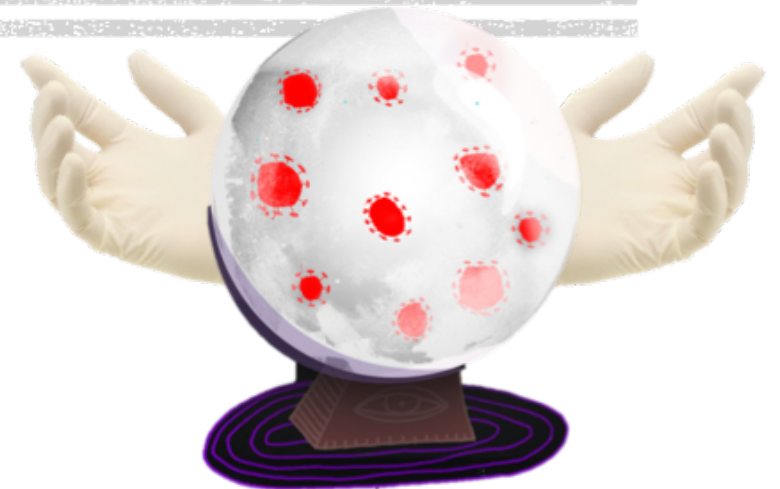


COVID-19 INTERVENTIONS: FACTS, LESSONS & PREDICTIONS

Glen Drobot

Jamie Falk



University
of Manitoba

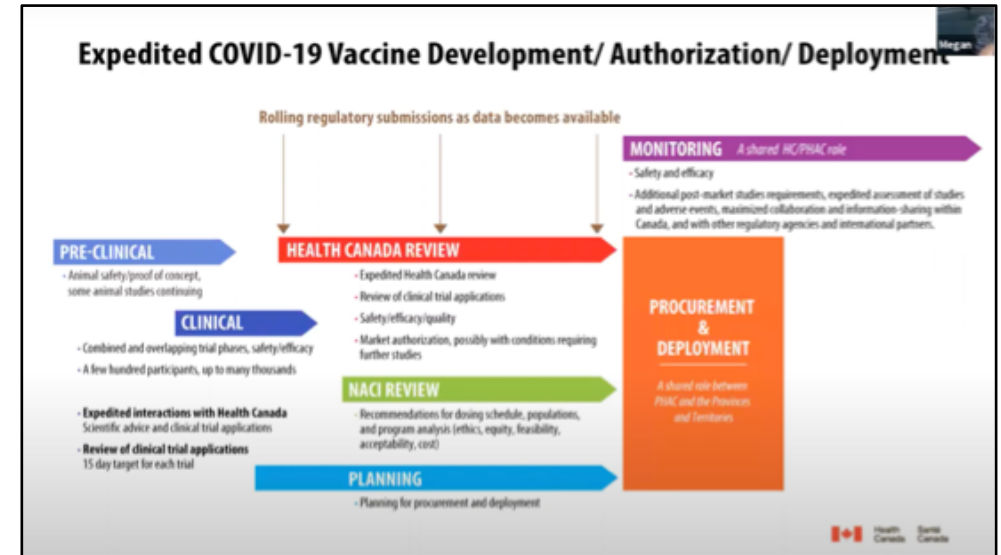
CONFLICTS OF INTEREST

- 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 Légaré⁵



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

PFIZER-BIONTECH (BNT162B2)

95%

21 d

EFFICACY*

- 95% reduction in the risk of acquiring COVID-19 infection after 2 doses

COMMON SIDE EFFECTS**

- Local: pain at injection site
- Systemic: headache, fatigue, muscle pain, joint pain, fever, malaise, nausea

NUMBER OF DOSES

- 2 intramuscular doses 21 days apart

STORAGE

- Vials must be kept frozen between -80°C to -60°C. Can be stored for 5 days, 2-8°C before administration.

MECHANISM OF ACTION

- Vaccine contains mRNA encoding the SARS-CoV-2 spike antigen that elicits both neutralizing antibody and cellular immune responses.

