LYMPHOMA SUPPORT GROUP OF OTTAWA

October 4, 2022

COVID-19 AND PATIENTS WITH COMPROMISED IMMUNE SYSTEMS

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Disclosures

- No conflicts of interest pertaining to this talk
  - *I have received honorariums for speaking engagements (Pfizer)*

- Relevant to this talk: Nominated PI on the VIP Study

Introduction

- In this presentation
  - *You will see a mix of*
    - Recommendations from Public Health, Scientific Panels and Immunization Authorities
      - *Including relevant slides available publicly*
    - Recommendations put out by specialist organizations
    - Data from peer reviewed publications, including systematic review & meta-analysis
  - *You may see several slides on my own research project, The VIP Study*
- Time for questions at the end

Overview

- Part 1: Vaccines
  - *Quick introduction to vaccines*
  - *COVID-19 vaccines in patients with blood cancers*
  - *Review regarding recommendations for primary series & boosters*
- Part 2: Non-Vaccine Prevention
  - *Monoclonal Antibodies*
  - *NPIs*
- Part 3: Treatment
  - *Current management of patients with COVID-19 Infection*
- Question Period

PART 1: VACCINES

Basics of Vaccines

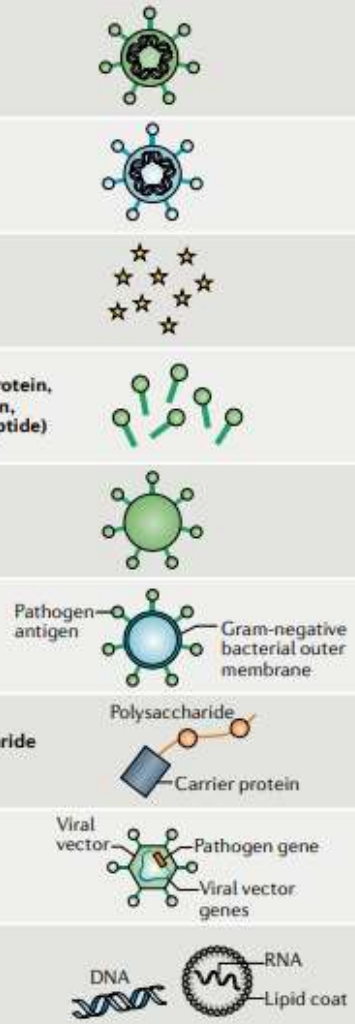

A guide to vaccinology: from basic principles to new developments

Andrew J. Pollard[1,2] and Else M. Bijker[1,2]

- Vaccine – biological product that can be used to safely induce an immune response that confers protection against infection and/or disease on subsequent exposure to a pathogen

Pollard, 2021

Type of vaccine	Licensed vaccines using this technology	First introduced
Live attenuated (weakened or inactivated)	Measles, mumps, rubella, yellow fever, influenza, oral polio, typhoid, Japanese encephalitis, rotavirus, BCG, varicella zoster	1798 (smallpox)
Killed whole organism	Whole-cell pertussis, polio, influenza, Japanese encephalitis, hepatitis A, rabies	1896 (typhoid)
Toxoid	Diphtheria, tetanus	1923 (diphtheria)
Subunit (purified protein, recombinant protein, polysaccharide, peptide)	Pertussis, influenza, hepatitis B, meningococcal, pneumococcal, typhoid, hepatitis A	1970 (anthrax)
Virus-like particle	Human papillomavirus	1986 (hepatitis B)
Outer membrane vesicle	Group B meningococcal	1987 (group B meningococcal)
Protein–polysaccharide conjugate	*Haemophilus influenzae* type B, pneumococcal, meningococcal, typhoid	1987 (*H. influenzae* type b)
Viral vectored	Ebola	2019 (Ebola)
Nucleic acid vaccine	SARS-CoV-2	2020 (SARS-CoV-2)



Live attenuated (LAV)

- Tuberculosis (BCG)
- Oral polio vaccine (OPV)
- Measles
- Rotavirus
- Yellow fever
- Varicella-Zoster virus (VZV)
- Seasonal influenza (nasal spray)

Inactivated (killed antigen)

- Whole-cell pertussis (wP)
- Inactivated polio virus (IPV)
- Hepatitis A
- Seasonal Influenza (injectable)

Subunit (purified antigen)

- Acellular pertussis (aP)
- Haemophilus influenzae type b (Hib)
- Pneumococcal (PCV-7, PCV-10, PCV-13)
- Hepatitis B (HepB)
- Human papillomavirus (HPV)

Toxoid (inactivated toxins)

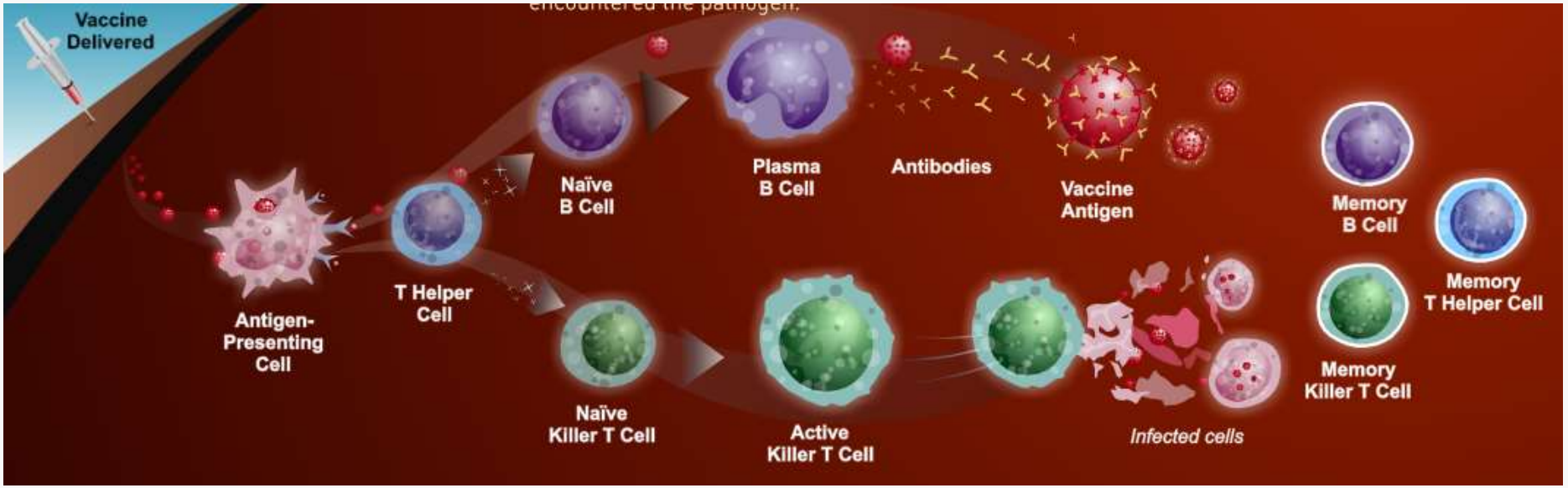
- Tetanus toxoid (TT)
- Diphteria toxoid

Viral vector vaccine

- Zaire Ebola virus (rVSV-ZEBOV)

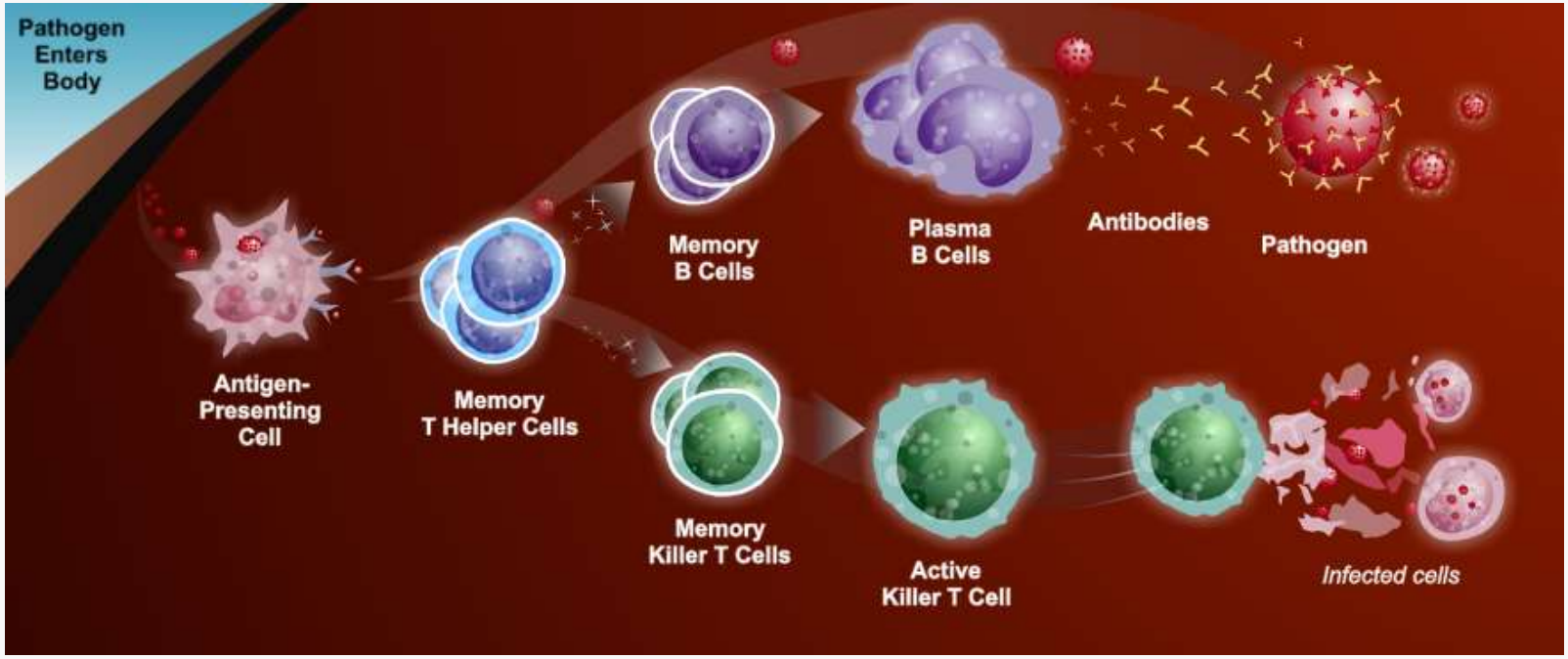
Pollard, 2021; WHO Vaccine Safety Basics

How vaccines work



https://www.historyofvaccines.org/content/how-vaccines-work

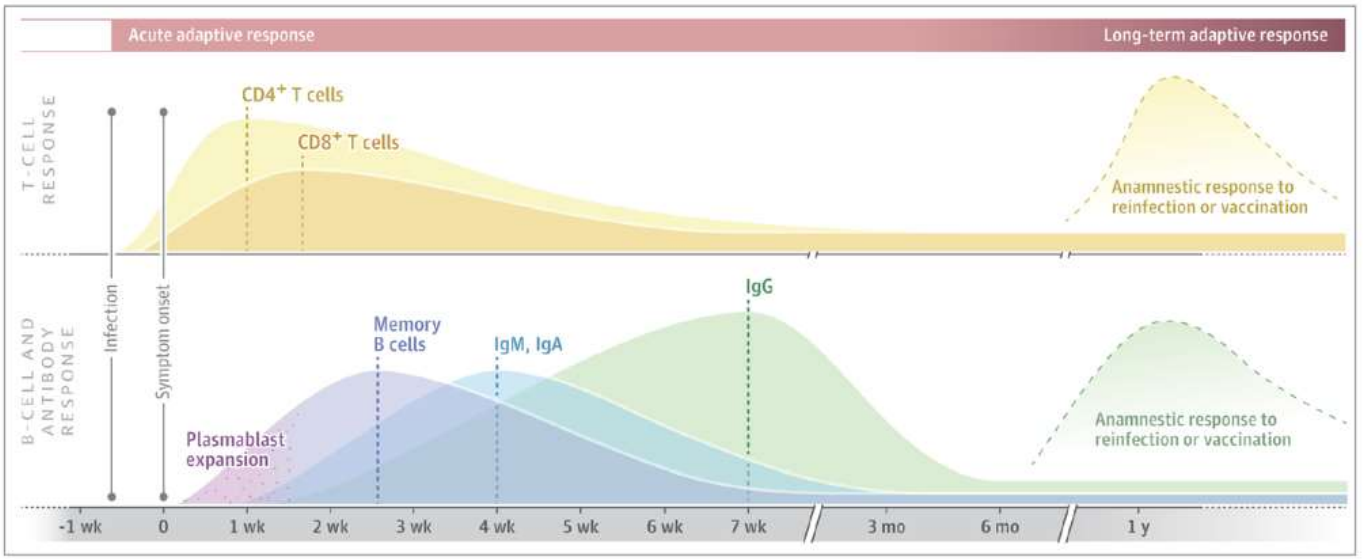
How vaccines work



https://www.historyofvaccines.org/content/how-vaccines-work

Immune response

Adaptive Immunity to Coronavirus Disease 2019:
Generalized model of T-cell and B-cell responses to SARS-CoV-2 infection projected over 1 year following infection



Slide credit: Dr. M. McGuinty

How do we know vaccines are working?

Population data

- Vaccine efficacy: measures the proportionate reduction in cases among vaccinated persons – this term is used in ideal conditions such as a clinical trial
- Vaccine effectiveness: measures the proportionate reduction in cases among vaccinated persons – this term is used in real world setting

CDC Principles of Epidemiology, accessed October 4, 2021

How do we know vaccines are working?

