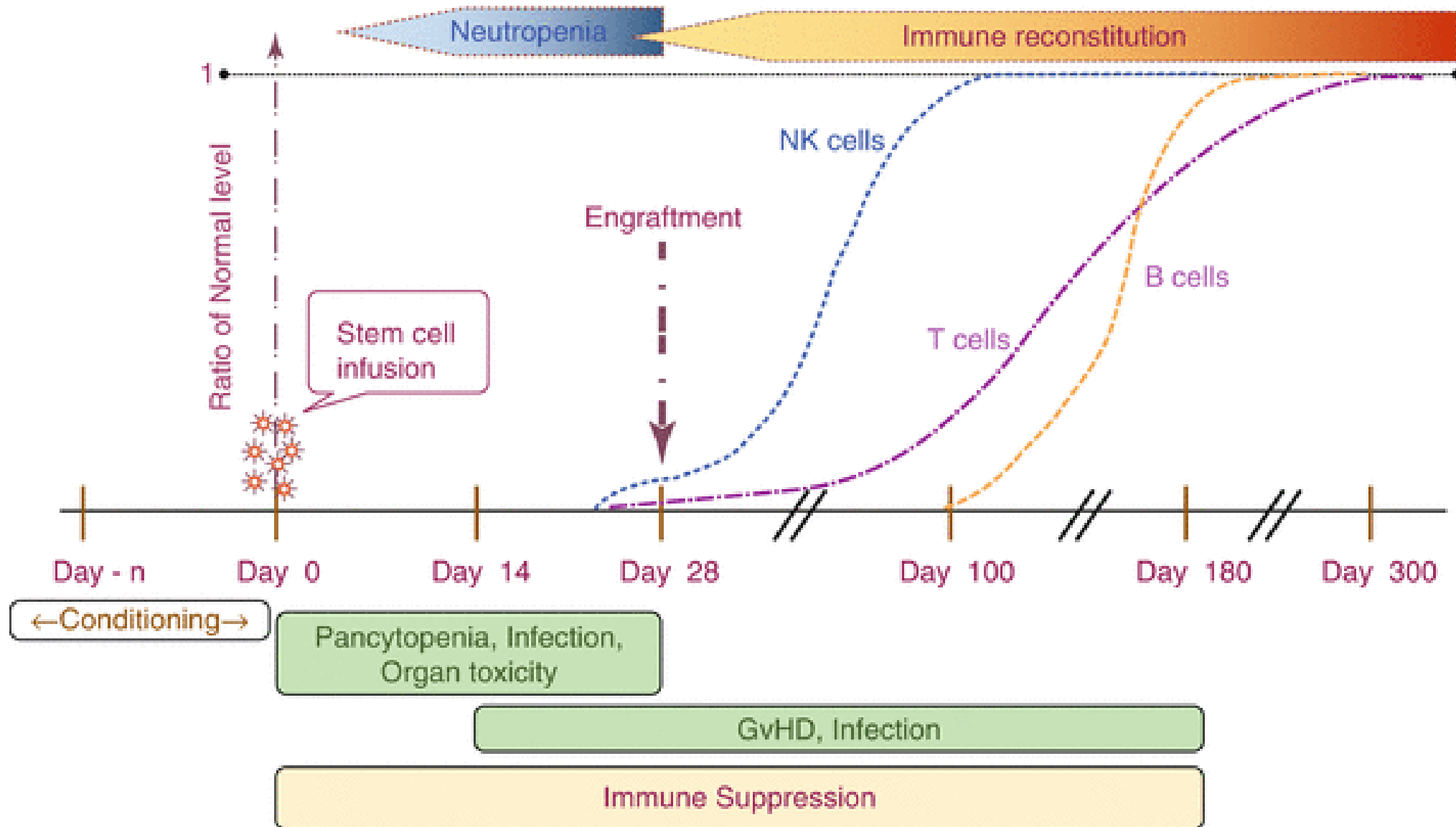
Agreement that post-therapy patients should be re-immunized

- How? When?
- No universal practice

Vaccine Timing – varies around the world

- North America
 - No sooner than 3 months post chemotherapy, 12 months post HSCT
- Europe
 - 6 months post chemotherapy or HSCT
- UK
 - 6 months post chemotherapy
 - Complete re-immunization 12 months post matched sibling HSCT and auto HSCT
 - Complete re-immunization 18 months post unrelated HSCT

Immune Reconstitution follow Hematopoietic Stem Cell Transplant





Local Practice: Vaccinations of BC
Pediatric Oncology Patients



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www.bccdc.ca/health-professionals/clinical-resources/communicable-disease-control-manual/immunization/immunization-of-special-populations

Part 2: Immunization of Special Populations

Part 2 of the BC Immunization Manual provides guidelines for the immunization of individuals at high risk for vaccine-preventable diseases.