PFIZER-BIONTECH (BNT162B2)

MODERNA (MRNA-1273)

94%

28 d

EFFICACY*

- 93.6% reduction in the risk of acquiring COVID-19 infection after 2 doses

COMMON SIDE EFFECTS**

- Local: pain at injection site
- Systemic: headache, fatigue, muscle pain, joint pain, fever, malaise, nausea

NUMBER OF DOSES

- 2 intramuscular doses 28 days apart

STORAGE

- Vials must be stored at 2-8°C. Doses could be held in syringes for up to 8 hours at room temperature before administration.

MECHANISM OF ACTION

- Lipid nanoparticle-encapsulated mRNA-based vaccine that encodes the prefusion stabilized full-length spike protein of SARS-CoV-2.

MODERNA (MRNA-1273)

70%

28 d? (4 - >12 wks)

EFFICACY*

- 70.4% reduction in the risk of acquiring COVID-19 infection
- 62.1% reduction in standard dose/standard dose (SDSD) group
- 90% reduction in low dose/standard dose (LDSD) group

COMMON SIDE EFFECTS**

- Local: pain, tenderness
- Systemic: fatigue, headache, muscle pain, joint pain, fever, malaise, nausea

NUMBER OF DOSES

- 2 doses, spaced 28 days apart

STORAGE

- Store at 2-8°C

MECHANISM OF ACTION

- Adenovirus-vectored vaccine expressing full-length SARS-CoV-2 structural surface glycoprotein

OXFORD-ASTRAZENECA VACCINE (AZD1222)

70%

28 d? (4 - >12 wks)

EFFICACY*

- 70.4% reduction in the risk of acquiring COVID-19 infection
- 62.1% reduction in standard dose/standard dose (SDSD) group
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STORAGE

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MECHANISM OF ACTION

- Adenovirus-vectored vaccine expressing full-length SARS-CoV-2 structural surface glycoprotein

PFIZER-BIONTECH (BNT162B2)

CRITICAL APPRAISAL

Based on the Centre for Evidence-Based Medicine critical appraisal tool

CRITERIA	COMMENTS
Randomized	Randomized in a 1:1 ratio via an interactive web-based system
Groups: similarity	Groups were similar at baseline
Groups: equal treatment	Groups were treated equally
Loss to follow-up	62037/760 patients (1.8%) were lost to follow up for the primary outcome
Intention-to-treat protocol	Intention-to-treat analysis - does not include all participants that received BNT162B2. Followed ITT for safety analysis
Blinding	Site staff and participants were blinded. Sponsor staff were not blinded
Treatment effect: size	BNT162B2 showed a 95.0% reduction in the risk of acquiring COVID-19 infection 7+ days after the second dose
Treatment effect: precision	Vaccine efficacy: 95.0% (95% CI: 90.3-97.6%)

Criteria met: ● Unclear: ● Criteria not met: ●

MODERNA (MRNA-1273)

CRITICAL APPRAISAL

Based on the Centre for Evidence-Based Medicine critical appraisal tool

CRITERIA	COMMENTS
Randomized	Randomized in a 1:1 ratio via centralized interactive response technology. Stratified, on the basis of age and Covid-19 complications risk criteria
Groups: similarity	Groups were similar at baseline
Groups: equal treatment	Groups were treated equally
Loss to follow-up	51 (0.17%) patients were lost to follow up
Intention-to-treat protocol	Full set (intention-to-treat), modified intention-to-treat and per-protocol sets analyzed. Primary efficacy endpoint reported from per-protocol set
Blinding	Observer-blind study - investigator, study staff, study participants, site monitors and sponsor personnel blinded
Treatment effect: size	mRNA-1273 showed a 94.1% reduction in the risk of acquiring COVID-19 infection 14+ days after the second dose
Treatment effect: precision	Vaccine efficacy: 94.1% (95% CI: 89.3 to 96.8%)

OXFORD-ASTRAZENECA VACCINE (AZD1222)

CRITICAL APPRAISAL

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NUMBER OF DOSES

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STORAGE

- Store at 2-8°C

MECHANISM OF ACTION

- Adenovirus-vectored vaccine expressing full-length SARS-CoV-2 structural surface glycoprotein

December 21, 2020

ALBERTA COLLEGE OF FAMILY PHYSICIANS

THE COLLEGE OF FAMILIAR PHYSICIANS OF CANADA

PEER

COVID-19 Rapid Reviews

Along with regular Tools for Practice, the PEER team will be writing rapid reviews to address COVID-19 topics relevant for primary care. The evidence is changing rapidly, and it is possible that as you read this, new evidence will already be available. We will try our best to stay in front and keep you up to date during these challenging times.