Immune parameters

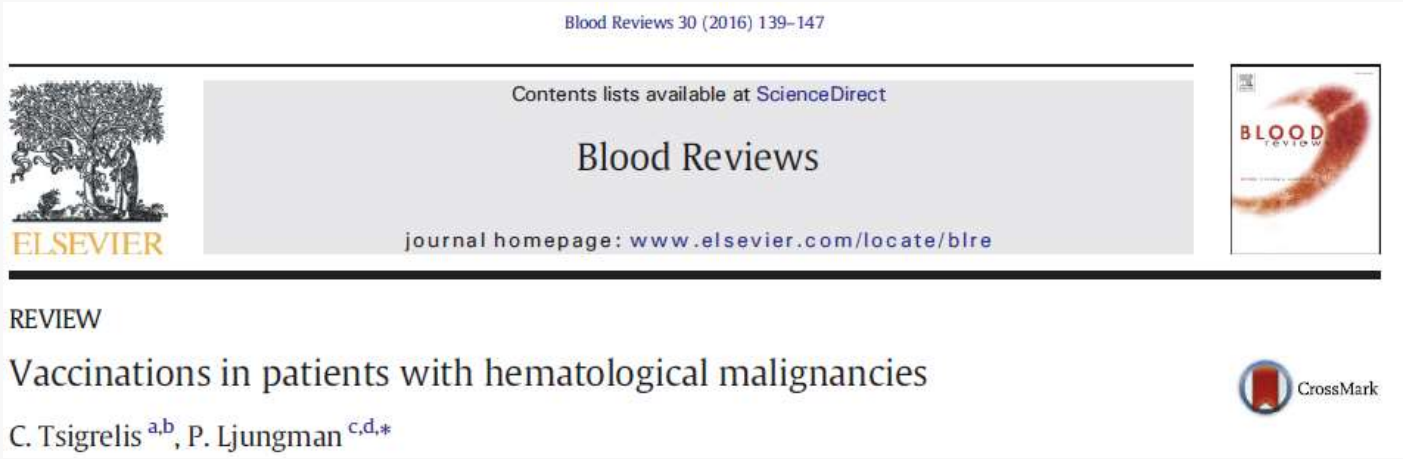
- Seroconversion: Usually defined as achieving a quantifiable antibody level post-vaccination – no detectable antibody prior to vaccination becomes detectable after vaccination
  - *In some cases, this could be a pre-defined fold-increase pre to post vaccine*
- Immunological correlation of protection: Type and amount of immunological response that correlates with vaccine-induced protection against a clinical infection diseases
  - *Sometimes, this is thought of as seroprotection*

- These parameters need to be defined in order to know if patients are protected

WHO, 2016

Vaccines for patients with Hematologic Malignancy or Blood Cancers

- Generally speaking, patients who are immunocompromised are at higher risk of infection including from vaccine-preventable diseases
  - *This includes people with hematologic malignancy*



Blood Reviews 30 (2016) 139–147

Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/blre

REVIEW

Vaccinations in patients with hematological malignancies

C. Tsigrelis [a,b], P. Ljungman [c,d,*]

Tsigrelis, 2016

Recommendations on vaccines exist

- Many recommendations exist with regards to vaccinating patients with blood cancers, especially post hematopoietic cell transplant
  - *IDSA Clinical Practice Guidelines, Canadian Immunization Guide, ECIL 7*
- We are used to routine vaccines and place an importance on ensuring patients are up to date
- Vaccine schedules are an important part of post-transplant or cellular therapy care
- Now, we have COVID-19 vaccines to add to the mix

Rubin, 2014; Canadian Immunization Guide; Antipolis, 2017

COVID-19 Vaccines Approved by Health Canada

- mRNA Vaccines
  - *Pfizer-BioNTech Comirnaty*
  - *Moderna Spikevax*
- Non-replicating viral vector vaccines
  - *AstraZeneca Vaxzevria*
  - *Janssen COVID-19 vaccine*
- Protein subunit vaccines
  - *Novavax Nuvaxovid*
- Plant based virus-like particle
  - *Medicago Covifenz*

Focus of today's talk

mRNA Vaccines

- Messenger RNA contains a code for the SARS-CoV-2 spike protein
- Once inside the recipient's cells – mRNA provides instructions to the cell to produce the spike protein antigen that they gets displayed on the cell's external surface
- The immune system "turns on" to induce humoral and cellular immune response
- Within days to weeks, the mRNA and the spoke protein are degraded → leaving the recipient with the protection induced by the immune response

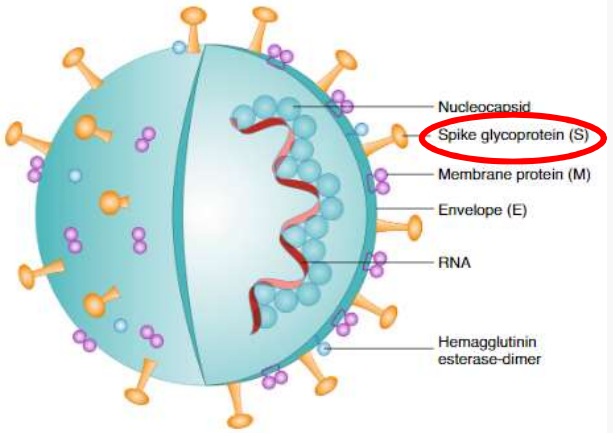


Fig. 1 | Schematic representation of SARS-CoV-2 structure. This is an enveloped, positive-sense RNA virus with four main structural proteins, including spike (S) and membrane (M) glycoproteins, as well as envelope (E) and nucleocapsid (N) proteins.

CDC, 2021

Current COVID-19 Vaccine Recommendations

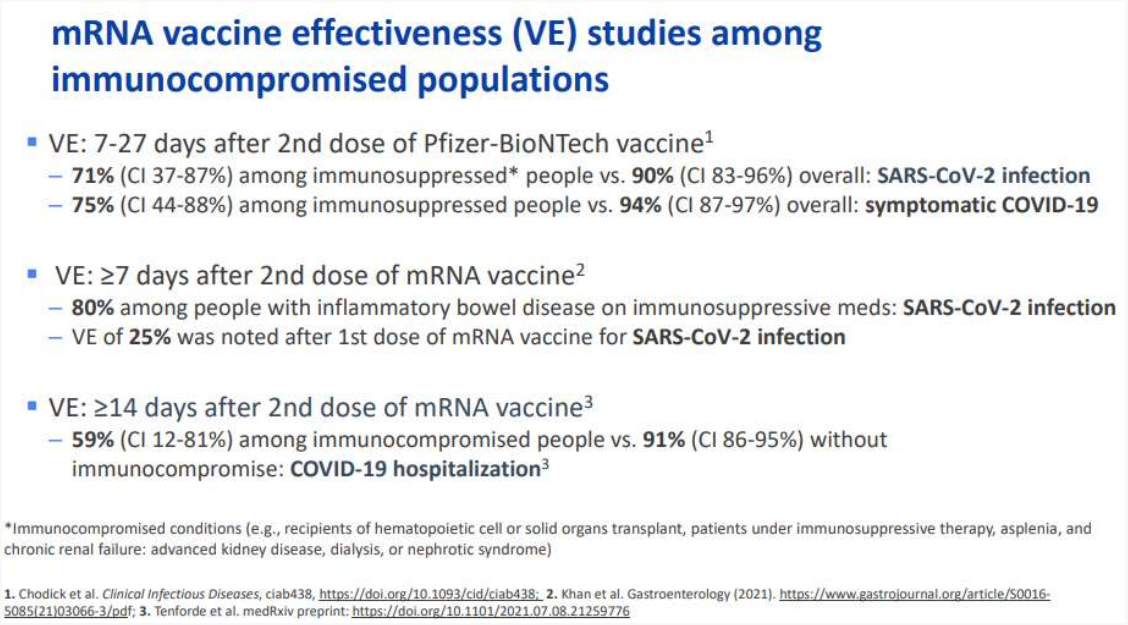
- For patients considered moderately to severely immunocompromised
  - *3-dose primary series*
  - *Eligible for 1st and 2nd booster (equates to 4th and 5th doses)*
  - *Eligible for bivalent booster, no matter the of number of previous vaccine doses*

3-Dose Primary Series

- 3-dose primary series is recommended for moderately-severely immunocompromised
  - *To enhance immune response and established improved protection in those that may have no or sub-optimal response to 2-dose primary series*
- Dose intervals
  - *First dose → 1 month → Second dose → 2 months → Third dose*
- Primary series should be with the original (monovalent) vaccines
  - *Pfizer 30mcg or Moderna 100mcg*
- But, these were not always the recommendations…

Why 3-dose Primary Series?

- Original clinical trial data for 2 doses series
  - *Both mRNA vaccine studies quoted ~ 94-95 % effective*
- Original clinical trials did not include many immunocompromised patients



mRNA vaccine effectiveness (VE) studies among immunocompromised populations

- VE: 7-27 days after 2nd dose of Pfizer-BioNTech vaccine[1]
  - **71%** (CI 37-87%) among immunosuppressed* people vs. **90%** (CI 83-96%) overall: **SARS-CoV-2 infection**
  - **75%** (CI 44-88%) among immunosuppressed people vs. **94%** (CI 87-97%) overall: **symptomatic COVID-19**
- VE: ≥7 days after 2nd dose of mRNA vaccine[2]
  - **80%** among people with inflammatory bowel disease on immunosuppressive meds: **SARS-CoV-2 infection**
  - VE of **25%** was noted after 1st dose of mRNA vaccine for **SARS-CoV-2 infection**
- VE: ≥14 days after 2nd dose of mRNA vaccine[3]
  - **59%** (CI 12-81%) among immunocompromised people vs. **91%** (CI 86-95%) without immunocompromise: **COVID-19 hospitalization**[3]

*Immunocompromised conditions (e.g., recipients of hematopoietic cell or solid organs transplant, patients under immunosuppressive therapy, asplenia, and chronic renal failure: advanced kidney disease, dialysis, or nephrotic syndrome)

1. Chodick et al. *Clinical Infectious Diseases*, ciab438, https://doi.org/10.1093/cid/ciab438; **2.** Khan et al. Gastroenterology (2021). https://www.gastrojournal.org/article/S0016-5085(21)03066-3/pdf; **3.** Tenforde et al. medRxiv preprint: https://doi.org/10.1101/2021.07.08.21259776

ACIP, July 22, 2021

Variable immune response

Patients have variable humoral responses

54% of patients responded to 2 doses of the mRNA vaccine

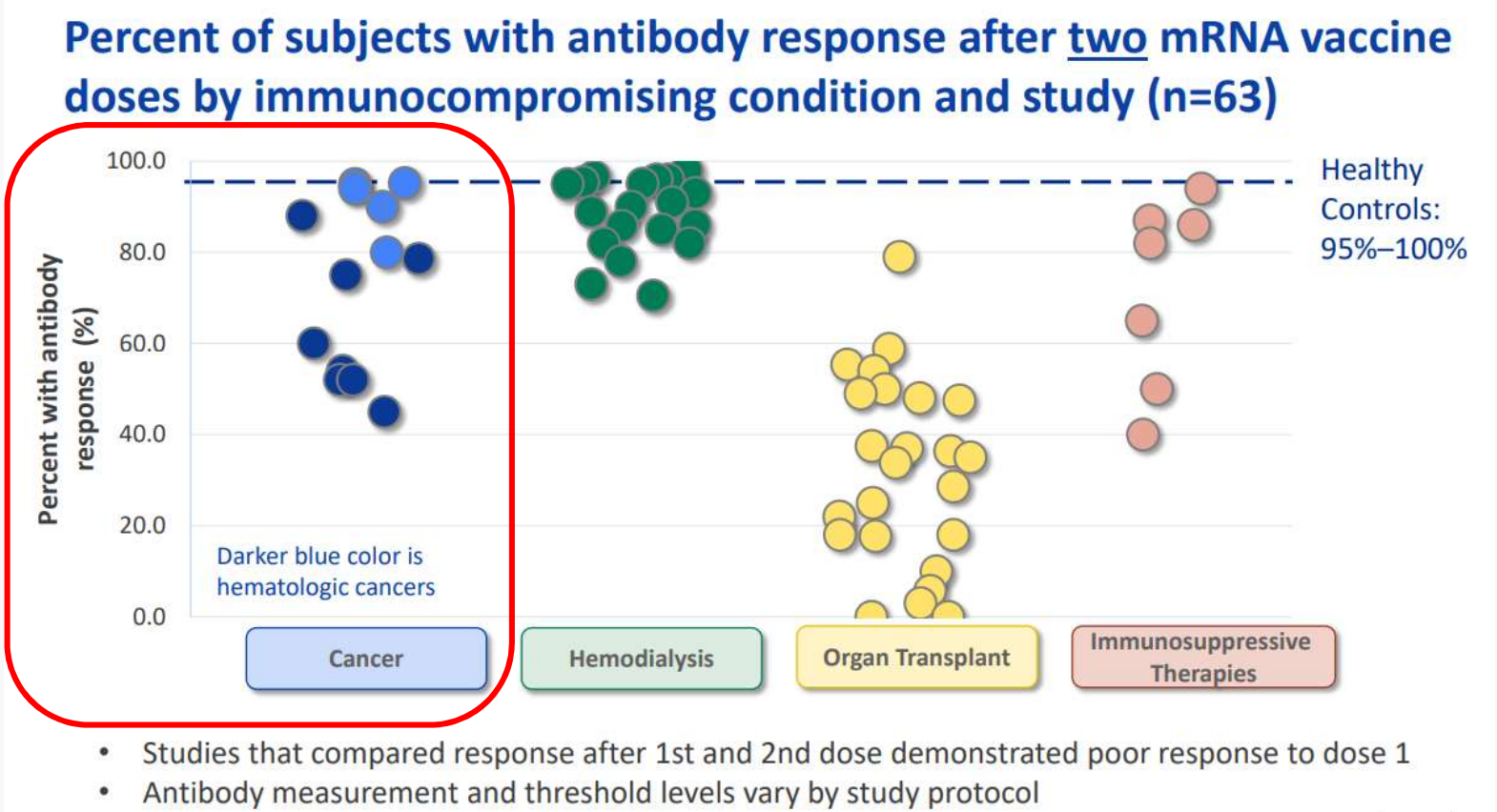
LEUKEMIA & LYMPHOMA SOCIETY OF CANADA

	Responders (N=36, 54%)	Non-responders (N=31, 46%)
Therapy		
-Active treatment	15 (50%)	15 (50%)
-Observation	21 (57%)	16 (43%)
Cancer type		
-CLL	3 (21%)	10 (77%)
-Non-CLL	33 (61%)	21 (39%)
Lymphomas	11 (52%)	10 (48%)
Multiple myeloma	19 (66%)	10 (35%)
Other (AML + CML)	3 (75%)	1 (25%)

Agha. MedRxiv Preprint Server. doi: https://doi.org/10.1101/2021.04.06.21254949

Slide courtesy of Dr. S Bhella

From ACIP



ACIP, July 22, 2021

From ACIP

For people with moderate to severe immune compromise due to a medical condition or immunosuppressive treatment, the potential to increase immune response coupled with an acceptable safety profile support consideration for an additional dose of mRNA COVID-19 vaccine following an initial 2-dose primary mRNA COVID-19 vaccine series in this population

- Serologic testing or immune testing to assess response to vaccine and guide clinical care has not been established and is NOT recommended
- Additional dose should be same mRNA vaccine as primary series, but alternate can be used
- At least 28 days after 2nd dose
- Patients should still continue prevention measures (masks, distancing, etc)
- Close contacts should be strongly encouraged to be vaccinated

ACIP, August 13, 2021

Canada follows suit

- In the US, ACIP = Advisory Committee on Immunization Practices
  - *August 12, 2021: FDA authorized additional vaccine dose for certain immunocompromised individuals*
  - *August 13, 2021: ACIP meeting → Recommends 3 dose series*
- In Ontario, Vaccine Clinical Advisory Group and Ministry of Health
  - *August 18, 2021: MOH → Consider 3rd dose for special populations*
- In Canada, NACI = National Advisory Committee on Immunization Practices
  - *September 10, 2021: Rapid Response → Recommends 3 dose series*

Ontario recommends 3rd dose at 8 week interval

Recommendations:

At this time third doses of the COVID-19 vaccines will be offered for the following populations eligible for vaccination with the vaccine product authorized for their age group, to complete an extended primary COVID-19 vaccine series.

