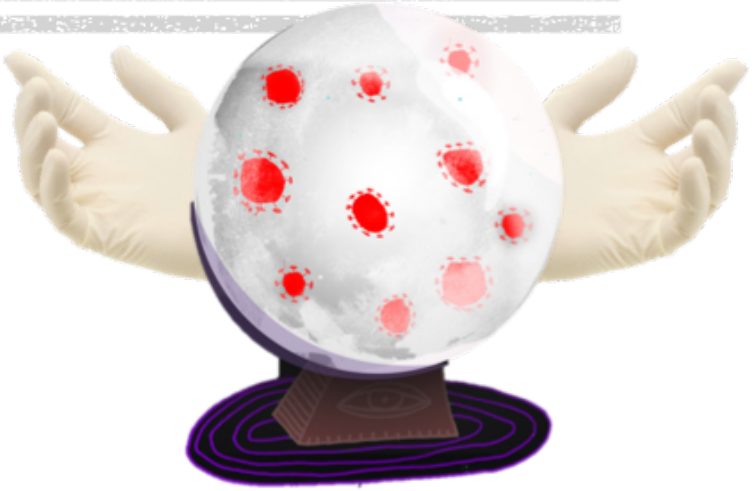
COVID-19 INTERVENTIONS:
FACTS, LESSONS & PREDICTIONS

Glen Drobot

Jamie Falk



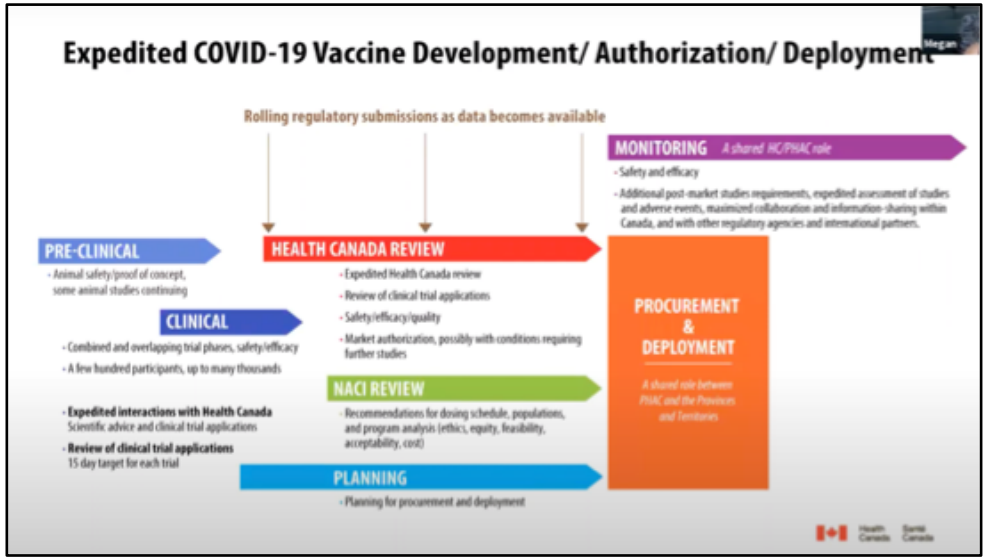
University of Manitoba

CONFLICTS OF INTEREST

- Presenter's Name: Jamie Falk, Glen Drobot
- **We have no conflicts to disclose**
- This program has received no financial or in-kind support from any commercial or other organization

LESSONS LEARNED?

1. If something really needs to get done, it often can be (especially with a collective global effort)
2. With enough regulatory resources, pretty much anything can be fast-tracked
3. There's a lot of low-value care out there
4. The Brady Bunch was way ahead of its time



