

An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)

Extended dose intervals for COVID-19 vaccines to optimize early vaccine rollout and population protection in Canada in the context of limited vaccine supply

PROTECTING AND EMPOWERING CANADIANS TO IMPROVE THEIR HEALTH



Public Health
Agency of Canada

Agence de la santé
publique du Canada

Canada

PREAMBLE

The National Advisory Committee on Immunization (NACI) is an External Advisory Body that provides the Public Health Agency of Canada (PHAC) with independent, ongoing and timely medical, scientific, and public health advice in response to questions from PHAC relating to immunization.

In addition to burden of disease and vaccine characteristics, PHAC has expanded the mandate of NACI to include the systematic consideration of programmatic factors in developing evidence-based recommendations to facilitate timely decision-making for publicly funded vaccine programs at provincial and territorial levels.

The additional factors to be systematically considered by NACI include: economics, ethics, equity, feasibility, and acceptability. Not all NACI Statements will require in-depth analyses of all programmatic factors. While systematic consideration of programmatic factors will be conducted using evidence-informed tools to identify distinct issues that could impact decision-making for recommendation development, only distinct issues identified as being specific to the vaccine or vaccine-preventable disease will be included.

This statement contains NACI's independent advice and recommendations, which are based upon the best current available scientific knowledge.

This document is being disseminated for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph(s). Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) of the Canadian manufacturer(s) of the vaccines. Manufacturer(s) have sought approval of the vaccines and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of PHAC's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

CONTENTS

I. INTRODUCTION.....	3
II. METHODS.....	3
III. EVIDENCE.....	4
IV. RECOMMENDATION	15
V. TABLES	18
LIST OF ABBREVIATIONS.....	33
ACKNOWLEDGEMENTS	34
REFERENCES	35

I. INTRODUCTION

Since COVID-19 vaccines were first authorized in Canada in December 2020, the National Advisory Committee on Immunization (NACI) has been providing evidence-informed guidance on the recommended interval between vaccine doses. On January 12, 2021, NACI provided advice on extending intervals for mRNA vaccines to six weeks. In February 2021, the Public Health Agency of Canada (PHAC) asked NACI to address the following context and question: Due to limited vaccine supply and logistical challenges, jurisdictions need to implement COVID-19 mRNA vaccine intervals beyond six weeks. Given emerging evidence as mRNA vaccines are rolled out to populations in Canada and elsewhere in the world, what extended interval would be recommended in order to balance individual protection and population impact? Are extended intervals a particular concern for any key populations?

A rapid response statement was published on [March 3, 2021](#) to advise on NACI's decision regarding extended intervals in the context of limited vaccine supply. The current statement provides a more detailed overview of NACI's considerations, including evidence available through daily scanning as of March 26, 2021 as well as some additional studies that became available after that date with regard to mRNA vaccines and AstraZeneca.

Guidance objective

The objective of this statement is to provide guidance for the equitable, ethical, and efficient allocation of authorized COVID-19 vaccines in the context of staggered arrival of vaccine supply. This guidance builds on the foundational framework of NACI's [Recommendations on the use of COVID-19 vaccines](#). The goal of Canada's pandemic response is to minimize serious illness and death while minimizing societal disruption as a result of the COVID-19 pandemic. The [goal of Canada's COVID-19 immunization response](#) is to enable as many Canadians as possible to be immunized against COVID-19 as quickly as possible, while ensuring that high-risk populations are prioritized.

II. METHODS

After receiving a request from PHAC and Chief Medical Officers of Health from across the country seeking advice about intervals between doses of COVID-19 vaccines given limited vaccine supply, NACI reviewed available evidence on extended intervals for COVID-19 vaccines in full Committee meetings (February 8, 2021; February 24-25, 2021; March 25, 2021; March 30, 2021) and Working Group meetings (February 19, 2021). This included evidence available from published peer-reviewed studies, pre-prints, and data available from population-based assessments from within and outside of Canada. The Public Health Ethics Consultative Group had been previously consulted by NACI (on December 15, 2020 and January 26, 2021) about the ethical implications of delaying the second dose in a COVID-19 vaccine series. On March 1, 2021, NACI voted on and approved the revised recommendations and between March 25 and 28, 2021 NACI members revisited the recommendations with regard to specific population groups. In arriving at its decisions, NACI considered the following factors, which are outlined in this document:

1. Efficacy and effectiveness of the first dose of the available COVID-19 vaccines
2. Duration of protection following the first dose of the available COVID-19 vaccines
3. Impact of extending the interval between the priming and boosting doses on the immune response and vaccine efficacy

4. Impact of more rapidly vaccinating a greater number of people with the available supply of COVID-19 vaccines
5. Modelling information on the impact of extending the interval between the first and second doses of COVID-19 vaccines
6. Impact of extending the interval between doses of COVID-19 vaccines on variants of concern
7. Impact on specific population groups
8. Ethics, equity, feasibility, and acceptability of extending the interval to the second dose of COVID-19 vaccines authorized as a two-dose series.