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Immunocompromised Individuals

Immunocompromised individuals are unable to mount an adequate immune response. The cause of the altered immunocompetent state can be primary (inherited) or secondary (acquired) and it can be temporary or permanent.

A variety of conditions and treatments can affect the immune system of an individual, making them more vulnerable to a range of communicable diseases. These conditions include:

- Asplenia (functional or anatomic)
- Congenital immunodeficiencies involving any part of the immune system, including B-lymphocyte (humoral) immunity, T-lymphocyte (cell-mediated) immunity, complement system (properdin, or factor D deficiencies), or phagocytic functions
- Hematopoietic stem cell transplantation (HSCT)
- Human Immunodeficiency Virus infection (HIV)
- Immunosuppressive therapy including corticosteroids, chemotherapy, radiation therapy, post-organ-transplant therapy, certain anti-rheumatic drugs, and drugs used for the management of inflammatory bowel disease
- Islet cell transplant (candidate or recipient)
- Chronic kidney disease
- Chronic liver disease (including hepatitis B and C)
- Malignant neoplasms including leukemia and lymphoma
- Solid organ transplant (candidate or recipient)

Immunization of Pediatric (those under 18 years of age) Oncology Clients who have Completed Treatment, Including Autologous HSCT

- Routine immunization is suspended at diagnosis
- Decision to start immunization post-treatment is made by the Oncologist
- Incomplete primary series should be completed
- **Reimmunization Strategy**
 - i. Chemotherapy / immunosuppressive therapy / Auto HSCT
 - ii. Allogeneic Hematopoietic Stem Cell Transplant

Auto vs Allo HSCT

Autologous HSCT

- Stem cells collected from patient prior to high dose chemo/radiation
- Returned to patient as a “stem cell rescue” to repopulate myeloablated bone marrow
- Same immune system, no risk of GvHD, no immune suppression needed

Allogeneic HSCT

- Stem cells transplanted from Donor to Recipient
- Used to correct a hematopoietic defect, or generate Graft versus Leukemia effect (immune therapy)
- Regenerates a new Donor immune system within the Recipient
- Risk of Graft versus Host Disease (GvHD), immune suppression used until immune tolerance achieved

1. Post Chemotherapy / Immunosuppressive Therapy / Auto HSCT

Booster Vaccinations

Inactive Vaccines – 6 months post-therapy

- DTaP-HB-IPV-Hib
(diphtheria, tetanus, acellular pertussis, hep B, inactivated polio, h. flu)
- Men C, PCV 13
(meningococcal, pneumococcal)
- HPV, Hep A if applicable
(human papilloma virus)

Live Vaccines – 12 months post-therapy

- MMR
(measles, mumps, rubella)
- Varicella

2. Post Allogeneic Hematopoietic Stem Cell Transplant

- **Immune System is New!**
 - Much of the immune system must develop from graft CD34+ progenitor cells, requires education
- **Immune Dysfunction**
 - Alloreactivity between host and recipient (mismatch)
 - Graft versus Host Disease (GvHD)
- **Immune Suppression on board**

2. Post Allo HSCT

Particular Risks (pertaining to vaccination related organisms)

- ❑ Viral Reactivation – **varicella and herpes zoster**
 - Related to T cell reconstitution
 - Types of transplants are higher risk
 - Eg. T-cell deplete HSCT, cord blood transplants

- ❑ Splenic dysfunction – **encapsulated bacteria** (meningococcus, pneumococcus, Hib)

2. Post Allo HSCT

Full Reimmunization – entire series (*not just a booster*)

