



**CANVAX WEBINAR SERIES**

# **PHAC: NACI Recommendations for COVID-19 Vaccine Interchangeability**

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## QUICK NOTES

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# MODERATOR/ SPEAKERS

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**Moderator:** Annie Fleurant-Ceelen, RN, MScN.  
Public Health Agency of Canada

**Speakers:**

**Dr. Bryna Warshawsky**, MDCM, FRCPC.  
Public Health Agency of Canada

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Chair, National Advisory Committee on Immunization (NACI)



The contents of this webinar reflect the recommendations published on June 1<sup>st</sup>, 2021 in *NACI rapid response: Interchangeability of authorized COVID-19 vaccines* and on June 17, 2021 in *Recommendations on the use of COVID-19 Vaccines*

# NACI Recommendations on interchangeability of authorized COVID-19 Vaccines

June 21 2021



## Conflicts of Interest

- Dr. Bryna Warshawsky- Nothing to Declare
- Dr. Shelley Deeks- Nothing to Declare

Moderator: Annie Fleurant-Ceelen - Nothing to Declare

## Objectives

1. Define how the National Advisory Committee on Immunization (NACI) provides advice in response to questions from PHAC relating to immunization.
2. Discuss the current scientific body of evidence on COVID-19 vaccine interchangeability.
3. Explain the NACI practice recommendations on COVID-19 vaccine interchangeability.

# BRIEF OVERVIEW OF NACI

## National Advisory Committee on Immunization (NACI)

- NACI is an expert advisory body that provides independent advice to the Public Health Agency of Canada (PHAC) on the optimal use of vaccines in Canada.
- It is normal for NACI recommendations to be broader or narrower than the conditions of use approved by Health Canada.
- NACI recommendations are advisory in nature as provinces and territories are responsible for their vaccine policies and immunization programs.



## Recommendations on authorized COVID-19 vaccines

- NACI has provided recommendations on the use of COVID-19 vaccines since the authorization of the first COVID-19 vaccine in Canada in December 2020.
- Recommendations aims to achieve Canada's pandemic response goal which is to minimize serious illness and overall deaths, as well as societal disruption.
- Recommendations support ongoing work between federal, provincial and territorial governments to rollout COVID-19 vaccines as efficiently, equitable and effectively as possible.

## Recommendations on authorized COVID-19 vaccines

- NACI assesses how best to use a COVID-19 vaccine to achieve the greatest public health benefits by considering:
  - The spread of COVID-19 in Canada and the risks for population subgroups;
  - Safety, efficacy and effectiveness data from clinical trials and real world use;
  - Expected vaccine supply in Canada; and
  - Elements of ethical decision-making.
- NACI updates their recommendations as new vaccines become authorized for use and as evidence on authorized vaccines evolves.
- To date, NACI has published recommendations on the use of the Pfizer-BioNTech, Moderna, AstraZeneca and Janssen COVID-19 vaccines, and on subjects such as extended dose intervals and the interchangeability of vaccines.

## Roles of Health Canada, PHAC and NACI

	<b>Health Canada</b> <i>Regulatory Review</i>	<b>PHAC</b> <i>National Vaccine Strategy</i>	<b>NACI</b> <i>Expert Vaccine Advice</i>
<b>Purpose</b>	Authorize <b>specific indications of a product</b> which is expected to be safe, immunogenic, and efficacious, for individuals	PHAC facilitates a national vaccination strategy. That strategy includes <b>reviewing and sharing NACI recommendations, sharing vaccination guidance, procurement, distribution and other supporting information to provinces and territories</b> on administration of COVID-19 vaccines	Independently recommend vaccination <b>strategies to promote health, prevent and control infectious diseases</b> , and prepare for or respond to public health emergencies
<b>Focus</b>	<b>Individual use of product</b>  Risks and benefits of the vaccine for the individual	The <b>number of vaccines</b> administered, <b>coverage</b> across Canada, adverse events following immunization, and evidence on safety, efficacy and effectiveness	Optimal <b>use of product for public programs</b> , and population health, and individuals. Benefits of the vaccine for public programs and the health needs within specific populations and for the individual
<b>Data reviewed</b>	<b>Pre-clinical and clinical trial data</b> and manufacturing information submitted by manufacturers; post-marketing monitoring and published scientific evidence that informs benefit-risk analysis	PHAC uses the <b>latest evidence</b> , regulatory and logistical information as well as NACI guidance	<b>All relevant/available evidence for specific vaccines</b> and similar vaccine formulations in the context of public health considerations, including existing vaccine programs and schedules, disease burden and distribution, and outbreak management