Covid-19: an opportunity to reduce unnecessary healthcare

Recovering health systems can prioritise genuine need

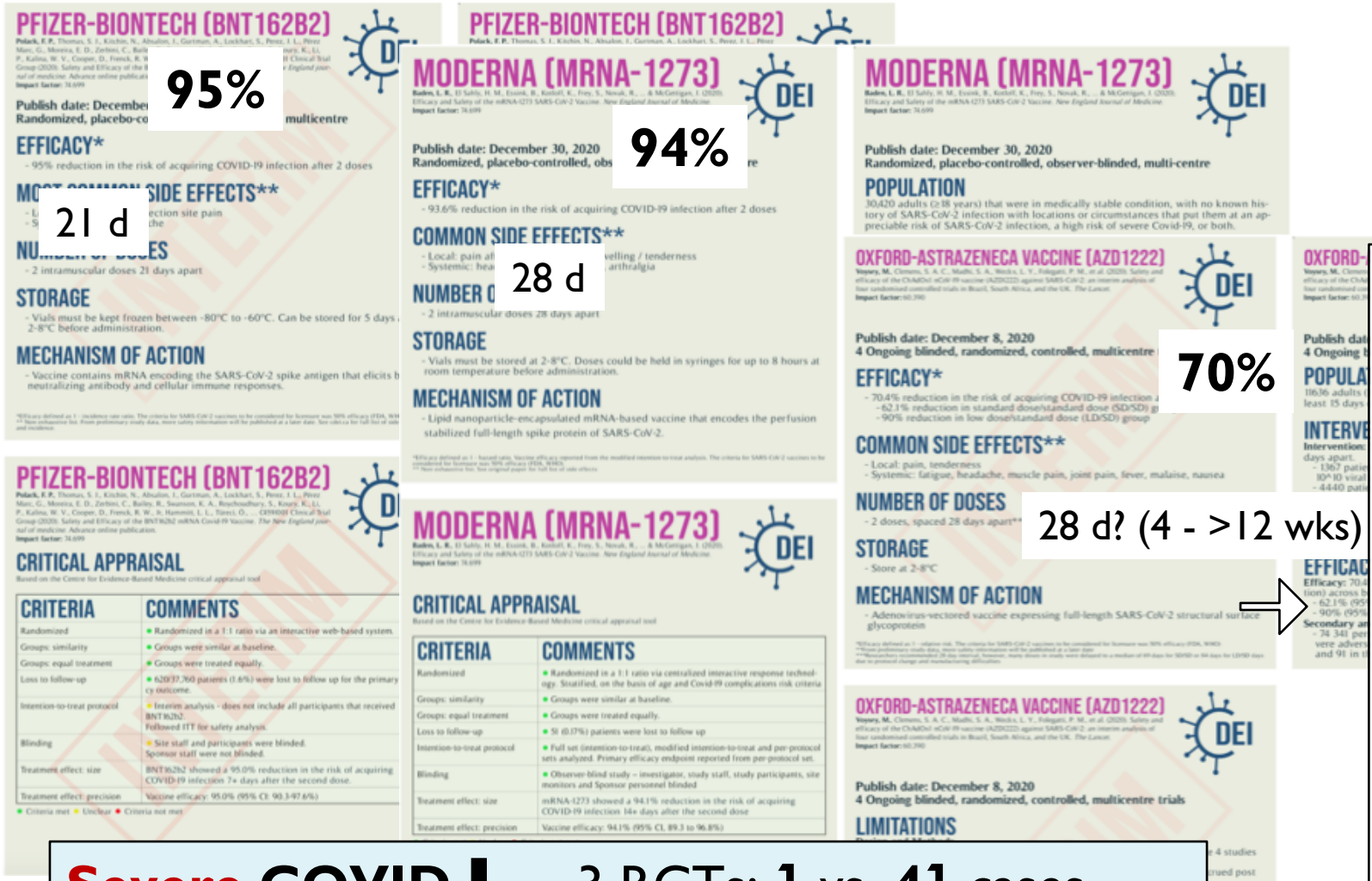
Ray Moynihan, [1] Minna Johansson, [2] Alies Maybee, [3] Eddy Lang, [4] France Légaré[5]

