COVID-19 Vaccine Update

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April 22, 2021

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CANADIAN IMMUNIZATION RESEARCH NETWORK

Disclosures

- **Research Funding**
  - Government
    - CIHR
    - Public Health Agency of Canada
    - Public Works Canada
  - Industry
    - GlaxoSmithKline
    - Sanofi Pasteur
    - Pfizer
    - Merck
    - Janssen
    - Entos
    - IMV
    - CanSino
    - VBI
  - The CIRN SOS Network is funded by CIHR, PHAC and by collaborative agreements or investigator-initiated research agreements with GSK (influenza) and Pfizer (CAP/IPD), respectively

- **Consultant/Advisory Board/Committee**
  - Government
    - NS Dept of Health Experts Group
    - C19 Vaccine Expert Panel
    - DHW COVID-19 Key Populations Task Group
  - Industry
    - GlaxoSmithKline
    - Sanofi Pasteur
    - Merck
    - Pfizer
    - Medicago

Learning Objectives

- To review current data on authorized and anticipated vaccinations for COVID-19
- To review NACI recommendations for COVID-19 vaccination
- To discuss use of COVID-19 vaccines in those who are pregnant or breastfeeding, immunocompromised or have underlying autoimmune conditions
- To review diagnosis and treatment of Vaccine Induced Immune Thrombotic Thrombocytopenia (VITT) associated with AstraZeneca (and J&J) vaccine

SARS-CoV-2 virion

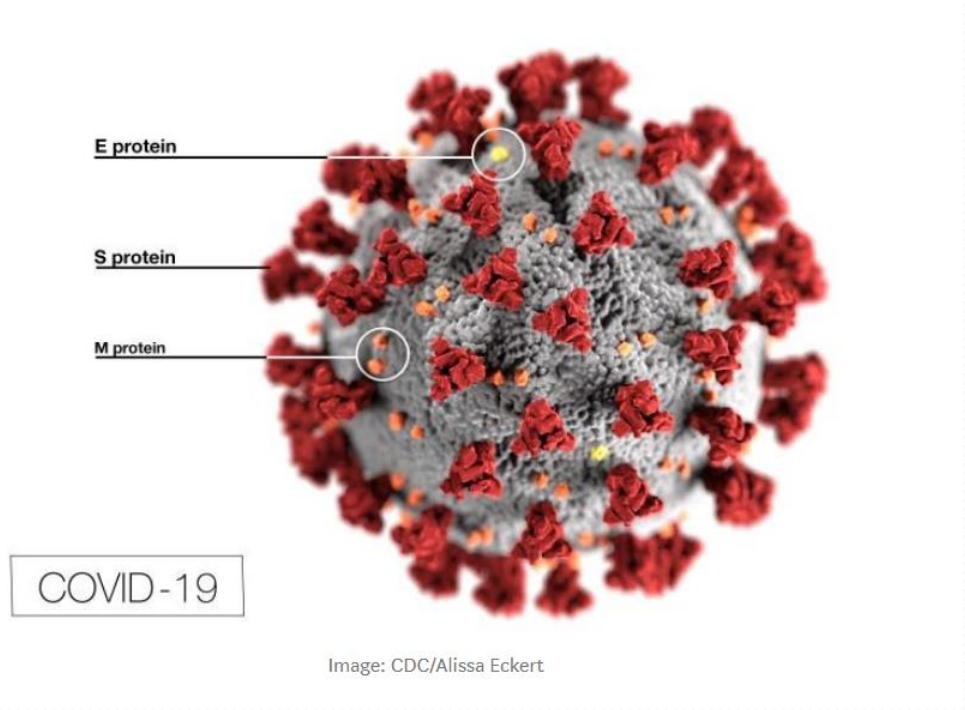
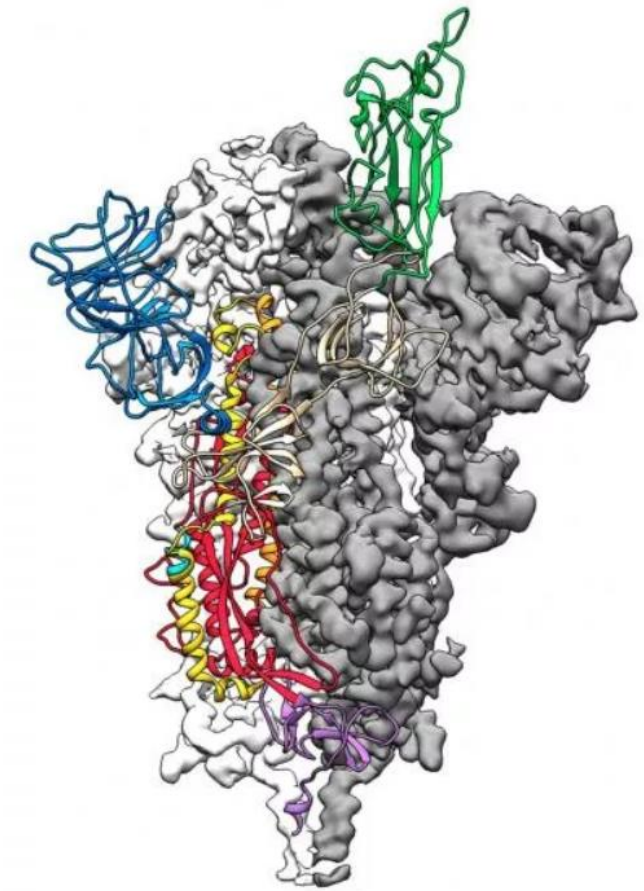