**NACI can make off-label vaccine recommendations when there is a clear need supported by vaccine characteristics, epidemiology, and a public health ethics analysis**

NACI Recommendations for COVID-19 Vaccine Interchangeability

# **BACKGROUND AND METHODOLOGY**

## Background

- In response to a request from the Public Health Agency of Canada (PHAC), NACI has provided advice on whether the use of a mixed two-dose primary series schedule for COVID-19 immunization in Canada is recommended.
- Similar vaccines from different manufacturers are routinely used interchangeably, particularly during transitions between public health programs over time and when vaccine supply changes. Examples include :
  - Hepatitis A, monovalent Hepatitis B, Influenza, Measles, Mumps, Rubella (MMR), Meningococcal conjugate vaccines and vaccines used for routine primary immunization series of diphtheria toxoid, tetanus toxoid, pertussis, poliomyelitis and Haemophilus influenzae type b (DTaP-IPV-Hib).

## Background

- To be considered interchangeable, vaccines should be authorized with the same indications and with similar schedules, for the same population, contain comparable type of antigen, and be similar in terms of safety, reactogenicity, immunogenicity and efficacy.
- All currently authorized COVID-19 vaccines in Canada use the spike protein as antigen.
  - The spike protein produced by the mRNA (Moderna and Pfizer/BioNTech) and Janssen vaccines is stabilized in the **prefusion** conformation.
  - The AstraZeneca vaccine produces a **wild-type spike protein** in various conformations, including **prefusion**.

## Methodology

- NACI reviewed all available direct and indirect evidence on the safety and immunogenicity of mixed schedules of mRNA and viral vector COVID-19 vaccines that was available up to **June 11, 2021**.
- **Ethical considerations** - NACI applied its Core Ethical Dimensions and Procedural Ethical Considerations Filters throughout recommendation development to ensure the principles of justice, trust, respect for persons and communities, and minimizing risks vs harms were upheld.
- **Ongoing monitoring** – NACI continues to monitor the evolving evidence and will update recommendations as needed.

## Methodology

- This was done using full Committee meetings that reviewed **evidence from 3 studies**;
  - CoM-Cov (Shaw et al., Oxford, UK) [DOI:10.1016/S0140-6736\(21\)01115-6](https://doi.org/10.1016/S0140-6736(21)01115-6)
  - CombiVacS (Spain) (Borobia et al., Spain) <https://ssrn.com/abstract=3854768>
  - Health Care Worker Study (Hillus et al., Germany) [DOI: 10.1101/2021.05.19.21257334v1](https://doi.org/10.1101/2021.05.19.21257334v1)
- Following the initial statement on June 1st, additional studies reporting on immunogenicity results of heterologous COVID-19 vaccine schedules have come out as preprints:
  - CoCo Study (Barros-Martins, J., et al, Germany). [DOI: 10.1101/2021.06.01.21258172](https://doi.org/10.1101/2021.06.01.21258172)
  - Groß, R., Zanoni, et al. (Germany) [DOI: 10.1101/2021.05.30.21257971](https://doi.org/10.1101/2021.05.30.21257971)
  - Hillus et al (newer version with immunogenicity data) [DOI:10.1101/2021.05.19.21257334v2](https://doi.org/10.1101/2021.05.19.21257334v2)



## Interchangeability and Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT)

- The risk of VITT is approximately:
  - 1/50,000 after the first dose of AstraZeneca
  - 1/600,000 to 1/750,000 after the second dose of AstraZeneca
- Following the emerging evidence on the risk of VITT associated with the use of AstraZeneca, several EU countries (Denmark, Finland, France, Germany, Sweden) issued guidance to complete a two-dose series started with AZ with an mRNA vaccine. The decision to implement a mixed schedule is being considered by other countries.
- In the case of COVID-19 vaccines NACI considered the risk of VITT associated with the use of viral vector vaccines, the availability of 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.

NACI Recommendations for COVID-19 Vaccine Interchangeability

# **SCIENTIFIC EVIDENCE**

## Preclinical Studies

- Previously conducted animal studies of mixed two-dose primary series schedules of adenoviral vector and mRNA COVID-19 vaccines have demonstrated robust immune responses following the second vaccine dose.
- Similar immune responses have also been reported in studies that evaluated immunogenicity of mixed schedules with the adenovirus and Modified Vaccinia virus Ankara (MVA) Ebola vaccines.