COVID Vax Fast Facts: Say That 10 Times Fast

Clinical Question: What are the benefits and risks of the three COVID-19 vaccines likely available soon in Canada?

Bottom Line: Interim results of two large randomized, placebo-controlled trials (RCTs) demonstrate ~95% relative efficacy in preventing COVID-19 (Pfizer, Moderna). The AstraZeneca/Oxford vaccine has ~70% relative efficacy. Absolute benefits will vary with baseline risk and time but if annual risk of developing COVID-19 is 20%, then vaccine would decrease risk to 1% (6% with AstraZeneca/Oxford). These vaccines appear safe and may decrease the likelihood of severe COVID-19. Ongoing studies should provide further details.

Evidence:

- Interim results from FDA submissions,^{1,2} or peer reviewed publications.^{3,4} Median

THIS JUST IN...

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

@ 28 days:

- Efficacy = 66% (72% in US)
- No severe cases (vax)

Severe COVID ↓ ... 3 RCTs: 1 vs. 41 cases

Asymptomatic transmission ↓ ... other vaccines would suggest yes, but we don't know

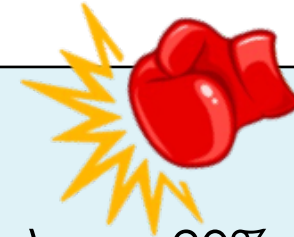
AND, majority of transmission from people with symptoms (?)

HARMS: SHORT-TERM

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%



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

What you need to know up to and including January 15, 2021



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 administered)

Adverse Events Following
Immunization that **individuals**
have reported

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



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
Early Release / Vol. 70

Morbidity and Mortality Weekly Report

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** VS. **2** FOR “ALL”
(maybe delayed) (on schedule)

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



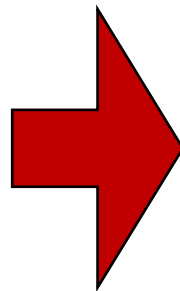
Lauren Pelley · CBC News · Posted: Dec 24, 2020 5:17 PM ET | Last Updated: December 24, 2020

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



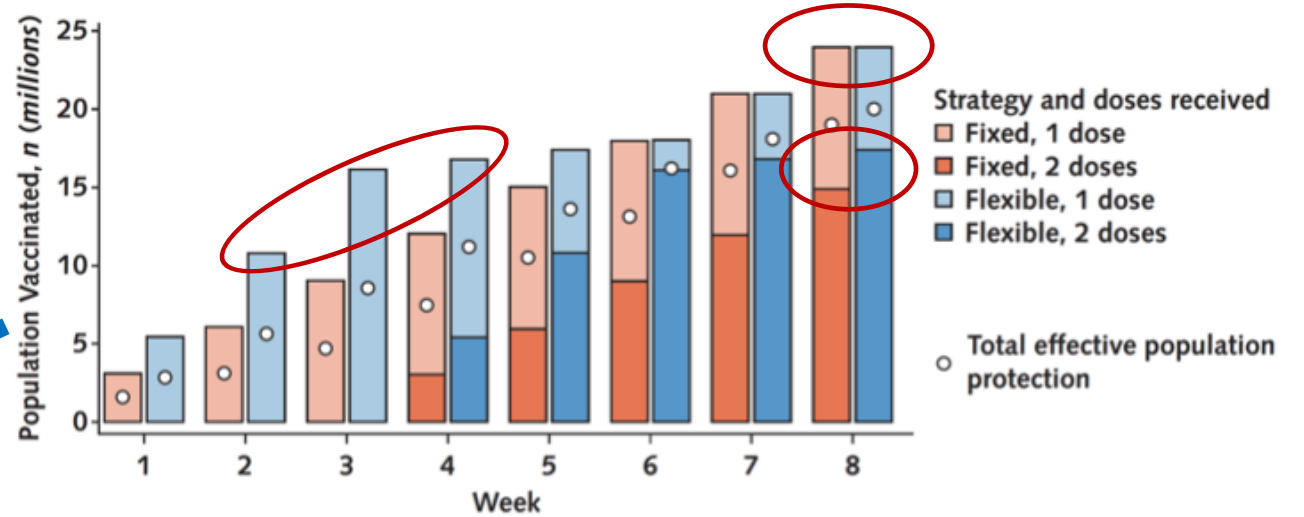
- **FIXED** strategy (based on Pfizer vaccine) modeled after current U.S. policy:
 - reserve **50%** of each vaccine installment for 2nd doses to be administered 3 wks later
- **FLEXIBLE** strategy:
 - reserve **10%** of weekly supply for 2nd doses during each of the first three weekly installments
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



