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CANVAX

Canada

COVID-19 and vaccines during pregnancy and lactation

A summary of the evidence

Speaker and disclosures

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- No conflicts to declare

Objectives

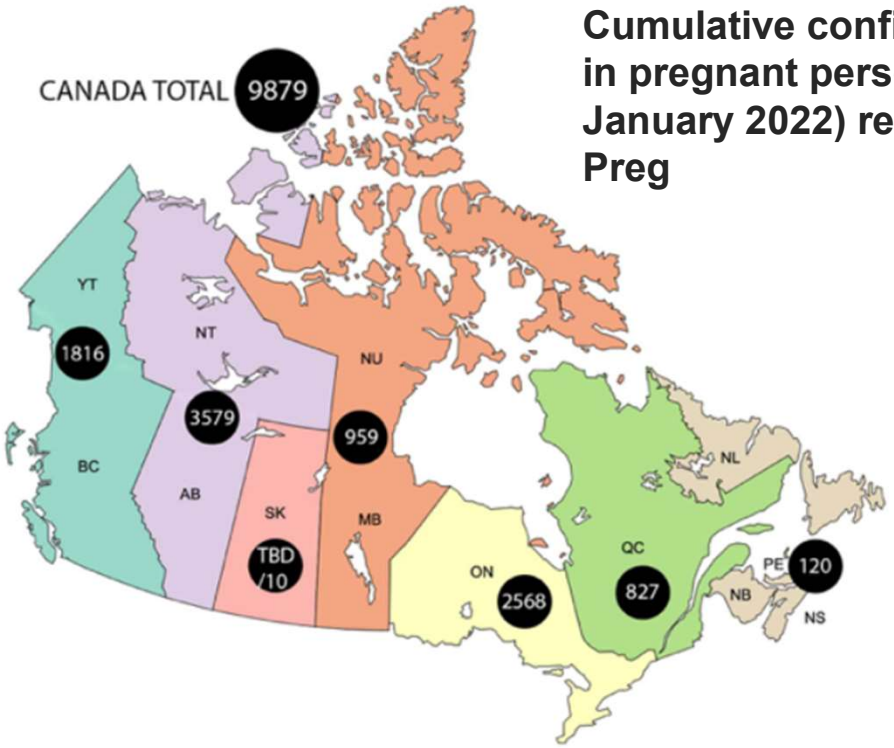
- Identify the risks associated with infection with SARS CoV-2 during pregnancy.

- Explain the safety and effectiveness of mRNA vaccines in pregnancy and lactation and for those intending to become pregnant.

Infection with SARS-CoV-2 during pregnancy

It is difficult to capture the burden of COVID-19 in pregnant people in Canada

- CANCOVID-Preg is a national surveillance project
- CANCOVID has identified almost 10,000 positive cases **as of January 2022**, but this picture is incomplete due to differences in reporting.



Cumulative confirmed COVID-19 cases in pregnant persons in Canada (as of January 2022) reported to CANCOVID-Preg

Last updated
BC + Yukon: Jan 7th, 2022
Alberta + NWT: Jan 4th, 2022
Saskatchewan: TBD/Nov 11, 2020
Manitoba + Nunavut: Jan 4th, 2022
Ontario: Oct 31, 2021
Quebec: Dec 14, 2020
The Atlantic Provinces: Dec 29, 2021

(CANCOVID-Preg, 2022)

COVID-19 outcomes among pregnant people in Canada

The **CANCOVID-Preg report #5** (unpublished) examined maternal and infant outcomes of positive COVID-19 cases during pregnancy in 5 provinces (BC, AB, MB, ON, QC):

- March 1, 2020 - September 30, 2021
- Outcomes of 6,991 positive cases among pregnant individuals were assessed
- Hospitalization data were available for 4,654 people
- Of those, 7.0% were hospitalized and 2.3% were admitted to the ICU or CCU
- Among those hospitalized, admitted to ICU/CCU, or ventilated, none had completed a primary series of vaccination

(CANCOVID-Preg Report #5, 2022 – unpublished data)

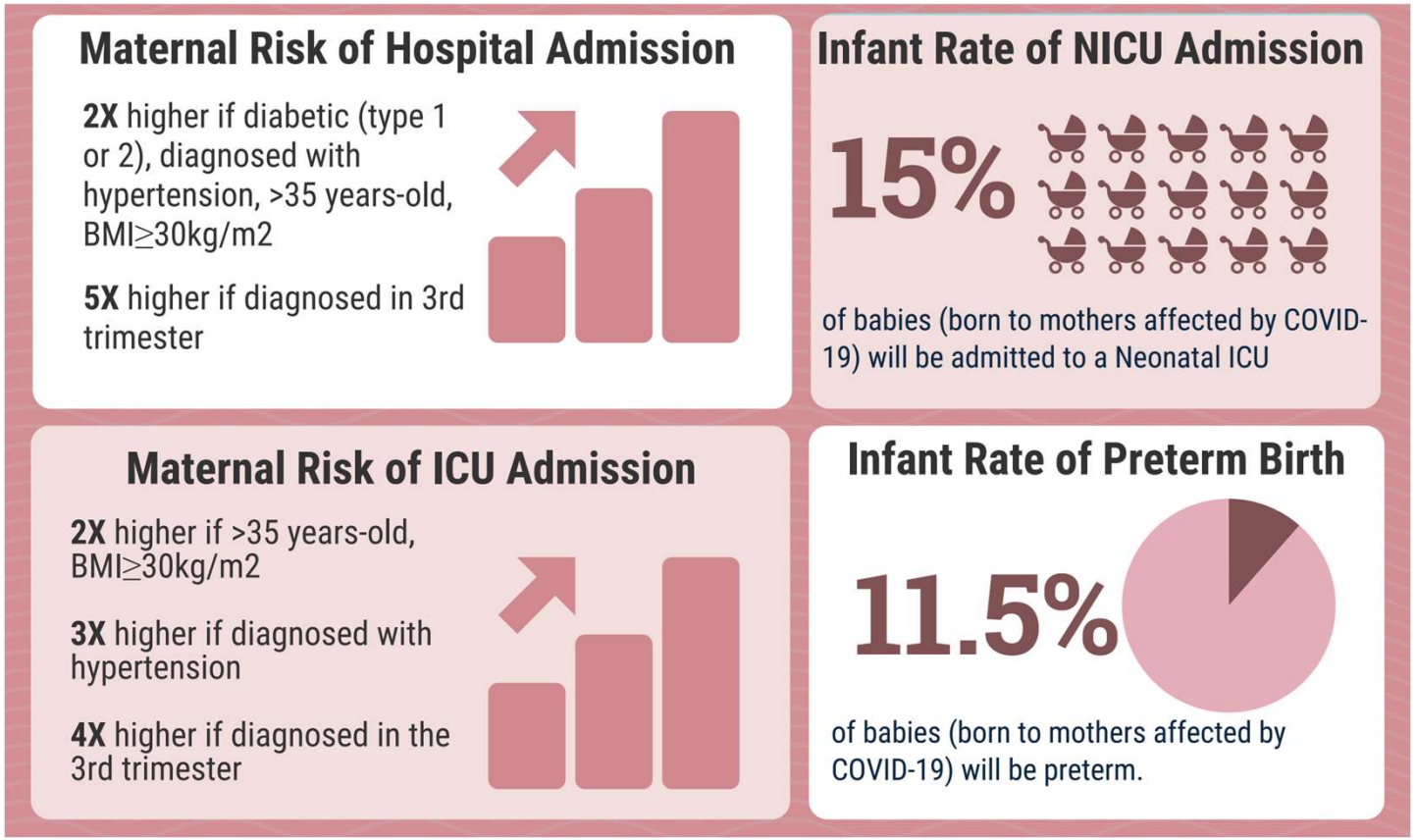
COVID-19 outcomes among pregnant people in Canada (continued)