### Heterologous or Mixed schedule

Vaccination series that uses **more than one vaccine product**

e.g. 1<sup>st</sup>  
AstraZeneca™ +  
2<sup>nd</sup> Pfizer-  
BioNTech™

# Safety

## Reactogenicity

Production of a local / systemic reaction

(fatigue, pain at injection site, chills, headache, muscle pain, joint pain, malaise, mild nausea, fever)

Reactogenicity	Method	Studies
Increased reactogenicity with heterologous schedules	<ul style="list-style-type: none"> <li>AZ + Pfizer <u>or</u> Pfizer + AZ 28 days apart</li> <li>vs</li> <li>AZ + AZ <u>or</u> Pfizer + Pfizer 4 weeks apart</li> </ul>	Com-COV (UK, Oxford)
No differences when reactogenicity compared to historical data	AZ + Pfizer, 8-12 weeks apart	CombiVacS study (Spain)
Decreased systemic reactogenicity after 2 <sup>nd</sup> dose with mixed schedules than for 1st dose AZ	<ul style="list-style-type: none"> <li>AZ + Pfizer, 10-12 weeks apart</li> <li>vs</li> <li>Pfizer + Pfizer, 3 weeks apart</li> </ul>	Healthcare Worker Study (Hillus & al., Germany)
Decreased systemic reactogenicity with the 2 <sup>nd</sup> dose compared to the 1 <sup>st</sup> dose for some types of reactions	<ul style="list-style-type: none"> <li>AZ + Pfizer, 8 weeks apart</li> </ul>	Groß et al. (Germany)

## Immunogenicity: CombiVacS trial in Spain

### Immunogenicity

Ability to produce  
a immune  
response  
(antibodies,  
cellular immunity)

450 participants received a Pfizer-BioNTech 2<sup>nd</sup> dose 8-12 weeks after the AZ 1<sup>st</sup> dose. Compared to the immune response at baseline (which represents the residual immune response from the first dose of AstraZeneca):

- **Anti-receptor binding domain (RBD) antibody titres** increased by approximately 80-fold, 14 days post-second dose, with increases observed as early as 7 days post-second dose.
- **Anti-spike antibodies** increased approximately 37-fold 14 days post-second dose.
- **Neutralizing antibodies** titres also increased by approximately 45-fold following the Pfizer-BioNTech dose.

<https://papers.ssrn.com/abstract=3854768>

## Immunogenicity : Groß et al. (Germany)

- 26 subjects received an AstraZeneca followed by Pfizer-BioNTech at a 8 week interval. The humoral and cellular immune response were compared to that of previously obtained sera from 28 subjects who were vaccinated twice with Pfizer-BioNTech (interval not provided).
  - Results issued from this limited sample size indicated an increase in IgG, IgA and neutralizing antibodies (NAbs) following the 2<sup>nd</sup> dose.
  - Cumulative IgG and IgM levels and NAb titres (against pseudovirus **B.1.1.7** [alpha], **B.1.351** [beta] and **B1.617** variants) were **higher** than those from **previously obtained for Pfizer-BioNTech + Pfizer-BioNTech sera.**

[www.medrxiv.org/content/10.1101/2021.05.30.21257971v1.full-text](https://www.medrxiv.org/content/10.1101/2021.05.30.21257971v1.full-text)

## Immunogenicity : Hillus & al. (Germany)

- 110 health care workers with no previous SARS-CoV-2 infection received a 1<sup>st</sup> dose of AstraZeneca followed 10-12 weeks later by a Pfizer-BioNTech were compared to 189 subjects who received 2 doses of Pfizer-BioNTech at a 3 week interval.
- Immune responses were measured 3-4 weeks after each dose
  - Antibody levels following 1st dose were lower for AstraZeneca than Pfizer-BioNTech.
  - Both regimens produced **high avidity antibodies after the 2nd dose**; avidity was **slightly higher with the AstraZeneca + Pfizer-BioNTech** compared to a 2-dose Pfizer-BioNTech series, which could be due to longer interval between the doses.
  - Levels of binding Abs and NAbs were **similar after 2nd dose BNT** in both regimens
  - Anti-S1 T cell responses were 35% higher after AstraZeneca + Pfizer-BioNTech compared to 2-dose Pfizer-BioNTech series.