Table 1 summarizes studies that provide vaccine effectiveness (VE) estimates with one dose of COVID-19 vaccine. Daily literature scans for articles in Table 1 were conducted using the following sources: PubMed, Scopus, BioRxiv, MedRxiv, ArXiv, SSRN, Research Square, and cross-referenced with the COVID-19 information centers run by Lancet, BMJ, Elsevier, Nature, Wiley, Epistemonikos' L·OVE, and McMaster PLUS. Table 1 contains literature available in the scan up to March 26, 2021, 11:00 am EST. A first level rapid screening of titles was performed in Distiller by a single reviewer using a combination of manual review and DistillerAI's natural language processing technology. A second reviewer screened full text results of potentially relevant articles to identify those related to vaccine efficacy or effectiveness of the first dose. All articles in Table 1 were abstracted by one author and reviewed by a second author. Only articles that provide a clear VE estimate and were available before 11:00 am EST March 26, 2021 are included in Table 1. Some additional studies that became available after that time are referred to in the text only.

III. EVIDENCE

1. Efficacy and effectiveness of the first dose of the available COVID-19 vaccines

Review of available data on efficacy and effectiveness of a single dose of mRNA vaccine was a critical factor in assessing the impact of extending the interval to the second dose. Evidence regarding efficacy and effectiveness of one dose of COVID-19 vaccines is summarized below. Additional details regarding evidence available up to March 26, 2021 are summarized in Table 1.

Data from the two clinical trials for mRNA vaccines (Pfizer-BioNTech ⁽¹⁾ and Moderna ⁽²⁾) provide evidence that indicates that efficacy against symptomatic disease begins as early as 12 to 14 days after the first dose. Excluding the first 14 days before vaccines are expected to offer protection, both vaccines showed an efficacy of 92% up until the second dose ⁽³⁾ ⁽⁴⁾ (the second dose was generally administered at approximately 21 days after the first dose for the Pfizer-BioNTech product and at approximately 28 days for the Moderna product). From the AstraZeneca clinical trial publication, one dose of the vaccine was found to have 76% efficacy between 22 and 90 days after administration ⁽⁵⁾.

Since publication of the clinical trials to March 26, 2021, studies with clear VE data have become available from Israel (5 studies ⁽⁶⁻¹⁰⁾, one of which was re-analyzed ⁽¹¹⁾), Canada (several study designs and target populations in two provinces ⁽¹²⁻¹⁴⁾), the United States (3 studies ⁽¹⁵⁻¹⁷⁾), the United Kingdom (9 studies ⁽¹⁸⁻²⁷⁾, some with multiple components) and Denmark (1 study ⁽²⁸⁾). Most of these studies are currently only available as unpublished preprints, and therefore have

not been peer reviewed. The available one dose data reflects the vaccination programs and products being used at the time in each country as follows:

- **Israel:** Israel was using the Pfizer-BioNTech vaccine with the second dose administered approximately 21 days after the first dose. Therefore, one dose data is available only up to the time the second dose was administered.
- **Canada:** The Pfizer-BioNTech vaccine was authorized on December 9, 2020 and the Moderna vaccine was authorized on December 23, 2020. From December 2020 to early April 2021, approximately 75% of Canada's vaccines were supplied as Pfizer-BioNTech and 25% as Moderna. Data from Quebec is based on one dose, as the second dose was delayed for at least three months almost from the start of the provincial program. In British Columbia, provincial policy deferred the second dose to 5-6 weeks following the first dose; second-dose recipients were excluded to reflect the effect of a single dose.
- **United States:** The United States was administering both the Pfizer-BioNTech and Moderna vaccines with approximately a 21- and 28-day interval between doses, respectively. Therefore, one dose data is available only up to the time the second dose was administered.
- **United Kingdom:** The United Kingdom (UK) used only Pfizer-BioNTech from December 8, 2020 to January 3, 2021 and both AstraZeneca and Pfizer-BioNTech were used from January 4, 2021 onwards. Both products were given with an extended interval of 12 weeks between doses, except for a small number of people who received two doses of the Pfizer-BioNTech vaccine at shorter intervals.
- **Denmark:** Based on the one included study ⁽²⁸⁾, Denmark appears to have a two-dose schedule.

As can be seen from Table 1 and the summary below, VE of one dose of COVID-19 vaccines varied considerably as did study design, study size, study population, outcome (asymptomatic and/or symptomatic PCR-confirmed SARS-CoV-2, COVID-19 hospitalizations or deaths) and outcome dates (symptom onset date, specimen collection date, laboratory result date, hospitalization and death dates). VE estimates may also be impacted by the duration of follow-up and the time period of the study. Observational studies are subject to biases that may influence their results. In addition, many of the studies are preprints which have not been peer reviewed. Some methodologic considerations with regard to studies available before the March 26, 2021 cut-off are highlighted in Table 1 and a review of general methodological considerations are summarized below.

The preponderance of one dose data pertains to mRNA vaccines (mostly Pfizer-BioNTech); the results summarized below pertain to one dose of mRNA vaccines unless AstraZeneca is specified and unless information regarding the second dose is provided. They do not include studies in long term care home residents which are covered in [Section 7 \(Impact on specific populations groups\)](#).

- **Symptomatic disease:**
 - A large study from the UK found VE against symptomatic disease for both the Pfizer-BioNTech and AstraZeneca vaccines of 58% in adults ≥70 years of age ⁽²⁶⁾.
 - Data from health care worker from four hospitals and associated facilities in the United Kingdom found a VE of 67% (combined results for Pfizer-BioNTech and AstraZeneca) ⁽²²⁾.