Image: CDC/Alissa Eckert

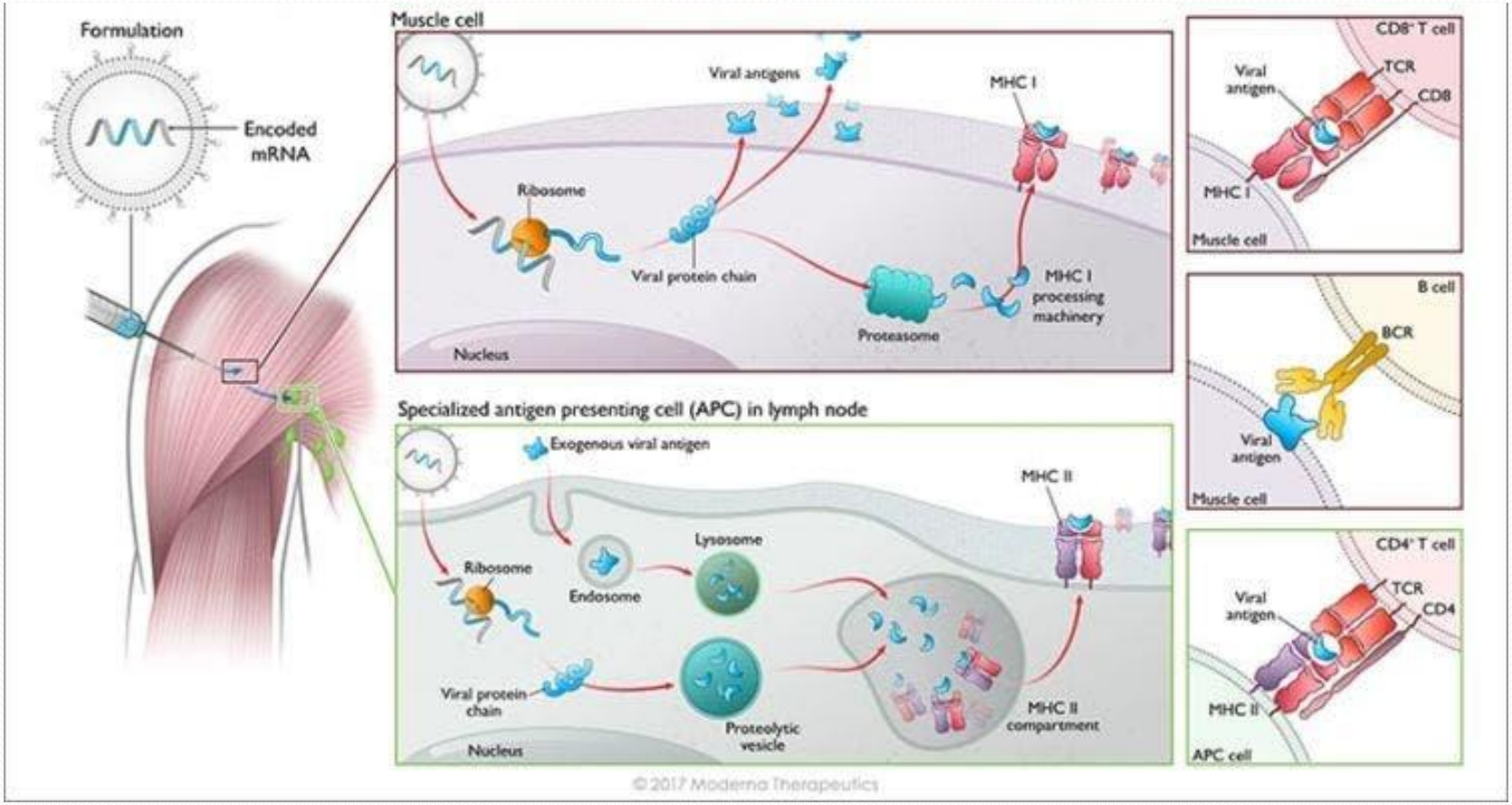
SARS-CoV-2 spike protein



This is the 3D atomic scale map or molecular structure of the SARS-2-CoV protein "spike" which the virus uses to invade human cells.
(Image: © Jason McLellan/Univ. of Texas at Austin)