- Individuals receiving active treatment[1] (e.g., chemotherapy, targeted therapies, immunotherapy) for solid tumour or hematologic malignancies.
- Recipients of solid-organ transplant and taking immunosuppressive therapy
- Recipients of chimeric antigen receptor (CAR)-T-cell therapy or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy).
- Individuals with moderate to severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome).
- Individuals with stage 3 or advanced untreated HIV infection and those with acquired immunodeficiency syndrome.
- Individuals receiving active treatment with the following categories of immunosuppressive therapies: anti-B cell therapies[2] (monoclonal antibodies targeting CD19, CD20 and CD22), high-dose systemic corticosteroids (refer to the CIG for suggested definition of high dose steroids), alkylating agents, antimetabolites, or tumor-necrosis factor (TNF) inhibitors and other biologic agents that are significantly immunosuppressive.

NACI & Dose 3

National Advisory Committee on Immunization (NACI) rapid response: Additional dose of COVID-19 vaccine in immunocompromised individuals following 1- or 2- dose primary series

Published September 10, 2021

- Why was a 3rd dose recommended?
  - *Increased risk of prolonged infection & serious complications*
  - *Although data limited, observational studies show reduction in vaccine effectiveness (VE) in immunocompromised patients compared to general population*
  - *Immunogenicity is decreased in immunocompromised adults compared to healthy population, especially malignancy, MS treated with immunosuppression, SOT recipients, primary immune deficiency*
    - Caveat: clinical significance of seroconversion and impact on VE is not known
  - *Safety profile in real world has shown no specific concern in immunocompromised patients*

NACI & Dose 3

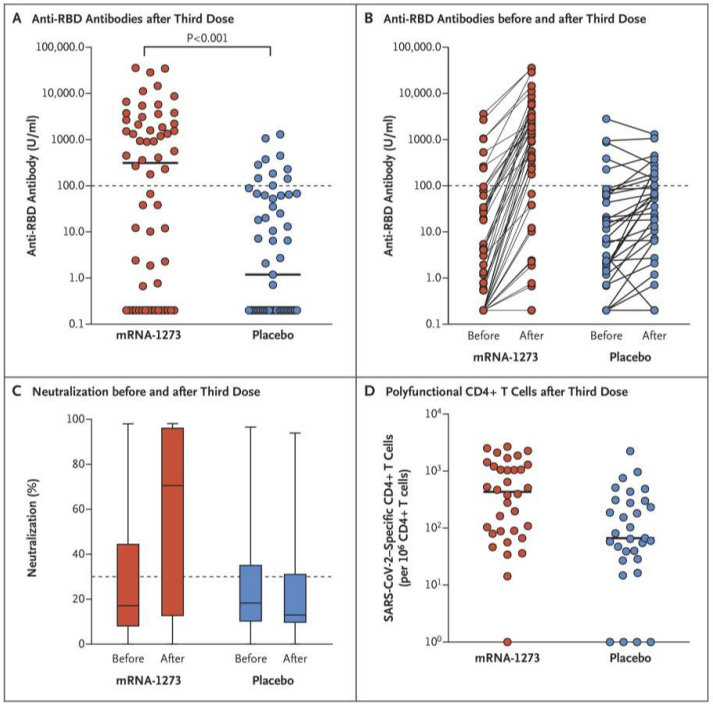
Recommendations

1. **For those who have not yet been immunized, NACI recommends that moderately to severely immunocompromised * individuals in the authorized age groups should be immunized with a primary series of three doses of an authorized mRNA vaccine. (Strong NACI Recommendation)**
2. **For those moderately to severely immunocompromised * individuals in the authorized age groups who have previously received a 1- or 2-dose complete primary COVID-19 vaccine series (with a homologous or heterologous schedule using mRNA or viral vector vaccines), NACI recommends that an additional dose of an authorized mRNA COVID-19 vaccine should be offered. (Strong NACI Recommendation)**
    - **2a. An additional dose of a viral vector vaccine should only be considered when other authorized COVID-19 vaccines are contraindicated or inaccessible. Informed consent for an additional dose of viral vector vaccine should include discussion about the lack of evidence on the use of an additional dose of viral vector COVID-19 vaccine in this population. (Discretionary NACI Recommendation)**

The efficacy/effectiveness of an additional dose of COVID-19 vaccine following a 1- or 2- dose primary series in immunocompromised individuals is currently unknown. A diminished immune response to the additional dose may also occur. Therefore, **immunocompromised individuals should continue to follow recommended public health measures for prevention and control of SARS-CoV-2 infection and transmission**. It is also important that household members, healthcare workers providing care, and other close contacts of the immunocompromised be vaccinated to provide indirect protection for these individuals.

Will dose 3 help?

- Evidence from solid organ transplant patients
  - *Study done in Toronto looking at solid organ transplant patients was published in the NEJM → one of the key studies used in determining recommendations for 3rd dose*
  - *Double blind, randomized, controlled trial of third dose mRNA01273 (Moderna) vs placebo*
  - *This study saw a increase in anti-RBD antibody levels, higher median percent virus neutralization and also provided data on T-cell response*
    - Importantly they do note that the threshold antibody value chosen was arbitrary
  - *Third dose was safe*



Hall, 2021

Cancer Cell

CellPress

Letter

Anti-spike antibody response to SARS-CoV-2 booster vaccination in patients with B cell-derived hematologic malignancies

Lee M. Greenberger,[1,*] Larry A. Saltzman,[1] Jonathon W. Senefeld,[2] Patrick W. Johnson,[3] Louis J. DeGennaro,[1] and Gwen L. Nichols[1]

[1]The Leukemia & Lymphoma Society, Rye Brook, NY, USA
[2]Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, MN, USA
[3]Department of Quantitative Health Sciences, Mayo Clinic, Jacksonville, FL
*Correspondence: lee.greenberger@lls.org
https://doi.org/10.1016/j.ccell.2021.09.001

★ 3rd dose (not booster)

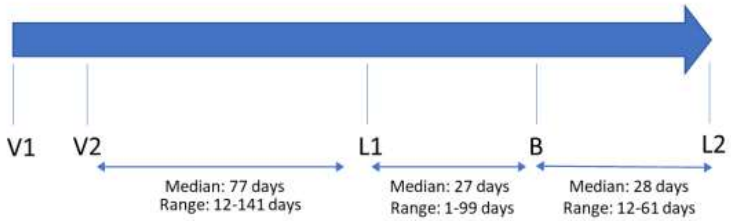


Figure S1. Timeline of analysis.

Patients received one (V1) or two (V2) vaccinations approximately one month apart. An analysis of anti-S antibody levels was done before (L1) and after (L2) booster vaccination (B). The median days and ranges between these intervals are shown.

Greenberger, 2021

Cancer Cell

CellPress

Letter

Anti-spike antibody response to SARS-CoV-2 booster vaccination in patients with B cell-derived hematologic malignancies

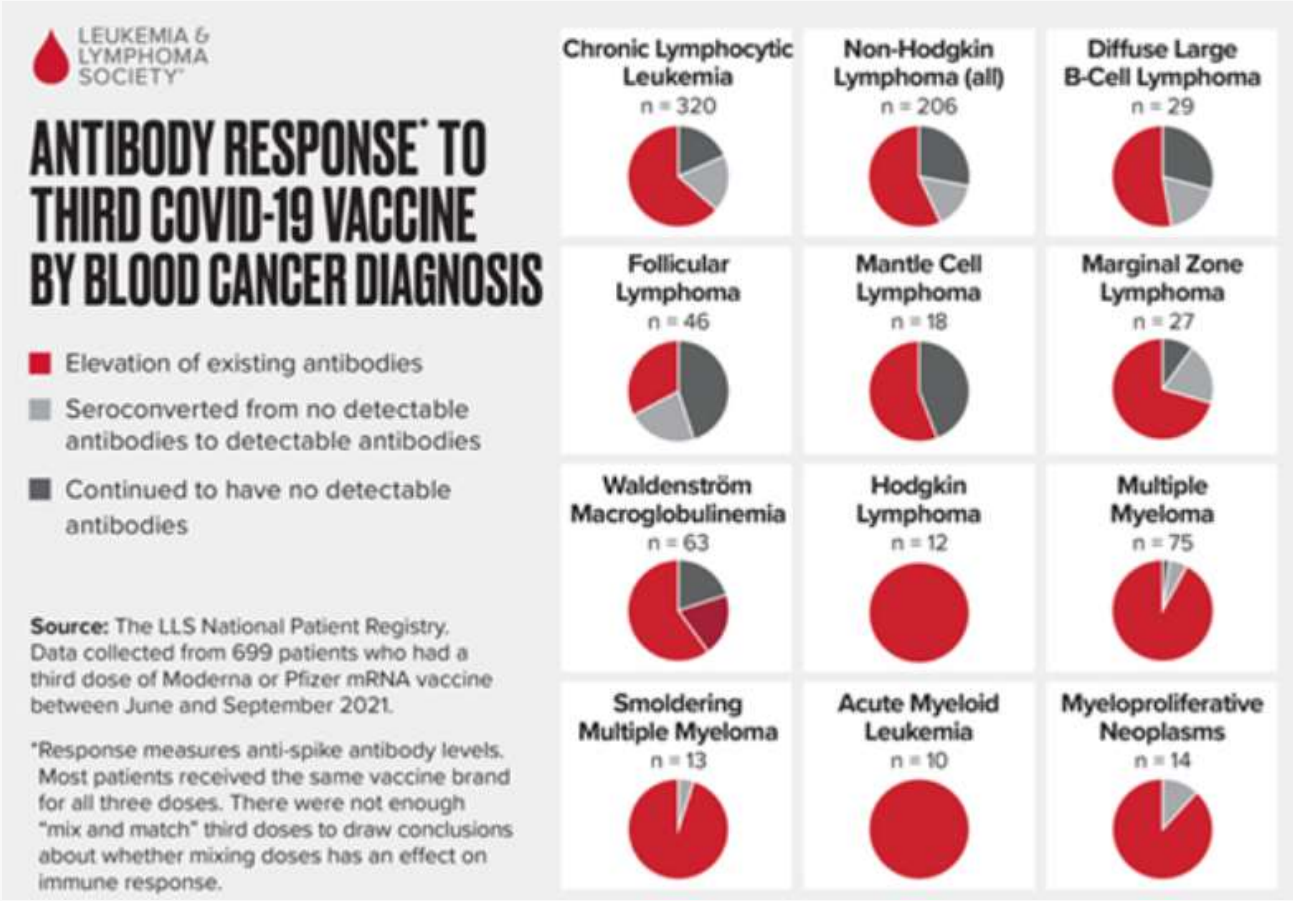
Lee M. Greenberger,[1,*] Larry A. Saltzman,[1] Jonathon W. Senefeld,[2] Patrick W. Johnson,[3] Louis J. DeGennaro,[1] and Gwen L. Nichols[1]
[1]The Leukemia & Lymphoma Society, Rye Brook, NY, USA
[2]Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, MN, USA
[3]Department of Quantitative Health Sciences, Mayo Clinic, Jacksonville, FL
*Correspondence: lee.greenberger@lls.org
https://doi.org/10.1016/j.ccell.2021.09.001

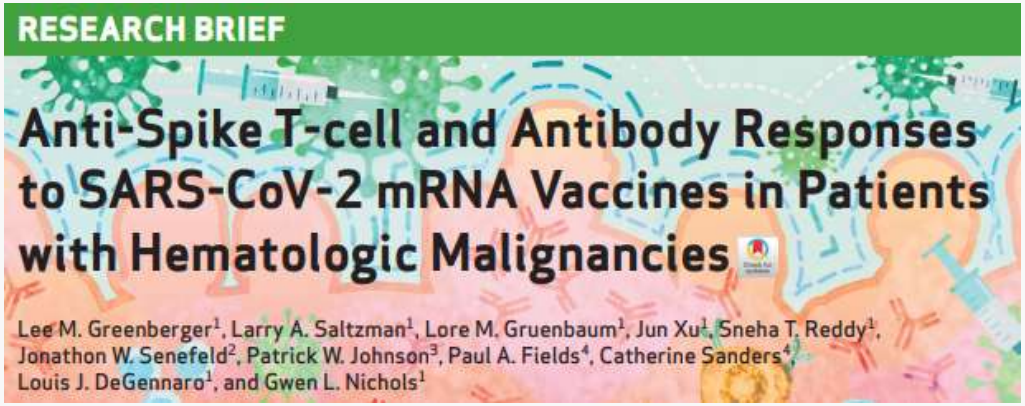
- The study's focus was not for subgroup analysis, but the authors point out
  - *Those who had completed treatment (2 years ago) mostly responded*
  - *The more time post anti-CD20 therapy (>7 months) the better the percentage of patients with response*
- Small cohort, so have to remember the study was not powered for other types of analysis
- Concluded
  - *In a small, limited observational study, 55% (21/38) patients with B-cell malignancies who did not produce antibodies to a 2 dose series, did with a 3rd dose*
  - *Risk factors for not responding included anti-CD20 therapy (especially in last 6 months)*
  - *Did not look at neutralizing antibody response or T cell responses*