- In studies in Israel, estimates of VE against symptomatic disease for Pfizer-BioNTech ranged from 57% in the general population ⁽⁹⁾ to 76% in health care workers ⁽⁶⁾.
- **Asymptomatic infection:**
 - VE of 79% was reported in one study based on patients tested before medical or surgical procedures at Mayo clinic sites in the United States ⁽¹⁷⁾.
 - VE of 75% was calculated based on test positivity in health care workers screened weekly in the UK ⁽¹⁸⁾.
 - An exploratory analysis from Israel found a lower rate **of 29%** ⁽⁹⁾, however there were methodological limitations noted in the study (see Table 1).
- **PCR positive SARS-CoV-2 (symptomatic or asymptomatic):** Many studies assessed this outcome with results as follows:
 - 55% in Scottish health care workers ⁽²⁰⁾;
 - 61% in the Meuhedet Health Maintenance Organization in Israel ⁽¹⁰⁾;
 - 64% in health care workers in Oxfordshire, United Kingdom ⁽²²⁾;
 - 65% in the Sheba Medical Centre in Israel ⁽⁶⁾;
 - 69% in the Mayo clinic health system in the United States ⁽¹⁶⁾;
 - 72% in health care workers in the SIREN study in the UK ⁽²⁴⁾;
 - 77% calculated from test positivity in health care workers screened weekly in the UK ⁽¹⁸⁾;
 - 80% in health care workers in a single hospital in the UK ⁽²⁷⁾;
 - 70 to 90% in health care workers in Canada using Pfizer-BioNTech and Moderna ⁽¹²⁻¹⁴⁾; and
 - 91% in the Maccabi Healthcare Services organization in Israel ^(8, 11).

The following studies provide additional information about symptomatic and/or asymptomatic infection:

- A study of frontline health care providers in Denmark found a 17% VE when adjusted for calendar time and 50% unadjusted vaccine effectiveness; methodologic limitations were noted in this study (see Table 1) ⁽²⁸⁾.
- A study of self-reported laboratory results found VE of 42% for AstraZeneca and 57% to 70% for Pfizer-BioNTech ⁽²¹⁾.
- A study using administrative data from Israel found unusually low VE against positive cases for those > 60 and <60 years of age (0 and 12%) 14-20 days after the first dose, which was much higher 0-6 days after the second dose (73 and 77%) which may reflect, in part, a first dose effect ⁽⁷⁾.
- A preprint released after March 26 (therefore not included in Table 1) describes vaccination of 2,116 health care workers in a medium-size hospital in Spain (including 30% of health care workers who were previously positive). New SARS-CoV-2 infections declined by 62% in the 2-4 weeks after the first dose of the Pfizer-BioNTech vaccine and virtually disappeared after the second dose. Community infection rates were also declining at the time but much less dramatically ⁽²⁹⁾.
- A study published after March 26 (therefore not included in Table 1) involved self-swabbing of 3,950 frontline workers in eight locations in the United States once

weekly for 13 weeks as well as after symptom onset, and found a VE of one dose of Pfizer-BioNTech and/or Moderna of 80% (95% CI: 59 to 90%) ⁽³⁰⁾.

- **Hospitalizations and deaths:** VE estimates against hospitalizations were generally higher than for symptomatic and/or asymptomatic PCR positive SARS-CoV-2.
 - In mostly frail elderly patients in Bristol, UK, the Pfizer-BioNTech vaccine was 71 to 79% effective against hospitalizations and the AstraZeneca vaccine was 80% effective ⁽²³⁾.
 - A study from Israel using administrative data found VE of 81% 0-6 days after the second dose which likely represents the effect from the first dose ⁽⁷⁾. See Table 1 for methodological considerations.
 - A study of health care workers from Scotland showed a VE against hospitalization of 84% ⁽²⁰⁾.
 - A study using national data for the population in Scotland found a VE of 85% for the Pfizer-BioNTech vaccine and 94% for AstraZeneca; some methodologic issues were noted with this study (see Table 1) ⁽¹⁹⁾.
 - A study in the Clalit Health Services organization in Israel showed VE against hospitalization, severe disease and death of 74%, 62% and 72%, respectively, however methodologic issues were noted with these estimates ⁽⁹⁾ (see Table 1).
 - The largest study from Public Health England likely provides the most reliable estimates and showed that the Pfizer-BioNTech and AstraZeneca vaccines were approximately 80% effective against preventing hospitalizations in those ≥80 years of age, and the Pfizer-BioNTech vaccine was approximately 85% effective against preventing death in the same age group (the AstraZeneca vaccine was not studied against deaths) ⁽²⁶⁾.
- [See Section 7 on specific population groups](#) for data on residents in long-term care facilities.

For the AstraZeneca vaccine, the one-dose effectiveness data (58% ⁽²⁶⁾ to 68% ⁽⁴⁴⁾), one-dose efficacy from the clinical trial (76%) ⁽⁵⁾, and two-dose efficacy (63%) ⁽⁵⁾ appear to be similar. For the mRNA vaccines, the one-dose effectiveness data is lower (generally between 60 and 80%, with some lower and higher estimates) than the one-dose efficacy from the clinical trials (92%) ⁽³⁾ ⁽⁴⁾ and lower than the two-dose effectiveness data (88% to 95% ⁽²⁵⁾ ⁽⁶⁾ ⁽³¹⁾ ⁽³⁰⁾) and two-dose efficacy data (94% to 95% ^(2, 1)).

