

Ministry of Health

Q&A for Health Care Providers on Mixed (Heterologous) COVID-19 Vaccine Schedules

Version 1.0 – July 16, 2021

This document provides basic information only and is not intended to provide or take the place of medical advice, diagnosis or treatment, or legal advice.

Background

- It is crucial for all individuals to complete their vaccine series with a second dose of a COVID-19 vaccine to receive the optimal level of protection. Data from clinical trials and real-world studies clearly demonstrate that a complete two dose vaccine series provides enhanced protection against COVID-19.
- The increased circulation of the B.1.617.2 (Delta) variant of concern (VOC) further emphasizes the importance of ensuring second doses are further accelerated for people living in Ontario.
- The National Advisory Committee on Immunization (NACI) [recommendations](#) on the use of a different COVID-19 vaccine product to complete a COVID-19 vaccine series (also known as a mixed or heterologous vaccine schedule) are being followed in Ontario.
 1. NACI recommends that, if readily available*, the same mRNA COVID-19 vaccine product should be offered for the subsequent dose in a vaccine series started with an mRNA COVID-19 vaccine.
 - However, when the same mRNA COVID-19 vaccine product is not readily available*, or is unknown, another mRNA COVID-19 vaccine product recommended for use in that age group should be offered to complete the vaccine series.
 - The previous dose should be counted, and the series need not be restarted.

*Readily available has been defined by NACI as easily available at the time of vaccination without delay or vaccine wastage

2. NACI recommends that while either an AstraZeneca/COVISHIELD COVID-19 vaccine or an mRNA COVID-19 vaccine product may be offered for the subsequent dose in a vaccine series started with an AstraZeneca/COVISHIELD COVID-19 vaccine, **an mRNA COVID-19 product is preferred as a subsequent dose**, due to emerging evidence, including the possibility of better immune response, and the safety of heterologous schedules.
 - Regardless of which product is offered, a complete two-dose series is important for protection; the previous dose should be counted, and the series need not be restarted.
 - Individuals who receive two doses of the AstraZeneca/COVISHIELD vaccine are considered protected and do not require further vaccination
- Where a different product is used to complete the vaccine series, the second dose should be given at the Health Canada product monograph authorized interval of the vaccine used for the first dose, or as soon as operationally feasible thereafter.

Vaccine for first dose	Vaccine for second dose	Interval between doses
Pfizer	Pfizer	21 days†*
Pfizer	Moderna	21 days†*
Moderna	Moderna	28 days†
Moderna	Pfizer	28 days†
AstraZeneca	Pfizer	8-12 weeks ^{oo}
AstraZeneca	Moderna	8-12 weeks ^{oo}
AstraZeneca	AstraZeneca	8-12 weeks ^{oo}

† Health Canada authorized interval as per product monograph of the vaccine used for the first dose.

*An interval of 28 days may be considered for operational feasibility

- ∞ AstraZeneca/COVISHIELD COVID-19 vaccine may be provided at the Health Canada authorized interval of 4-12 weeks as per the product monograph for those with medical exceptions to the extended dose intervals.
- More information on dose intervals for different population groups can be found on the ministry's website in a [quick reference guide](#).

Patients should understand which product they are receiving and have the opportunity to ask questions.

What do we know about mixed (heterologous) vaccine schedules?

Using a heterologous vaccine schedule is an established process in immunization programs. Similar vaccines from different manufacturers are used when vaccine supply or public health programs change.

Foundational vaccine science principles indicate that similar vaccines, from different manufacturers can be substituted when: they are authorized for the same purpose; for the same populations; have similar schedules; have similar or produce similar type(s) of antigens and are similar in terms of vaccine safety, immune responses and protection provided.

- Use of a heterologous vaccine series for COVID-19 vaccines is consistent with the current [NACI guidance](#) for vaccines that are used for the same indication and contain comparable antigens.
- In line with basic principles of vaccinology, it is expected that combining different COVID-19 vaccines that induce an immune response against the SARS-CoV-2 spike protein will lead to a robust immune response.
- In providing COVID-19 heterologous vaccine product recommendations, NACI considered the risk of Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT) associated with the use of viral vector vaccines, the availability of alternative mRNA COVID-19 vaccines without this risk, general principles of vaccinology, as well as evidence on the safety and immunogenicity of a heterologous COVID-19 vaccine schedule.