- Compared to their non-pregnant counterparts, pregnant individuals who were COVID-19 positive were:
  - **more than twice as likely to be hospitalized** (RR 2.45, 95% CI: 2.20 – 2.72)
  - **more than six times as likely to be admitted to the ICU** (RR 6.30, 95% CI: 5.12 – 7.58)

- Increased risk may be due to physiological and immunological changes during pregnancy which increase susceptibility to more severe consequences of infection.
  - Pregnancy also increases risk of severe illness from influenza

(CANCOVID-Preg Report #5, 2022-Unpublished; Wise et al., 2006; Abu-Raya et al., 2020)

COVID-19 outcomes among pregnant people and their infants in Canada

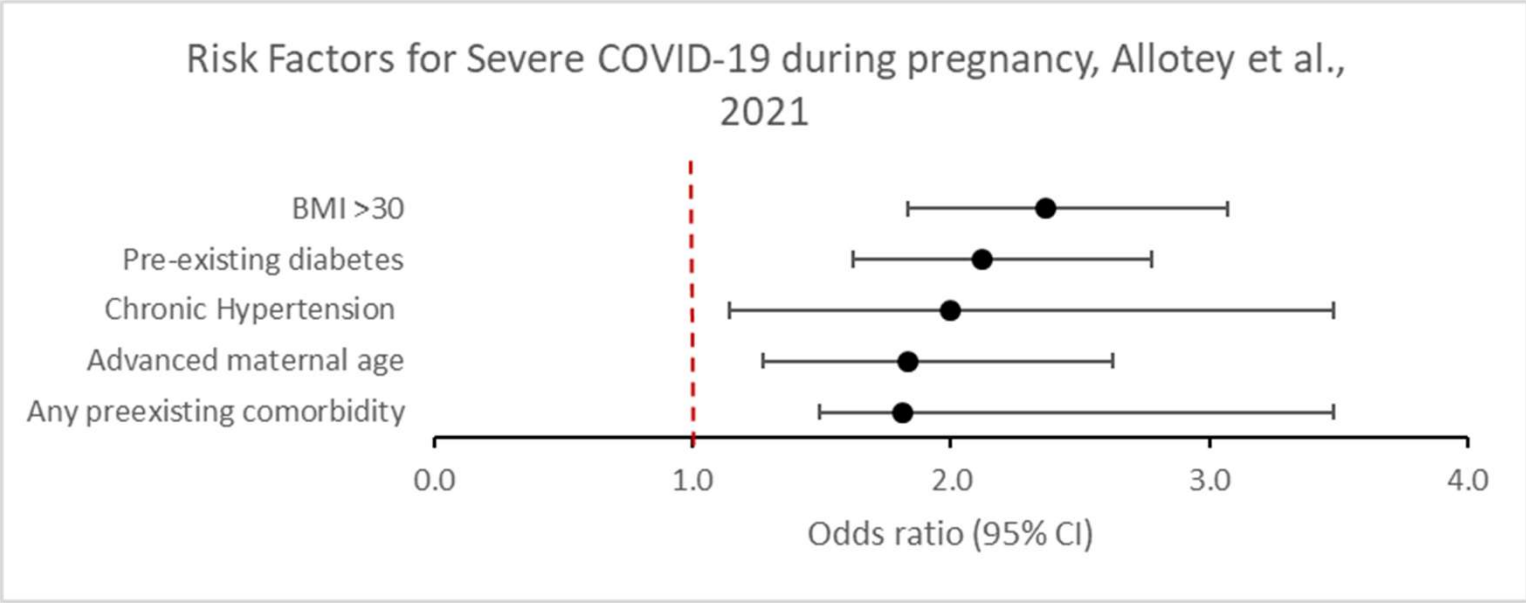


(CANCOVID-Preg Report #5, 2022- Unpublished)

Several common risk factors increase the likelihood of severe COVID-19 during pregnancy