DOI: 10.1126/science.abb2507

mRNA Vaccines: Mechanism of Action



Vaccine characteristics

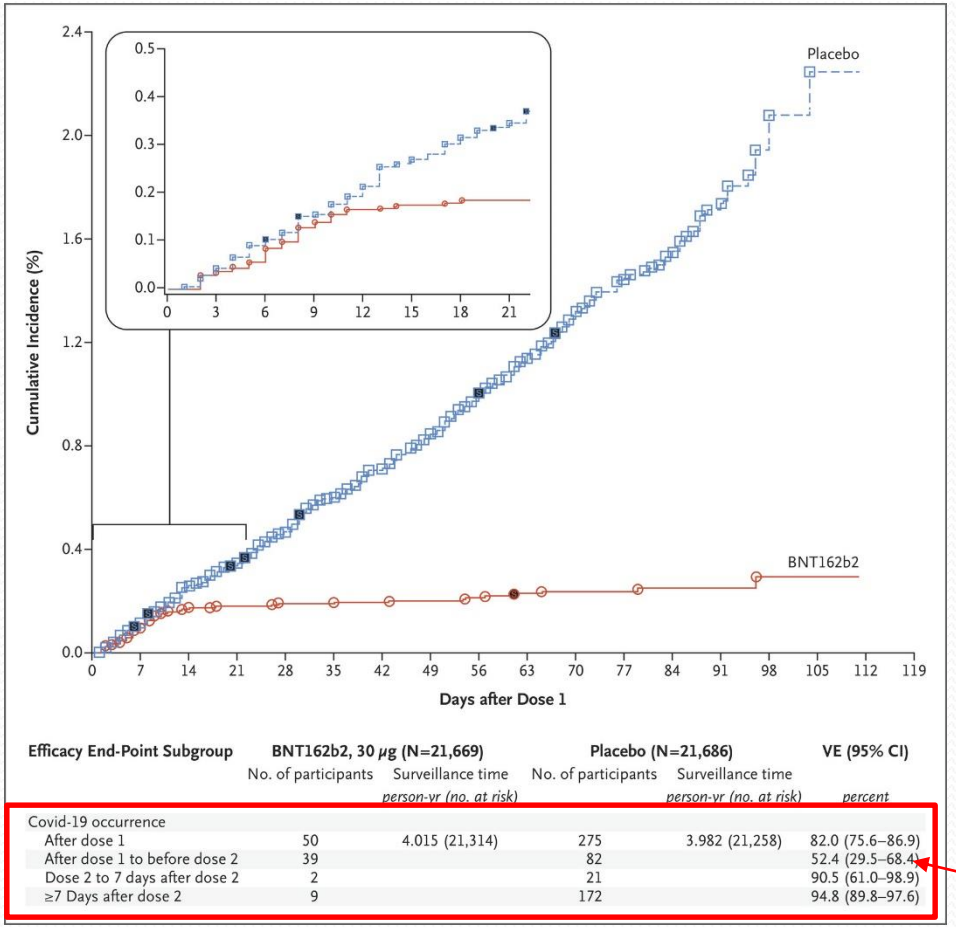
	Moderna (mRNA-1273)	Pfizer/BioNTech (BNT162b2)
Vaccine components	mRNA formulated into a lipid nanoparticle (LNP)	mRNA formulated into a lipid nanoparticle (LNP)
Authorized population	18y +	16y +
Vial size	10 dose multi-vial	5 (6) dose multi-vial
Reconstitution	None needed	Normal saline
Administration and dosing	2 x 0.5ml IM; 28d apart	2 x 0.3ml IM; 21d apart (alt 28d schedule OK per NACI)
Freezer storage	-20°C	-75°C
Transport	Frozen only (-20°C)	Ultrafrozen only (-75°C)
Fridge storage	30d	5d
Room temperature (unpunctured)	12h	2h
Once punctured	6h	6h

mRNA Vaccines: Summary Results (Efficacy)

	Moderna (mRNA-1273)[1]	Pfizer/BioNTech (BNT162b2)[2]
	Phase 3 - Age: 18+ - No LTCF residents - Size: 30,413 in US - dosing: 2xIM, 28d	Phase 3 - Age: **12-15y, 18-55y, 65-85y** - No LTCF residents - Size: 44,000 in US - Dosing: 2xIM, 21d
Efficacy Data	*Final Analysis* 185 Placebo/ 11 vaccine Data from 2 months post dose 2 **Primary endpoint: 94.1% vaccine efficacy (89.3- 96.8%)** **Efficacy in 65+: 86.4% (61.4-95.2)** **Secondary endpoint**: 30 severe cases and 1 death- all in Placebo group	Final analysis at 170 cases (162 Placebo/ 8 vaccine) Data from 1 week after dose 2 **Primary endpoint**: **95% vaccine efficacy (90.3-97.6%)** **Efficacy in 65y+: 94.7% (66.7-99.9)** **Secondary endpoint:** 10 severe cases- 9 in Placebo group.
Safety Data	Median follow up only approx. ≤ 14 weeks; quite reactogenic; no serious safety concerns	Median follow up only approx. ≤14 weeks; quite reactogenic; no serious safety concerns