One dose of both Pfizer-BioNTech and AstraZeneca vaccines provided very good protection against more serious outcomes, particularly hospitalization ⁽²⁶⁾ ⁽²³⁾ ⁽¹⁹⁾, with one study also showing very good protection against deaths for the Pfizer-BioNTech vaccine ⁽²⁶⁾.

VE estimates, which are obtained from observational studies, are typically lower than vaccine efficacy estimates from clinical trials. For the studies on one dose effectiveness of COVID-19 vaccines, differences between observational data and clinical trial data may be due to the following:

- Observational studies include populations generally excluded from clinical trials (e.g., elderly residents in long term care facilities).
- Both symptomatic and asymptomatic infection are often being studied in observational studies, whereas the clinical trials looked mainly at symptomatic disease.

- It is also possible that relaxing of public health measures and precautions by vaccinated people in the real world may be increasing their risk of infection, leading to lower VE estimates.

In addition, the following methodologic considerations could explain some of the differences between observational studies and clinical trials and should be noted when assessing the effectiveness data:

Unlike the clinical trials that assessed symptom onset dates, many of the effectiveness studies ⁽⁸⁾ ⁽¹⁰⁾ ⁽¹²⁻¹⁴⁾ ⁽¹⁶⁾ ⁽¹⁸⁾ ⁽²⁰⁾ ⁽²²⁾ ⁽²⁴⁾ ⁽²⁷⁾ ⁽²⁸⁾ used dates related to specimen collection or positive PCR results. Because specimen-related dates are often later than symptom onset dates, the impact of the first dose may only be noted later in the 14-to-21 day window, therefore underestimating the vaccine impact in that time period.

- Some studies assessing hospitalization or severe disease used the date of hospitalization or onset of severe disease ^(7, 9, 19) instead of the date of symptom onset in those who subsequently required hospitalization or developed severe disease. Two of these studies ^(9, 19) noted unexpectedly high VE against hospitalization and/or severe disease in the early periods before the vaccine is expected to offer protection against infection and much sooner than the vaccine is expected to offer protection against hospital admission or onset of severe illness, raising methodological concerns.
- Unlike the clinical trials, most of the population included in effectiveness studies were not screened by PCR before entering the study (although those known to be previously positive were excluded in some studies). As a result, some subjects found to be PCR positive after vaccination may have acquired their infection before vaccination or in the earlier period after vaccination before the vaccine is expected to offer protection, which would underestimate the impact of the vaccine. The exceptions to this were the SIREN study by Hall et al. ⁽²⁴⁾ and the study by Lumley et al. ⁽²²⁾, which screened all health care workers on a regular basis and assessed VE in only those who had no prior COVID-19.
- Studies that compare infection rates in the early post-vaccination period with the later period may be affected by the decreasing trends in community rates at the time ^(12, 13, 14), which could overestimate VE in these studies.

2. Duration of protection following the first dose of the available COVID-19 vaccines

Data and exploratory modeling from the AstraZeneca clinical trial publication indicated that the protection from one dose did not wane up to 90 days from vaccination ⁽⁵⁾. Effectiveness data from Canada and the UK demonstrates protection from the mRNA vaccines based on analyses extending to about 8 weeks from vaccination ^(14, 23, 25, 26). Experience with other multi-dose vaccines after a single dose suggests protection could last for six months or longer in adolescents and adults ⁽³²⁾ (e.g., hepatitis A and human papillomavirus vaccines). Longer-term follow-up of clinical trial participants and populations receiving vaccinations in public programs will assist in determining the duration of protection following both one and two doses of COVID-19 vaccines.

3. Impact of extending the interval between the priming and boosting doses on the immune response and vaccine efficacy after the second dose

As a general vaccination principle, interruption of a vaccine series resulting in an extended interval between doses does not require restarting the vaccine series, regardless of the interval between doses ⁽³³⁾. Principles of vaccinology support at least a three-week interval between doses in a multi-dose primary series to avoid immune interference in the primary response to the vaccine ⁽³⁴⁾. Furthermore, a longer interval between the priming and boosting doses allows maturation of the memory B cells, resulting in a higher and more durable response ⁽³⁴⁾.

Data from the AstraZeneca COVID-19 vaccine clinical trial showed maximum efficacy when the interval was extended to ≥ 12 weeks, with efficacy at < 6 weeks between doses of 55.1% (95% CI: 33.0 to 69.9%) and efficacy at ≥ 12 weeks of 81.3% (60.3 to 91.2%) ⁽⁵⁾.

4. Impact of rapidly vaccinating a greater number of people with the available supply of COVID-19 vaccines

Extending the interval between the first and second doses will allow many more people to be vaccinated rapidly with the available supply of vaccines. Based on the expected supply of mRNA vaccines alone, 90% of older adults (50 years of age and over) and 75% of younger adults (16 to 49 years of age) could be offered a dose of mRNA vaccine by the middle of June 2021. Second doses could be offered as soon as all eligible individuals had been offered their first dose, or prioritized earlier for certain cohorts or specific population groups if indicated based on emerging data.