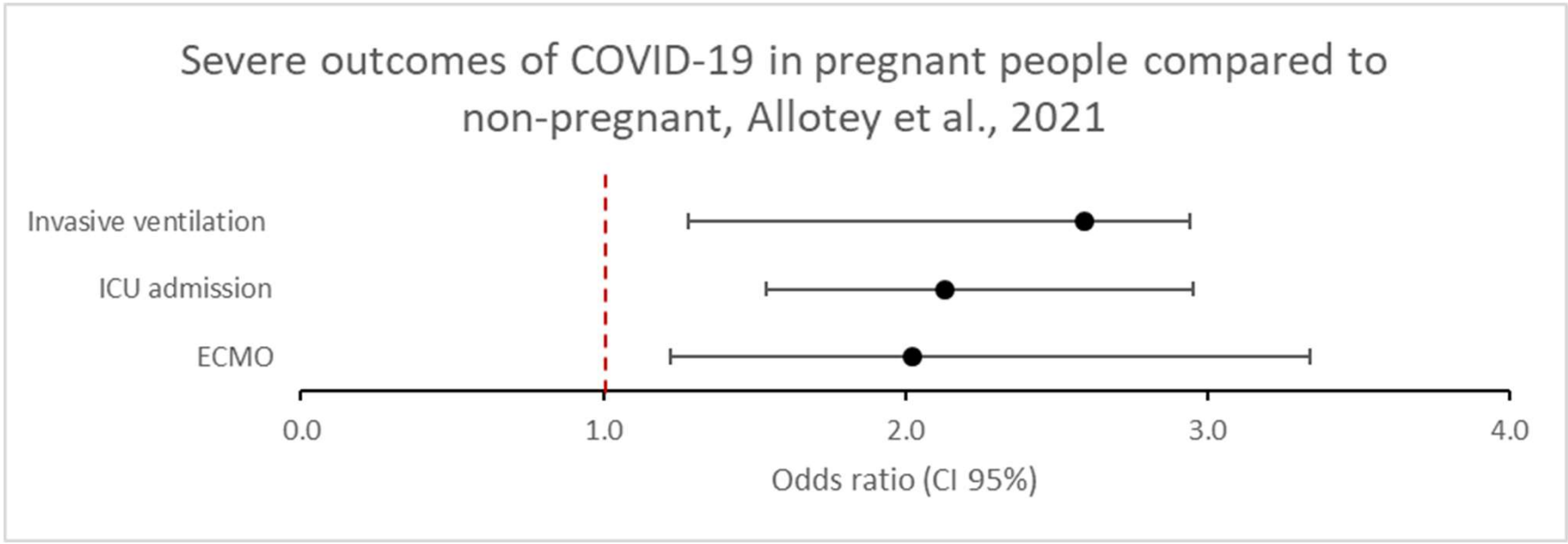
Living systematic review by Allotey et al., published in BMJ, updated Feb 2021

- 192 studies included
- 64,676 pregnant and recently pregnant people with COVID-19
- 569,981 non-pregnant reproductive aged women with COVID-19



(Allotey et al., 2021)

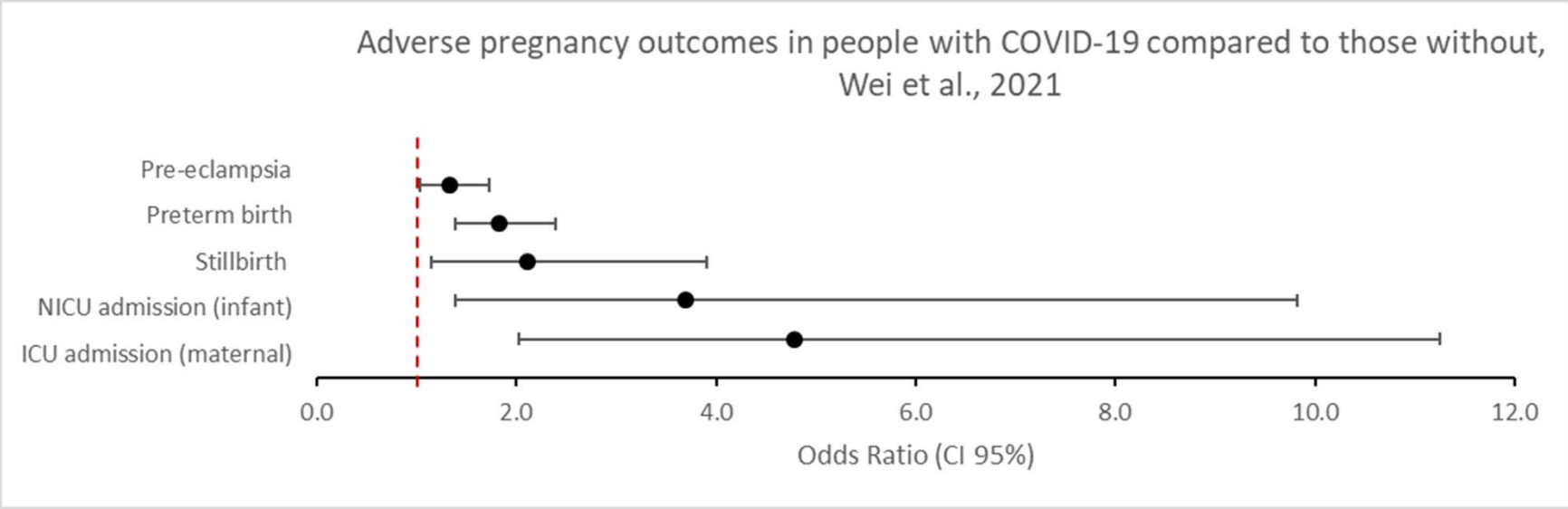
Pregnancy is associated with significantly higher rates of severe outcomes of COVID-19



(Allotey et al., 2021)

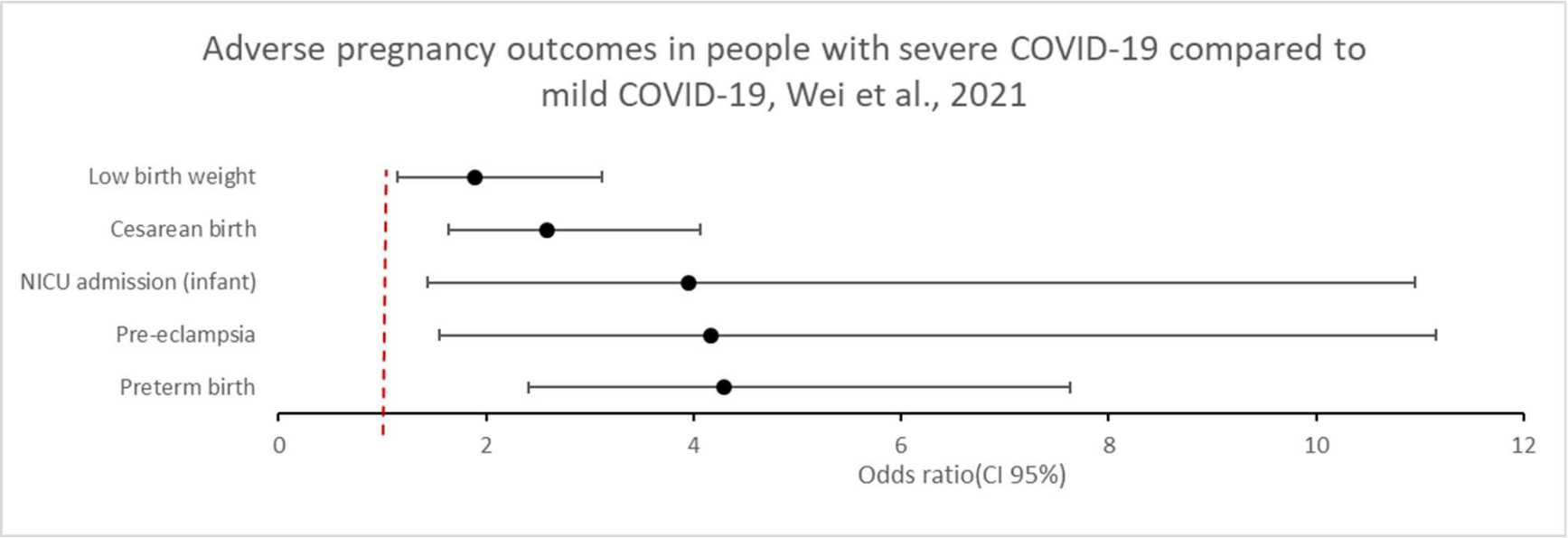
COVID-19 is associated with increased adverse pregnancy outcomes