Greenberger, 2021

Leukemia & Lymphoma Society

- 699 patients
- 3rd dose of mRNA vaccine June-Sept 2021





- Studied 505 patients with hematologic malignancy (CLL n = 285, NHL n = 154)
  - *Data on anti-S antibody response (humoral immunity) and added benefit of third dose*
    - Among those who were seronegative after second vaccine, 40% achieved an antibody response after third vaccination (wide range of anti-S antibody level) but not all acquired “meaningful” response
  - *Data on T-cell response*
    - % of patients with T-cell response was higher in seropositive patients, but of 221 seronegative patients 45% did have a T-cell response

Greenberger 2022

Third dose data

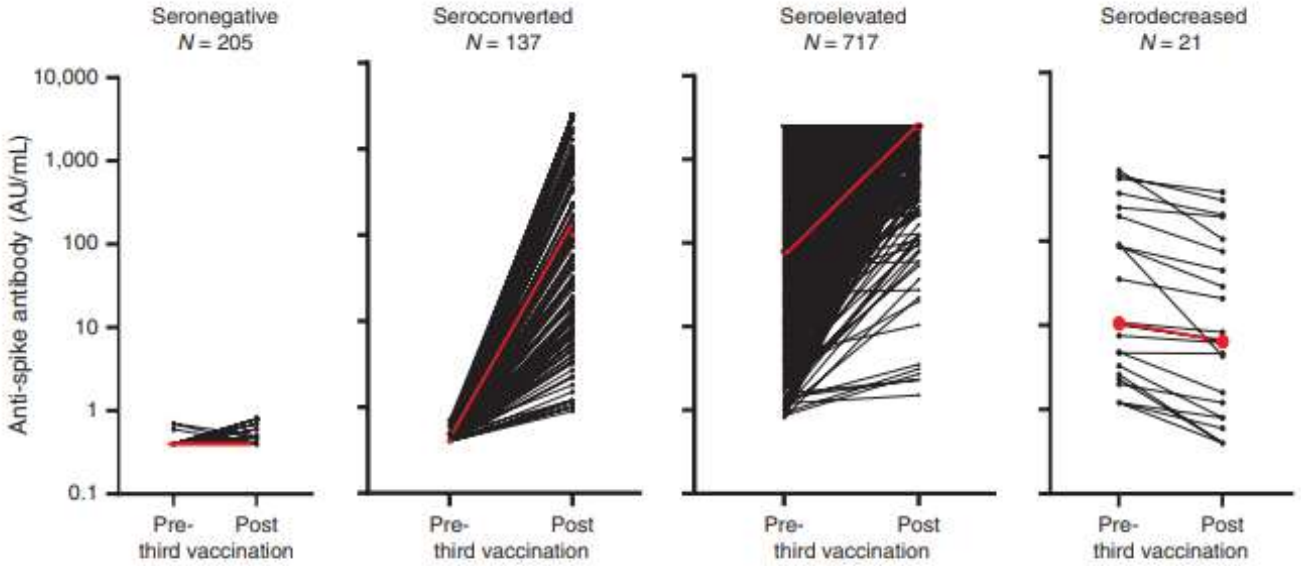


Figure 2. The serological response to second and third vaccinations in individual patients with hematologic malignancies was analyzed for anti-S antibodies as described in the Methods. Individual lines represent each patient. Four types of responses were observed. Those patients who were seronegative prior to the third vaccination either remained persistent seronegative or seroconverted. Those patients who were seropositive prior to the third vaccination either had an increase in anti-S antibody levels (seroelevated) or had a small decrease in anti-S antibody levels (serodecreased). The red line in each graph represents the median anti-S antibody level.

Greenberger 2022

Booster Doses

- Booster = a dose given after completion of primary series

- First Booster
  - *For immunocompromised patients this would be 4th dose*
- Second Booster
  - *For immunocompromised patients this would be 5th dose*

- Recommended dose intervals and minimum dose intervals are not always the same
  - *Minimum interval is 3 months between booster doses*
  - *But recommended is longer – for improved immune response*

Why do we boost?

- Vaccine effectiveness (VE)
  - *Data from ancestral strain and earlier variants demonstrated VE to be high after completion of primary series*
  - *VE against Omicron is lower and decreases over time*
  - *VE improves with booster of mRNA vaccine*
  - *Reassuringly, VE still reasonable for severe outcomes, also improves with booster*

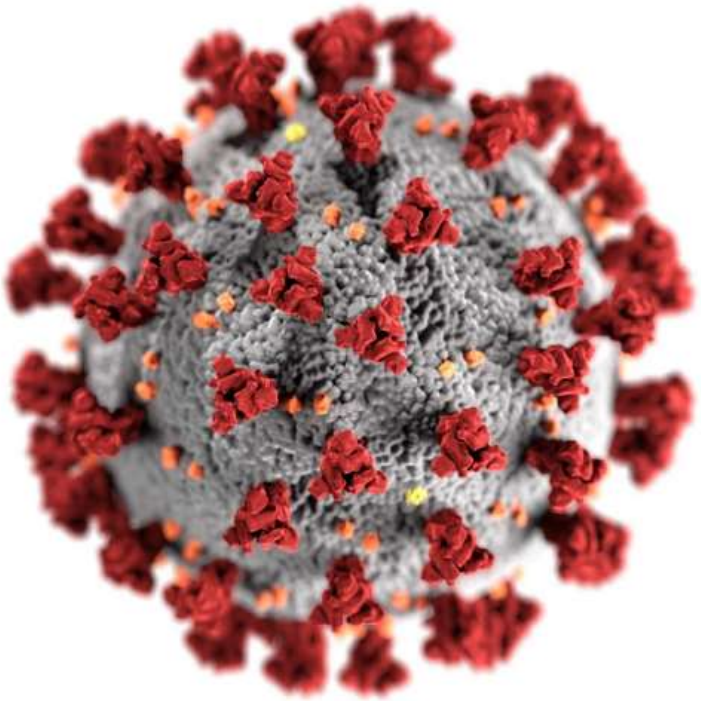
- Studies have shown this in patients with hematologic malignancy, although initial research uses 2nd dose as starting time point
  - *Immunity post dose wanes over time, more significant in patients with hematologic malignancy*

ACIP

COVID-19 Vaccine Effectiveness during Omicron

Ruth Link-Gelles, PhD, MPH
LCDR, US Public Health Service
Program Lead, COVID-19 Vaccine Effectiveness
Epidemiology Task Force, CDC

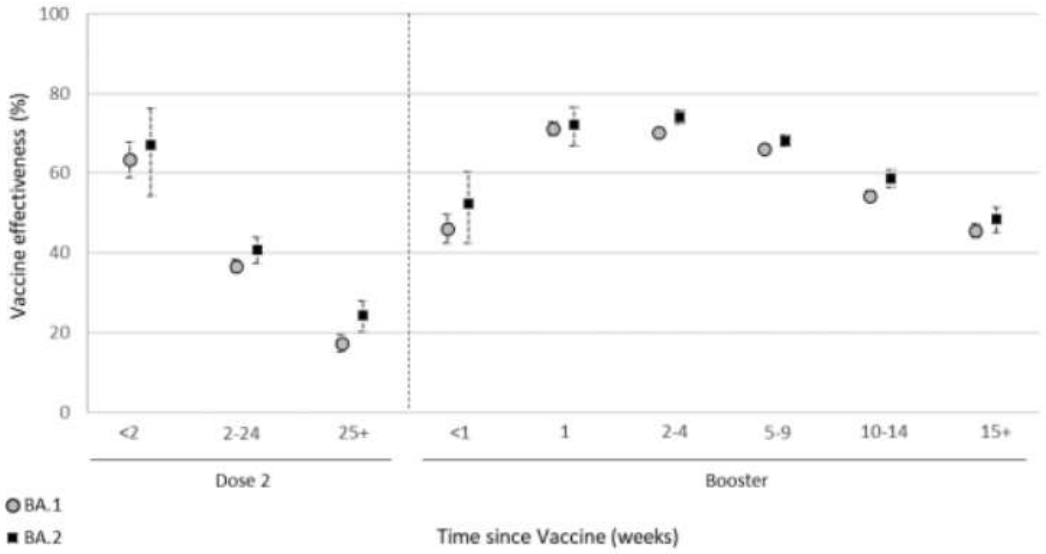
ACIP
April 20, 2022



cdc.gov/coronavirus

Data from the UK: VE vs. symptomatic infection comparing Omicron sublineages (BA.1 vs BA.2) by time since booster

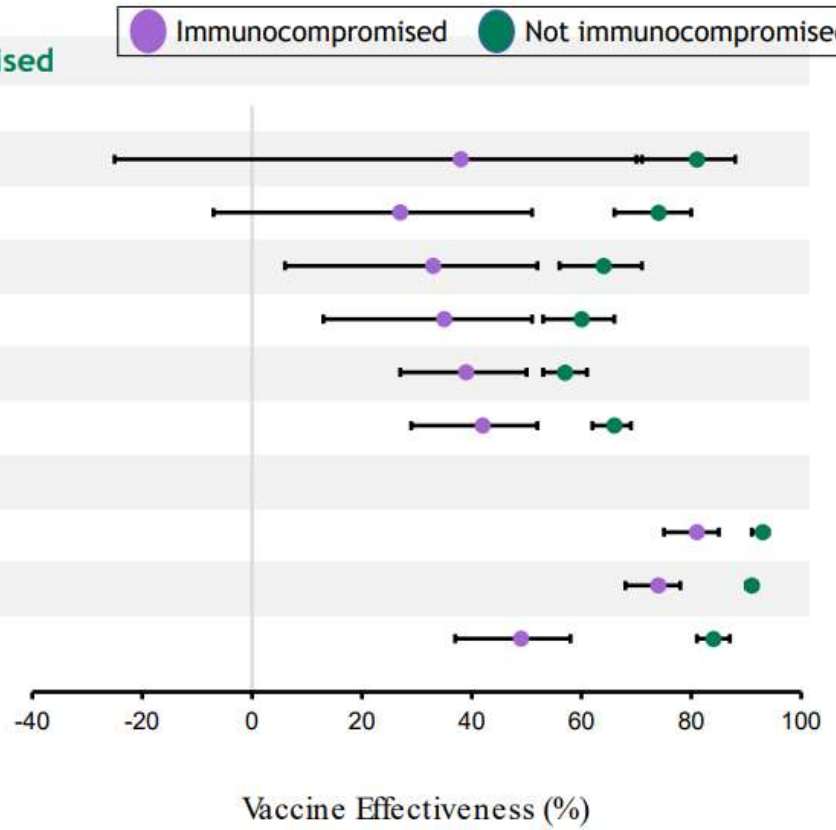
- Pfizer-BioNTech, Moderna, or ChAdOx1-S primary series, Pfizer-BioNTech or Moderna booster
- VE was generally comparable by Omicron sublineage



https://www.medrxiv.org/content/10.1101/2022.03.22.22272691v1.full.pdf

VISION: mRNA VE for hospitalization by number of doses and time since last dose receipt for adults ≥50 years, Dec 2021–Mar 2022, by immunocompromised status

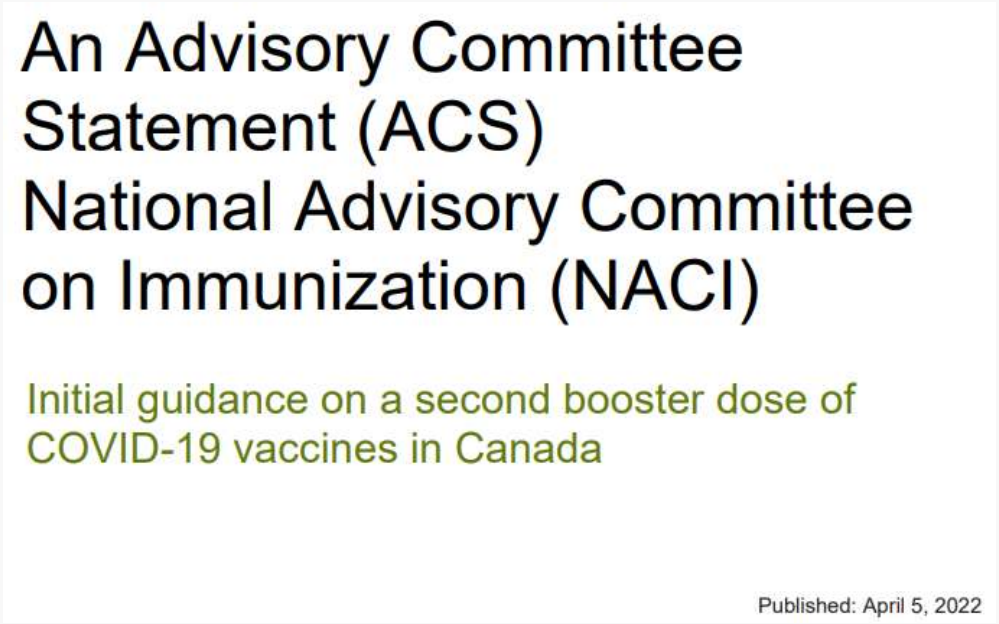
	Adjusted VE% (95% CI)	
Status:	Immunocompromised	Not immunocompromised
2 doses		
14-59 days	38 (-25-71)	81 (70-88)
60-119 days	27 (-7-51)	74 (66-80)
120-179 days	33 (6-52)	64 (56-71)
180-239 days	35 (13-51)	60 (53-61)
240-299 days	39 (27-50)	57 (53-61)
300+ days	42 (29-52)	66 (62-69)
3 doses		
14-59 days	81 (75-85)	93 (91-94)
60-119 days	74 (68-78)	91 (90-92)
120-179 days	49 (37-58)	84 (81-87)