[www.medrxiv.org/content/10.1101/2021.05.19.21257334v1](https://www.medrxiv.org/content/10.1101/2021.05.19.21257334v1) ;  
[www.medrxiv.org/content/10.1101/2021.05.19.21257334v2](https://www.medrxiv.org/content/10.1101/2021.05.19.21257334v2)

## Immunogenicity: Contact COVID (CoCo) Study (Barros-Martins et al.; Germany)

- Observational study of healthcare professionals previously vaccinated with AstraZeneca with no previous SARS-CoV-2 infection who were offered AstraZeneca (AZ) or Pfizer-BioNTech (BNT), with a 73-74 day interval: 32 chose AZ and 55 chose BNT
- Immune responses were measured 30 and 68 days post-dose 1 and 16-18 days post-dose 2
- Results after 2<sup>nd</sup> dose:
  - Boosts in anti-spike IgG and IgA were higher after a 2<sup>nd</sup> dose of Pfizer-BioNTech compared to 2<sup>nd</sup> dose of AstraZeneca (**11.5** fold ↑ for AZ + BNT IgGs vs **2.9** ↑ fold for AZ + AZ IgGs)
  - Neutralizing antibodies were detected after 2<sup>nd</sup> dose Pfizer-BioNTech against Wuhan strain, Alpha, Beta and Gamma variants (in all participants, except for 2 against the Beta variant).
    - AZ homologous boost led to a modest increase in neutralizing antibody levels against Alpha but showed no effect against Gamma and Beta.
- Greater fold-increase in anti-spike specific B cells, CD4 and CD8 T cells after 2<sup>nd</sup> dose in heterologous schedule
- The heterologous series was also associated with increase in spike protein-stimulated serum IFN-γ

[www.medrxiv.org/content/10.1101/2021.06.01.21258172v1](https://www.medrxiv.org/content/10.1101/2021.06.01.21258172v1)



## **Efficacy and Effectiveness**

- No evidence on efficacy was available at the time of the review
- Immunogenicity data on interchangeability continues to emerge

# **NACI RECOMMENDATIONS ON INTERCHANGEABILITY OF COVID-19 VACCINES**

## Series initiated with an mRNA vaccine

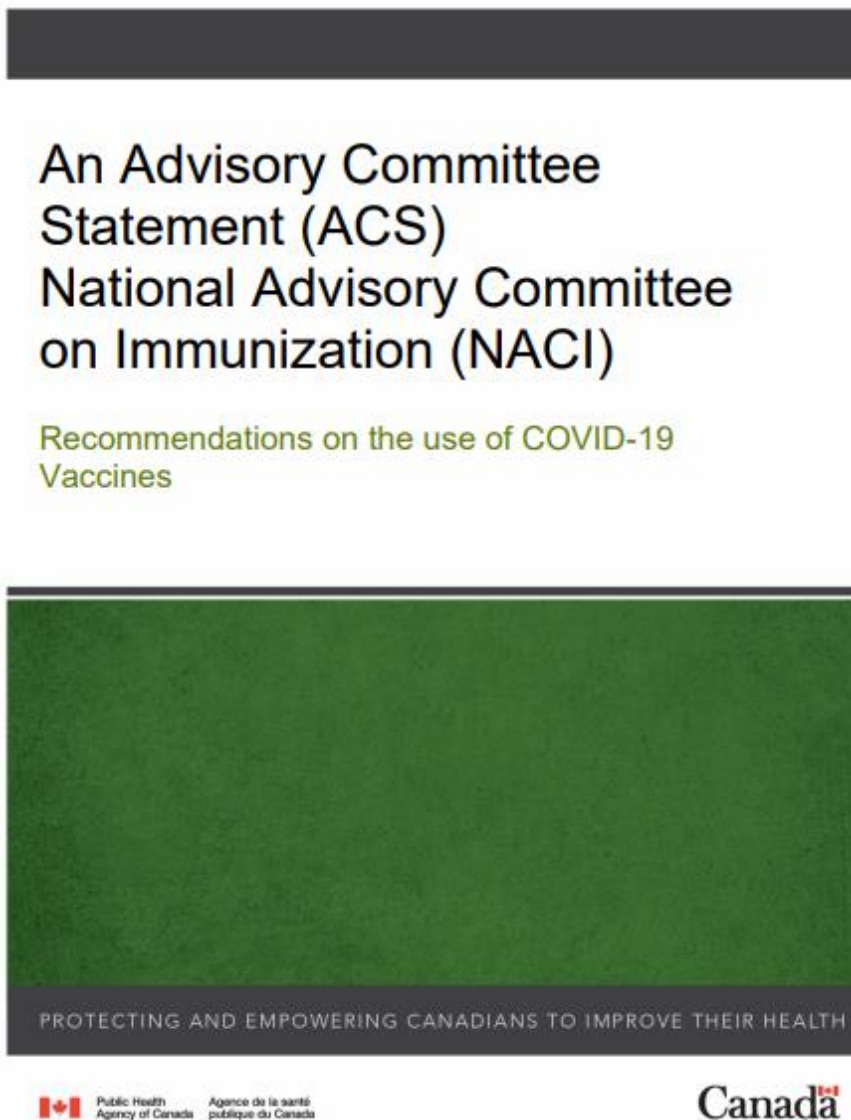
- If readily available, the same mRNA COVID-19 vaccine product should be offered for the subsequent dose in a vaccine series started with an mRNA. (*Strong NACI Recommendation*)
  - *Readily available* refers to easily available at the time of vaccination without delay or vaccine wastage
- When the same mRNA COVID-19 vaccine product is not readily available, the other mRNA product should be offered (if authorized in that age group) and can be considered interchangeable (e.g., complete a series started with the Pfizer-BioNTech COVID-19 vaccine with the Moderna COVID-19 vaccine and vice versa). (*Strong NACI Recommendation*). The previous dose should be counted, and the series need not be restarted.