What do we know about mRNA mixed (heterologous) vaccine schedules?

- The mechanism of action in both Pfizer-BioNTech and Moderna mRNA vaccines is the same. Both use the pre-fusion conformation of the spike protein of the SARS-CoV-2 virus as the antigen. The spike protein encoded by either of the authorized mRNA vaccines is stabilized in the same manner, although other vaccine components like the lipid nanoparticle and the mRNA sequence may be different.
- During clinical trials, both mRNA vaccines (Pfizer-BioNTech, Moderna) demonstrated similar safety profiles and side effects ([NACI](#)).
- Both mRNA vaccines showed similar vaccine efficacy in clinical trials against symptomatic COVID-19 disease following the second dose, 95% and 94% respectively for Pfizer-BioNTech and Moderna vaccines ([NACI](#)). Recent vaccine effectiveness estimates against symptomatic disease from Ontario have also demonstrated similar estimates of 91% and 94% respectively for Pfizer-BioNTech and Moderna vaccines (Chung et al., 2021)
- There is no published data on immunogenicity of a heterologous mRNA vaccine schedule available at this time.
- There is no reason to believe that mRNA vaccine series completed with a different authorized mRNA vaccine product would result in any additional safety issues or reduction in immune protection against COVID-19 at this time ([NACI](#)).
- The Ministry of Health in consultation with the Chief Medical Officer of Health supports a heterologous model approach to mRNA COVID-19 immunization where necessary to support the completion of a COVID-19 vaccine series.
 - Individuals who received a first dose of an mRNA vaccine (Pfizer-BioNTech or Moderna) should be offered the same mRNA product for their second dose when both vaccines are simultaneously available

- If the same product is not readily available, or the product used for the first dose is unknown, the available mRNA vaccine product should be used for the 2nd dose, to complete the series.
- A heterologous model approach does not apply to individuals aged 12-17 as there is only one vaccine product authorized for use in this age group at this time

What do we know about AstraZeneca/COVISHIELD-mRNA mixed (heterologous) vaccine schedules?

- The second dose interval for individuals who received their first dose of an AstraZeneca/COVISHIELD COVID-19 vaccine has been accelerated to no less than eight weeks.
- Recently released immunogenicity data shows that a heterologous schedule (AstraZeneca/COVISHIELD for the first dose and Pfizer-BioNTech for the second dose) results in increased humoral and cellular immune responses, including against VOCs, compared to a homologous schedule of AstraZeneca followed by AstraZeneca ([Barros-Martins et al.](#)).
- Individuals who received a first dose of the AstraZeneca/COVISHIELD COVID-19 vaccine may want to complete their series with this same vaccine product, while others may prefer to receive an mRNA vaccine for their second dose. A tool has been developed to assist individuals in their decision-making that must be reviewed with a health care provider prior to vaccination: [COVID-19 Vaccine Information for Individuals who received a first dose of the AstraZeneca/COVISHIELD COVID-19 vaccine.](#)
- Individual decision-making should assess the risks and benefits based on the available evidence, individual circumstances and preferences.
- All individuals who received the AstraZeneca/COVISHIELD COVID-19 vaccine as a first dose will be eligible to receive their second dose no less than 8 weeks after their first dose, regardless of which vaccine product they choose.

- Individuals with medical exceptions to the extended dose interval, may continue to receive the vaccine at the Health Canada authorized product monograph interval of 4-12 weeks.