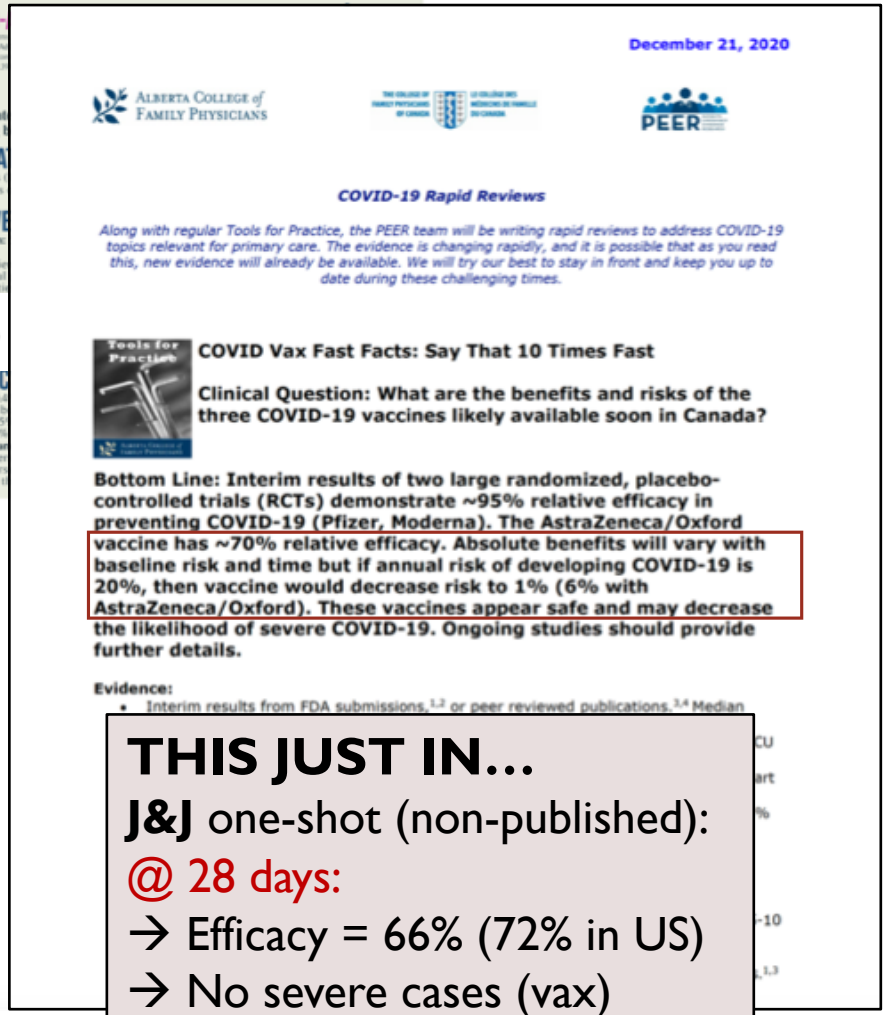
OUTLINE

1. Efficacy overview
2. Harms: short- & long-term
3. 1 *vs.* 2 doses
4. Mixing
5. More questions:

   → boosters, variants, pregnancy, immunocomp

BIG TRIALS, LOTS OF EARLY DATA





Severe COVID⬇… 3 RCTs: **1** vs. **41** cases

Asymptomatic transmission⬇… other vaccines would suggest yes, but we don't know

AND, majority of transmission from people with symptoms (?)

THIS JUST IN…

J&J one-shot (non-published):

@ 28 days:

→ Efficacy = 66% (72% in US)

→ No severe cases (vax)

https://cdei.ca/our-mission

https://gomainpro.ca/tools-for-practice/

HARMS: SHORT-TERM

X1-2d
(~10% >7d)

RCT DATA…

- **REACTOGENICITY**
  - Local: **85%** (vax) vs. ~20% (placebo)
  - Systemic: **75-80%** vs. 35-45%
    - Fever: **15%** vs. <1%
- Unsolicited reporting **5-20X** less common
- **SERIOUS:** 0.5-0.8% vs. 0.5-0.7%

What you need to know up to and including January 15, 2

No safety signals
(potential safety issues) have been identified

66
New AEFI reports since last update
(49 new non-serious and 17 new serious)

90
Total AEFI reports
(0.015% of all doses admini

63
Total AEFI reports were non-serious
(0.010% of all doses administered)

27
Total AEFI reports were serious
(0.004% of all doses administered)

601,901
Total doses administered
as of January 9, 2021

Adverse **E**vents **F**ollowing **I**mmunization that **individuals have reported**

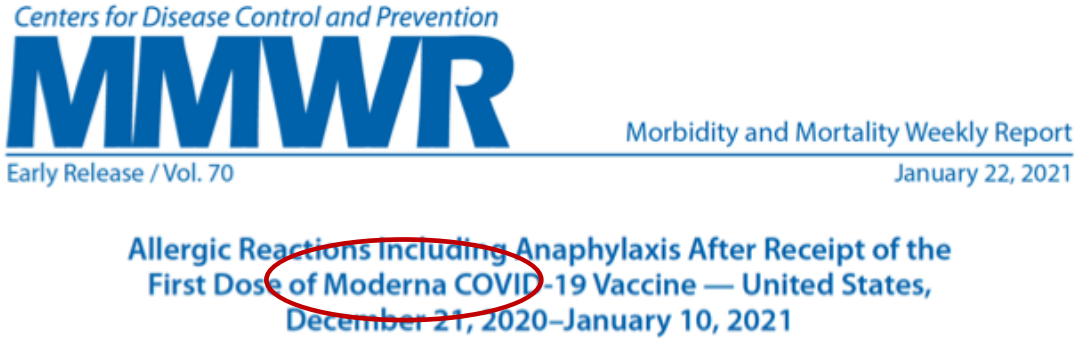
https://health-infobase.canada.ca/covid-19/vaccine-safety/

HARMS: SHORT-TERM (ANAPHYLAXIS)


Morbidity and Mortality Weekly Report (*MMWR*)

Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine — United States, December 14–23, 2020

Weekly / January 15, 2021 / 70(2);46–51


Centers for Disease Control and Prevention

MMWR

Morbidity and Mortality Weekly Report

Early Release / Vol. 70

January 22, 2021

Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Moderna COVID-19 Vaccine — United States, December 21, 2020–January 10, 2021