CDC, preliminary unpublished data. Individuals with prior infections excluded. Logistic regression conditioned on calendar week and geographic area, and adjusted for age, sex, race, ethnicity, local virus circulation, respiratory or nonrespiratory underlying medical conditions, and propensity to be vaccinated

ACIP, April 20, 2022

Canadian Second Booster Recommendations



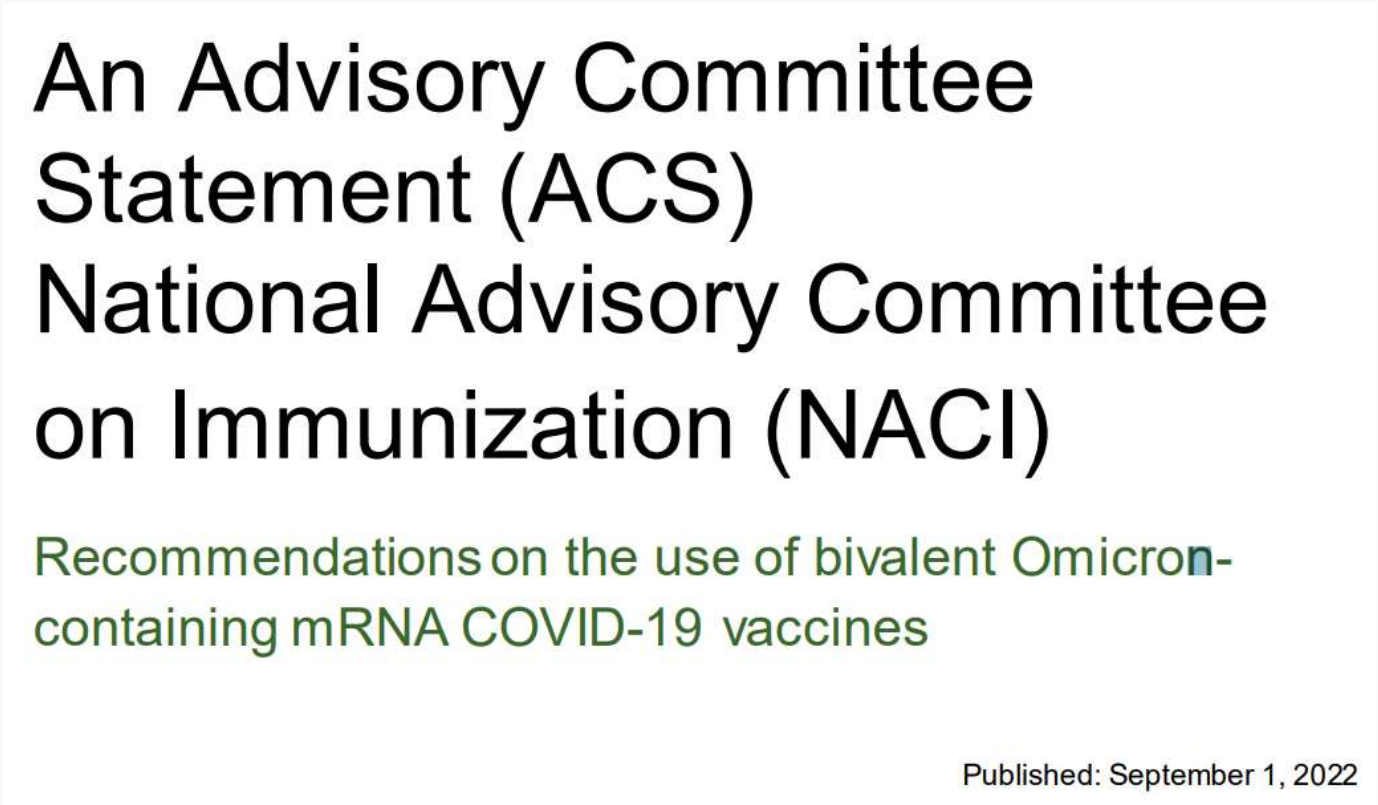
VE over time following a first booster

- Current data suggest that COVID-19 vaccines offer reduced protection against Omicron infection and symptomatic disease and somewhat lower protection against hospitalization/ severe disease compared to the protection offered against the ancestral strain and previous VOCs. This lower protection is also occurring in the context of decreasing protection over time since the previous dose.
- VE against infection/symptomatic disease for the Omicron variant from a first booster of mRNA vaccine is approximately 60% and decreases over time since vaccination in most studies.
- Vaccine protection against severe disease and hospitalization due to COVID-19 has been more durable than protection against symptomatic disease or infection and is approximately 10 to 20% higher following a first booster compared to those who have only completed a primary series, reaching ~90% or more shortly following vaccination [4-9]. Evidence regarding the duration of protection of a first booster against severe disease is limited, with a few studies suggesting some decrease over time [4, 6]. As an example, VE against hospitalization was 78% (95% CI: 67 to 85%) at ≥4 months in one US study [4].

VE following a second booster

- Evidence on second booster VE is limited and has mainly been assessed as a relative benefit compared to the first booster [10-12]. Preliminary data indicates that a second booster dose provides additional protection compared to a first booster, including against severe disease. However, the duration of protection is currently unknown, and the absolute benefit will depend on the residual protection from the first booster dose and on the level of circulating disease in the community.
- In a study of a second booster among older adults ≥60 years of age who were vaccinated at least 4 months from their first booster [11], the rates of SARS-CoV-2 infection and COVID-19 severe illness were lower in those 12 or more days after the fourth dose (2.0-fold and 1.8-fold for infection and 4.3-fold and 4.0-fold for severe disease) compared to the two control groups, respectively (those eligible for the second booster dose but who did not receive it, and those who received the second booster dose but were within 3 to 7 days after receiving the second booster dose, which is before it is expected to take effect [11]).
- In a separate study of healthcare workers who received a second booster dose given at least 4 months after the first booster dose, there was a relative adjusted VE after a second booster compared to a first booster against symptomatic disease of 43% (95% CI: 7 to 65%) in the Pfizer-BioNTech group and 31% (95% CI: -18 to 60%) in the Moderna group [10].

Bivalent Booster



Bivalent Booster

- Bivalent booster is now preferred over monovalent booster in Ontario
  - *Bivalent booster currently available:*
    - Moderna Spikevax Bivalent (50mcg) = 25 mcg ancestral strain + 25mcg BA.1
  - *Elicits higher neutralizing antibody response compared to second booster of monovalent vaccine (Moderna Spikevax Original 50mcg)*
    - Clinical outcomes and VE are yet to be established
  - *Similar reactogenicity and frequency of adverse events*
  - *Plan is for post-marketing surveillance*

RECOMMENDATIONS

Consistent with NACI's Interim guidance on planning considerations for a fall 2022 COVID-19 vaccine booster program in Canada:

1. **NACI strongly recommends that individuals ≥12 years of age* who are at increased risk of severe illness from COVID-19** should be offered a fall COVID-19 vaccine booster dose regardless of the number of booster doses previously received.** ***(Strong NACI recommendation)***

2. **NACI recommends that all other individuals 12 to 64 years of age may be offered a fall COVID-19 booster dose regardless of the number of booster doses previously received.** ***(Discretionary NACI recommendation)***

With regard to the product offered;

3. **NACI recommends that the authorized dose of a bivalent Omicron-containing mRNA COVID-19 vaccine should be offered as a booster dose to the authorized age groups (≥18 years of age). If the bivalent Omicron-containing mRNA COVID-19 vaccine is not readily available, an original mRNA COVID-19 vaccine should be offered to ensure timely protection.** ***(Strong NACI recommendation)***
    - Individuals eligible for a fall booster dose, particularly those in groups at a higher risk of severe outcomes from COVID-19, should not delay their planned vaccination in anticipation of a bivalent Omicron-containing mRNA vaccine. Individuals choosing to delay a booster dose in anticipation of a new vaccine formulation should carefully assess their individual risks (i.e., risks of SARS-CoV-2 infection and severe outcomes from COVID-19) and benefits associated with deferring a booster dose.
    - NACI continues to recommend that COVID-19 booster doses may be offered at an interval of 6 months after a previous COVID-19 vaccine dose or SARS-CoV-2 infection, regardless of the product offered. However, a shorter interval of at least 3 months may be warranted in the context of heightened epidemiologic risk, as well as operational considerations for the efficient deployment of the vaccine program.

Current Vaccine Schedule in Ontario

Ontario

Age	Recommended Intervals[1]	Minimum Intervals[2]

Moderately or severely immuno-compromised individuals ≥6 months of age[3]	**Primary Series**
	• 1st dose
	• 2nd dose, 8 weeks after 1st dose
	• 3rd dose, 8 weeks after 2nd dose
	
	Booster Doses
	• 1st booster dose
	  ○ (if under 5) not eligible
	  ○ (if 5-17) 6 months
	  ○ (if 18+) 5 months after 3rd dose
	• 2nd booster dose
	  ○ (if under 11) not eligible
	  ○ (if 12-17) 6 months after first booster
	  ○ (if 18 and over) 5 months after first booster
		Primary Series
		• 1st dose
		• 2nd dose, 19 days (Pfizer-BioNTech) or 21 days (Moderna for 6 years and over) or 28 days (Moderna for 6 months to 5 years) after 1st dose
		• 3rd dose, 28 days after 2nd dose
		
		Booster Doses
		• 1st booster dose
		  ○ (if under 5) not eligible
		  ○ (if 5 and over) 3 months after 3rd dose
		• 2nd booster dose
		  ○ (if under 11) not eligible
		  ○ (if 12 and over) 3 months after first booster

PLUS

Now eligible for **bivalent booster**, regardless of how many previous doses

Recommended interval is 6-months, but can be minimum 3-months since last dose.

Are these vaccines safe?

- YES, but there are common side effects and rare adverse events
  - *Side effects*
    - Local reaction – pain at injection site, localized welling including axillary swelling or lymphadenopathy. Usually mild-moderate, resolve within a few days.
    - Systemic reactions – fatigue, headache, muscle pain, chills and joint pains. Fever especially after second dose. Usually mild-moderate, resolve within a few days.
  - *Adverse events following immunizations (AEFI)*
    - Thrombosis with Thrombocytopenia (viral vector covid-19 vaccines)
    - Myocarditis or pericarditis (mRNA covid-19 vaccines)

AEFI: Reporting system is in place

- How often are these rare AEFIs happening?
  - *Very rare*

Table 1. Summary of AEFI reports by vaccine product: Ontario, December 13, 2020 to September 25, 2022

	Pfizer-BioNTech Comirnaty COVID-19 vaccine	Moderna Spikevax COVID-19 vaccine	AstraZeneca Vaxzevria/ COVISHIELD COVID-19 vaccine	Janssen (Johnson & Johnson) COVID-19 vaccine	Novavax Nuvaxovoid COVID-19 vaccine	All vaccine products combined
Total number of AEFI reports	13,047	6,826	1,673	21	23	21,591
Number of non-serious reports	12,365	6,446	1,542	20	23	20,397
Number of serious reports	682	380	131	1	0	1,194
Proportion of total AEFI reports that are serious	5.2	5.6	7.8	4.8	0.0	5.5
Doses administered	23,496,308	9,564,771	1,087,604	3,893	11,161	34,323,145
Total reporting rate per 100,000 doses administered	55.5	71.4	153.8	539.4	206.1	62.9
Serious reporting rate per 100,000 doses administered	2.9	4.0	12.0	25.7	0.0	3.5

PHO, 2022

Are these vaccines safe in immunocompromised patients?

- YES
- Although these populations were not specifically studied in the clinical trials, the safety profile in real-world observational studies is comparable to the general population
- To date, no unexpected or concerning safety signals are seen in those with immunocompromising conditions

Take Home Points

- In general, these vaccines are safe and effective
  - *The important piece is the protection against hospitalization/ICU stays, severe outcomes and death*
- Immunocompromised patients including those with hematologic malignancy have been found to have less robust immune response based on current data
  - *3 dose primary series is recommended*
  - *Boosters are recommended (1st and 2nd boosters)*
  - *Bivalent booster is recommended*
- All close contacts of these patients should be vaccinated
  - *Even if you are not immunocompromised, by vaccinating yourself you are helping to protect others*

COVID-19 IMMUNITY TASK FORCE

Public Health Agency of Canada

The VIP study

COVID-19 Vaccine Immunogenicity in Patients with Hematologic Malignancies: A Prospective Real World Observational Multi-Site Canadian Study

- **Lead Investigators:** Arianne Buchan, Sita Bhella, Abi Vijenthira, Peng Wang, Michael Sebag
- **ON Co-Investigators:** Anca Prica, Vikas Gupta, Lisa Hicks, Matt Cheung, Donna Reece, Chris Bredeson, Natasha Kekre, David Allan, Stephen Betschel, Graeme Fraser, Andrew Aw, Joy Mangel, Annette Hay, Deepali Kumar, Curtis Cooper, Arleigh McCurdy, Sasan Hosseini, Jonas Mattsson
- **QC Co-Investigators**: Anna Nikonova, Sarit Assouline
- **NS Co-Investigators**: Tony Reiman
- **MB Co-Investigators**: Caroline Moltzan
- **SK Co-Investigators**: Julie Stakiw
- **AB Co-Investigators**: Joseph Brandwein, Carolyn Owen
- **BC Co-Investigators**: Laurie Sehn
- **Public Health Co-Investigators:** Shelly Bolotin, James Brooks
- **Lab Co-Investigators:** Anne-Claude Gingras, Michael Chu, Marc-Andre Langlois, Angela Crawley