Systematic review & meta-analysis by Wei et al., 2021 (CMAJ), included 42 studies involving 438,548 people who were pregnant



(Shu Qin Wei et al., 2021)

Adverse pregnancy outcomes were significantly greater amongst those with severe* COVID-19 compared to mild COVID-19



*Severe COVID-19 defined as the presence of dyspnea, respiratory rate at 30 breaths per minute or more and oxygen saturation at 93% or less on room air, or findings consistent with pneumonia.

(Shu Qin Wei et al., 2021)

COVID-19 During Pregnancy Key Takeaways

- Burden of COVID-19 infection during pregnancy in Canada is difficult to accurately capture with provincial, territorial, and federal surveillance systems.
- Pregnancy increases risk of severe outcomes due to COVID-19, including ICU admission, and the need for mechanical ventilation and ECMO.
- Risk factors for severe COVID-19 during pregnancy are common. People who are pregnant should be made aware of these risk factors to help inform their understanding of their own risk.
- COVID-19 during pregnancy is associated with adverse pregnancy outcomes, including preeclampsia, preterm birth, and stillbirth.
- Severe COVID-19 in pregnancy increases risk of adverse pregnancy outcomes.

Effectiveness of mRNA COVID-19 vaccines during pregnancy and lactation

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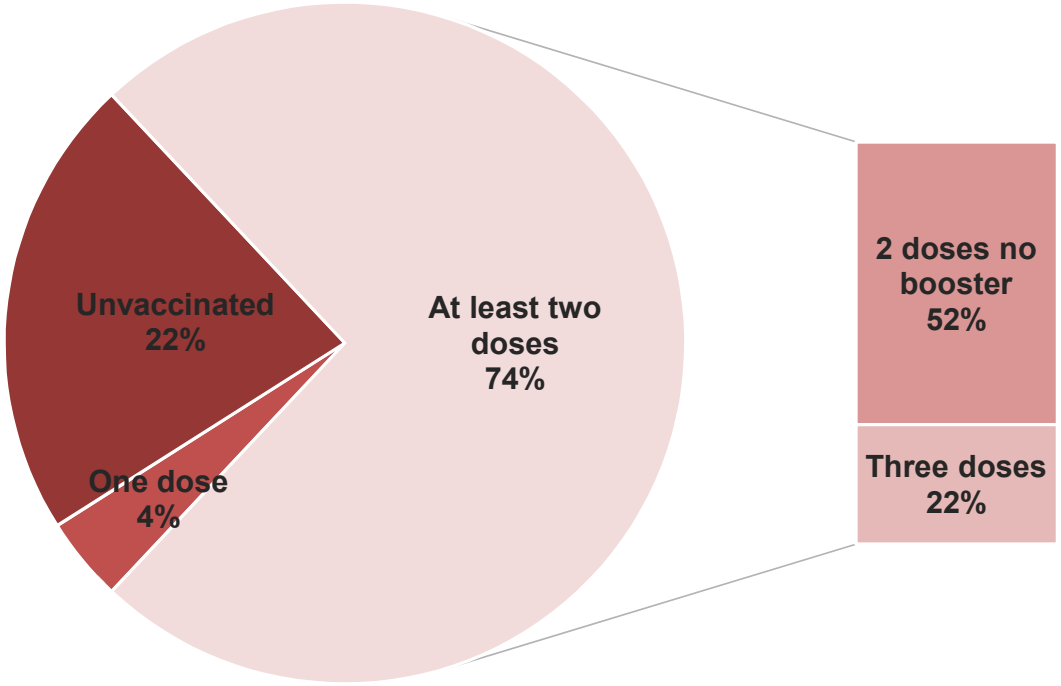
Uptake of COVID-19 vaccines among pregnant people

Estimated vaccine coverage in pregnant Ontarians (ICES, Jan 9, 2022)



- Vaccine coverage in pregnant persons across Canada is difficult to estimate.
- According to available estimates, vaccine coverage in pregnant individuals is lower than in the general population.

(ICES COVID-19 Dashboard, 2022)

Slide 15

R(1 Perhaps not for this slide, but the speaker should know and I would recommend they should reference in speaking remarks the results from the Cdn Immunity Task Force's COVID-19 Vaccine Registry for Pregnant and Lactating Individuals - including their national survey of pregnant women showing 86% of their survey respondents (total sample n=5006) report having had 2 doses of COVID vaccine. Will send the deck presented to FPT CIC committee on this study

Robinson, Kerry (PHAC/ASPC), 2022-02-09

How vaccine effectiveness and immunogenicity is assessed in pregnant people

- Initial vaccine efficacy research (pre-licensure randomized clinical trials) did not include pregnant people.
- Prospective and retrospective cohort studies assess quantity and quality of immune response
  - Titres of SARS-2-CoV antibodies (Ab) and T-cell responses in participant sera
  - Neutralization assays to quantify neutralizing Ab titres
- Vaccine effectiveness estimates rely on real-world (observational) evidence:
  - Test-negative case control and cohort studies to assess vaccine effectivenes

(CITF, 2021; Public Health Agency of Canada, Centre for Immunization and Respiratory Infectious Diseases (CIRID), COVID-19 Surveillance Team)

Immunogenicity of mRNA vaccines in pregnancy and lactation

- COVID-19 vaccination in people who are pregnant induces good immune responses.
- Similarly high vaccine-induced immune responses in pregnant and lactating people compared to non-pregnant people.
  - Both humoral and cellular immunity
- Antibody titres are higher in pregnant people who are vaccinated than those who had a COVID-19 infection during pregnancy.