1,893,360 first doses:

→ 175 case reports as possible of severe allergic reactions

→ 21 cases of anaphylaxis
(**17**/21 had documented hx of allergies/allergic rxns)
= **11.1 cases/million doses**

- median interval from vaccine to symptom **onset = 13 min** (range = 2–150 min)

4,041,396 first doses:

→ 108 case reports as possible of severe allergic reactions

→ 10 cases of anaphylaxis
(**9**/10 had documented hx of allergies/allergic rxns)
= **2.5 cases/million doses**

- median interval from vaccine to symptom **onset = 7.5 min** (range = 1–45 min)

HARMS: LONG-TERM

"We don't know at this point" "Results are pending"

- **ENCOURAGING?**
  - Unprecedented oversight
  - most AEs happen in first 4-6 wks… we now have several months of follow-up with no strong signals
- **2 YEARS OF FOLLOW-UP** will be helpful, but…
  - For rare events, difficult to ever know (10s X thousands of participants may not be able to determine causality)
  - IF rare events found → translation of **BENEFIT:risk** will be essential

AT LEAST **1**, THEN **2** (maybe delayed) *vs.* **2** FOR "ALL" (on schedule)

Growing 'consensus' provinces should offer COVID-19 vaccine more widely, instead of holding back 2nd dose

Lauren Pelley · CBC News · Posted: Dec 24, 2020 5:17 PM ET | Last Updated: December 24, 2020

Annals of Internal Medicine
Jan 5, 2021 doi:10.7326/M20-8137
OBSERVATION: BRIEF RESEARCH REPORT

Alternative Dose Allocation Strategies to Increase Benefits From Constrained COVID-19 Vaccine Supply

- **FIXED** strategy (based on Pfizer vaccine) modeled after current U.S. policy:
  → reserve **50%** of each vaccine installment for 2nd doses to be administered 3 wks later
- **FLEXIBLE** strategy:
  → reserve **10%** of weekly supply for 2nd doses during each of the first three weekly installments
  → reserve 90% of supply for the next 3 wks
  → reserve 50% of doses for remaining 2 wks