Vaccines that reduce both symptomatic and asymptomatic infection are expected to also reduce transmission of SARS-CoV-2. A number of the studies in this review found that the Pfizer-BioNTech vaccine was effective against SARS-CoV-2 infection (which is symptomatic or asymptomatic infection combined ^{(6) (8) (10) (11) (12-14) (16) (18) (20) (21) (22) (24) (27) (28)}).

Tande et al. assessed asymptomatic individuals undergoing pre-procedural screening and found a VE of 79% (95% CI: 63 to 88%) from > 10 days after the first dose to the second dose of the Pfizer-BioNTech or Moderna vaccines (compared to unvaccinated people) ⁽¹⁷⁾. In addition, a recently released preprint from Israel showed 90.4% (95% CI: 89.1 to 91.5%) VE against asymptomatic infection based on two doses of the Pfizer-BioNTech vaccine ⁽³¹⁾. The clinical trial results for the Moderna ⁽²⁾ and Janssen ⁽³⁵⁾ vaccines suggested that one dose of these vaccines may decrease asymptomatic infection. The AstraZeneca vaccine has not been shown to reduce asymptomatic infection, which appears to be due to poor efficacy against preventing asymptomatic infection with the B.1.1.7 variant ⁽³⁶⁾; its ability to prevent transmission is unknown.

Vaccination of larger numbers of people with vaccines that prevent infection and transmission will not only protect the vaccinated individual but those around them as well (indirect protection). In addition, extending the interval between doses in order to more rapidly vaccinate an increased number of people is likely to decrease the overall circulation of the virus in the community contributing to community protection.

5. Modelling information on the impact of extending the interval between the first and second doses of COVID-19 vaccines

Public Health Agency of Canada model

An internal PHAC model, examining dose intervals between 12 and 24 weeks, suggested that accelerating vaccine coverage by extending dose intervals of mRNA vaccines could have short-term (12 months) public health benefits in reducing symptomatic disease, hospitalizations, and deaths compared to a 6-week interval while vaccine supply is constrained. The model used the following assumptions for effectiveness after the first dose: effectiveness against all infections representing 90% of effectiveness against symptomatic disease (e.g., 60.3% effectiveness against infection / 67% effectiveness against disease); effectiveness against symptomatic disease of 67% in adults aged 20-64 years and 58% in adults 65+ years; effectiveness against hospitalizations of 80% for all ages, and effectiveness against deaths of 85% for all ages. In addition, the model employed the following assumptions:

- mRNA vaccines were prioritized in descending order of age groups (given the risk of severe outcomes) until age 55 years and then vaccine was offered to those 20 to 54 years of age in no particular order;
- Coverage rates for adults aged 20-64 years and 65+ years were 65% and 80%, respectively
- The daily vaccination capacity was 150,000 doses in the first quarter (January to March, 2021) and increased to 350,000, 450,000, and 525,000 in the second quarter (April to June, 2021) and 525,000 (June to December, 2021);
- Given the limited evidence regarding waning protection for COVID-19 vaccines, first dose protection was lost at a rate of 1% per week (additional scenarios were run to test 4% and 8% loss per week).

The model projected that extending the dose interval would reduce overall symptomatic disease, hospitalizations, and deaths in the population while vaccine supply is constrained. Projected benefits were driven by accelerating access to vaccines in adults aged 20-74 years. A 16-week interval was projected to have the largest reductions in severe outcomes of hospitalizations and deaths in individuals 75+ years. A 24-week interval was projected to have the largest reductions in hospitalizations and deaths in individuals aged 20-74 years.

Sensitivity analysis indicated that dose intervals as long as 24 weeks would reduce symptomatic disease and hospitalizations across first dose effectiveness against disease and hospitalization values of 50% to 85%. All extended intervals were projected to reduce deaths while effectiveness against death was at least 65% but increased deaths when effectiveness was less than 65%. An effectiveness against death less than 65% could still reduce deaths if the third wave was more severe than the base case scenario.

Sensitivity analysis projected that extending the mRNA dose interval as far as 24 weeks would still have short-term public health benefits in reducing symptomatic disease, hospitalizations, and deaths if first dose protection was lost at a rate of 4% per week. A 24-week interval was no longer projected to reduce deaths under a scenario in which first dose protection was lost at a rate of 8% per week, though 12-week and 16-week intervals were still projected to reduce symptomatic disease, hospitalizations, and deaths.

Models available in publications or pre-prints

A multi-model comparison included five external vaccine modelling studies on alternate dosing strategies available as publications or pre-prints as of February 14, 2021 ⁽³⁷⁻⁴¹⁾. The studies were

on mRNA vaccines and examined different delay intervals, single dose strategies, strategies where some subpopulations received one dose while others received two doses, and strategies that reserved some proportion of supply for two doses while the remainder were for one dose. One model ⁽³⁷⁾ directly compared different extended dosing intervals (up to 15 weeks) against no delay.

External modelling suggested that extended dosing intervals (between 9 to 12 weeks) can reduce infections, hospitalizations and deaths compared to no delays when vaccine supply is limited ⁽³⁷⁾. The population benefits come from providing greater vaccine coverage to more people, even when the level of protection of one dose is not as high as the protection offered by two doses.