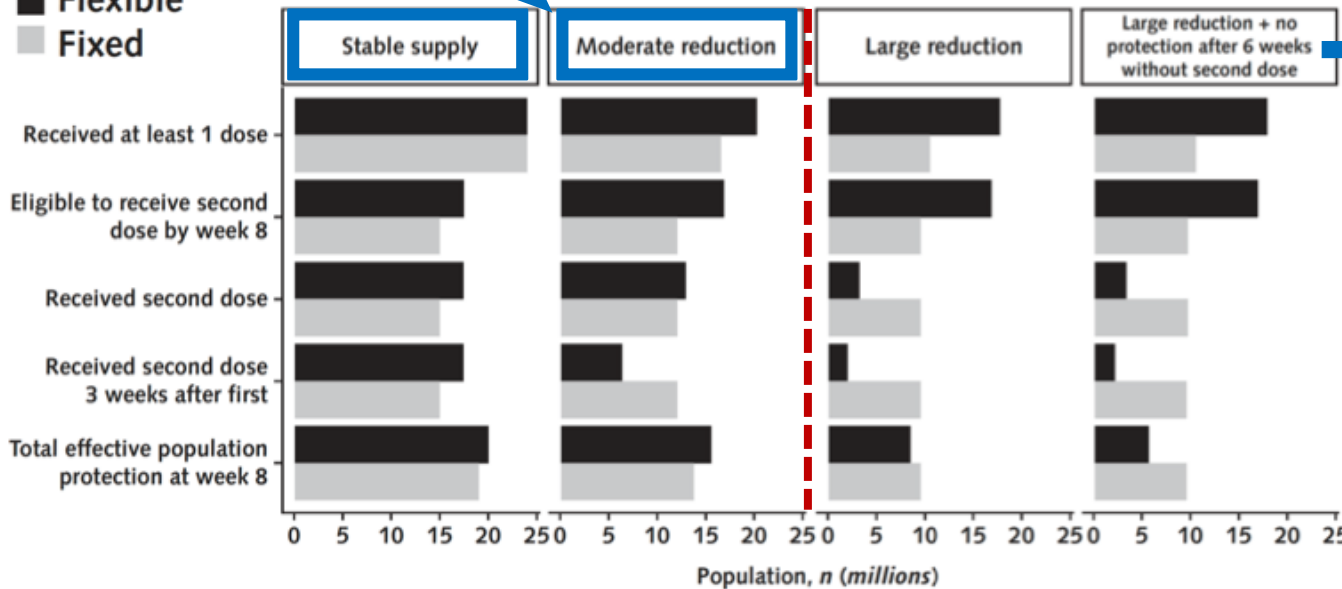
Annals of Internal Medicine

OBSERVATION: BRIEF RESEARCH REPORT

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



Strategy
■ Flexible
■ Fixed



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)

NACI (Health Canada)