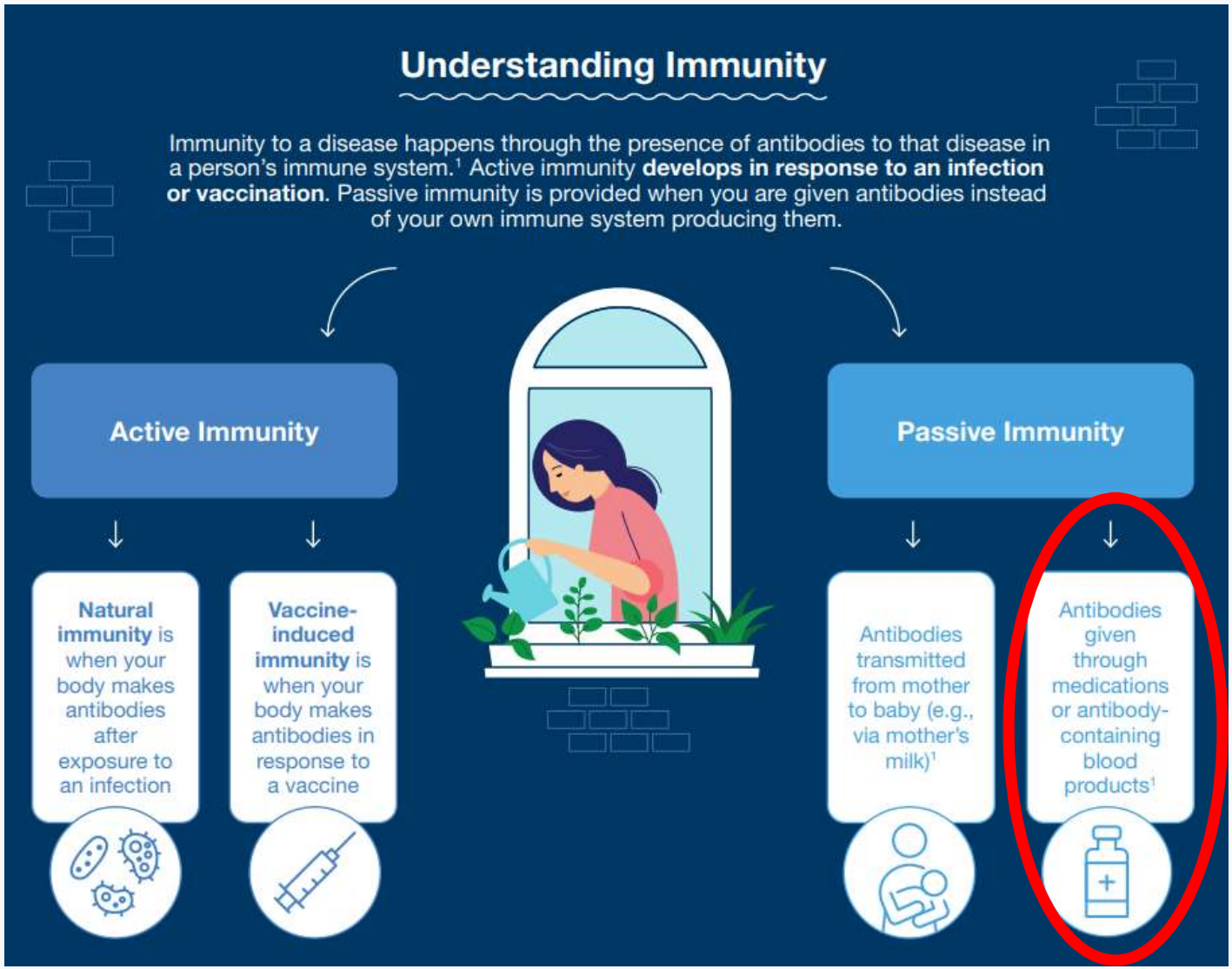
uOttawa | UHN Princess Margaret Cancer Centre | McGill University Health Centre | Alberta Health Services | Public Health Agency of Canada | COVID-19 IMMUNITY TASK FORCE

Approved by Ontario Cancer Research Ethics Board: Aug 31/21, approved until June 15/22

PART 2: NON-VACCINE PREVENTION

Monoclonal Antibodies

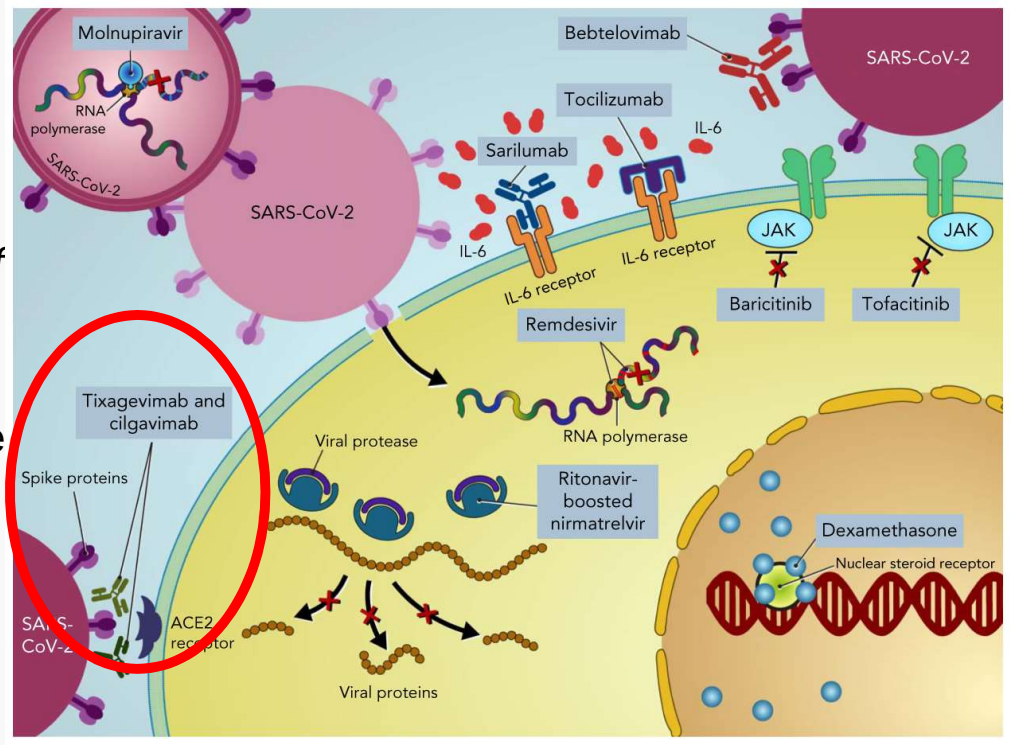
- Monoclonal antibodies have been used for a variety of conditions for many years
- Specifically as these related to COVID-19
  - *Designed to provide passive immunity through administration of neutralizing antibodies against SARS-CoV-2*
- There have been various monoclonal antibodies used over the course of COVID-19 Pandemic – both for treatment and prevention
  - *Current focus in Canada is for use as prevention*
    - NOT a substitute for vaccines → to be used in combination with vaccines in individuals who may not develop an adequate immune or vaccine response to SARS-CoV-2 putting them at higher risk



Canadian Public Health Association, 2022

Tixagevimab/ Cilgavimab (Evusheld)

- Combination of recombinant IgG1 monoclonal antibodies directed against the SARS-CoV-2 spike protein
  - *2 different long acting antibodies*
  - *Bind to non-overlapping epitopes of the spike-protein RBD*
- Goal: block interaction with the host cellular receptor, inhibiting entry into the cell and neutralizing the virus



El Chaer, 2022

Tixagevimab/ Cilgavimab (Evusheld)

- PROVENT Study published April 2022 (e)
- Randomized control trial (blinded)
- 5197 adults patients without prior COVID-19 infection
- Incidence of symptomatic COVID-19 was lower than in placebo
- Limitations: coincided with vaccines, fewer cases of COVID-19 infection in immunocompromised patients, not current circulating variant

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Intramuscular AZD7442 (Tixagevimab–Cilgavimab) for Prevention of Covid-19

Levin MJ et al. DOI: 10.1056/NEJMoa2116620

CLINICAL PROBLEM

Despite widespread Covid-19 vaccination, some persons — especially immunocompromised persons and those who cannot be vaccinated — remain at risk for severe disease. AZD7442 is a combination of two human, SARS-CoV-2–neutralizing monoclonal antibodies (tixagevimab and cilgavimab) that have an extended half-life and prophylactic and therapeutic effects in nonhuman primates. Safety and efficacy data in humans are needed.

CLINICAL TRIAL

Design: An ongoing phase 3, multinational, double-blind, randomized, placebo-controlled trial evaluated a single dose of AZD7442 as preexposure prophylaxis against Covid-19 in adults who had an increased risk of an inadequate response to Covid-19 vaccination, an increased risk of exposure to SARS-CoV-2, or both.

Intervention: 5197 adults without previous SARS-CoV-2 infection were randomly assigned (in a 2:1 ratio) to receive a single 300-mg dose of AZD7442 (one 1.5-ml intramuscular injection of each antibody administered consecutively) or matching placebo. The primary safety end point was the incidence of adverse events. The primary efficacy end point was the first episode of symptomatic Covid-19 on or before day 183 after administration.

RESULTS

Safety: The incidence of adverse events was similar in the AZD7442 and placebo groups; most events were mild or moderate.

Efficacy: During a median follow-up of 83 days, the incidence of symptomatic Covid-19 was significantly lower with AZD7442 than with placebo.

LIMITATIONS AND REMAINING QUESTIONS

- Enrollment occurred between November 2020 and March 2021, when Covid-19 vaccines became available; participants who wanted to consider vaccination could become aware of their randomized assignment, and data were censored after unblinding or vaccination.
- Few Covid-19 cases occurred in key subgroups, including immunocompromised persons, so efficacy in these groups could not be estimated.
- These data are from the period before the delta and omicron waves; thus, activity against those strains cannot be directly assessed.

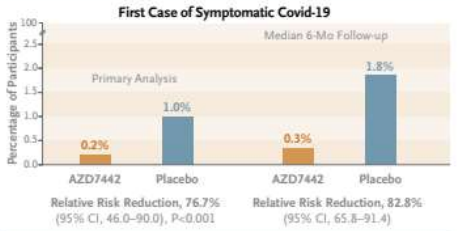
Links: Full Article | NEJM Quick Take | Editorial

Risk factors for an inadequate response to Covid-19 vaccination

- Age ≥60 years
- Obesity
- Immunocompromised status
- Inability to receive vaccines without adverse effects
- Congestive heart failure
- Chronic obstructive pulmonary disease
- Chronic kidney disease
- Chronic liver disease

Persons at increased risk for SARS-CoV-2 exposure

- Health care workers (including staff working in long-term care facilities)
- Workers in industrial settings shown to increase risk of SARS-CoV-2 transmission
- Military personnel
- Students living in dormitories
- Others living together in close or high-density proximity



CONCLUSIONS

A single dose of the monoclonal-antibody combination AZD7442 appeared to be efficacious as preexposure prophylaxis against symptomatic Covid-19 in adults who were at increased risk for severe illness, without any evident safety concerns.

CellPress

Cancer Cell

Letter

Activity of AZD7442 (tixagevimab-cilgavimab) against Omicron SARS-CoV-2 in patients with hematologic malignancies

Robert Stuver,[1] Gunjan L. Shah,[2] Neha S. Korde,[3] Lindsey E. Roeker,[4] Anthony R. Mato,[4] Connie L. Batlevi,[1] David J. Chung,[2] Sital Doddi,[5] Lorenzo Falchi,[1] Boglarka Gyurkocza,[2] Audrey Hamilton,[1] Ya-Hui Lin,[5] Ann A. Jakubowski,[2] Erel Joffe,[1] Heather L. Landau,[2] Richard J. Lin,[2] Sham Mailankody,[3] M. Lia Palomba,[1] Jae H. Park,[4] Miguel-Angel Perales,[2] Doris M. Ponce,[2] Lakshmi V. Ramanathan,[5] Gilles A. Salles,[1] Michael Scordo,[2] Susan K. Seo,[6] Urvi A. Shah,[3] Eytan M. Stein,[4] David Straus,[1] Saad Z. Usmani,[3] James W. Young,[2] Andrew D. Zelenetz,[1] Ariela Noy,[1,8,*] and Santosha A. Vardhana[1,7,8,*]

- Data from Memorial Sloan Kettering Cancer Centre
  - *Adult patients with hematologic malignancy, observational study*
  - *Measured response using antibody levels before & after dose*
  - *Results*
    - 52 patients enrolled, of which 2 patients had documented infection
    - Patients included did not all receive the same dose (recommendations changed during study period)
    - All patients achieved high anti-S (spike) IgG titers
    - Failed to achieve meaningful neutralization of Omicrobn-RBD at singe dose of 150mg, but neutralization significantly increased after a 300mg dose

Outstanding Questions

- Omicron subvariants
  - *Concern re. neutralizing abilities of monoclonal antibodies to VOCs and sub-variants of Omicron in vitro (lab)*
    - Resulted in increased dose of Evusheld in some jurisdictions
- Duration of response
  - *Estimated to be ~ 6 months*

- More research and clinical data needed to answer these questions

Takashita, 2022; Yamasoba 2022

Current Recommendations for Evusheld

- Intra-muscular (IM) injection x 2
  - *Total dose 300mg : 150mg tixagevimab + 150mg cilgavimab*
  - *With BA.4 and BA.5 → FDA has suggested increasing dose to 600mg*
    - Ontario Health reports emerging evidence that it has decreased activity with these subvariants and that clinical judgement should be exercised when determining dose
- Recommended to administer 2 weeks after a dose of covid-19 vaccination
- Patients should receive all eligible doses of vaccination prior to Evusheld, limited data on administration of vaccines post-Evusheld
- Considerations re side/effects: Generally well tolerated – local site reactions, rash, generalized reactions.
  - *Specific mention re cardiovascular or thromboembolic events**

Ontario Health, Oct 3, 2022

In Ontario:

- Consider for people at highest risk of an inadequate response to vaccination, upon discussion of risks & benefits:
  - *Solid Organ Transplant recipients*
  - *Stem Cell Transplant recipients*
  - *CAR-T Cell Therapy recipients*
  - *Other hematologic cancer patients undergoing treatment*
  - *People receiving anti-B-Cell Therapy (ex. Rituximab)**
  - *People with significant primary immunodeficiency**
- Must be
  - *At least 12 years old, weigh at least 40kg*
  - *NOT have had a current COVID-19 infection OR recent exposure*

Ontario Health, Oct 3, 2022

Non-Pharmaceutical Interventions

- NPIs: actions (apart from vaccines or pharmaceutical products) that slow spread of infection → apply to COVID-19 and other communicable diseases