## Series initiated with a viral vector vaccine

- 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.

## NACI Statement on COVID-19 Vaccines

Visit [NACI recommendations on the use of COVID-19 vaccines](#) for more guidance on COVID-19 vaccines.



# Subscribe for NACI publications and updates to the Canadian Immunization Guide

The screenshot shows the top navigation of the NACI website. It includes the Government of Canada logo, a search bar, and a 'MENU' dropdown. The breadcrumb trail is: Canada.ca > Health > Healthy living > Vaccines and immunization. The main heading is 'National Advisory Committee on Immunization (NACI): Statements and publications'. Below this are several menu items: 'Statements and publications' (highlighted), 'About us', 'Meeting', 'Workplan', 'Methods and process', and 'Related'. At the bottom of the page, there are two buttons: 'Subscribe for updates' and 'Canadian Immunization Guide'.

### Subscribe

To receive information regarding updates to the Canadian Immunization Guide and new National Advisory Committee on Immunization (NACI) recommendations, statements and literature reviews, please enter your e-mail address below and click on the "Subscribe" button.

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- Nurse
- Nurse Practitioner/Extended Class
- Pharmacist
- Laboratory Scientist/Laboratory Technician
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If other category, please specify:

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

# PHAC Health Care Provider Toolkit:



## Contents

- **About COVID-19:** General information including symptoms, prevention and guidance for health care providers, culturally safe care, and statements from the Chief Public Health Officer of Canada
- **Overview of Vaccines:** COVID-19 vaccines in Canada, how to get vaccinated, national vaccination coverage, shipments and deliveries, how vaccines are developed, as well as information for Indigenous Peoples
- **Authorized Vaccines:** Information about COVID-19 vaccines that have been authorized by Health Canada
- **Guidance for Health Care Providers:** Planning guidance on vaccine administration and immunization clinics, NACI recommendations, and guidance on anaphylaxis, vaccine components and pain mitigation
- **Vaccine Confidence:** Information and training on addressing vaccine confidence, and answers to common questions
- **Vaccine Safety:** Overview of vaccine safety, surveillance and reporting, information on possible side effects, and reported side effects in Canada
- **Additional Resources:** Provincial, territorial and stakeholder resources, communications and digital tools, and content and resources for social media platforms
- **Terms of Use:** Information about the Canada wordmark and how the tool kit resources can be used

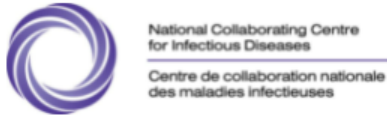
<https://www.canada.ca/content/dam/phac-aspc/documents/services/diseases-maladies/2019-novel-coronavirus-infection/health-professionals/covid-19-healthcare-professionals-vaccine-toolkit.pdf>