(CITF, 2021; Gray et al., 2021; Atyeo et al., 2021; Collier et al., 2021)

mRNA vaccines are effective in pregnant people

- Effectiveness against infection, symptomatic infection and hospitalization for pregnant people have been demonstrated for ancestral, Alpha and Beta variants.
  - Comparable to the general population
- Note: Vaccine effectiveness studies cited occurred before the Omicron variant became the dominant strain of COVID-19.

Vaccine effectiveness estimates following 2 mRNA vaccine doses	
Documented or symptomatic infection	Hospitalization
87 – 97%	89%

- In the CANCOVID-Preg Report #5 (Unpublished), between March 1, 2020 and September 30, 2021, among the pregnant people who were hospitalized, admitted to ICU/CCU or ventilated **none were fully vaccinated** (i.e., two doses).

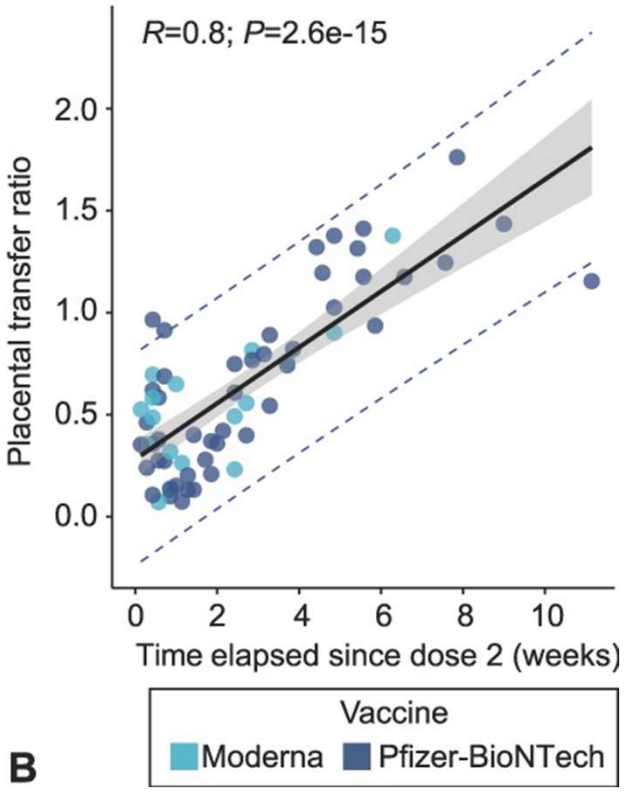
(CANCOVID-Preg Report #5, 2021 -Unpublished; Engjom et al., 2022; Dagan et al., 2021; Butt et al., 2021; Public Health Agency of Canada, Centre for Immunization and Respiratory Infectious Diseases (CIRID), COVID-19 Surveillance Team)

Vaccine protection against variants for pregnant people

- In the general population, vaccine effectiveness against infection is significantly lower for the Omicron variant.
- Protection against severe disease and hospitalization has remained strong for Omicron, especially following a booster dose.
- Reduced serum neutralizing antibodies in pregnant persons and infant cord blood against variants with immune evasion (Alpha, Beta).
  - Cellular immunity (CD4 and CD8 T-cell responses) appeared to be preserved.

(Collier et al., 2021)

Longer time between first or second dose and delivery are associated with higher IgG titers and placental transfer ratios



Antibody transfer is assessed by quantifying IgG antibodies in cord blood, sometimes as a placental transfer ratio:

$$\text{Placental transfer ratio} = \frac{\text{cord blood Ab concentration}}{\text{maternal serum Ab concentration}}$$

- Binding and neutralizing antibodies are found in cord blood, suggesting efficient transfer through the placenta.
- Suggest vaccination earlier in pregnancy may confer optimal protection for fetus and pregnant individual.

(Prabhu et al., 2021)

mRNA vaccine-induced antibody transfer through human milk

- Antibody transfer is assessed by quantifying antibodies in human milk at various time points after vaccine doses during pregnancy or lactation.
- Many components of human milk are known to have beneficial antiviral properties.
- SARS-CoV-2 virus is unlikely to be transmitted into human milk.
- Human milk transmits vaccine-induced antibodies (IgM, IgA and IgG) to newborns:
  - Robust secretion of IgA and IgG antibodies in human milk was continued for 6 weeks after vaccination.
  - Peak antibody titres in human milk may occur from 7 to 28 days after the second dose.
  - Unclear how antibody protection for the newborn differs between those of lactating parents vaccinated vs. infected with COVID-19 during lactation.
- The degree of protection conferred to the infant by antibodies in human milk is unknown.

(Fu et al., 2021)

Importance of vaccination in pregnancy

- Most of the adverse outcomes occur in pregnant persons who are **unvaccinated** or only **partially vaccinated** against COVID-19.
- According to the recent CANCOVID-Preg report, none of the of 328 pregnant persons hospitalized with COVID-19 included in the study were fully vaccinated.
- The National Advisory Committee on Immunization (NACI), the Society of Obstetricians and Gynecologists of Canada (SOGC) and the World Health Organization (WHO) all **recommend immunization with COVID-19 vaccines at any time during pregnancy**.
- Pregnant individuals are at high-risk of severe outcomes and are recommended to get a booster dose of an mRNA COVID-19 vaccine.

(CITF, 2021)

Vaccine Effectiveness Key Takeaways

- Immunogenicity and vaccine effectiveness are similar for the pregnant and non-pregnant population.
- Studies occurred before Omicron was the dominant strain.
- In the general population, vaccine effectiveness against infection with Omicron variant is low, though protection against severe illness remains strong.
- Antibodies pass through the placenta and human milk following vaccination, although the degree of protection is unknown.
- Vaccination appears to be highly protective against hospitalization for pregnant individuals.
- Booster doses are important to increase protection against infection and severe disease.