Pfizer/Mod RCTs
1st → 2nd:
20-42 d

Step 2: Identify the ethical considerations (using the Core Ethical Dimensions Filter of the BEA Framework)	
Core Ethical Dimension for Public Health (Reorganized)	Considerations
Respect for persons and communities (Right to exercise informed choice based on all available evidence)	<ul style="list-style-type: none"> Individual autonomy, choice and perspectives of unique and diverse populations need to be respected. Keeping doses in reserve to ensure completion of a vaccine series enhances autonomy and respect for persons and communities. The public also expects that public health authorities will fulfil their responsibility to determine which course of action is in the best interest of the public when making recommendations. There is an obligation to be truthful and honest with those requests. If credible evidence is responsibly anticipated, there should be a clear and strong rationale available to the affected population. NACI's guidance is transparent about what is known and unknown regarding COVID-19 vaccines. This is included in the rationale for its recommendations to offer a complete two-dose vaccine series. Informed consent of those receiving vaccine will be vital. If half the initial doses are kept in reserve so that all initial vaccine recipients can receive both doses in accordance with the recommended interval, individuals can make a comparatively better informed choice than would be the case if no doses were kept in reserve. <ul style="list-style-type: none"> Evidence on the safety and efficacy available from clinical trials could be provided with assurance if a second dose would be provided on schedule. It is likely that the preferences of individuals willing to be vaccinated would be to complete the vaccine series within the recommended interval for optimal protection. If all doses are immediately distributed without reserving doses to complete the vaccine series in accordance with the recommended interval, then the ability to make an informed choice will be limited to deciding whether to accept one dose of the vaccine in the face of considerable uncertainty about: <ul style="list-style-type: none"> The timing of a second shipment of the authorized vaccine and Safety and efficacy.
Beneficence and non-maleficence (Promotion of well-being, avoidance of harm or benefits)	<ul style="list-style-type: none"> If half the initial doses are kept in reserve so that all initial vaccine recipients can receive both doses in accordance with the recommended interval, they will experience benefit and minimize risks for those vaccinated in high-risk key populations (13, 14) that have been identified to receive initial doses of COVID-19 vaccine by NACI. If all doses are immediately distributed without reserving doses to complete the vaccine series in accordance with the recommended interval, then they will be at least a slight benefit to a greater number of individuals identified as high-risk key populations (13, 14) with a broader distribution of the vaccine. This will promote the health of the population and reduce the overall burden of disease as much as possible, especially in the face of significant mortality and morbidity. The timing of administration of the first dose will likely be more important if administration of a second dose is delayed. However, there is a possible risk of harm in the longer term if subsequent vaccine supply does not arrive as planned with limited evidence on the efficacy of one dose compared to two doses, no evidence on interchangeability, and the potential for a second possible shipment if one dose is found not to offer sufficient protection. Other risks of harm include: <ul style="list-style-type: none"> Risk of increased vaccine hesitancy for COVID-19 vaccines and vaccines in general. Decreased acceptability for vaccine if vaccinated individuals get disease. Decreased trust in public health officials making recommendations. Decreased compliance to complete other vaccines in accordance with recommended intervals. Risk of behaviour associated with a false sense of security in individuals vaccinated with an incomplete series. Historical concerns of distributing the vaccine in a manner that is not consistent with the recommendations from the manufacturer. Risk of anxiety in the vaccinated individual related to uncertainties in degree of protection and vaccine availability for a second dose.
Proportionality (Measures should be proportionate to the level of risk and benefits)	<ul style="list-style-type: none"> If half the initial doses are kept in reserve so that all initial vaccine recipients can receive both doses in accordance with the recommended interval, the level of risk is proportionate to the anticipated benefits for those vaccinated in the high-risk key populations identified by NACI (13, 14). If all doses are immediately distributed without reserving doses to complete the vaccine series in accordance with the recommended interval and subsequent supply is insufficient, the level of risk may not be proportionate to the anticipated benefits given the uncertainty of supply for a second dose. Limited comparative evidence on the level and duration of protection offered by one vs two doses, and the absence of evidence on interchangeability of vaccine doses.