Jan 5, 2021 doi:10.7326/M20-8137

Annals of Internal Medicine

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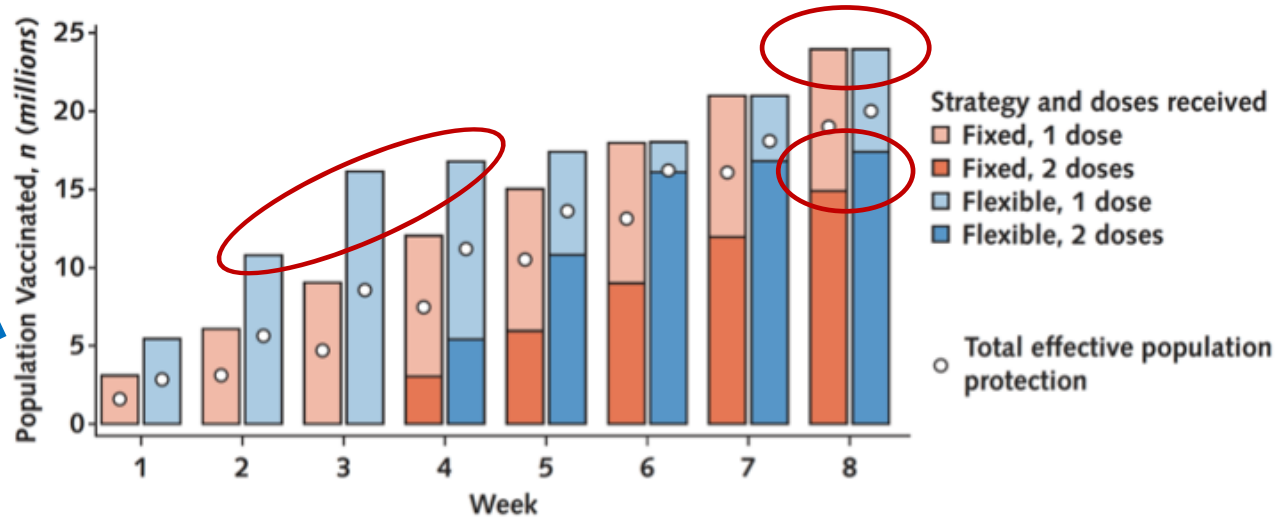
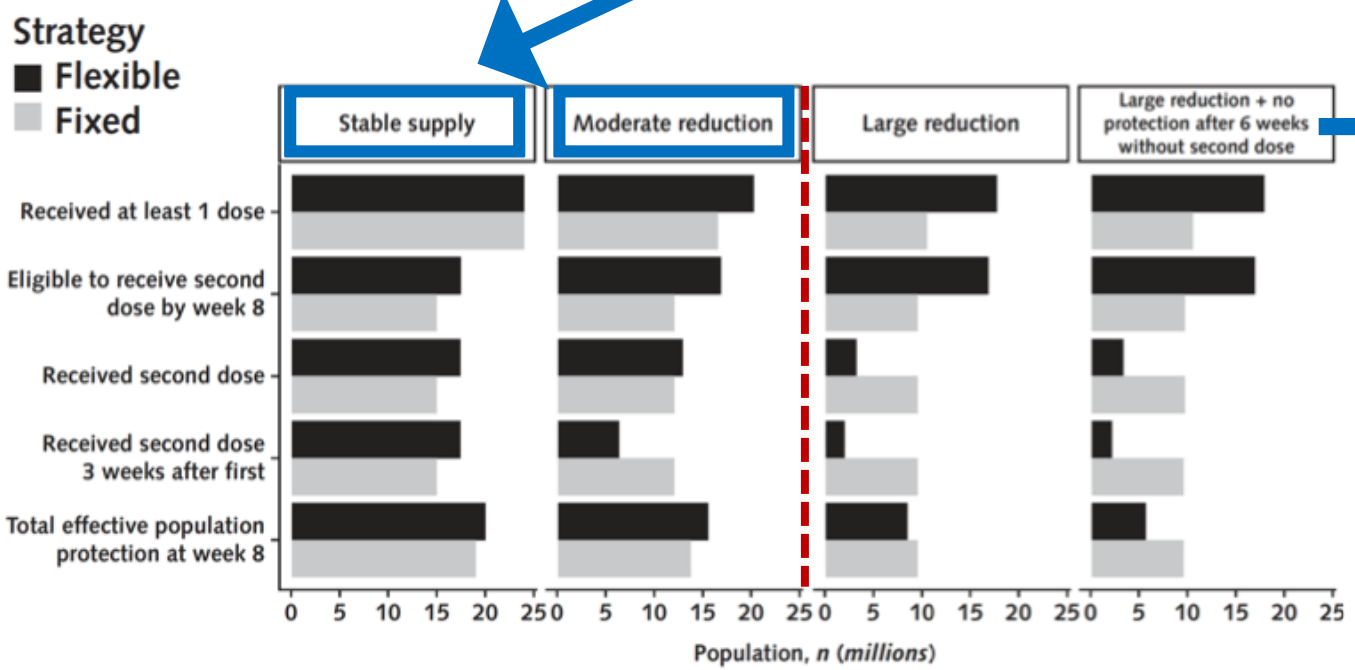




favors fixed model

- **steady** vaccine supply: **23-29%** more COVID-19 cases averted with flexible vs. fixed strategy
- **moderate** supply reduction: **27-32%** more COVID-19 cases averted with flexible vs. fixed strategy

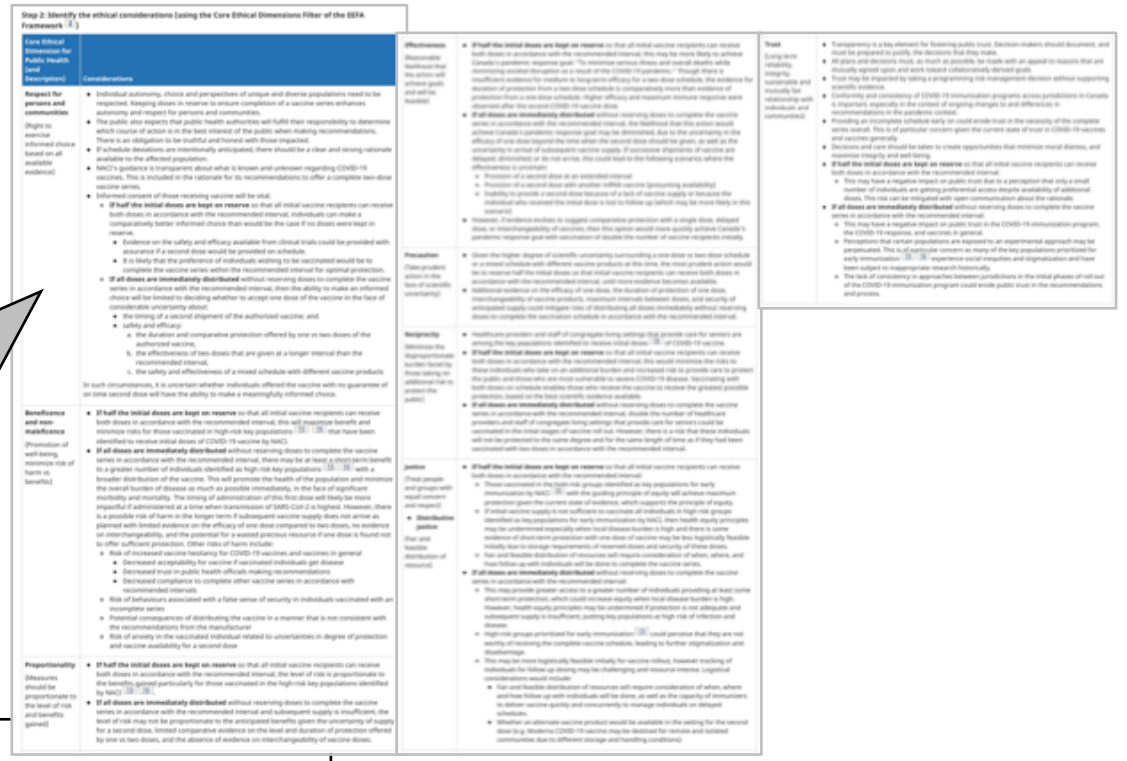
DOSING INTERVAL…WHO'S SAYING WHAT?