Common NPIs:

- Staying at home when sick
- Hand hygiene
- Appropriate use of face masks
- Ventilation – outdoors, indoor improve ventilation
- Limiting contact*

Helpful Resources:

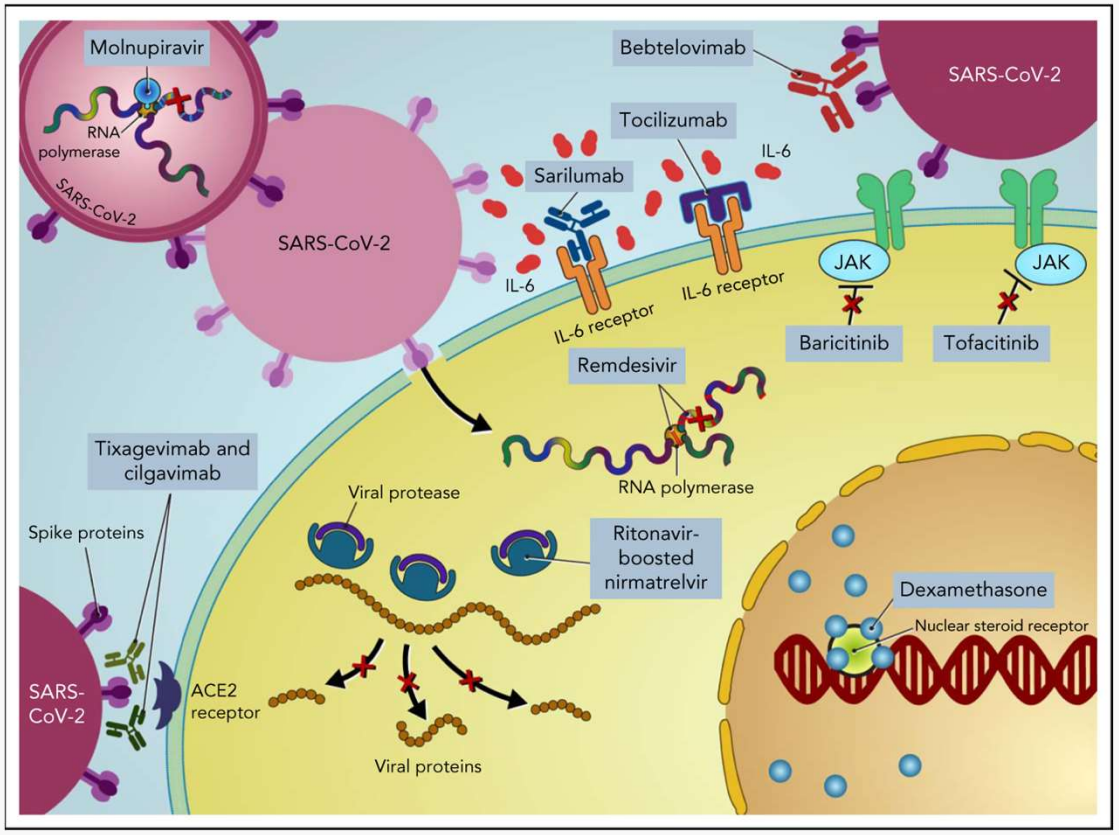
- Ontario: https://www.ontariohealth.ca/sites/ontariohealth/files/2022-05/Patient%20Handout%20-%20Evusheld%20-%20EN.pdf
- Quebec: https://www.quebec.ca/en/health/health-issues/a-z/2019-coronavirus/symptoms-transmission-treatment/preventive-treatment-against-covid-19-evusheldtm
- The Ottawa Hospital: https://www.ottawahospital.on.ca/en/2019-novel-coronavirus/covid-19-treatment-information/

PART 3: TREATMENT

Treatment of COVID-19

- Significant progress has been made since March 2020
  - *Some of the initial therapies used early in → found not to work*
  - *Data accumulated on therapies that did work*
- Trials such as RECOVERY, ACTT I & II and REMAP-CAP
  - *Generated data → used to guide recommendations for treatment*
- Now rely on treatment recommendations for management
  - *Generally consistent across jurisdictions*

How I treat and prevent COVID-19 in patients with hematologic malignancies and recipients of cellular therapies



Firas El Chaer,Jeffery J. Auletta,Roy F. Chemaly, How I treat and prevent COVID-19 in patients with hematologic malignancies and recipients of cellular therapies, Blood, 2022

Treatment of COVID-19

- Until late 2021, treatment guidelines have focused on hospitalizations patients
- Recommendations are based on severity of illness
- In Ontario, hospital practice generally reflects recommendations from the Ontario Science Table (OST)

Treatment of COVID-19: In Hospital

Severity of Infection	Definition	Treatment Recommendations
Moderately Ill	New oxygen requirements	Dexamethasone Remdesivir Consider: Tocilizumab or alternative
Critically Ill	Patient require ventilatory and/or circulatory support	Dexamethasone Tocilizumab or alternative

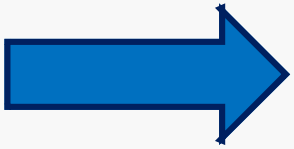
Adapted from Ontario Science Table (OST)

Treatment of COVID-19: Early Infection

- Late 2021 – attention shifted to **early intervention & outpatient therapies** for patients at high risk → What qualifies as **High Risk**?

Mildly Ill Patients

Patients who do not require new or additional supplemental oxygen from their baseline status



HIGHER RISK OF SEVERE DISEASE

Individuals who have a ≥5% risk of hospitalization or are immunocompromised

Ontario Science Table: Clinical Practice Guidelines
Updated: April 1, 2022

Treatment of COVID-19: Early Infection

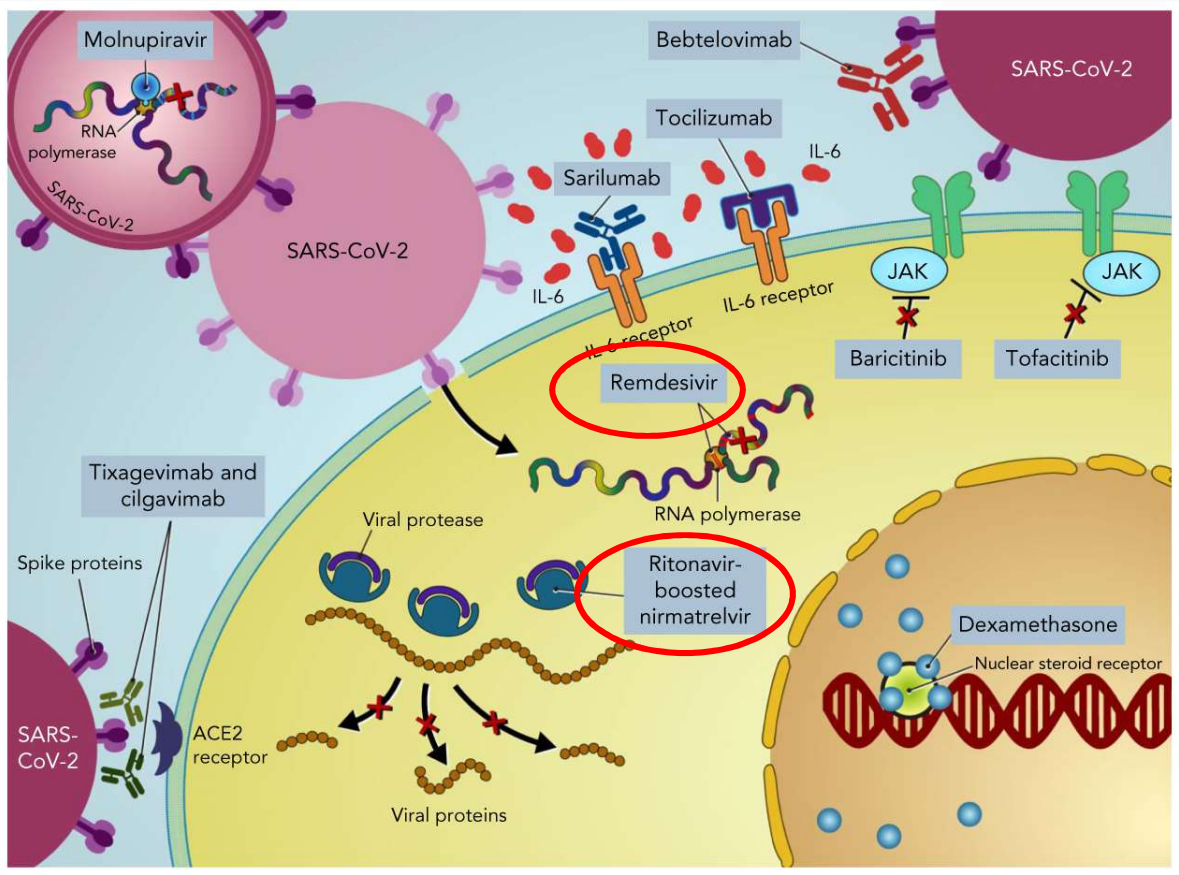
Original early treatments – Late 2021 – Early 2022

- Monoclonal antibodies were the initial main driver
  - *Casirivamb-imdevimab (Regen-CoV)*
    - Stopped when omicron variant became dominant
  - *Sotrovimab*
    - Used during early Omicron wave
    - Stopped when subvariants BA.2, BA.4 and BA.5 became dominant strains
- Despite discontinuation of use, set precedence for early and outpatient management of high-risk patients diagnosed with COVID-19 infection

Treatment of COVID-19: Early Infection

Current early treatments

- Shifted to antivirals
  - *Paxlovid (PO)*
  - *Remdesivir (IV)*



El Chaer, 2022

Treatment of COVID-19: Paxlovid

- Paxlovid = Nirmatrelvir / ritonavir
  - *Nirmatrelvir = SARS-CoV-2 protease inhibitors*
    - Stops viral replication
  - *Ritonavir = HIV protease inhibitor, but also a CYP3A4 inhibitor*
    - Boosts the action of Nirmatrelvir
- 1 dose is 3 tabs:
  - *300mg Nirmatrelvir (2 x 150mg tabs)*
  - *100mg ritonavir (1x 100mg tab)*

    *Dose is adjusted for kidney function
- Given twice a day for 5 days
- Approved by Health Canada January 2022

Treatment of COVID-19: Paxlovid

- EPIC HR Study Published in April 2022
- Randomized control trial (double-blind)
- 2246 adult patients with COVID-19
- Results: reduced risk of progression to hospitalization and death at 28 days
- Limitation: unvaccinated patients and those at high risk of progression to severe infection

Hammond, 2022

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19

Hammond J et al. DOI: 10.1056/NEJMoa2118542

CLINICAL PROBLEM

Safe and effective oral therapies for mild-to-moderate Covid-19 are needed for symptomatic, unvaccinated outpatients at high risk for progression to severe disease. Although monoclonal antibodies are currently available for this indication, they require administration and monitoring in a health care setting and may not work as well against emerging SARS-CoV-2 variants.

CLINICAL TRIAL

Design: An international, phase 2–3, double-blind, randomized, controlled trial assessed the efficacy and safety of the antiviral agent nirmatrelvir plus ritonavir (a pharmacokinetic enhancer) in preventing disease progression in unvaccinated adults with mild-to-moderate Covid-19 who were at high risk for progression to severe Covid-19.

Intervention: 2246 adults with confirmed SARS-CoV-2 infection were randomly assigned to receive nirmatrelvir (300 mg) plus ritonavir (100 mg) or matching placebo every 12 hours for 5 days, beginning within 5 days after the onset of Covid-19 symptoms. The primary outcome of the final analysis involving 1379 patients was the incidence of Covid-19–related hospitalization or death from any cause by day 28 in patients receiving treatment within 3 days after symptom onset.

RESULTS

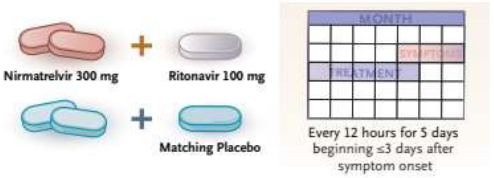
Efficacy: Nirmatrelvir plus ritonavir resulted in risk of progression to hospitalization or death at 28 days that was significantly lower than the risk with placebo.

Safety: The incidence of adverse events during or after treatment was similar in the two groups. Dysgeusia and diarrhea were more frequent with nirmatrelvir plus ritonavir than with placebo.

LIMITATIONS

- The trial was restricted to unvaccinated patients and those at high risk of progression to severe Covid-19.

Links: Full Article | NEJM Quick Take | Editorial



Treated ≤3 Days after Onset of Symptoms through Day 28 (modified intention-to-treat population)

	Nirmatrelvir Group N = 697	Placebo Group N = 682
Total number of patients with event	5	44
Covid-19–related hospitalization	5	44
Death from any cause	0	9
Estimated percentage with event (95% CI)	0.72 (0.30–1.73)	6.53 (4.90–8.68)
Difference ±SE from placebo — percentage points	−5.81±1.01	
Relative risk reduction	88.9%	

Adverse Events during Treatment Period (safety-analysis population)

	Nirmatrelvir Group N = 1109	Placebo Group N = 1115
No. of adverse events	476	525
Patients with any adverse event — no. (%)	251 (22.6)	266 (23.9)
Serious adverse event	18 (1.6)	74 (6.6)
Maximum grade 3 or 4 adverse event	45 (4.1)	93 (8.3)
Maximum grade 5 adverse event	0	13 (1.2)
Discontinued drug or placebo because of adverse event	23 (2.1)	47 (4.2)
Had dose reduction or temporary discontinuation owing to adverse event	4 (0.4)	4 (0.4)

CONCLUSIONS

As compared with placebo, nirmatrelvir plus ritonavir reduced the risk of Covid-19–related hospitalization or death from any cause in symptomatic, unvaccinated, nonhospitalized patients at high risk for progression to severe Covid-19.