No active GvHD

Off immune suppression

- Can check for T & B lymphocyte subsets, IgG level

12 months post HSCT

- Inactive immunizations

24 months

- Live immunizations

3. Extended encapsulated bacteria prophylaxis

❑ Anatomic asplenia

❑ Functional asplenia

- Total Body Irradiation
- Radiation to spleen, left abdomen/flank
- Sickle cell disease
- Post-transplant patients with splenic dysfunction
- Chronic Graft versus Host disease

❑ PPV 23 (extended pneumococcal)

❑ Meningococcal quadrivalent
(extended meningococcal)

❑ Haemophilus influenza type b

- Complement inhibitor *Eculizumab* (paroxysmal nocturnal hemoglobinuria, Transplant-associated TMA, atypical HUS, etc.)

Meningococcal quadrivalent vaccination or empiric antibiotic prophylaxis for *Neisseria*

4. Household Members

- ❑ Ensure routine immunizations are up to date
- ❑ No contraindication to immunization
- ❑ Live Vaccinations:
 - Avoid Flu Mist (live intranasal), and oral polio (inactive formulation is fine)
 - No contraindication to MMR, as transmission via live viral shedding is low
 - Varicella
 - If vaccine recipient develops a rash within 42 days, cover lesions and minimize close contact with patient until rash resolves

Special Immunizations

**VACCINATIONS GIVEN
DURING THERAPY**

Influenza Annual Vaccination

❑ During chemotherapy

- ❑ Recommended at discretion of treating oncologist
- ❑ Non-live strain
- ❑ Absolute neutrophil count $\geq 0.5 \times 10^9/L$
- ❑ Ideally would have some circulating absolute lymphocyte count

❑ After chemotherapy

- Recommended

COVID 19 Vaccination

- ❑ **Age 12 and older, until age limit is lowered (as of Oct 2021)**
 - Recommended even during therapy, 2 (and if eligible 3) doses
 - Discuss timing with primary oncologist

- ❑ **Post HSCT**
 - Recommended sooner than other vaccinations, ideally ≥ 3 months post-HSCT
 - May delay while on intensive immune suppression

COVID 19 Vaccination

❑ Post B-cell directed therapy (CD19, CD20, CD22)

E.g. rituximab, blinatumomab, inotuzumab, CAR T cells

- Recommended at the discretion of treating physician. Ideally would have some evidence of circulating B-cells, but would not delay if reconstitution is protracted
- 3rd dose particularly recommended

Cell Therapy Transplant Canada (CTTC) Position Statement on COVID 19 vaccinations:



www.cttcanada.org/resource/resmgr/covid-19__2020-2021_/cttc_vaccine_rev24aug2021.pdf

Pegylated asparaginase anaphylaxis and COVID 19 Vaccination

www.hematology.org/covid-19/covid-19-and-pediatric-all:

- ❑ Both the Pfizer and Moderna vaccines contain elements of a form of polyethylene glycol (PEG), PEG2000 that is slightly different than the PEG that is conjugated to asparaginase (PEG5000).
- ❑ For patients who have had serious anaphylaxis to a dose of PEG-asparaginase, we would recommend skin testing such patients to PEG and if not tolerated, would advise against receiving the mRNA vaccines.
- ❑ It would be reasonable to proceed with the vaccine per local guidelines if patients had mild reactions to PEG-asparaginase and had tolerated other medications containing PEG (laxatives, pegylated G-CSF, some cosmetics and skin care products, etc).



How to vaccinate your post-treatment patients

Sections



Individuals at high risk for vaccine-preventable diseases (overview)	+
Immunocompromised individuals (general information)	+
Referral forms	-
<ul style="list-style-type: none">• Referral Form for Varicella Vaccination• Referral Form for MMR Vaccination• Referral Form for Rotavirus Vaccination• Referral Form for Live Attenuated Influenza Vaccination	
Specific immunocompromising conditions	+
Other high risk conditions	+
Select populations	+

Date:

YYYY/MM/DD

MMR VACCINATION OF IMMUNOCOMPROMISED CLIENTS REQUIRES PHYSICIAN OR NURSE PRACTITIONER APPROVAL: the primary care physician, medical specialist or nurse practitioner most familiar with the client's current medical status.