[1]NEJM 2020:Dec 30 [2]NEJM 2020:Dec 10

Pfizer/BioNTech: Single dose efficacy

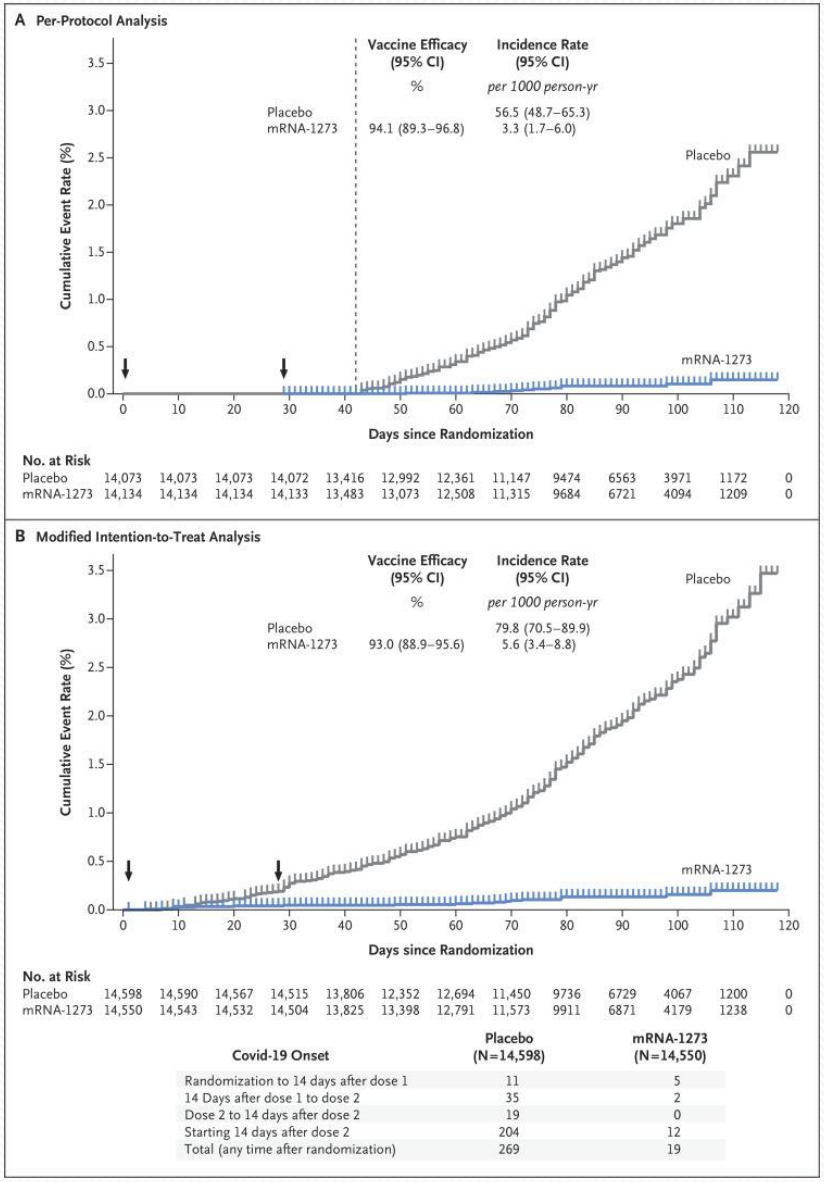


Efficacy End-Point Subgroup	BNT162b2, 30 μg (N=21,669) No. of participants	BNT162b2, 30 μg (N=21,669) Surveillance time *person-yr (no. at risk)*	Placebo (N=21,686) No. of participants	Placebo (N=21,686) Surveillance time *person-yr (no. at risk)*	VE (95% CI) *percent*
Covid-19 occurrence					
After dose 1	50	4.015 (21,314)	275	3.982 (21,258)	82.0 (75.6–86.9)
After dose 1 to before dose 2	39		82		52.4 (29.5–68.4)
Dose 2 to 7 days after dose 2	2		21		90.5 (61.0–98.9)
≥7 Days after dose 2	9		172		94.8 (89.8–97.6)

VE 14d after dose 1 to before dose 2 = **92.3% (69-98%)**

NB- Median duration of follow-up = 28d

Moderna: Single dose efficacy



Covid-19 Onset	Placebo (N=14,598)	mRNA-1273 (N=14,550)
Randomization to 14 days after dose 1	11	5
14 Days after dose 1 to dose 2	35	2
Dose 2 to 14 days after dose 2	19	0
Starting 14 days after dose 2	204	12
Total (any time after randomization)	269	19

Single dose efficacy:
After Dose 1 to before Dose 2: **80.2%** (55.2- 92.5%)
14d after dose 1 to before dose 2: **92.1%** (68.8- 99.1%)

NB: Median duration of follow-up= 28d

Why has NACI recommended a 0, 4 month interval for COVID-19 vaccines?

- While studies have not yet collected 4 months of data on VE following first dose, first 2 months of real world data (3 in UK- no exceptions to intervals) show sustained high level of protection (70-80%; UK, Israel; Quebec; BC)
- Immunologic principles and vaccine science do not predict rapid waning in adults over a short time
- Modelling by PHAC demonstrated higher overall population level protection even with a 6 month interval
- Given limited vaccine supply, extending interval establishes population immunity faster, thereby protecting the vulnerable
- No evidence that extending interval will impact VOC

Are there populations that should be vaccinated on schedule?