Study results were dependent on particular model inputs used. Of note, the single dose effectiveness appeared influential - if a high single dose effectiveness was applied, then the extended interval strategy was preferred over no delay; however, if a low single dose effectiveness was applied, then the strategy of no delay was preferred. Studies considered single dose effectiveness between 72% to 80% as high and between 18% to 55% as low ⁽³⁷⁻³⁹⁾. Model inputs on waning may also be influential - if the vaccine began to wane many weeks after the first dose, then the extended interval strategy was preferred; however, if the waning began soon after the first dose, then the strategy of no delay was preferred ⁽³⁷⁾. Vaccine coverage and background transmission may also influence the preferred vaccine strategy ⁽³⁸⁾.

Overall, internal and external modelling indicate the benefits of extending dose intervals by reducing symptomatic disease, hospitalizations, and deaths while vaccine supply is constrained.

6. Impact of extending the interval between doses of COVID-19 vaccines on variants of concern

The impact of extending the interval between doses on the emergence and/or circulation of variants of concern is unknown. There is currently no evidence that an extended interval between doses will either increase or decrease the emergence of variants of concern, although preventing transmission in the community by vaccination may decrease the chance of the emergence and/or spread of variants as suggested in a recent publication ⁽⁴²⁾. COVID-19 mRNA vaccines and the AstraZeneca vaccine have shown promising early results against variant B.1.1.7 based on effectiveness studies in the UK (Pfizer-BioNTech and AstraZeneca ⁽²⁶⁾) and Israel (Pfizer-BioNTech ⁽³¹⁾) where this is the dominant strain. Two doses of the AstraZeneca vaccine were not found to be efficacious against the B.1.351 variant in a randomized clinical trial conducted in South Africa ⁽⁴³⁾, however a recent press release stated that two doses of the Pfizer-BioNTech vaccine were efficacious against B.1.351. Ongoing monitoring, including genetic sequencing of PCR positive samples in previously vaccinated people, will be required to assess the effectiveness of one and two doses of COVID-19 vaccines against variants of concern.

Manufacturers are currently exploring the need for, and development of, booster doses specific to variants of concern. Additional information may be available about updated formulations of the vaccines to inform the second dose recommendations by the time that dose is indicated.

7. Impact on specific population groups

Older adults

The following studies assessed one dose VE in older adults:

- In a large study from Public Health England, VE of one dose of Pfizer-BioNTech or AstraZeneca vaccines against symptomatic disease in those ≥ 70 years of age was 58% with approximately 80% protection against hospitalization in those ≥ 80 years of age ⁽²⁶⁾. In addition, the Pfizer-BioNTech vaccine provided approximately 85% protection against death in those ≥ 80 years of age ⁽²⁶⁾.
- In mostly frail elderly patients in Bristol, United Kingdom, the Pfizer-BioNTech vaccine was 71 to 79% effective against hospitalizations and the AstraZeneca vaccine was 80% effective ⁽²³⁾.
- Surveillance-based data from long term care facilities in British Columbia ⁽¹³⁾ and Quebec (INSPQ) ^(12, 14) showed protection of 80 to 90% against PCR positive SARS-CoV-2 using Pfizer-BioNTech or Moderna vaccines in residents, noting that health care workers were also vaccinated which could provide indirect protection to residents as well.
- A study from Denmark found low VE against PCR-confirmed outcomes (symptomatic and asymptomatic combined) using the Pfizer-BioNTech vaccine in the adjusted analysis (21%, after adjustment for calendar time) from day 14 after the first dose to the second dose on approximately day 24, with higher VE of 60% in the unadjusted analysis, although methodological limitations were noted in this study (see Table 1) ⁽²⁸⁾.
- VE of 63% against SARS-CoV-2 infection, regardless of symptoms, using the Pfizer-BioNTech vaccine was noted in two outbreaks in skilled nursing facilities in the United States ⁽¹⁵⁾.
- A more recently released preprint from the UK (Vivaldi study) (became available after March 26 therefore is not included in Table 1) assessed VE against PCR-positive SARS-CoV-2 among 10,412 residents from 310 long term care facilities. The vast majority (85%) of PCR positive tests were identified following routine screening of residents; 7.5% of residents with a positive test were symptomatic at the time of routine testing. VE reached 65% (95% CI: 29 to 83%) for Pfizer-BioNTech and 68% (95% CI: 34 to 85%) for AstraZeneca, both between days 35 to 48 after vaccination ⁽⁴⁴⁾.

In assessing VE in long term care homes, it should be noted that the extent to which indirect protection from also vaccinating health care workers and visitors (in addition to direct protection) is contributing to these VE estimates is not known.

Immunogenicity studies are also available to assess antibody response in older adults. However, it is difficult to interpret immunogenicity studies as the mechanism by which vaccines protect against COVID-19 is not certain and there is currently no correlate of protection.

- Based on home testing using lateral flow immunoassays, the percentage of participants with an IgG positive test was lower ≥ 21 days after one dose of the Pfizer-BioNTech vaccine in those ≥ 70 years of age, compared to younger age groups. IgG positivity was similarly high across all age groups after two doses of vaccine ⁽⁴⁵⁾.
- A small study using one dose of the Pfizer-BioNTech vaccine from British Columbia also showed lower binding and neutralizing antibody titres (based on a pseudovirus surrogate

neutralization assay) among 12 residents of long term care homes compared to 18 health care workers ⁽⁴⁶⁾.