Vaccine safety writ large – where do pregnant populations fit?

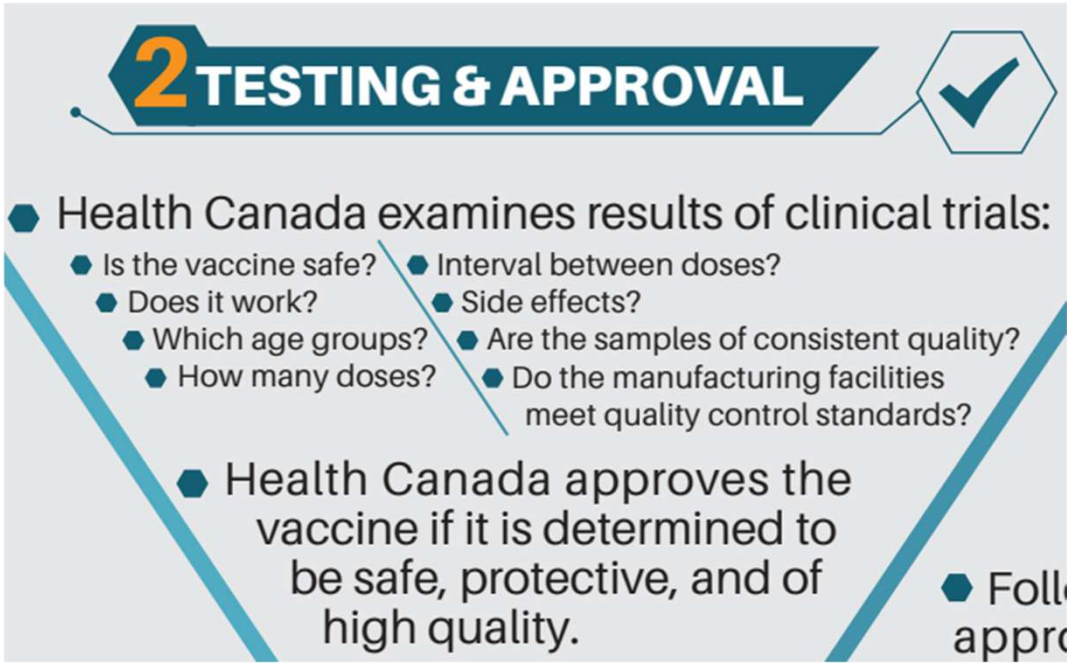
(PHAC, 2020)

How vaccine safety is assessed in pregnant people.

- Pre-market evidence in pregnant people:
  - Clinical trials: a handful of people may become pregnant during large clinical trials
  - Developmental and reproductive toxicology (DART) studies - animal studies
    - Developmental – pre-natal development of embryo/fetus
    - Reproductive – all aspects of fertility

(PHAC, 2020)

How vaccine safety is assessed in pregnant people (cont'd).

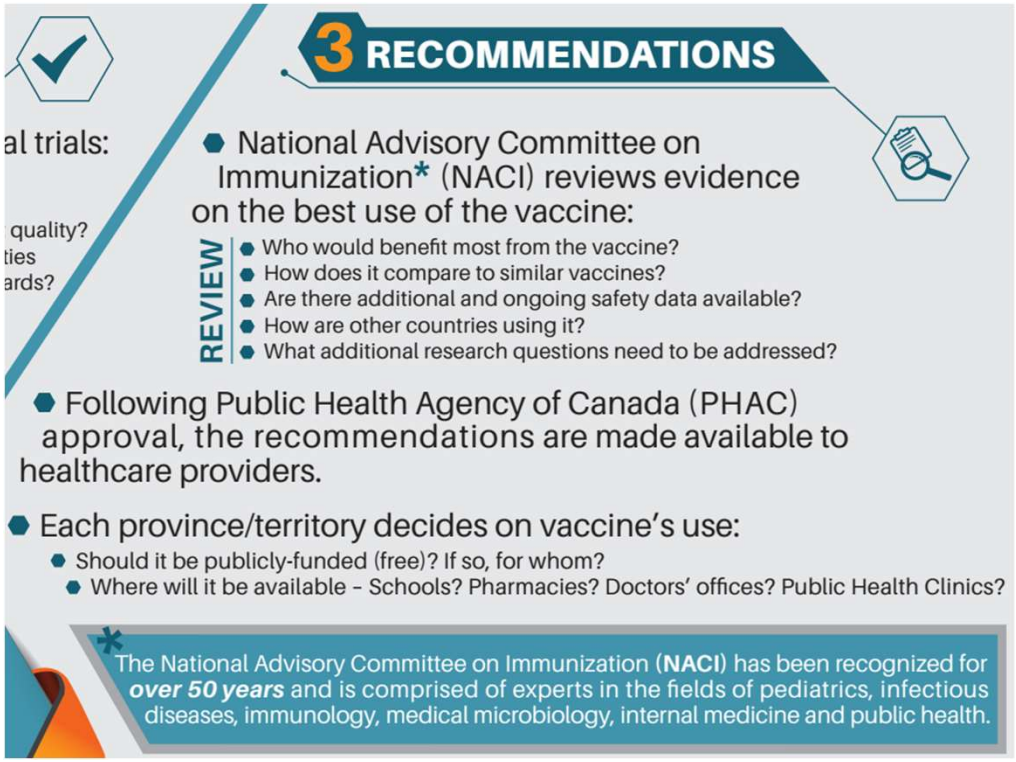


Product Monograph – typical pregnancy/lactation language:

- "The safety and efficacy of _____ in pregnant women have not yet been established. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition, or post-natal development..."
- "It is unknown whether _____ is excreted in human milk. A risk to the newborns/infants cannot be excluded."

(PHAC, 2020)

How vaccine safety is assessed in pregnant people (cont'd).



NACI recommendations typically make stronger recommendations specifically for pregnancy and lactation once evidence emerges that clearly indicate that the benefits outweigh the risks of vaccination.