- NACI has a process for ongoing review of emerging data that could influence recommendations
- Thus far, only small immunogenicity trials are available suggesting reduced response to first dose in some people
- Real-world effectiveness data from UK have not shown clinically important reductions in effectiveness in any group witn 0, 3 month interval
- Small trials of interest:
  - Cancer patients: SOAP trial (pre-print: medRxiv)
    - Pfizer vaccine; n= 151 elderly patients with ST and haem malignancy vs 54 controls
    - 39% of solid cancer and 13% of heam cancer had anti-SARS-CoV-2 Ab 2 weeks post dose 1 vs 97% controls
    - If dose 2 given at 3 weeks, 95% of solid cancer patients had anti-SARS-CoV-2 Ab 2 weeks post dose 2 vs 43% of solid cancer and 8% of haematologic cancer if dose 2 delayed (single dose)
  - Seniors: 12 LTCF residents (age 82) vs 36 HCW
    - Neutralizing Ab post dose 1 was 2-4-fold lower in LTCF than HCW controls

Are there populations that should be vaccinated on schedule?

- Solid organ transplant recipients (JAMA online Mar 15)
  - 436 transplant recipients; median age 56y
  - 52% received Pfizer and 48% rec'd Moderna
  - Median time since transplant = 6.2y
  - Immunosuppression included tacrolimus, steroids, mycophenolate, azathioprine, sirolimus and everolimus
  - Ab detected in 17% 20d post dose 1
  - Recipients receiving antimetabolites, older transplant recipients and those who received Pfizer vaccine less likely to have Ab

    NOTE: no assessment of CMI; response post dose 2 not measured so not clear giving second dose rectifies response

Asymptomatic transmission

- Pfizer VE: US – 40K asymptomatic pre-op patients
  - 72% decrease ≥10d post dose 1; 80% post dose 2
- Pfizer VE: UK HCW- 75% decrease post dose 1
- Pfizer VE: Israel- 75% decrease post dose 1; 94% post dose 2
- mRNA: US CDC (3h ago!)- 4000 HCW- 80% decrease post dose 1; 90% post dose 2 (MMWR March 29, 2021)
- Moderna in clinical trials: asymptomatic infn in 15/14,000 (0.1%) in vaccine arm vs 39/14,000 (0.3%) in placebo arm suggesting reduction in asymptomatic infection of about 2/3
- J&J (clinical trials): 74% decrease
- Several studies showing decreased viral load with breakthrough infection
- AstraZeneca: no impact on asymptomatic infection

Local injection site reactions

VACCINE	Any reaction	Pain/tenderness	Swelling	Redness	Swollen lymph nodes
Moderna					
Dose 1	85%	80%	5%	2%	10%
Dose 2	90%	90%	10%	8%	15%
Pfizer					
Dose 1	85%	83%	6%	5%	-
Dose 2	85%	78%	6%	6%	-
AstraZeneca					
Dose 1	75%	54%/ 64%	10%	14%	NA
Dose 2	less				