## For more PHAC webinars on COVID-19, visit:



COVID-19 for health professionals: Training

[www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/health-professionals/training.html](http://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/health-professionals/training.html)



National Collaborating Centre for Infectious diseases

[nccid.ca/phac-webinars-on-covid-19-vaccines](http://nccid.ca/phac-webinars-on-covid-19-vaccines)



Canadian Vaccination Evidence Resource and Exchange Centre

[www.canvax.ca/canvax-webinar-series](http://www.canvax.ca/canvax-webinar-series)

### **Topics include:**

- COVID-19 vaccines foundations
- Vaccine-induced immune thrombotic thrombocytopenia (VITT)
- Allergies and low dead volume syringes
- Delayed injection site reactions
- Planning for immunization clinics
- Other recommendations from NACI on the use of COVID-19 vaccines



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**THANK YOU FOR  
JOINING US!**

NACI Recommendations for COVID-19 Vaccine Interchangeability

# **SUPPLEMENT**

# Reactogenicity evidence with heterologous schedules

		Groß et al	Shaw et al (ComCOV)	Borobia et al (CombiVacS)	Hillus et al
	Population	Individuals age 25-46	Individuals ≥50 years old with no or mild-moderate, well controlled comorbidity	Adults <60 years old	Healthcare professionals with no previous SARS-CoV-2 infection
	Intervention	<b>AZ + BNT (n=26); 8 week interval</b>	4 different 2-dose series, <b>28</b> and 84 day intervals:	<b>AZ + BNT (n=450); 8-12 week interval</b>	<b>AZ + BNT (n=110); 10-12 week interval</b>
	Comparator	None in study; previously obtained sera from BNT + BNT vaccinated (28 day interval*) collected 13-15 days post boost	<ul style="list-style-type: none"> <li>- <b>AZ + AZ (n=112)</b></li> <li>- <b>BNT + BNT (n=117)</b></li> <li>- <b>AZ + BNT (n=114)</b></li> <li>- <b>BNT + AZ (n=110)</b></li> </ul>	No 2 <sup>nd</sup> dose comparator; <b>AZ single dose only (n=226)</b>	<b>BNT + BNT (n=189); 3 week interval</b>
O u t c o m e s	Local reactogenicity	- Compared to 1 <sup>st</sup> dose AZ, injection site pain was slightly less frequent with 2 <sup>nd</sup> dose BNT (92.3% vs 84.6%)	<ul style="list-style-type: none"> <li>- For series with <b>28 day intervals</b> only: <b>Increased</b> local and systemic reactogenicity with <b>heterologous</b> schedules</li> <li>- E.g. for fatigue:               <ul style="list-style-type: none"> <li>- AZ + AZ – 50%</li> <li>- BNT + BNT – 55%</li> <li>- AZ + BNT – 68%</li> <li>- BNT + AZ – 77%</li> </ul> </li> <li>- Similar trend for injection site pain and other systemic reactions</li> </ul>	<ul style="list-style-type: none"> <li>- Only reported for 2<sup>nd</sup> dose BNT: Injection site pain, induration, erythema very common</li> </ul>	Frequency of <b>local reactions similar after all doses</b> (pain and tenderness very common)
	Systemic reactogenicity	<ul style="list-style-type: none"> <li>- Fatigue was equally common after 1<sup>st</sup> AZ and 2<sup>nd</sup> dose BNT</li> <li>- Compared to 1<sup>st</sup> dose AZ, following reactions were less common after 2<sup>nd</sup> dose BNT: chills, myalgia, fever</li> <li>- 73% had a milder reaction to 2<sup>nd</sup> dose compared to 1<sup>st</sup> dose</li> </ul>		<ul style="list-style-type: none"> <li>- Only reported for 2<sup>nd</sup> dose BNT: Headache (44%), myalgia (43%), malaise (43%)</li> </ul>	% of any systemic reaction (highest to lowest): <ul style="list-style-type: none"> <li>- 1<sup>st</sup> dose AZ &gt; 2<sup>nd</sup> dose BNT (BNT + BNT) &gt; <b>2<sup>nd</sup> dose BNT (AZ + BNT)</b> &gt; 1<sup>st</sup> dose BNT</li> <li>- Similar trend for specific systemic reactions and severe systemic reactions</li> </ul>
	Serious adverse events (SAEs)	No hospitalizations or SAEs reported	No hospitalizations, SAEs or thrombocytopenia reported	No hospitalizations or SAEs reported	No hospitalizations or SAEs reported
	Risk of Bias	High (4 stars; Newcastle-Ottawa Quality Assessment Scale)	Low (Cochrane RoB2)	Some concerns (Cochrane RoB2)	Moderate (6 stars; Newcastle-Ottawa Quality Assessment Scale)
	Additional considerations	<ul style="list-style-type: none"> <li>- No AZ + AZ cohort or any other direct comparator group</li> <li>- Reporting period for solicited events not given</li> </ul>	<ul style="list-style-type: none"> <li>- Randomized trial</li> <li>- Solicited events reported within 7 days after any dose</li> </ul>	<ul style="list-style-type: none"> <li>- No AZ + AZ cohort or any other direct comparator group</li> <li>- Randomized trial</li> <li>- Solicited events reported within 7 days after any dose</li> </ul>	<ul style="list-style-type: none"> <li>- No AZ + AZ cohort</li> <li>- Groups have different intervals</li> <li>- Solicited events reported within 7 days after any dose</li> </ul>