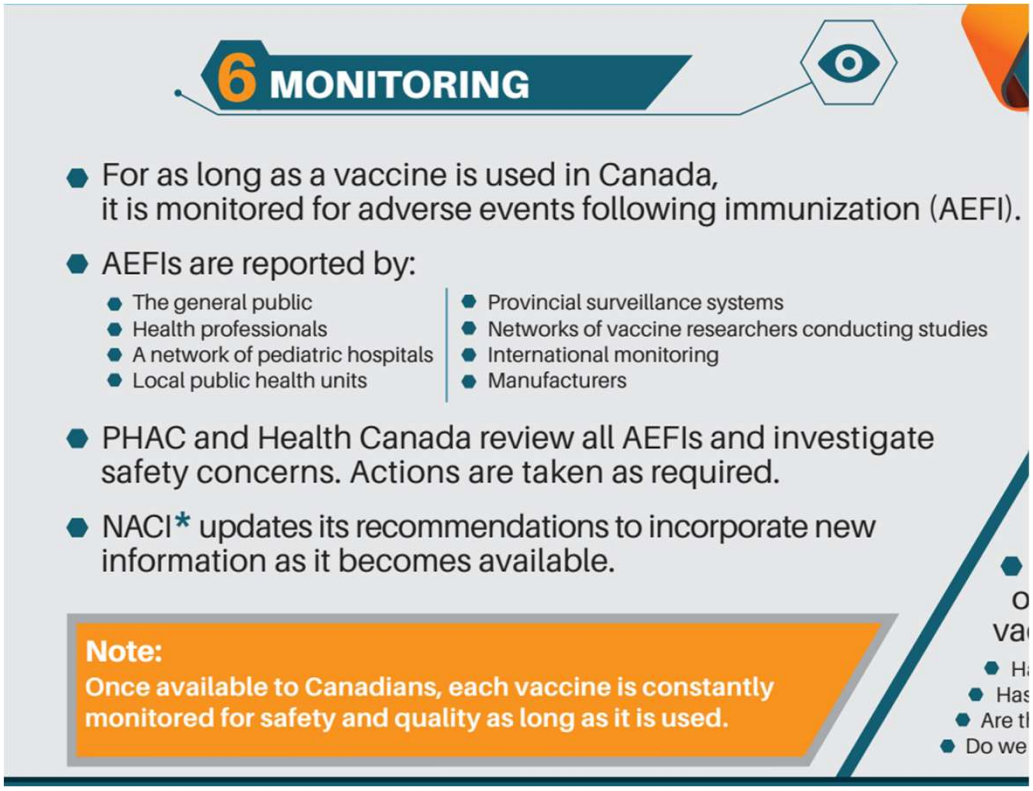
NACI guidance on COVID-19 vaccines in pregnancy:

- December 12, 2020: Vaccine "**may be offered**"
  - Informed consent about limited evidence

- May 28, 2021: mRNA "**should be preferentially offered**" to individuals in the authorized age group who are pregnant or breastfeeding.

(PHAC, 2020; CIG, 2022)

How vaccine safety is assessed in pregnant people (cont'd)



Post-market:

- Detects rare adverse events not captured in clinical trials
- Detects events that may occur over long time periods
- Detects events in populations not included in clinical trials
- Types: post-licensure clinical trials and Phase IV surveillance studies
  - Passive and active surveillance systems at the national and province/territories
  - Pregnancy registries (C-VIPER, COVERED, BORN Ontario, VIP, CDC, Moderna, CONSIGN)
  - Research studies

(PHAC, 2020)

Safety data for pregnancy and lactation

- Growing evidence consistently indicates that mRNA COVID-19 vaccines do not cause pregnancy complications or adversely affect human milk (hundreds of thousands of pregnant people across the world).
- Pregnant people experience the same rates of common side effects as those experienced by the general public, including mild or moderate:
  - Pain at the injection site
  - Headache
  - Redness and swelling at injection site
  - Muscle pain
  - Chills
- Side effects improve within a few days of vaccination

(EMA, 2022)

Many large studies have examined vaccine safety during pregnancy

- European Medicines Agency, Jan 18, 2022
  - n=~65,000
  - Detailed review of multiple studies
- CDC's V-safe registry, Sept 22, 2021
  - n=>35,000 pregnancies reported, 5096 registry participants, 1,614 pregnancies completed
  - Participants interviewed during each trimester, postpartum, and during early infancy
- CDC's Vaccine Safety Datalink, July 31, 2021
  - n=>40 000
  - Health administrative data of eight health care organizations included directly comparable controls
  - looked specifically at SGA and preterm birth
- UK's Health Security Agency, November 25, 2021
  - n=~18,000
  - Health administrative data NHS, with directly comparable unvaccinated controls

(EMA, 2022; CDC, 2021; Lipkind et al., 2021; Shimabukuro et al., 2021)

Large studies did not identify any increases in adverse pregnancy events above expected background rates at any gestation FA(6

- Outcomes assessed included local and systemic reactogenicity, as well as specific perinatal outcomes:
  - Range of pregnancy complications, miscarriages
  - Neonatal: preterm birth <37 wk, small size for gestational age, congenital anomalies, neonatal death

(UK Health Security Agency, 2021; Magnus et al., 2021)

Slide 31

FA(6 Did you mean gestation stage or just gestation? The translator indicated "stage" in French and it made me wonder.

Fleurant, Annie (PHAC/ASPC), 2022-02-15

No safety concerns have been identified regarding vaccination during lactation

- Limited data suggest safety of COVID-19 vaccines in lactating people, with no effects on the infant/child being fed human milk or milk production or excretion.
- Several cohort studies studying lactating individuals who received an mRNA vaccine did not detect any safety signals.
- As in the general population, local and systemic symptoms in lactating people were more frequent with Moderna than Pfizer, and more frequently experienced after Dose 2.
  - None of the events in studies of lactating people were serious
  - No safety signals were identified in children being fed human milk, some increased irritability
- Human milk does not contain detectable mRNA from COVID-19 vaccines after a lactating person is vaccinated.

(Golan et al., 2021; Low et al., 2021; Falsaperla et al., 2021; Bertrand et al., 2021; Lechosa-Muñiz et al., 2021; Golan et al., 2021; McLaurin-Jiang et al., 2021; Jia Ming Low et al., 2021; Golan et al., 2021; Mattar et al., 2021)

mRNA vaccines and fertility

- Pre-clinical, clinical, and post-market studies have provided emerging, but consistent evidence that COVID-19 mRNA vaccines have no impact on fertility:
  - No effect on anti-Müllerian hormone
  - No reduction in semen levels
  - ART/IVF studies: no difference in pregnancy rates, ectopic pregnancies, spontaneous miscarriages, intrauterine pregnancies, ovarian follicular function, number of fertilized embryos
- Infection with SARS-CoV-2 may reduce fertility in males transiently, and for a minority, longer term.
- Major professional and public health organizations agree that alleged links between vaccines and infertility are unfounded and recommend vaccination for pregnant people and those intending to become pregnant.