Option 1: Receive an AstraZeneca COVID-19 vaccine for the second dose

- Clinical trial data and real-world evidence have demonstrated that a complete two dose series of the AstraZeneca/COVISHIELD COVID-19 vaccine provides good protection against symptomatic COVID-19 and severe outcomes.
- Clinical trials demonstrated that when two doses of the AstraZeneca/COVISHIELD COVID-19 vaccine are spread out by ≥ 12 weeks, it provided an estimated 82% protection against symptomatic disease. When the two doses were given closer together (9-12 weeks), protection was estimated at 69%.
- Vaccine effectiveness data of a two dose AstraZeneca/COVISHIELD COVID-19 vaccine schedule was found to be 66.1% (95% CI: 54.0 to 75.0) against the Alpha variant and 59.8% (95%CI: 28.9 to 77.3) against the Delta variant in preventing symptomatic lab confirmed infection ([Bernal et al., 2021](#))
 - Rare cases of a specific syndrome that involves serious blood clots (at unusual sites such as cerebral venous sinus) associated with thrombocytopenia have been reported after vaccination with viral vector vaccines. Investigations to better understand this syndrome, often referred to as Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT), are ongoing. These events often occur between 4 and 28 days after receipt of the vaccine.
 - Early identification and appropriate treatment are critical.
 - Clots related to VITT can be very aggressive and can be challenging to treat with potential associated long-term morbidity. Ontario's Science Advisory Table has provided treatment and diagnosis guidance for [Emergency Department and Inpatient settings](#) and [Outpatient settings](#).

- The case fatality rate of VITT also varies between countries, and ranges between 20 and 50% ([NACI](#)).
- Currently, the reported risk of VITT after the second dose of AstraZeneca / COVISHIELD COVID-19 vaccine is lower than after the first dose. With increased observation times, VITT rates have generally increased, including the risk estimate following the second dose. Risk estimates are continually updated as new data become available.
 - The rate of VITT is estimated to be between 1 per 26,000 and 1 per 100,000 persons vaccinated with a first dose of an AstraZeneca/COVISHIELD COVID-19 vaccine ([NACI](#)). The rate of VITT in Canada after a first dose has been estimated to be approximately 1 per 55,000 doses administered ([Ontario Science Advisory Table](#)).
 - At this time, data from the United Kingdom (UK) suggests that the rate of VITT following the second dose is approximately 1 per 600,000 doses administered (31 events following 19.6 million second doses administered in the UK as of June 16, 2021). Information from the UK is regularly reviewed and reported because many millions of second doses of AstraZeneca COVID-19 vaccine have been administered in this country. This report is updated weekly and can be found here: [Coronavirus vaccine - weekly summary of Yellow Card reporting - GOV.UK \(www.gov.uk\)](#).

Option 2: Receive an mRNA (Pfizer-BioNTech or Moderna) vaccine for a second dose

- In line with basic principles of vaccinology, it is expected that combining different COVID-19 vaccines that induce an immune response against the SARS-CoV-2 spike protein will lead to a robust immune response.
- There is evidence that providing an mRNA vaccine after AstraZeneca COVID-19 vaccine will boost the immune response
 - A recent study from Spain ([Borobia et al., 2021/CombiVacS](#)) demonstrated that a heterologous vaccine schedule of an AstraZeneca COVID-19 vaccine followed by a dose of the Pfizer BioNTech COVID-19 vaccine produces a strong immune response, as measured by antibodies following the second dose, when compared to study participants with only a single dose of the AstraZeneca COVID-19 vaccine.

- In a recent observational study ([Barros-Martins et al., 2021](#)), using a ~10.5 week interval between doses, a Pfizer-BioNTech boost following AstraZeneca COVID-19 vaccine was found to induce a heightened humoral and T cell immune response compared to the homologous AstraZeneca COVID-19 vaccine schedule, including an increased neutralizing antibody response against the Alpha, Beta and Gamma VOCs. The significance of these findings with regard to effectiveness and duration of protection is unknown due to a lack of a defined immunological correlate of protection for SARS-CoV-2 infection.
- Studies involving heterologous schedules with vaccines using different platforms are ongoing, including the [MOSAIC CIRN Canadian study](#). The CoM-Cov randomised clinical trial from the United Kingdom (UK), compared four combinations of the AstraZeneca and Pfizer-BioNTech vaccines at 28 and 84 day intervals. Published results of the 28 day interval comparison demonstrated a more robust immune response for the AstraZeneca/COVISHIELD COVID-19 vaccine followed by the Pfizer-BioNTech vaccine one month following the second dose, compared to a homologous schedule with the AstraZeneca/COVISHIELD COVID-19 vaccine (Liu et al., 2021). Data on immunogenicity for the 84 day schedule is forthcoming. For more information, see the study website: <https://comcovstudy.org.uk/home>
- Emerging evidence indicates that heterologous COVID-19 schedules have an acceptable safety profile. There is direct evidence on the safety of heterologous COVID-19 immunization schedules (AstraZeneca and Pfizer-BioNTech) from three studies at dosing intervals between 4 and 12 weeks.
- There is a possibility of increased short-term side effects when using heterologous COVID-19 vaccine schedules, including headache, fatigue and myalgia. These side effects are relatively mild, temporary and resolved without complications.