CLIENT INFORMATION

Name:

Last

First

DOB:

YYYY/MM/DD

PHN:

MMR vaccine is available for susceptible immunocompromised clients listed below.

Check the appropriate box for your client:

- HSCT recipient ≥ 2 years post-transplant (provided there is no GVHD, immunosuppression has been discontinued for at least 3 months, and the client is deemed immunocompetent by a transplant specialist).
- Pediatric oncology treatment, including autologous HSCT (12 months after discontinuation of therapy).
- Acute lymphocytic leukemia in remission for at least 12 months (total lymphocyte count must be $\geq 1.2 \times 10^9/L$), and client **not** receiving radiation therapy at the time of immunization. If client is still receiving maintenance chemotherapy, it should be withheld for at least 1 week before to 1 week after immunization.
- Chronic Kidney Disease/Dialysis
- Solid Organ Transplant Candidate: complete MMR at least 4 weeks prior to transplantation.
- Asplenia/Hyposplenia (congenital, surgical removal or functional)
- Adults who are no longer immunocompromised due to malignant disease **and** ≥ 3 months after completion of immunosuppressive treatment [≥ 6 months if treated with anti-B-cell antibodies (e.g., rituximab)], not including SOT or HSCT recipients.
- ≥ 1 month after completion of high dose (≥ 2 mg/kg or ≥ 20 mg daily) oral corticosteroid therapy ≥ 14 days duration.
- ≥ 3 months after completion of immunosuppressive therapy [≥ 6 months if treated with anti-B-cell antibodies (e.g., rituximab)].
- Isolated immunodeficiencies:
 - Humoral (Ig) deficiency diseases
 - Neutrophil deficiency diseases
 - Complement deficiency diseases
- Other (specify): _____
- HIV-infected client, by age group ^A

Immunologic category	<12 months		1-5 years		≥ 6 years	
	CD4+ T-lymphocyte counts ($\times 10^6/L$)	Percent (%) of total lymphocytes	CD4+ T-lymphocyte counts ($\times 10^6/L$)	Percent (%) of total lymphocytes	CD4+ T-lymphocyte counts ($\times 10^6/L$)	Percent (%) of total lymphocytes
1	$\geq 1,500$	≥ 34	≥ 1000	≥ 30	≥ 500	≥ 26
2	750-1,499	26-33	500-999	22-29	200-499	14-25

PHYSICIAN OR NURSE PRACTITIONER APPROVAL IS REQUIRED FOR LIVE VACCINES: the primary care physician, medical specialist or nurse practitioner most familiar with the client's current medical status.

CLIENT INFORMATION

Name:		
	<i>Last</i>	<i>First</i>
DOB:		PHN:
	<i>YYYY/MM/DD</i>	

**To be completed by physician or nurse practitioner and sent to Public Health Nurse.
Must be renewed after 4 months.**

I have verified on (YYYY/MM/DD) _____, this client has no medical contraindications to the receipt of live attenuated MMR vaccine. I understand that individuals may require up to 2 doses given up to 3 months apart, and verify that this client's condition is sufficiently stable to permit receipt of 2 doses, during a period of 4 months from the date above.

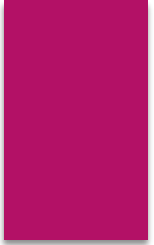
Signature:		Clinic:	
Phone #:		Fax #:	

To be completed by Public Health Nurse and returned to physician or nurse practitioner.

Public Health Nurse Name:			
Phone #:		Fax #:	

MMR Vaccine (2 doses, if indicated):

Date:		Lot #:		Site:	
Date:		Lot #:		Site:	



- **Once signed, is valid for 4 months**
- **Separate forms for each of MMR, varicella, and inactive vaccines**

Where?

- Public Health Nurse
- BC Children's Hospital Family Immunization Clinic

Family Immunization Clinic
Ambulatory Care Building (Main Level, Entrance 21)
4480 Oak Street, Vancouver BC V6H 3V4
Clinic phone: 604-875-3000
Clinic fax: 604-875-2311
FamilyImmunizationClinic@cw.bc.ca

Regular Clinic hours: Monday - Friday, 8:30 am - 4:30 pm

Dr. Manish Sadarangani
Dr. Jane Finlay



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Thank you

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