- A small study in the UK showed 8 of 15 (53%) subjects over 80 years of age reached the threshold titre for neutralizing antibodies three weeks after a first dose of the Pfizer-BioNTech vaccine, compared to 8 of 8 subjects under 80 years of age. All subjects developed a response after the second dose given three weeks after the first ⁽⁵⁴⁾.
- A study in a retirement home in Germany assessed immunogenicity in 93 participants <60 years of age (mean age 42 years) compared to 83 participants >80 years of age (mean age 88 years), 17-19 days after the first dose and 17 days after the second dose of the Pfizer-BioNTech vaccine. For the older group, 65.9% of participants and 10.6% of participants had spike specific IgG antibodies below the cut-off value after the first and second dose respectively, compared to 4.4% and 0% in the younger group. Both age groups showed low percentage of people developing neutralizing antibodies after the first dose (16.1% in the younger group and 1.2% in the older group). After the second dose, 97.8% of the younger group had a neutralizing antibodies compared to 68.7% of the older age group ⁽⁴⁷⁾.
- A survey of blood donors in England found that 75.8% (95% CI: 71.2 to 79.9%) of blood donors 70 to 84 years of age had antibodies against SARS-CoV-2 (with only 5.6% testing positive due to disease, as determined by antibodies against nucleoprotein) ⁽⁴⁸⁾.
- A study from the UK of adults aged 70-90 years assessed immunogenicity using five different tests (two assessing nucleoprotein to determine past SARS-CoV-2 infection and three assessing spike protein, to indicate vaccine response in those who are nucleoprotein negative) three weeks after first and second doses of Pfizer-BioNTech vaccination. Of the 92 individuals without evidence of previous infection (nucleoprotein negative) 77%, 77% and 95% were seropositive 3 weeks after one dose, depending on the spike protein assay used. Antibody levels were lower in those ≥80 years of age, compared to the younger age group. All 86 two-dose vaccine recipients were seropositive against spike protein in all three assays, with higher titres ⁽⁴⁹⁾.

Underlying medical conditions

Vaccine efficacy following a complete series of COVID-19 vaccines among immunocompromised patients is not known, as these patients were excluded from clinical trials. Effectiveness studies with clear data are not available regarding underlying medical conditions. Three immunogenicity studies are available, noting the limitations of interpreting immunogenicity studies due to the unknowns about the immune mechanism for protection against COVID-19 and no available correlate of protection.

- A study of 436 solid organ transplant recipients showed that only 17% (95% CI: 14 to 21%) of people developed an antibody response a median of 20 days after one dose of the Pfizer-BioNTech or Moderna vaccines. Participants were more likely to have a detectable antibody level with the Moderna vaccine compared to the Pfizer-BioNTech vaccine, if they were not receiving anti-metabolite maintenance immunosuppression or if they were younger. The study did not assess the response after a second dose ⁽⁵⁰⁾.

- A study of 151 cancer patients (who had an average age of 73 years) compared to 54 younger healthier controls (40.5 years of age; most of whom were health care workers) found low antibody response 3 and 5 weeks after one dose of the Pfizer-BioNTech vaccine in those with solid tumors (that subsequently increased significantly after a booster dose at 21 days) and even lower antibody response in those with hematological malignancies. T cell responses were better than antibody responses in patients with both types of cancer. This study also assessed results of nose and throat swabs tested for SARS-CoV-2 by PCR in some patients (noting that there was limited compliance with this portion of the study). Up to day 21 post-vaccination, six patients were positive, two of whom died, while no new positive results were noted after day 21 post-vaccination ⁽⁵¹⁾.
- A study of 241 kidney transplant recipients in France found that 10.8% had an antibody response 28 days after their first dose of Moderna vaccine. Patients who seroconverted had a longer time after their transplant, were receiving less immunosuppressive therapy and had better kidney function ⁽⁵²⁾.

It should be noted that a number of populations known to be at higher risk of severe COVID-19 outcomes have not been studied with regard to immunogenicity or effectiveness.

8. Ethics, equity, feasibility, and acceptability of extending the interval to the second dose of COVID-19 vaccines authorized as a two-dose series

NACI applies the ethics, equity, feasibility, and acceptability (EEFA) Framework for the systematic consideration of factors critical for comprehensive immunization program decision-making and successful implementation of recommendations ⁽⁵³⁾. This framework empowers the Committee to review and balance available evidence and transparently summarize the rationale for appropriate, timely COVID-19 immunization program recommendations. Key considerations for ethics, equity, feasibility and acceptability of the recommendation to extend the interval to the second dose are summarized below.

- **Ethics:** Given the evolution of evidence on the level of protection offered by one dose of authorized COVID-19 vaccines, the balance of risks and benefits favours extending the interval between doses, especially in the context of high disease burden. This option could more quickly achieve Canada's immunization and pandemic response goals of enabling as many Canadians to be immunized against COVID-19 as quickly as possible, and minimizing serious illness and overall deaths while minimizing societal disruption as a result of the COVID-19 pandemic. In situations where informed consent included assumptions about second dose timing, jurisdictions may consider offering second doses at shorter intervals for those who provided consent for the vaccine series prior to the extended-interval recommendation.
- **Equity:** Extending the interval between doses allows many more eligible people to be vaccinated earlier, which considerably enhances equity compared to leaving large groups of people unvaccinated until the summer. However, some individuals who would have received two doses without the delayed second dose may become infected and symptomatic in the interval between the first and second dose, although these individuals are likely to experience less severe disease compared to if they had not been vaccinated ^(20, 26).
- **Feasibility:** The same number of doses need to be administered if vaccines are offered with an extended interval between doses or with a shorter interval, so extending the interval to the second dose will not require more vaccine administration capacity. Attention will need to be

paid to ensure that people return for their second dose when it is offered, and this may be more logistically challenging with a longer interval. It should be noted that the second dose should be offered as soon as possible once first dose administration to all eligible populations approaches completion. The anticipated vaccine supply should support an interval of less than four months between doses.