What do we know about the importance of getting the second dose when it is offered?

- It is essential to complete the vaccine series to boost the initial immune response and because it is anticipated to provide protection in the longer term.
- There are risks associated with delaying the 2nd vaccine dose with the emergence of the Delta VOC in Ontario. Recent evidence examining the Pfizer-BioNTech vaccine and the AstraZeneca vaccine ([Bernal et al., 2021](#)) indicates there is lower vaccine effectiveness with one dose compared to two doses for both Pfizer-BioNTech and AstraZeneca COVID-19 vaccines against the Delta VOC.
 - Pfizer Bio-NTech vaccine effectiveness against symptomatic disease was estimated at 88% (95% CI:78.2 to 93.2) with two doses, compared to 36% (95% CI: 8.3 to 51.5) with one dose ([Bernal et al., 2021](#)).
 - AstraZeneca vaccine effectiveness was estimated at 60% (95% CI: 28.9 to 77.3) with two doses of AstraZeneca, compared to 33% (95% CI: 19.3 to 44.3) with one dose ([Bernal et al., 2021](#)).
- A significant delay in receiving a second dose of an mRNA vaccine in order to match the mRNA COVID-19 vaccine product, delays the improved protection provided by a completed vaccine series

Additional Information

- Bernal, J. L., Andrews, N., Gower, C., Gallagher, E., Simmons, R., Thelwall, S., Stowe, J., Tessier, E., Groves, N., Dabrera, G., Myers, R., Campbell, C., Amirthalingam, G., Edmunds, M., Zambon, M., Brown, K., Hopkins, S., Chand, M., & Ramsay, M. (2021). Effectiveness of COVID-19 vaccines against the B.1.617.2 variant. *medRxiv* [Preprint]. <https://doi.org/10.1101/2021.05.22.21257658>
- Barros-Martins, J., Hammerschmidt, S. I., Cossmann, A., Odak, I., Stankov, M. V., Ramos, G. M., Dopfer-Jablonka, A., Heidemann, A., Ritter, C., Friedrichsen, M., Schultze-Florey, C., Ravens, I., Willenzon, S., Bubke, A., Ristenpart, J., Janssen, A., Ssebyatika, G., Bernhardt, G., Münch, J., . . . Behrens, G. M. (2021). Humoral and cellular immune response against SARS-CoV-2 variants following heterologous and homologous ChAdOx1 nCoV-19/BNT162b2 vaccination. *medRxiv* [Preprint] <https://doi.org/10.1101/2021.06.01.21258172>
- Borobia, A. M., Carcas, A. J., Pérez Olmeda, M.T., Castaño, L., Jesús Bertrán, M., García-Pérez, J., Campins, M., Portolés, A., Gonzalez-Perez, M., García Morales, M. T., Arana, E., Aldea Novo, M., Díez-Fuertes, F., Fuentes-Camps, I., Ascaso, A., Lora, D., Imaz-Ayo, N., Baron-Mira, L. E., Agustí, A., . . . Frías, J. , CombiVacS Study, (2021). Reactogenicity and Immunogenicity of BNT162b2 in Subjects Having Received a First Dose of ChAdOx1s: Initial Results of a Randomised, Adaptive, Phase 2 Trial (CombiVacS). [Preprint] Available at SSRN: <https://ssrn.com/abstract=3854768>
- Chung, H., He, S., Nasreen, S., Sundaram, M., Buchan, S., Wilson, S., Chen, B., Calzavara, A., Fell, D., Austin, P., Wilson, K., Schwartz, K., Brown, K., Gubbay, J., Basta, N., Mahmud, S., Righolt, C., Svenson, L., MacDonald, S., Janjua, N., Tadrous, M. & Kwong, J. (2021) Effectiveness of BNT162b2 and mRNA-1273 COVID-19 vaccines against symptomatic SARS-CoV-2 infection and severe COVID-19 outcomes in Ontario, Canada. *medRxiv*. [Preprint] <https://doi.org/10.1101/2021.05.24.21257744>
- [Comparing COVID-19 Vaccine Schedule Combinations | Com-CoV \(comcovstudy.org.uk\)](https://www.comcovstudy.org.uk)