1st dose efficacy: 53% if <6wks
65% if >6wks

- **JCVI/UK:**
  - max interval = 12 wks for both A-Z & Pfizer vaccines
- **FDA**:
  - Stick to RCT schedules (= 3 or 4 wks)
- **Eur Medicines Agency, WHO, US CDC:**
  - Stick to RCT schedule (but 2nd dose could be as late as 6 wks after 1st)

Pfiz/Mod RCTs
1st→2nd: 20-42 d

NACI (Health Canada)



Conclusion:

Provinces and territories will have to determine the best course of action based on their own analysis and logistical contexts, including risks and unintended consequences that may occur as a result of delaying the second dose of vaccine, and in consideration of the in-depth ethical analysis provided here, recognizing that decisions made by provincial/territorial jurisdictions have impact throughout the country. Transparency in decision-making will be vital to foster continued trust. This ethics analysis may evolve as more evidence (e.g. effectiveness and duration of protection from the first dose of COVID-19 vaccine) emerges and as the certainty of vaccine supply increases. Research and evaluation in this area is encouraged.

MIXING BRANDS

UK trial to mix and match Covid vaccines to try to improve potency

Pilot planned for January will give subjects a shot of both Oxford/AstraZeneca and Pfizer/BioNTech versions

theguardian.com

IMPORTANT: **no data exist** on interchangeability of COVID-19 vaccines

BMJ 2021;372:n12 Jan 4…

Covid-19: Vaccine brands can be mixed in "extremely rare occasions," says Public Health England

?

Mary Ramsay, head of immunisations at PHE, told *The BMJ* that "every effort should be made to give [patients] the same vaccine, but where this is not possible it is better to give a second dose of another vaccine than not at all."

CDC

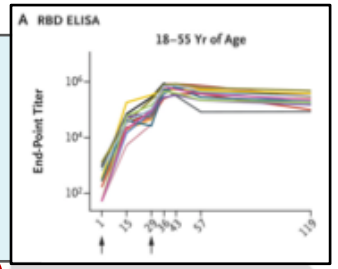
Jan 21… *"In **exceptional situations** in which the first-dose vaccine product **cannot be determined or is no longer available**, any available mRNA COVID-19 vaccine may be administered at a minimum interval of 28 days between doses"*

NACI

Jan 12… *"**If** the vaccine product used for a previously received dose is **not known, or not available**, attempts should be made to complete the vaccine series with a **similar type** of COVID-19 vaccine (e.g. mRNA vaccine)"*

MORE QUESTIONS

Based on **immunogenicity** data showing only slight decline up to 3 months post-2nd dose, **BUT**, we don't have a **disease correlate** to confirm protection



Widge, *NEJM* Jan 7, 2021

- When will **BOOSTERS** be necessary… info changes every week
  - Post-COVID19 infection → protection ≥3 months, ≥8 months → **to be continued**
  - Post-Pfizer or Moderna vaccine → protection ≥3-4 months → **to be continued**

(Reuters) - Immunity from Moderna Inc's COVID-19 vaccine should last at least a year, the company said on Monday at the J.P. Morgan Healthcare conference.

- Effects of **VARIANTS**…

NEWS · 26 JANUARY 2021

COVID research updates: Moderna vaccine vanquishes viral variants

Nature wades through the literature on the new coronavirus – and sur key papers as they appear.

