What has changed?

- The second dose interval for individuals who received their first dose of an AstraZeneca/COVISHIELD COVID-19 vaccine has been further accelerated to no less than eight weeks.
  - In general, longer intervals between vaccine doses result in stronger final immune responses. The circulation of the B.1.617.2 (Delta) variant of concern in some areas of Ontario, however, warrants consideration of a shorter interval. There is lower vaccine effectiveness with one dose compared to two doses for both Pfizer-BioNTech and AstraZeneca vaccines against the Delta variant (as per the Lopez Bernal et al study).
  - The interval of not less than 8 weeks balances the apparent benefit of protection associated with a longer dose interval against earlier enhanced protection from COVID-19 infection.

- Recently released immunogenicity data shows that a mixed schedule (AstraZeneca for the first dose and Pfizer-BioNTech for the second dose) results in an increased immune response, including against variants of concern, than a homologous schedule of AstraZeneca followed by AstraZeneca (as per Barros-Martins et al.). 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.
Background

The National Advisory Committee on Immunization (NACI) released their recommendation on the use of an mRNA vaccine to complete a COVID-19 vaccine series that was started with the AstraZeneca/COVISHIELD COVID-19 vaccine on June 1st 2021. Based on the available evidence NACI provided the following recommendation:

- 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. The previous dose should be counted, and the series need not be restarted.

In providing these 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 mixed COVID-19 vaccine schedule.

Read the full statement with rationale and evidence base here: NACI Rapid Response: Interchangeability of Authorized COVID-19 Vaccines

All second dose appointments have been accelerated in Ontario in response to improved vaccine supply. Aligned with the province’s accelerated second dose plan, all individuals who received AstraZeneca/COVISHIELD COVID-19 vaccine as a first dose will be eligible to receive their second dose at an 8-12-week interval, regardless of which vaccine product they choose.

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 that is to be reviewed together
with their 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 individual circumstances and preferences. The information in this document is intended to help support this decision-making process and providers in their conversations with patients.

What is the evidence to support each option for my patient/client?

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

A. What do we know about how well the AstraZeneca/COVISHIELD COVID-19 vaccine (AZ) protects against COVID-19?
   - Clinical trial data and real-world evidence have demonstrated that a complete 2 dose series of the AstraZeneca/COVISHIELD COVID-19 vaccines provide good protection against symptomatic COVID-19 and severe outcomes.
   - Clinical trials demonstrated that when two doses of the AstraZeneca 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 AZ-AZ 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 (as per the Lopez Bernal et al. study).

B. What do we know about the risk of VITT associated with receiving this series of 2 doses of AstraZeneca?
   - Rare cases of a specific syndrome that involves serious blood clots (at unusual sites such as cerebral venous sinus) associated with thrombocytopenia have recently been reported after vaccination with viral vector vaccines. These cases often occur between 4 and 28 days after receipt of the vaccine.
     - Early identification and appropriate treatment are critical.
Investigations to better understand this syndrome, often referred to as Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT), are ongoing.

- 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 in Canada after a first dose has been estimated to be approximately 1 in 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 in 600,000 doses administered (23 events following 15.7 million second doses administered in the UK as of June 2, 2021). Information from the UK is regularly reviewed and reported because many millions of second doses of AstraZeneca 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).

C. When are those who received their first dose of AstraZeneca/COVISHIELD COVID-19 vaccine eligible to receive their second dose of AstraZeneca and how will they book?

- All individuals who received the AstraZeneca/COVISHIELD COVID-19 vaccine as a first dose will be eligible to receive their second dose at an 8-12 week interval, regardless of which vaccine product they choose.
- Individuals with medical exceptions to the extended dose interval, may continue to receive the vaccine at the product monograph interval (between 4 to 12 weeks).
• Beginning June 14, 2021, individuals who received their first dose of the AstraZeneca vaccine 8 -12 weeks prior and who would like their second dose of the AstraZeneca vaccine, can contact the pharmacy or primary care provider where they received their first dose to book an appointment.

Option 2: Receive an mRNA vaccine for a second dose

A. What do we know about how well an AstraZeneca/COVISHIELD COVID-19 vaccine followed by an mRNA vaccine protects against COVID-19?