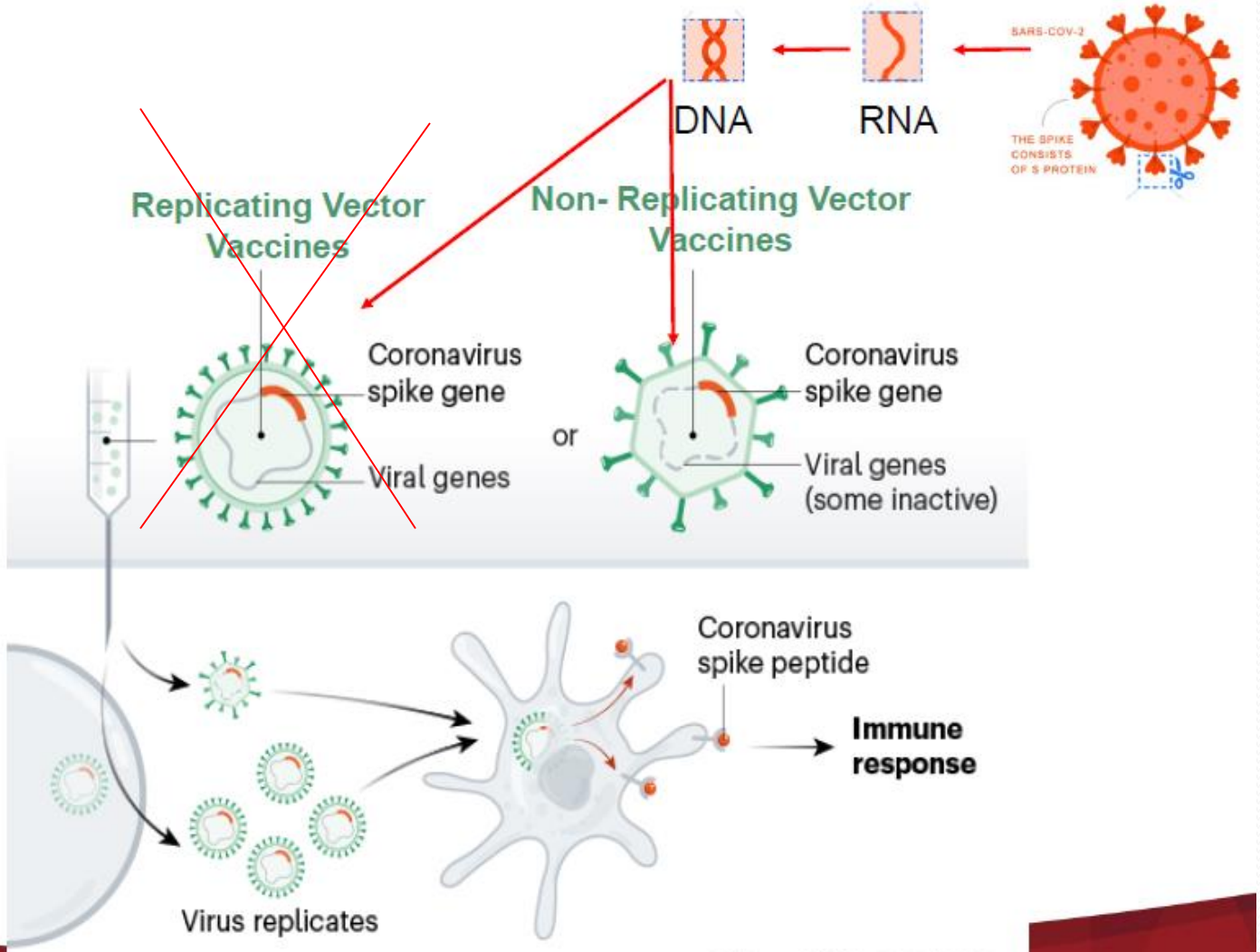
General reactions

VACCINE	Any reaction	Fever	Headache	Fatigue	Sore muscles	Chills	Nausea /vomiting
Moderna							
Dose 1	60%	1%	30%	35%	20%	5%	5%
Dose 2	80%	15%	60%	65%	60%	50%	20%
Pfizer							
Dose 1		1%	25%	34%	14%	6%	0%
Dose 2		11%	39%	51%	29%	23%	1%
AstraZeneca							
Dose 1	73%	8%	53%	53%	44%	32%	22%
Dose 2	less						

Implications for Occupational Health

- Local and systemic AEs common, particularly after Dose 2
- ~15% will experience fever post-dose 2; fatigue, headache and chills common (worse post dose 2)
- No role for prophylactic acetaminophen/ibuprophen but can be used to treat symptoms
- In NS HCW meeting COVID case definition (fever OR 2 or more of sore throat, runny nose, headache or SOB) should NOT REPORT TO WORK and should arrange a COVID test
- Attempt to avoid many people from same clinical area being vaccinated on same day to avoid service implications of AEs

Viral Vector Vaccines



Callaway 2020 ©nature

Viral Vector Vaccines

Advantages	- Established activation of humoral and cellular responses without an adjuvant - Potential boosted immunity to vector virus - Technology authorized in 3 vaccines – 2x Ebola and a dengue/yellow fever vaccine
Disadvantages	- Potential for reduced immune responses due to vector seropositivity (increased impact with age) - Potential blunting of response to Dose 2 and to future vaccines using the same platform

AstraZeneca Vaccine Efficacy

	AstraZeneca/Oxford
	Phase 3 - Age: 18+ - Size: 12,158 SD/SD - dosing: 2xIM, 29d
Efficacy Data	**Symptomatic illness** >14d post dose 2: **62%** (51.8-71.7) ≤65y = 63% (51-72%) >65 = 51% (-66 TO 85%) **82.4%** (47- 94%) if interval **>12wks in ≤65y** No estimate >65y (n= 1375) **Asymptomatic illness** >14d post dose 2: **-4.3%** (-416- 79) Symptomatic illness >21d post **dose 1: 71%** (59-86) (x 3 mos)
Safety Data	N/A: trial paused for investigation a neurological in a participant

1Lancet 2020: Dec 8; 2NEJM 2021: Jan 14

AstraZeneca Vaccine Effectiveness

- Currently available effectiveness data for the AstraZeneca COVID-19 vaccine is for a single dose in the United Kingdom population
- In adults **≥70** years of age, effectiveness against confirmed symptomatic COVID-19 is:
  - 60% (95% CI: 41–73%) at 28–34 days post-vaccination
  - **73% (95% CI: 27–90%) at 35+ days post-vaccination**
- In adults **≥80** years of age, effectiveness against hospitalizations is **37% (95% CI: 3–59%)** at 14-28 days post-vaccination
- In adults **≥18** years of age, effectiveness against hospitalization is **94% (95% CI: 73–99%)** at 28-34 days post-vaccination
  - **Pooled** analysis of Pfizer and AstraZeneca estimated effectiveness in older adults of:
    - 65–79 years: **79%** (95% CI: 17–95%) at 28–34 days post-vaccination
    - ≥80 years: **81%** (95% CI: 65–90%) at 28–34 days post-vaccination

Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT)

Summary

- Rare, serious blood clots, including cerebral venous sinus thrombosis with thrombocytopenia
- Cases have primarily been in women <55y
- Most have occurred 4-16d after AZ vaccine
- MOA- development of antibodies that “activate” platelets leading to formation of clots and low platelets (similar to heparin-induced thrombocytopenia)
- No underlying risk factors for VITT have been identified
- Rate not yet known
  - March 18 EMA 1 per 800k vaccinated; CVST 8.9X increased over background rate; DIC “at least” 5X increased over background rate
  - Paul Ehrlich Institut (Germany) 1 per 100,000 vaccinated; CVST 7X higher than baseline
- Case fatality rate 40%
- 3 cases reported in Canada (Quebec-F ; Alberta-60yoM; NB- 30yo)

Mechanism of action

Spontaneous heparin-induced thrombocytopenia

Heparin-induced thrombocytopenia (HIT)

- A rare syndrome
- 99% of the time occurs after heparin administration
- Heparin binds to platelet factor 4 which then bind antibodies
- The antibodies in this complex "activate" platelets, thrombosis formation and destruction of platelets (often to very low levels)
- Clots can form in venous (more common) or arterial systems

Spontaneous heparin-induced thrombocytopenia (HIT) / Autoimmune HIT

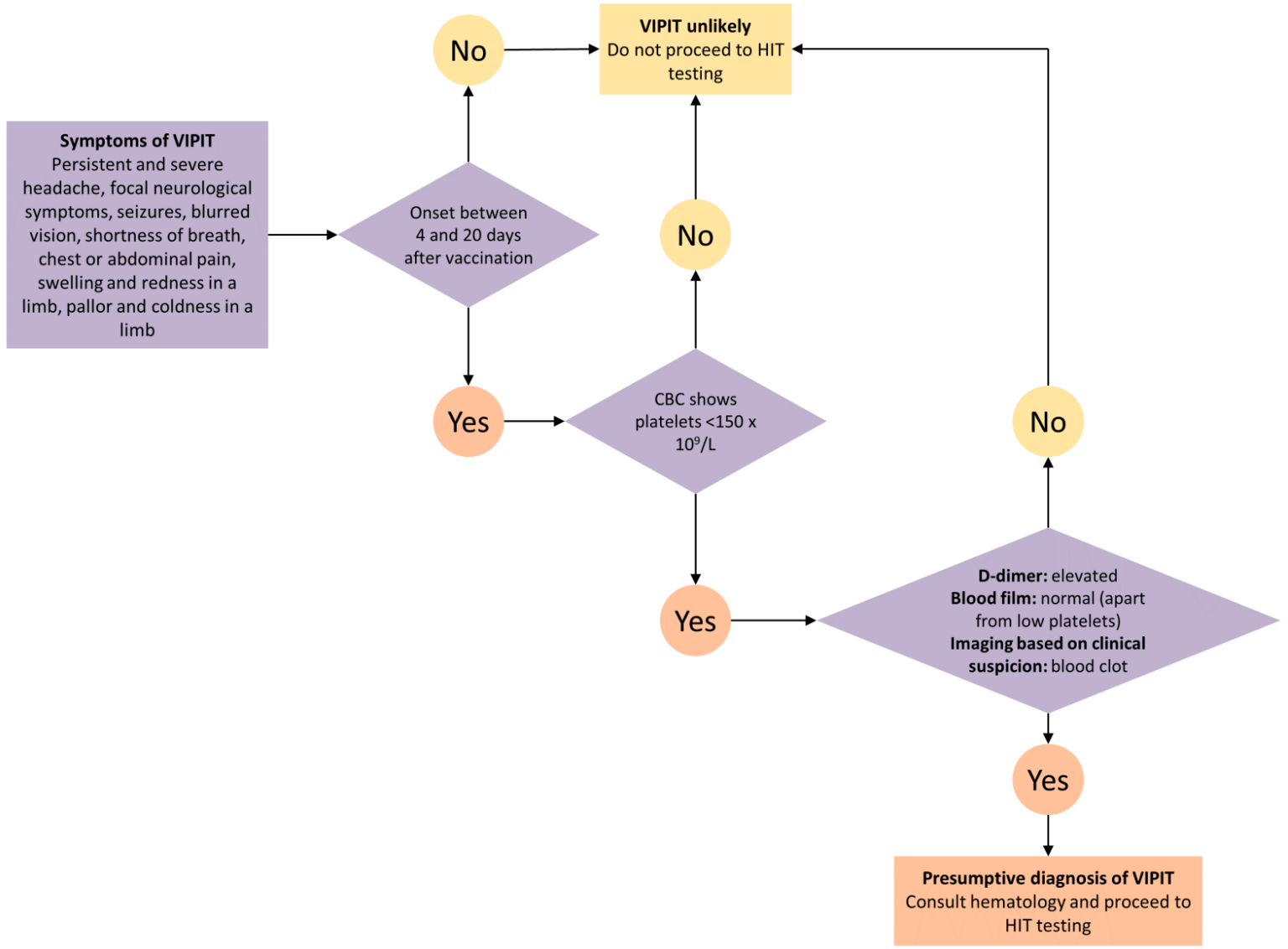
- No exposure to heparin
- Another substance serves the function of heparin (polyanionic substance that binds to platelet factor 4)
- Can be post-surgery (usually knee surgery) or infection
- Unsure what is triggering it post-vaccination – adenoviral vector; inflammation post-vaccination?
  - **Suggested new name is Vaccine-Induced Prothrombotic Immune Thrombocytopenia (VIPIT)**