Treatment of COVID-19: Paxlovid

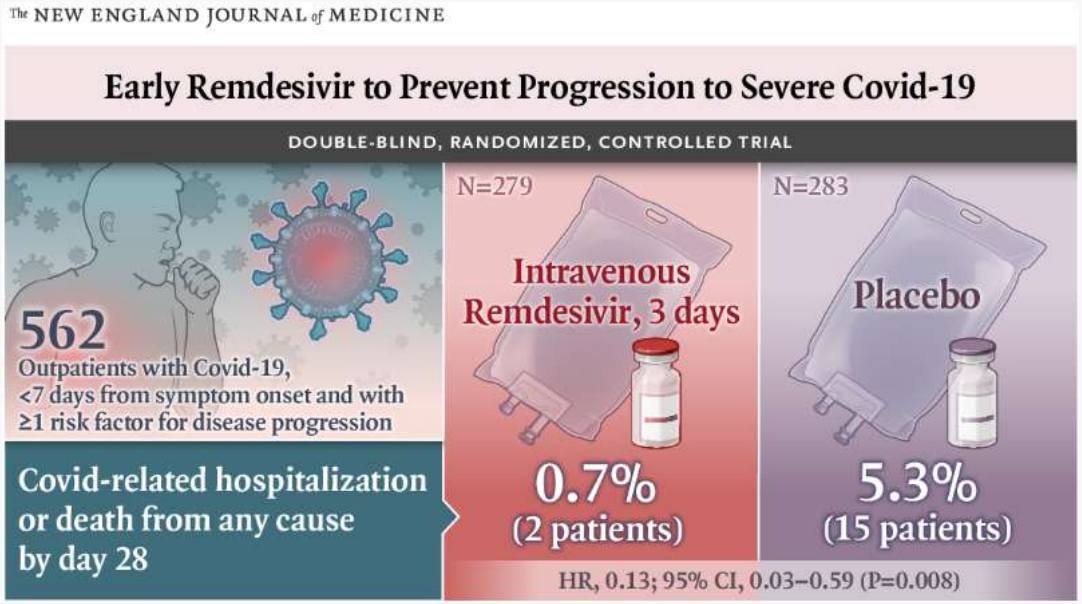
- Important to know → drug-drug interactions
- A physician or pharmacist should review other medications that a patient is taking to make sure no interactions
- Some medications cannot be given with Paxlovid, while other medications need to be adjusted
- Resources to manage this safely are available for physicians and pharmacists

Treatment of COVID-19: Remdesivir

- Remdesivir
  - *Direct-acting antiviral*
    - Inhibits viral replication by terminating RNA synthesis prematurely
- Given IV, once a day for 3 day course
  - *Day 1: 200mg IV*
  - *Day 2 & 3: 100mg IV*

Treatment of COVID-19: Remdesivir

- PINETREE Study Published in January 2022
- Randomized control trial (double-blind)
- 562 patients with COVID-19
- Results: reduced risk of progression to hospitalization and death at 28 days
- Limitation: patients had > 1 risk factor for severe infection, but many at risk-groups were underrepresented (inc. immunocompromise and cancer)
- Note study stopped early, original design was to enroll 1264 patients



Gottlieb, 2022

Current Practice

- **Nirmatrelvir/ritonavir (Paxlovid)** at a dose of 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all three tablets taken together orally twice daily for 5 days, **is recommended** for these patients if they present within 5 days of symptom onset.
  - In patients with moderate renal impairment (eGFR ≥30 to <60 mL/min), the dose should be reduced to 150 mg nirmatrelvir (one 150 mg tablet) and 100 mg ritonavir (one 100 mg tablet) taken together twice daily for 5 days. Paxlovid is not recommended in patients with severe renal impairment (eGFR <30 mL/min).
  - Specialized pharmacist consultation is important to mitigate any significant drug-drug interactions with other drugs.
  - Paxlovid should be preferentially deployed in regions and to populations where administration is a barrier to intravenous medication.
- **Remdesivir** 200 mg IV on day 1, then 100 mg IV daily for 2 days **is recommended** for these patients if they present within 7 days of symptom onset.

- Paxlovid
  - *5 day course, given orally for patients who are at high risk of severe illness within first 5 days of symptoms*
  - *Ensure drug-drug interactions are checked*
- Remdesivir
  - *3 day course, given IV for patients who are at high risk of severe illness within first 7 days of symptoms*

Treatment of COVID-19: Who is High Risk?

AGE (years)	NUMBER OF VACCINE DOSES			RISK FACTORS
	0 doses	1 or 2 doses	3 doses	
<20[1]	**Higher risk** if ≥3 risk factors[1]	Standard risk[1]	Standard risk[1]	• Obesity (BMI ≥30 kg/m²) • Diabetes • Heart disease, hypertension, congestive heart failure • Chronic respiratory disease, including cystic fibrosis • Cerebral palsy • Intellectual disability • Sickle cell disease • Moderate or severe kidney disease (eGFR <60 mL/min) • Moderate or severe liver disease (e.g., Child Pugh Class B or C cirrhosis)
20 to 39	**Higher risk** if ≥3 risk factors	**Higher risk** if ≥3 risk factors	Standard risk	
40 to 69	**Higher risk** if ≥1 risk factors	**Higher risk** if ≥3 risk factors	Standard risk	
≥70	**Higher risk**	**Higher risk** if ≥1 risk factors	**Higher risk** if ≥3 risk factors	
Immunocompromised[2] individuals of any age	**Higher risk**: Therapeutics should always be recommended for immunocompromised individuals not expected to mount an adequate immune response to COVID-19 vaccination or SARS-CoV-2 infection due to their underlying immune status, regardless of age or vaccine status.[1,2]			
Pregnancy	**Higher risk**[3]	Standard risk	Standard risk	

1. Evidence for the safety and efficacy of sotrovimab and nirmatrelvir/ritonavir (Paxlovid) in children <18 years of age is limited. While early evidence on risk factors for moderate and severe COVID-19 in children is emerging, the ability to reliably predict disease progression in children remains very limited, and the frequency of progression is rare. While not routinely recommended in children <18 years of age, the use of these agents may be considered in exceptional circumstances (e.g., severe immunocompromise and/or multiple risk factors, clinical progression) on a case-by-case basis. Multidisciplinary consultation with Infectious Diseases (or Pediatric Infectious Diseases) and the team primarily responsible for the child's care is recommended to review the individual consideration of these medications.
2. Examples of immunocompromised or immunosuppressed individuals include receipt of treatment for solid tumors and hematologic malignancies (including individuals with lymphoid malignancies who are being monitored without active treatment), receipt of solid-organ transplant and taking immunosuppressive therapy, receipt of chimeric antigen receptor (CAR)-T-cell or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy), moderate or severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome, common variable immunodeficiency, Good's syndrome, hyper IgE syndrome), advanced or untreated HIV infection, active treatment with high-dose corticosteroids (i.e., ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor-necrosis factor (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory. These individuals should have a reasonable expectation for 1-year survival prior to SARS-CoV-2 infection.
3. Therapeutics should always be recommended for pregnant individuals who have received zero vaccine doses.

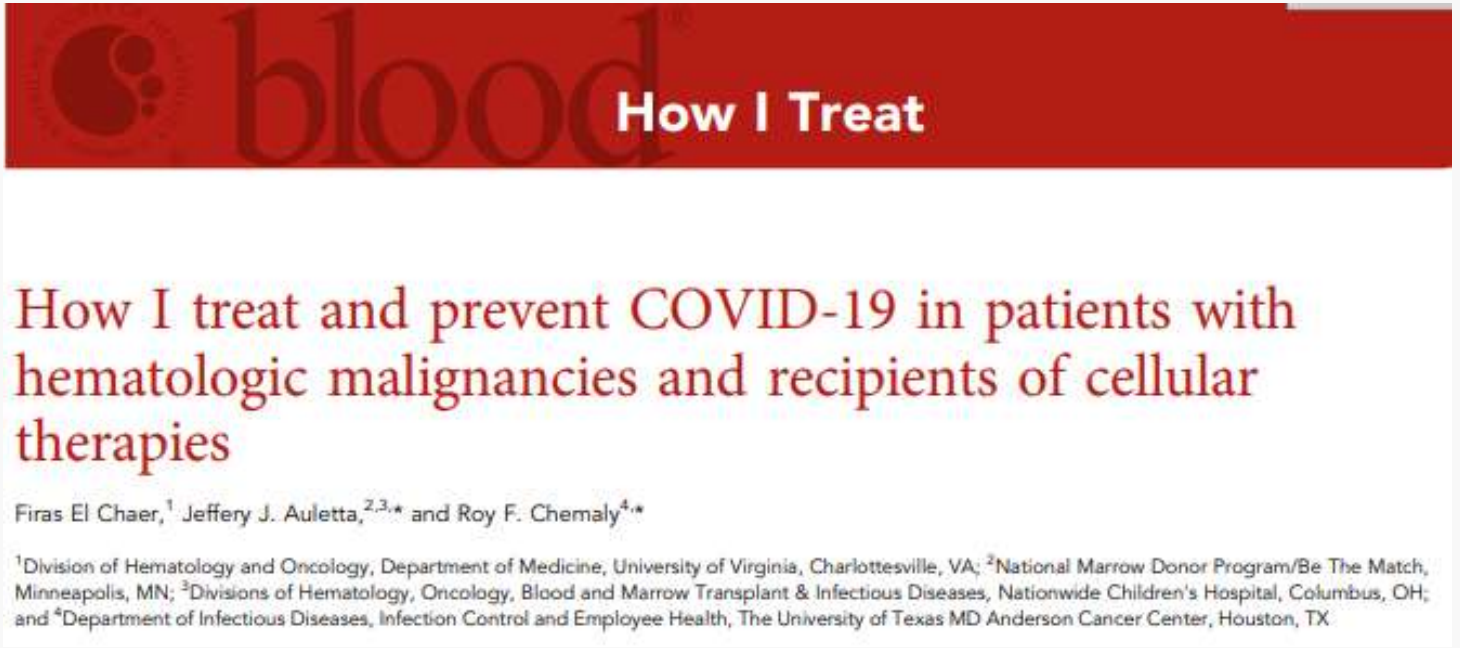
Ontario Science Table: Clinical Practice Guidelines
Updated: April 1, 2022

In Ontario:

- Health Care Provider should assess if patients are at high risk, if they should receive antiviral treatment and if any contraindications → through primary care provider (your doctors) or a clinical assessment centre
- Groups that are considered higher-risk include
  - *Immunocompromised*
  - *Age 70 and older*
  - *Age 60 and older, with less than 3 vaccine doses*
  - *Age 18 and older, with less than 3 vaccine doses AND 1 risk condition*
- Available antivirals in Ontario
  - *Paxlovid (oral)*
  - *Remdesivir (IV)*

Ontario Health, September 29, 2022

Treatment of COVID-19: Is this the same for patients with hematologic malignancies?



Treatment of COVID-19: Hematology

- Patients with hematologic malignancies are at higher risk of severe illness and may not respond as well to COVID-19 vaccines
  - *Highlights importance of early therapies to prevent progression of illness*
- Although there are not robust studies in these patients specifically, data from other trials in high risk patients, expert opinion and clinical experience support treatments recommended previously

El Chaer, 2022

Treatment of COVID-19: Hematology Early / Outpatient Treatment

Table 1.

Considerations for therapeutic management of nonhospitalized adults with cancer and mild to moderate COVID-19 without hypoxia

Supportive and symptomatic management	As per standard of care
Anti–SARS-CoV-2 monoclonal antibodies	Bebtelovimab within 7 d after symptom onset, as it retains activity against B.1.1.529 (0) and its BA.1 and BA.2 variants (evidence of in vitro activity against SARS-CoV-2, but no clinical efficacy data from placebo-controlled trials. Consider as alternative therapy when preferred therapies are not available.
Antiviral agents	5 d of ritonavir-boosted nirmatrelvir within 5 d of symptom onset (preferred agent with careful consideration for drug-drug interactions)
	3 d of IV remdesivir within 7 d of symptom onset (preferred agent but logistically challenging)
	5 d of molnupiravir within 5 d of symptom onset (alternative therapy when preferred therapies are not available)
Systemic steroids	No benefit of systemic steroids (including dexamethasone) in nonhospitalized patients and in the absence of another indication

El Chaer, 2022

Treatment of COVID-19: Hematology In-Hospital Treatment

Table 2.

Considerations for therapeutic management of hospitalized adults with cancer and COVID-19

Hospitalized not requiring supplemental oxygen*	Consider management as nonhospitalized adults with cancer and mild or moderate COVID-19 without hypoxia
	Insufficient evidence for the use of corticosteroids in the absence of another indication
Hospitalized requiring supplemental oxygen*	Remdesivir
	Dexamethasone
	Second immunomodulator for patients with increasing oxygen needs and systemic inflammation (tocilizumab or baricitinib: tofacitinib if baricitinib is not available and sarilumab if tocilizumab is not available)
Hospitalized requiring mechanical ventilation or extracorporeal membrane oxygenation	Remdesivir is not effective at this stage
	Dexamethasone
	Tocilizumab (sarilumab if tocilizumab is not available)

El Chaer, 2022

Helpful Resources:

- Ontario: https://www.ontario.ca/page/covid-19-testing-and-treatment
- Quebec: https://www.quebec.ca/en/health/health-issues/a-z/2019-coronavirus/symptoms-transmission-treatment/oral-treatment-against-covid-19-paxlovidmc
- Ottawa Public Health: https://www.ottawapublichealth.ca/en/shared-content/assessment-centres.aspx#Will-I-get-tested-for-COVID-19-during-my-in-person-assessment
- The Ottawa Hospital: https://www.ottawahospital.on.ca/en/2019-novel-coronavirus/covid-19-treatment-information/

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Blood Cancer Patients and COVID-19

https://www.lls.org/who-we-are/covid-19-vaccines-faq-patients-and-caregivers#latest-updates

- Take into consideration, some recommendations are specific to the US

Take Home Points

- Reduce the risk
  - *Receive appropriate COVID-19 vaccines*
    - 3-dose primary series
    - Booster doses including bivalent booster
  - *Your health care team may consider Evusheld (monoclonal antibody)*
  - *Continue to reduce risk with use of masks, avoiding sick contacts, etc*
- If you test + for COVID-19 or think you have symptoms
  - *Notify your health care provider!*
  - *Early treatment options are available*
    - Best if given early on in symptoms
    - Some patient requires medication review for important interactions

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