# Immunogenicity evidence with heterologous schedules

		<u>Barros-Martins et al</u> <u>(CoCo study)</u>	<u>Hillus et al</u>	<u>Groß et al</u>	<u>Borobia et al</u> <u>(CombiVacS study)</u>
	Population	Healthcare professionals with no previous SARS-CoV-2 infection	Healthcare professionals with no previous SARS-CoV-2 infection	Individuals age 25-46	Adults <60 years old
	Intervention	<b>AZ + BNT</b> (n= 55); <b>73-74 day interval (~10.5 weeks)</b>	<b>AZ + BNT</b> (n=110); <b>10-12 week interval</b>	<b>AZ + BNT</b> (n=26); <b>8 week interval</b>	<b>AZ + BNT</b> (n=450); <b>8-12 week interval</b>
	Comparator	<b>AZ + AZ</b> (n= 32); <b>73-74 day interval</b>	<b>BNT + BNT</b> (n=189); <b>3 week interval</b>	None in study; previously obtained sera from BNT + BNT vaccinated (28 day interval*)	No 2 <sup>nd</sup> dose comparator; <b>AZ single dose only</b> (n=226)
O u t c o m e s	Humoral immune responses:	- Fold-increases in IgG and IgA after 2 <sup>nd</sup> dose: <b>BNT &gt; AZ</b> (e.g. 11.5 fold ↑ for AZ + BNT IgG vs 2.9 fold ↑ for AZ + AZ IgG)	- For binding Abs and NAbs: Levels were <b>similar after 2<sup>nd</sup> dose BNT</b> in both regimens - Fold increases between dose 1 & 2: <b>AZ + BNT &gt; BNT + BNT</b> (since 1 <sup>st</sup> dose AZ < 1 <sup>st</sup> dose BNT)	- IgG, IgA levels and NAbs increased after 2 <sup>nd</sup> dose with BNT	- 14 days post-2 <sup>nd</sup> dose (BNT), <b>anti-RBD IgG titres, anti-spike IgGs and NAb titres</b> increased by <b>80-fold, 37-fold and 45-fold</b> , respectively
	binding antibodies (IgG, IgA, IgM), neutralizing antibodies (NAbs)	NAbs: - Fold increases after 2 <sup>nd</sup> dose: <b>BNT &gt; AZ</b> - <b>Detected</b> after 2 <sup>nd</sup> dose BNT against spike protein of Wuhan strain, <b>B.1.1.7</b> and <b>P.1</b> variants for all samples; detected against <b>B.1.351</b> variant in all but 2 samples - <b>Not detected</b> after 2 <sup>nd</sup> AZ dose against <b>B.1.351</b> or <b>P.1</b> variants	- Both regimens produced <b>high avidity antibodies after the 2<sup>nd</sup> dose</b> ; avidity was <b>slightly higher with the AZ + BNT</b> compared to BNT + BNT; may be due to longer interval	- Cumulative <b>IgG + IgM levels and NAb titres</b> (against pseudovirus <b>B.1.1.7, B.1.351 and B1.617 variants</b> ) were <b>higher</b> than those from <b>previously obtained BNT + BNT sera</b>	
	Cellular immune responses	- Fold increase in anti-spike <b>B cell, CD4 and CD8 T cell</b> responses: <b>BNT &gt;AZ</b> - 2 <sup>nd</sup> dose BNT also associated with increase in spike-stimulated <b>serum IFN-γ</b> levels	Anti-S1 <b>T cell responses were 35% higher</b> after <b>AZ + BNT</b> compared to BNT + BNT	Cytokine (IFN <sub>γ</sub> , IL2, TNF <sub>α</sub> )-secreting CD4 and CD8 cells were detected post-BNT boost; no comparator	2 <sup>nd</sup> dose BNT also associated with increase in spike-stimulated serum IFN-γ levels
	Risk of Bias	Moderate (5 stars; Newcastle-Ottawa Quality Assessment Scale)	Moderate (6 stars; Newcastle-Ottawa Quality Assessment Scale)	High (4 stars; Newcastle-Ottawa Quality Assessment Scale)	Some concerns (Cochrane RoB2)
	Additional considerations		- No AZ + AZ cohort - Groups have different intervals	No AZ + AZ cohort or any other direct comparator group	- No AZ + AZ cohort or any other direct comparator group - Randomized trial