• 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 (AZ) will boost the immune response, which is what we expect from a second dose.
  o A recent study from Spain (CombiVacS trial) has demonstrated that that a mixed 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.
  o A recent observation study using a ~10.5 week dose interval has released immunogenicity data (see: Barros-Martins et al.). In this study, a Pfizer-BioNTech (BNT) boost following AstraZeneca COVID-19 vaccine (AZ) induced a heightened humoral and T cell immune response compared to the homologous AZ + AZ schedule, including an increased neutralizing antibody response against the Alpha, Beta and Gamma variants of concern. 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.
  o Studies involving mixed schedules with vaccines using different platforms are ongoing. 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 with data on immunogenicity forthcoming. For more information, see the study website: https://comcovstudy.org.uk/home
• This is not a new concept. Similar vaccines from different manufacturers are used when vaccine supply or public health programs change. General vaccine principles indicate that vaccines from different manufacturers can be used interchangeably when vaccines are authorized for the same purpose, for the same populations, have similar schedules, have similar or produce similar type(s) antigens and are similar in terms of vaccine safety, immune responses and protection provided.
• The National Advisory Committee on Immunization (NACI) has recommended that either AstraZeneca/COVISHIELD COVID-19 vaccine or an mRNA COVID-19 vaccine product (Pfizer BioNTech or Moderna) may be offered as the second dose in a vaccine series for those that received a first dose of AstraZeneca/COVISHIELD COVID-19 vaccine.

B. What do we know about the risks associated with an AstraZeneca/COVISHIELD COVID-19 vaccine followed by an mRNA vaccine?
• Emerging evidence indicates that mixed COVID-19 schedules have an acceptable safety profile. There is direct evidence on the safety of mixed 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 mixed COVID-19 vaccine schedules, including headache, fatigue and myalgia. These side effects are relatively mild, temporary and resolve without complications.

C. When are those who received their first dose of the AstraZeneca/COVISHIELD COVID-19 vaccine eligible to receive their second dose of an mRNA vaccine and how will they book?
• All individuals who received AstraZeneca/COVISHIELD COVID-19 as a first dose will be eligible to receive their second dose at a 8-12-week interval, regardless of which vaccine product they choose.
• Individuals with medical exceptions to the extended dose interval, may receive the vaccine at the AstraZeneca product monograph interval (between 4 to 12 weeks).
• Beginning June 14, 2021, individuals who received their first dose of the AstraZeneca vaccine and are opting to receive an mRNA vaccine have the option to schedule their second dose appointment at a participating pharmacy where the Pfizer or Moderna vaccines are administered, through
the provincial booking system, or to schedule their second dose appointment directly through public health units that use their own booking system. Primary care settings and pharmacies may also be reaching out to eligible Ontarians.

Will the guidance about second dose for those who received a first dose of AstraZeneca change again?

Studies involving mixed schedules with vaccines using different vaccine platforms are ongoing and real-world evidence will also be forthcoming. Immunogenicity data from the UK Com-Cov clinical trial is expected later in June 2021 and recommendations may be updated upon review of the findings. Investigations continue into the risk of VITT with both first and second doses of the AstraZeneca/COVISHIELD COVID-19 vaccine and the data will continue to be monitored closely. Guidance will be updated as needed based on emerging data.

Additional Information

National Advisory Committee on Immunization's (NACI) Recommendations on the use of COVID-19 vaccines - Canada.ca

NACI Rapid Response: Interchangeability of Authorized COVID-19 Vaccines

Public Health Agency of Canada: Interchangeability of Authorized COVID-19 vaccines

Vaccine Safety | Public Health Ontario

Comparing COVID-19 Vaccine Schedule Combinations | Com-CoV (comcovstudy.org.uk)

Lancet Correspondence: Heterologous prime-boost COVID-19 vaccination: initial reactogenicity data


The Canadian MOSAIC Study *(Mix and match of the second COVID-19 vaccine dose for SAfety and ImmunogeniCity)*


*Risk of Vaccine-Induced Thrombotic Thrombocytopenia (VITT) following the AstraZeneca/COVISHIELD Adenovirus Vector COVID-19 Vaccines - Ontario COVID-19 Science Advisory Table (covid19-sciencetable.ca)*

Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT) Following Adenovirus Vector COVID-19 Vaccination: Interim Guidance for Healthcare Professionals in the Outpatient Setting - Ontario COVID-19 Science Advisory Table (covid19-sciencetable.ca)

Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT) Following Adenovirus Vector COVID-19 Vaccination: Interim Guidance for Healthcare Professionals in Emergency Department and Inpatient Settings - Ontario COVID-19 Science Advisory Table (covid19-sciencetable.ca)
Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT) Following Adenovirus Vector COVID-19 Vaccination: Lay Summary - Ontario COVID-19 Science Advisory Table (covid19-sciencetable.ca)