Autonomy (Individuals should be able to make their own choices)	<ul style="list-style-type: none"> If half the initial doses are kept in reserve so that all initial vaccine recipients can receive both doses in accordance with the recommended interval, this may be more likely to achieve Canada's pandemic response goal "To minimize serious illness and overall deaths while maintaining normal life as much as possible in the context of COVID-19 pandemic." Though there is insufficient evidence for evidence to long-term efficacy for a two-dose schedule, the evidence for duration of protection from a one-dose schedule is comparatively more than evidence of protection from one dose schedule. Higher efficacy and maximum immune response dose observed after the second COVID-19 vaccine dose. If all doses are immediately distributed without reserving doses to complete the vaccine series in accordance with the recommended interval, the evidence for the second dose would be insufficient to support the recommendation that they be distributed. Due to the uncertainty in the efficacy of one dose beyond the time when the second dose should be given, as well as the uncertainty in arrival of subsequent vaccine supply, if increased distribution of vaccine is always determined or in no time, this could lead to the following scenarios where the effectiveness of the vaccine would be reduced: <ul style="list-style-type: none"> Provision of a second dose at an extended interval. Provision of a second dose without sufficient (or no) follow-up. Inability to provide a second dose because of a lack of vaccine supply or because the recipient is unavailable to return to the site for follow-up (which may be more likely in this scenario). However, if evidence indicates a higher comparative protection with a single dose, despite this, the proportionality of vaccine, then this option would have benefits. Canada's pandemic response goal with vaccination of a greater number of vaccine recipients would be to receive half the initial doses so that initial vaccine recipients can receive both doses in accordance with the recommended interval, and dose evidence becomes available. Additional evidence on the efficacy of one dose, the duration of protection of one dose, and interchangeability of vaccine products, maximum immune response, and security of additional supply would mitigate risks of distributing all doses immediately without reserving doses to complete the vaccination schedule in accordance with the recommended interval.
Justice (Fair and equitable distribution of resources)	<ul style="list-style-type: none"> If half the initial doses are kept in reserve so that all initial vaccine recipients can receive both doses in accordance with the recommended interval, the number of healthcare workers and staff of long-term care facilities being vaccinated will be reduced. This will reduce the burden on the healthcare system and increase the availability of staff to care for other patients. If all doses are immediately distributed without reserving doses to complete the vaccine series in accordance with the recommended interval, the number of healthcare workers and staff of long-term care facilities being vaccinated will be increased. This will increase the burden on the healthcare system and reduce the availability of staff to care for other patients.
Transparency (Decision-makers should be open to scrutiny and feedback)	<ul style="list-style-type: none"> Transparency is a key element for fostering public trust. Decision-makers should document, and be prepared to justify, the choices that they make. All plans and decisions must, as much as possible, be made with an open and honest process that is mutually agreed upon and seeks broad collaboration and input. Trust may be repaired by being a programming the management decision without supporting scientific evidence. Confidence and credibility of COVID-19 immunization programs across jurisdictions in Canada is important, especially in the context of ongoing changes to and differences in recommendations in the pandemic context. Keeping an open schedule early on could create trust in the necessity of the complete series itself. This is in particular concern given the current state of trust in COVID-19 vaccines and vaccine generally. Decisions and care should be taken to create opportunities that minimize moral distress and maximize trust in and well-being. If half the initial doses are kept in reserve so that all initial vaccine recipients can receive both doses in accordance with the recommended interval: <ul style="list-style-type: none"> This may have a negative impact on public trust due to a perception that only a small number of individuals are getting preferential access despite availability of additional doses. This risk can be mitigated with open communication about the rationale. If all doses are immediately distributed without reserving doses to complete the vaccine series in accordance with the recommended interval: <ul style="list-style-type: none"> This may have a negative impact on public trust in the COVID-19 immunization program. Perceptions that certain populations are expected to an experimental approach may be generated. This is particularly concerning as many of the high-priority populations for early immunization (13, 14) experience social inequalities and degradation and have been subject to stigmatization and discrimination. The lack of consistency in approaches between jurisdictions in the initial phases of roll-out of the COVID-19 immunization program could also erode public trust in the recommendations and program.