Advice to those receiving AZ vaccine

- People who have received AZ vaccine should be counselled to seek emergency assessment if they develop any of the following between 4-20 days pose vaccine:
  - Persistent and severe headache
  - Focal neurological symptoms
  - Seizures
  - Blurred vision
  - Shortness of breath
  - Chest or abdominal pain
  - Swelling and redness in a limb
  - Pallor and coldness in a limb
  - Persistent bleeding
  - Multiple small bruises, reddish or purplish spots or blood blisters

Ontario Science Table Guidance

https://covid19-sciencetable.ca/science-briefs



Treatment of presumed VIPIT

- NO heparin
- No platelet transfusions
- First line anticoagulants: direct oral anti-Xa inhibitors (e.g. rivaroxaban, apixiban)
- **Consult hematology**
- IVIG 1g/kg daily for 2 days for severe or life-threatening blood clots

Data limitations re available COVID vaccines

- No/little safety or efficacy data in:
  - Women who are pregnant or breastfeeding
  - People who are immunosuppressed
  - People with underlying autoimmune conditions
- NACI recommends that these people be offered vaccination “if risk assessment deems that the benefit outweighs potential risks and if informed consent included discussion about the absence of evidence on the use of COVID-19 in these populations”

NACI Recommendations

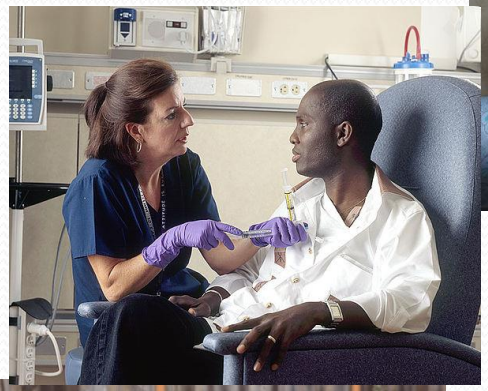
- https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/recommendations-use-covid-19-vaccines.html
- Updated Jan 12, 2021
- https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/rapid-response-extended-dose-intervals-covid-19-vaccines-early-rollout-population-protection.html
- Updated March 8, 2021

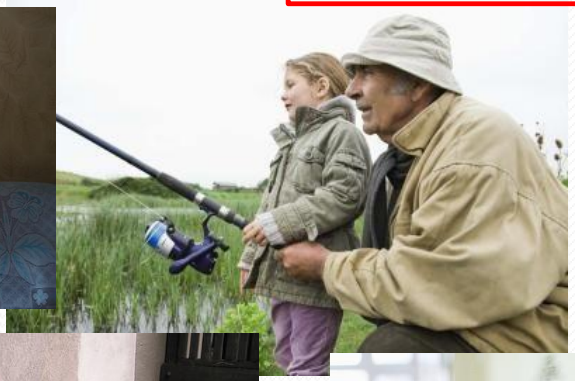
Other

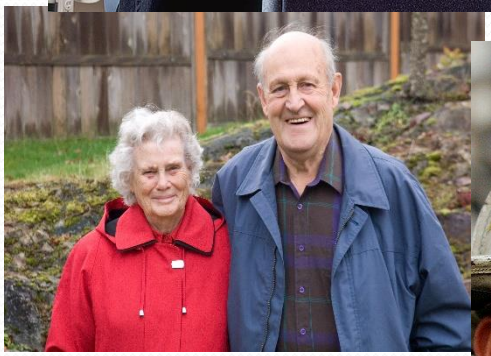
- Vaccination series should be completed with same product (same lot number not necessary)
- Do not give simultaneously with other vaccines- wait 14 days after another vaccine to give COVID vaccine; wait 28d after COVID vaccine to give another vaccine
- Place and read TST (or draw IGRA) before COVID-19 vaccine OR defer until 4 weeks post dose 2 (per CDC)

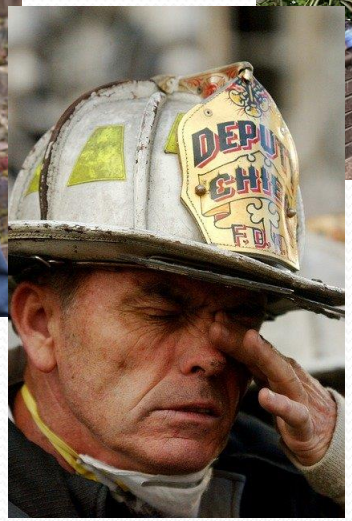
We're all in this together!

Insert your parent/grandparent here









Thanks!

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