NEWS · 29 JANUARY 2021

Novavax offers first evidence that COVID vaccines protect people against variants

Novavax's experimental shot is highly effective against the variant identified in Britain – but saw a worrying drop in efficacy against a lineage detected in South Africa.

- The **UNSTUDIED**: pregnancy, breastfeeding, immunocompromised, autoimmune
  - other non-live vaccines have had a good track record
  - additional studies planned… in the mean time → **shared decisions**

RISK:BENEFIT

* **NACI** (Jan 12): "…a complete vaccine series with a COVID-19 vaccine may be offered"

Faculty/Presenter Disclosure

- **Faculty: Dr. Glen Drobot**

- **Relationships with commercial interests:**
  - **Grants/Research Support: local principal investigator for hydroxychloroquine & anticoagulation for Covid19 trials**

Mitigating Potential Bias

- **Being open and honest about the trials I've been involved in**
- **Results from ATTACC interim analysis is publicly available**

An Intervention that Didn't work

- **Hydroxychloroquine has in vitro activity against SARS-CoV-2**
- **Hypothesis: early prophylaxis of close contacts would reduce symptomatic Covid19**
- **Randomized over 800 patients with a close contact within 4 days**
  - 5 days of HCQ vs matched placebo
  - Novel internet based screening, courier delivery

- **Approx 13% of subjects in both groups developed Covid19 symptoms/PCR confirmed**

An Intervention that Does work

- **Corticosteroids are used in a wide array of medical conditions, but often cause *harm* in ARDS (acute resp distress syndrome)**
- **Hypothesis: dexamethasone is hospitalized patients with confirmed Covid19**
- **Randomized over 4000 patients in the UK in the RECOVERY trial**
  - Up to 10 days of dexa 6mg vs standard of care
- **Absolute risk reduction of death at 28 days: 2.9%, NNT 33**
- **NNT 8.5 in ventilated patients, 29 in non-vent O2**

An Intervention that Probably Works

- **Early observational data from hard-hit areas showed increased frequency of thrombotic events in Covid19**
  - Observational, retrospective data suggested apparent benefit with full-dose anticoagulation
- **Hypothesis: full-dose anticoagulation is superior to standard of care in hosp Covid19 patients**
- **Multi-platform (3 trials), randomized, open-label, adaptive, Bayesian trial**
  - PI in the ATTACC trial, initiated in Manitoba/Canada in 4 countries

An Intervention that Probably Works

- **Primary outcome: Organ support-free days (OSFDs to day 21)**
  - Ordinal scale combination of in-hospital mortality and organ support-free days
  - A composite measuring clinically relevant morbidity and mortality

- **Key Secondary outcomes:**
  - Safety: Major hemorrhage (ISTH criteria) and HIT
  - Efficacy: Mortality, intubation, major thrombosis, PE, VTE, stroke, MI, length of stay in ICU and hospital

An Intervention that Probably Works

- **What happened?**
  - Data safety monitoring board (DSMB) recommended stopping ICU enrollment in December 2020 due to futility/possible harm
  - DSMB recommended stopping non-ICU enrollment January 21 for benefit in primary outcome
- **Results (n=2895 so far)**
  - Proportional odds ratio, approx 1.5 (CI 1.1- 2.2) for non-ICU patients

ATTACC, REMAP-CAP, and ACTIV IV-4a mpRCT

Primary outcome

State & D-dimer Strata	Proportional Odds Ratio Median (95% CrI)	Trial Statistical Conclusion
Moderate state, low D-dimer	1.57 (1.14 - 2.19)	**Superiority** [Probability of OR>1 = 0.997]
Moderate state, high D-dimer	1.53 (1.09 - 2.17)	**Superiority** [Probability of OR>1 = 0.991]
Moderate state, missing D-dimer	1.51 (1.06 – 2.15)	n/a⏃
Severe state	0.76 (0.60 – 0.97)	**Futility*** [Probability of OR>1.2 < 0.001]

* Posterior probability of **inferiority** [Probability of OR<1 = 0.985]

⏃ Not evaluated for stopping at interim

OR >1 represents benefit. A higher OR occurs when either mortality is improved and/or if those who survive have reduced requirement for organ support