(Mohr-Sasson et al., 2021; Lu-Culligan et al., 2021; Lifshitz et al., 2021; Safrai et al., 2021; Bentov et al., 2021; Morris et al., 2021; Orveito et al., 2021; Wesselink et al., 2022; Collins et al., 2022; Donders et al., 2021; Best et al., 2021; Setti et al., 2021)

COVID-19 vaccines and menstruation: considerations

- Anecdotal reports of menstrual irregularities following COVID-19 vaccination.
- Finding an association is difficult without a research study that has a control group.
  - Routine passive surveillance systems don't typically receive these types of reports unless very severe, don't capture rates in the unvaccinated
  - Need to use background rates to estimate the number of expected events using health administrative data
  - Self-limited menstrual irregularities are common, are rarely cause for seeking medical attention

mRNA COVID-19 vaccines and menstruation: available evidence.

- Early, unconfirmed evidence emerging that there might be an increased risk of prolonged bleeding, short intermenstrual interval, and increased pain during periods.
  - Norwegian self-controlled case series preprint, Trogstad et al. – questionnaire in vaccinated and unvaccinated (n=5,688)
- Edelman et al. conducted a prospective US study of menstruating individuals tracking pre and post vaccination cycles through an app.
  - n=3,959, (vaccinated 2,403; unvaccinated 1,556)
  - Pfizer-BioNTech vaccine 55%; Moderna 35%; Johnson & Johnson/Janssen 7%.
  - Found a transient, subtle, but statistically significant change in cycle length among vaccinated by <1 day
  - No change in duration of bleeding

(Trogstad L et al., 2022; Edelman A et al., 2022)

Vaccine Safety Key Takeaways

- Pregnant people were not included in clinical trials.
  - Post-market safety studies and surveillance are the primary means of assessing safety during pregnancy
- Studies have found no safety concerns specific to pregnancy or lactation.
- There is no evidence that COVID-19 vaccines cause infertility.
- There is some evidence that vaccination may temporarily change menstrual cycle length by <1 day.

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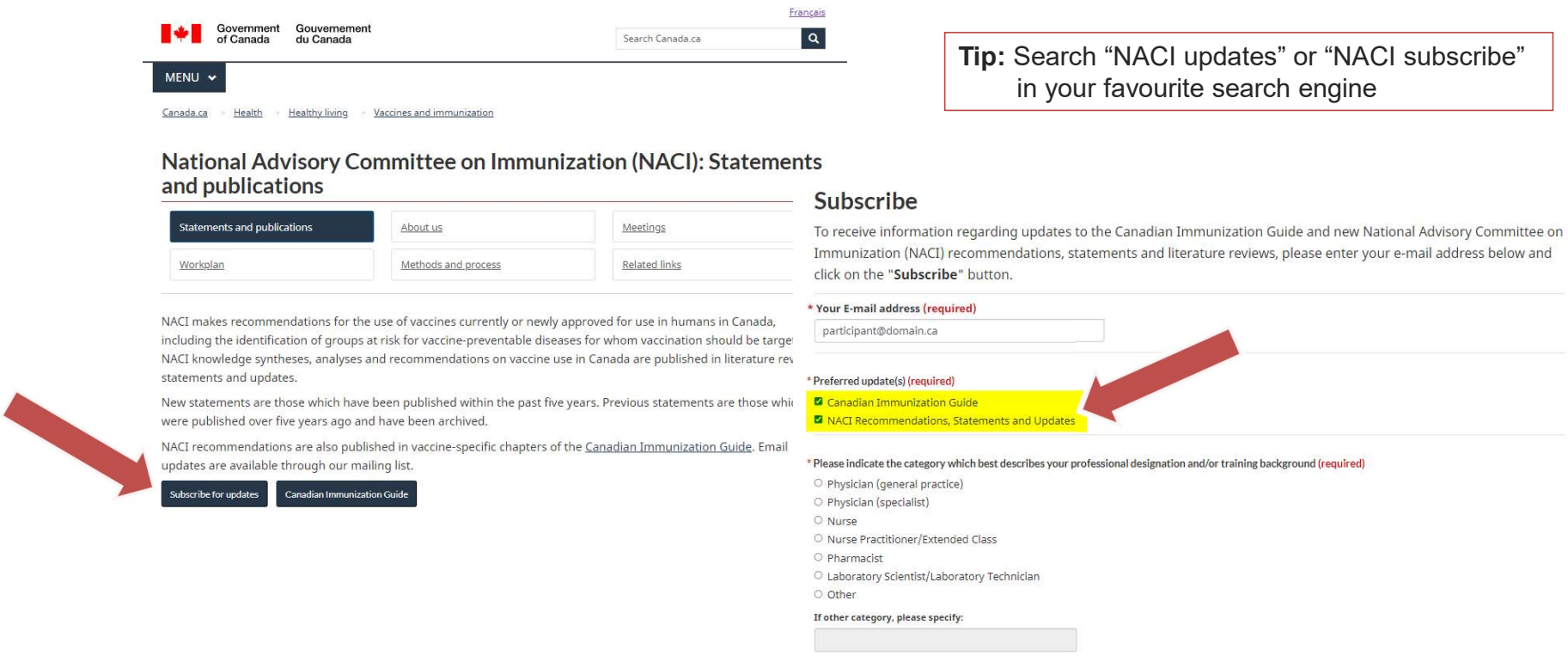

Tip: Search “NACI updates” or “NACI subscribe” in your favourite search engine

https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci.html

For more PHAC webinars and videos on COVID-19, visit:

Canada

COVID-19 for health professionals: Training
www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/health-professionals/training.html

National Collaborating Centre for Infectious Diseases
Centre de collaboration nationale des maladies infectieuses

National Collaborating Centre for Infectious diseases
nccid.ca/phac-webinars-on-covid-19-vaccines

CANVAX

Canadian Vaccination Evidence Resource and Exchange Centre
https://canvax.ca/canvax-presents-phac-webinar-series-covid-19-vaccines

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C(33 Update with link to report once published.
Charbonneau, Danielle (PHAC/ASPC), 2022-02-05

FA(8 Removed for the time being and replaced by "pending publication".
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