- Liu, X., Shaw, R., Arabella, S., Greenland, M., Dinesh, T., Provstgaard-Morys, S., Clutterbuck, E., Ramasamy, M., Aley, P., Farooq Mujadidi, R., Long, F., Lested, E., Robinson, H., Singh, N., Walker, L., White, R., Andrews, N., Cameron, J., Collins, A., . . . Snape, M. and the Com-COV Study Group. (2021). Safety & Immunogenicity Report from the Com-COV Study – a Single-Blind Randomized Non-Inferiority Trial Comparing Heterologous and Homologous Prime-Boost Schedules with an Adenoviral Vectored and mRNA COVID-19 Vaccine. [Preprint]. Available at SSRN: <http://dx.doi.org/10.2139/ssrn.3874014>
- National Advisory Committee on Immunization (NACI). (2021, June 17). [Recommendations on the use of COVID-19 vaccines - Canada.ca](#)
- National Advisory Committee on Immunization (NACI). (2021, June 1). [Rapid Response: Interchangeability of Authorized COVID-19 Vaccines](#)
- Ontario COVID-19 Science Advisory Table (2021, May 11) *Risk of Vaccine-Induced Thrombotic Thrombocytopenia (VITT) following the AstraZeneca/COVISHIELD Adenovirus Vector COVID-19 Vaccines*. <https://doi.org/10.47326/ocsat.2021.02.28.1.0>
- Ontario COVID-19 Science Advisory Table (2021, May 10) *Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT) Following Adenovirus Vector COVID-19 Vaccination: Interim Guidance for Healthcare Professionals in the Outpatient Setting* <https://doi.org/10.47326/ocsat.2021.02.20.2.0>
- Ontario COVID-19 Science Advisory Table (2021, May 10) *Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT) Following Adenovirus Vector COVID-19 Vaccination: Interim Guidance for Healthcare Professionals in Emergency Department and Inpatient Settings*. <https://doi.org/10.47326/ocsat.2021.02.21.2.0>
- Ontario COVID-19 Science Advisory Table (2021, May 7) *Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT) Following Adenovirus Vector COVID-19 Vaccination: Lay Summary*. <https://doi.org/10.47326/ocsat.2021.02.16.2.0>
- Public Health Agency of Canada (2021, June 1) [Interchangeability of Authorized COVID-19 vaccines](#)
- Public Health Ontario (n.d.) [Vaccine Safety](#)

- Shaw, R., Stuart, A., Greenland, M., Liu, X., Nguyen Van-Tam, J., Snape, M and the Com-COV Study Group (2021, May 29). Heterologous prime-boost COVID-19 vaccination: initial reactogenicity data [Correspondence]. *The Lancet*, 397, 2043-2045. [https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736\(21\)01115-6.pdf](https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(21)01115-6.pdf)
- The Canadian MOSAIC Study: [Mix and match of the second COVID-19 vaccine dose for SAFety and ImmunogeniCity](#)
- Weekly summary of Yellow Card reporting from the UK: <https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting> (under the section: Blood clots with concurrent low platelets)
- This document will be updated as important new information becomes available.