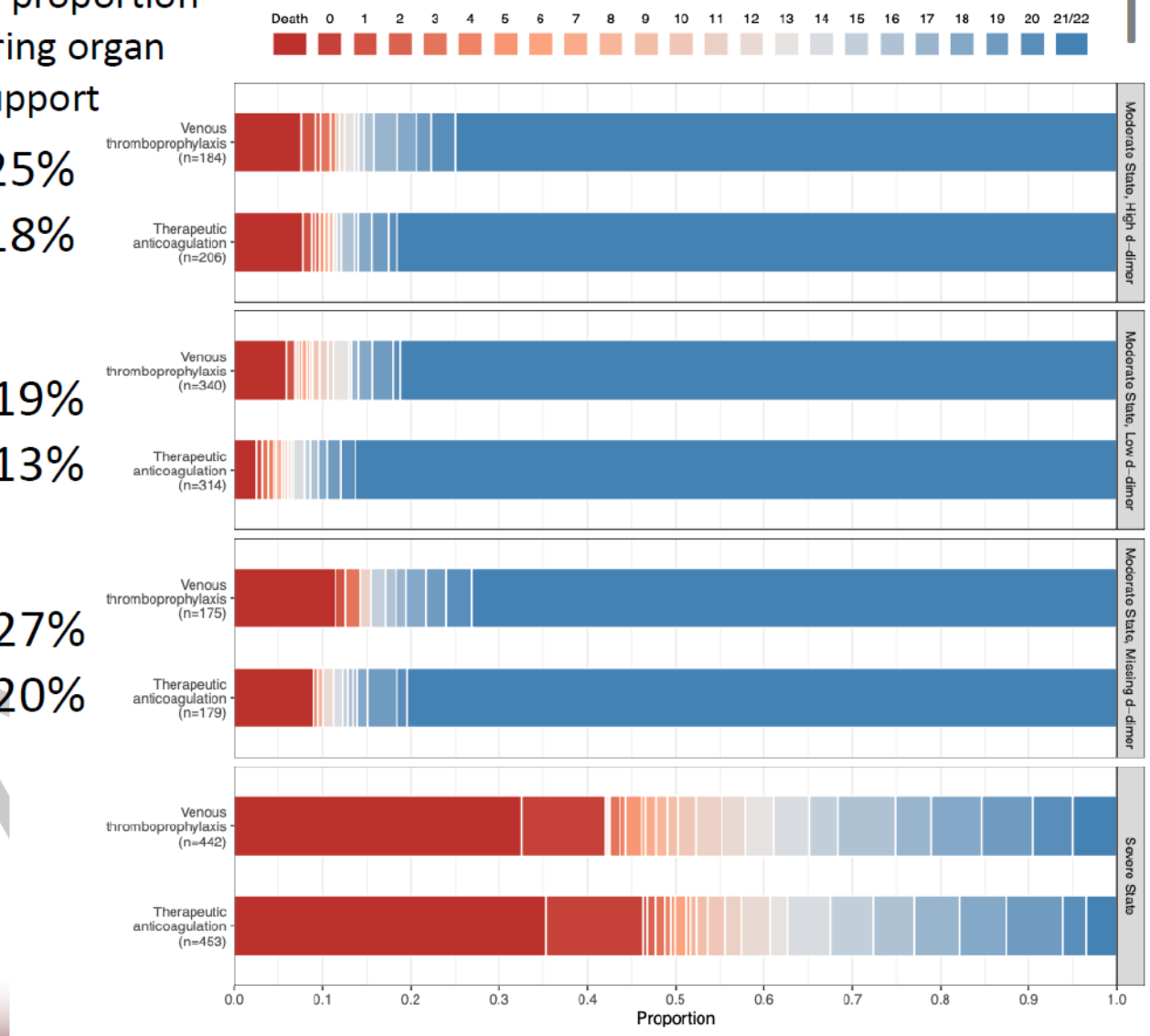
Release date: January 28, 2021

Pre-publication interim data, not from a locked database and not peer reviewed

Organ support-free days

INTERIM

Approx. proportion requiring organ support



~25%
~18%

Moderate state; HIGH D-dimer

~19%
~13%

Moderate state; LOW D-dimer

~27%
~20%

Moderate state; MISSING D-dimer

Severe state

Overall moderate state:

Requirement for organ support
Prophylactic anticoagulation – **~23%**
Therapeutic anticoagulation – **~16%**

Proportion requiring organ support represents a post-hoc analysis and is included to enhance clinical interpretation

Release date: January 28, 2021

Interim conclusion

- **In Moderate State:** Hospitalized, not on ICU Organ-Support
  - Therapeutic dose superior to usual care venous thromboprophylaxis with regard to organ support-free days in each d-dimer subgroup
  - Positive effect across morbidity and mortality components of primary endpoint
  - Major bleeding rate <2% on therapeutic anticoagulation

References

Boulware DR, Pullen MF, Bangdiwala KA. Randomized trial of hydroxychloroquine as post exposure prophylaxis for Covid19. NEJM 2020; 383: 517-25. 2017; DOI: 10.1056/NEJMoa2016638.

RECOVERY collaborative group. Dexamethasone in hospitalized patients with Covid19 – Preliminary report. NEJM 2020; DOI: 10.10156/NEJMoa2021436.

ATTACC trial: https://www.attacc.org/presentations