## Summary of immunogenicity studies of AstraZeneca followed by Pfizer-BioNTech

Study	Comparison	Results (measured 1-4 weeks after booster dose)
<a href="#">Spain (ComibiVacs)</a>	AZ + BNT at <b>8 to 12</b> week interval <b>vs.</b> Only a single dose of AZ	Robust humoral immune response with AZ + BNT schedule compared to pre-booster
<a href="#">Hillus (Germany)</a>	AZ + BNT with a <b>10 to 12</b> week interval <b>vs.</b> Pfizer + Pfizer with a <b>3</b> week interval	Similar antibody response with both schedules; High T cell reactivity with the AZ + BNT
<a href="#">Gross (Germany)</a>	AZ + BNT with an <b>8</b> week interval <b>vs.</b> BNT + BNT that seemed to have been assessed separately (perhaps from another study)	Higher antibody response in the AZ + BNT than the BNT + BNT, including against Beta (B.1.351) and B.1.617 variants; A robust cellular immune response was also demonstrated with the AZ + BNT schedule
<a href="#">Barros-Martins (Germany)</a>	AZ + BNT with a <b>10.5</b> week interval <b>vs.</b> AZ + AZ with a <b>10.5</b> week interval	Higher antibody response in the AZ + BNT than the AZ +AZ, including a better response against Gamma (P.1) and B.1.351 (Beta) variants of concern; A higher T cell response was also observed with the AZ + BNT schedule compared to the AZ + AZ schedule.

## Recommendations on the use of authorized COVID-19 vaccines

December 12, 2020	Pfizer-BioNTech mRNA vaccine
December 23, 2020	Moderna mRNA vaccine
January 12, 2021	Management options for rollout in the context of limited vaccine supply
March 1, 2021	AstraZeneca viral vector vaccine; Management options for the use of difference types of COVID-19 vaccines
March 3, 2021	Rapid response: Extending dose intervals to up to four months for all two-dose authorized COVID-19 vaccines
March 16, 2021	AstraZeneca recommendation updated to include use in those 65 years of age and older
March 29, 2021	Rapid response: Pause of AstraZeneca in those under 55 years of age due to vaccine-induced immune thrombotic thrombocytopenia (VITT)
April 7, 2021	Full statement: Extended dose intervals for COVID-19 vaccines to optimize early vaccine rollout and population protection in Canada in the context of limited vaccine supply
April 23, 2021	AstraZeneca recommendation updated to 30 years of age and older if benefits outweigh risks
May 3, 2021	Janssen vaccine may be considered for 30 years of age and older if benefits outweigh risks
May 18, 2021	Pfizer-BioNTech vaccine should be offered to adolescents 12 to 18 years of age
May 28, 2021	Recommendations for those who are immunosuppressed, have an autoimmune condition, are pregnant or are breastfeeding are now the same as recommendation for general adult population; Second doses should be offered as soon as possible, with priority given to those who are at highest risk of severe illness or death, after or concurrent with first doses being offered to all remaining eligible populations
June 1, 2021	Recommends same mRNA vaccine administered for first dose should be offered for second dose, but another mRNA vaccine can be considered interchangeable. Recommends individuals who received a first dose of the AstraZeneca/COVISHIELD vaccine may receive either the AstraZeneca/COVISHIELD vaccine or an mRNA vaccine for their second dose.