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.”



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”

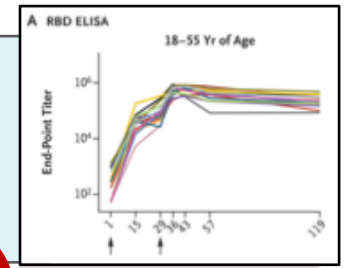


Jan 12... “**If** the vaccine product used for a previously received dose is **not known, or not available**, attempts should be made to complete the vaccine series with a **similar type** of COVID-19 vaccine (e.g. mRNA vaccine)”



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 surfs on 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 dexamethasone 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

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

Organ support-free days

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

Approx. proportion requiring organ support

~25%

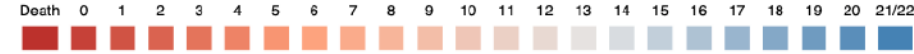
~18%

~19%

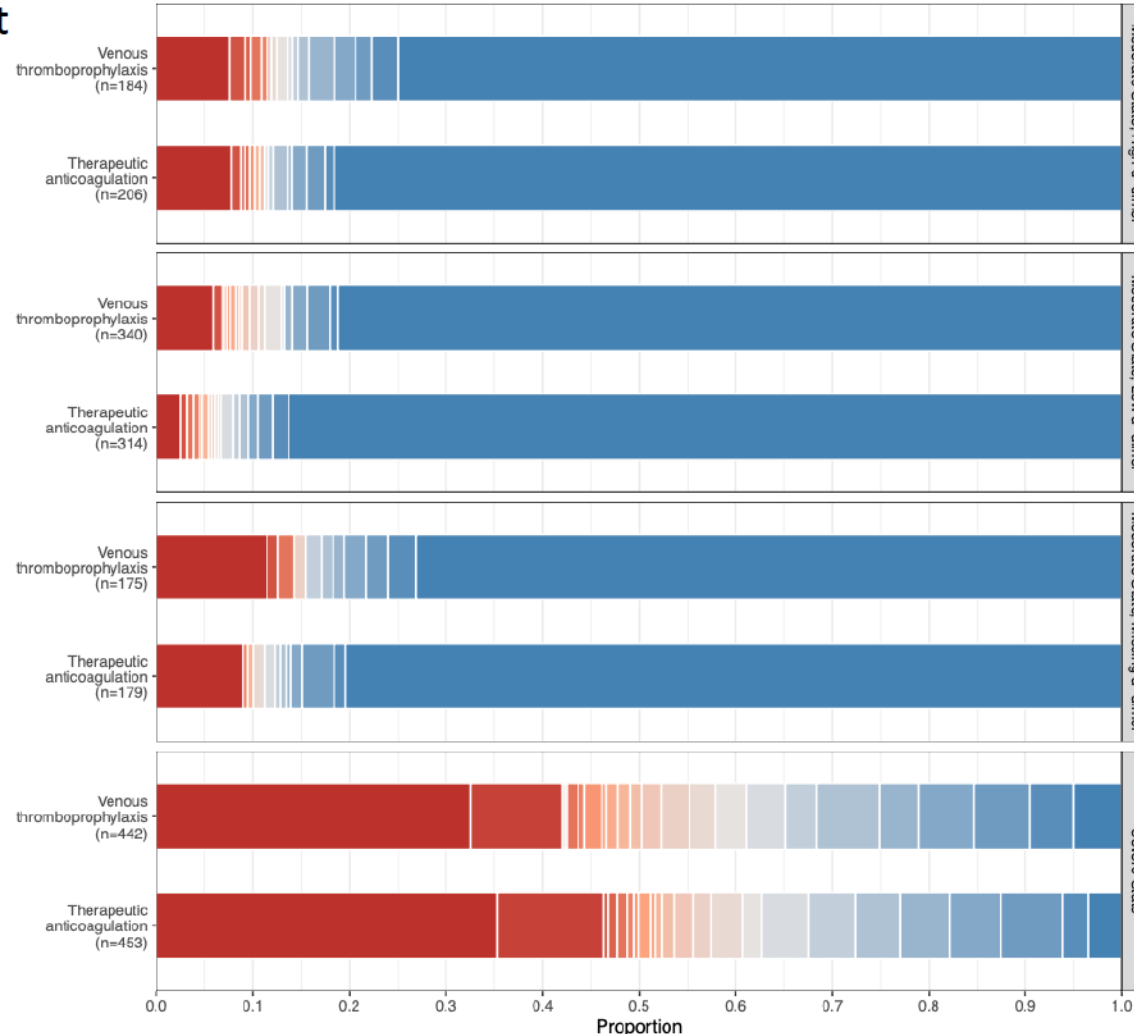
~13%

~27%

~20%



INTERIM



Moderate state;
HIGH D-dimer

Moderate state;
LOW D-dimer

Moderate state;
MISSING D-dimer

Severe state

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>