- **Acceptability:** To minimize any adverse impact on public trust due to the off-label use of the COVID-19 vaccines and the change from the previous recommendation, transparent and clear communication with the public and those offered vaccines regarding the rationale for this recommendation will be important and should include the:
 - individual benefit for most people who will be receiving earlier vaccination that will provide good protection from COVID-19 disease and very good protection against its complications,
 - more robust and durable immune response that can be expected when a second dose is administered with a longer interval, and
 - the potential to provide indirect and community protection more rapidly.

IV. RECOMMENDATION

Following the thorough review of available evidence summarized above, as well as the systematic assessment of ethics, equity, feasibility and acceptability considerations with the EEFA Framework, NACI makes the following recommendation for public health program level decision-making for the effective and equitable use of COVID-19 vaccines authorized for use in Canada. NACI will continue to carefully monitor the scientific developments related to COVID-19 and COVID-19 vaccines, as well as ongoing vaccine pharmacovigilance, and will update recommendations as evidence evolves.

Please note:

- A **strong recommendation** applies to most populations/individuals and should be followed unless a clear and compelling rationale for an alternative approach is present.
- A **discretionary recommendation** may be offered for some populations/individuals in some circumstances. Alternative approaches may be reasonable.

Please see Table 2 for a more detailed explanation of the strength of NACI recommendations.

Based on emerging evidence of the protection provided by the first dose of a two-dose series for COVID-19 vaccines currently authorized in Canada, NACI recommends that in the context of limited COVID-19 vaccine supply and ongoing pandemic disease, jurisdictions should maximize the number of individuals benefiting from the first dose of vaccine by extending the second dose of COVID-19 vaccine up to four months after the first. Second doses should be offered as soon as possible after all eligible populations have been offered first doses, with priority given to those at highest risk of severe illness and death from COVID-19 disease. Vaccinated people (with one or two doses) should continue to follow recommended public health measures. NACI will continue to monitor the evidence on effectiveness of an extended dose interval and will adjust recommendations as needed. (Strong NACI Recommendation)

Jurisdictions may choose to shorten the time between the first and second dose of a two-dose series for COVID-19 vaccines in specific population groups based on their local epidemiology, vaccine supply and vaccine delivery mechanisms.

Summary of evidence and rationale:

- Morbidity and mortality from COVID-19 is ongoing and vaccine supply is limited. Extending the interval to the second dose allows vaccination of the largest number of people as quickly as possible, providing more people with direct protection and the possibility of indirect and community protection.
- An extended interval of up to four months allows as many eligible populations as possible to be offered vaccination with one dose before proceeding to offering second doses. However, as soon as all eligible groups have been offered their first dose of vaccine, second doses should be offered. The interval between first and second dose should not be extended any longer than needed to offer first doses of vaccine to all eligible individuals.
- This recommendation applies to all two-dose COVID-19 vaccines currently authorized for use and available in Canada.
- Should adolescents and/or children less than 16 years of age become eligible for vaccination in the near future, NACI will assess how these age groups are prioritized relative to those needing their second dose.
- Current evidence summarized in this document suggests very good vaccine efficacy against symptomatic COVID-19 from one dose of COVID-19 vaccines (92% efficacy for the mRNA vaccines ^(3, 4); 76% efficacy for the AstraZeneca vaccine ⁽⁵⁾), with good effectiveness shown in observational studies (generally between 60 and 80%, with some lower and higher estimates) against symptomatic disease and/or asymptomatic infection, as well as very good effectiveness against hospitalization (approximately 80%) and death (approximately 85% based on one study from the UK ⁽²⁶⁾). While two doses of mRNA vaccines have shown excellent efficacy and effectiveness, one dose of mRNA vaccines appear to perform similarly to one or two doses of the AstraZeneca vaccine ⁽⁵⁾ and the single-dose Janssen vaccine ⁽⁵⁵⁾.
- Effectiveness has been documented for up to two months after the first dose of the mRNA vaccines, and the AstraZeneca clinical trial publication modelled one-dose efficacy up to 90 days after vaccination ⁽⁵⁾.
- Informed expert opinion based on principles of immunology indicate that a longer interval between priming and boosting doses of a vaccine series results in a better, more durable response ⁽³⁴⁾. The AstraZeneca COVID-19 vaccine clinical trial demonstrated optimal efficacy when the interval between the first and second doses was ≥ 12 weeks ⁽⁵⁾.
- In situations where informed consent included assumptions about second dose timing, jurisdictions may consider offering second doses at shorter intervals for those who provided consent for the vaccine series prior to implementation of this recommendation.
- Because of ongoing disease transmission and less than complete individual protection from vaccination in either one-dose or two-dose vaccinated people, ongoing compliance with public health measures (masking, physical distancing and limiting social interactions as per public health guidance) should continue at this time.
- The VE of the first dose will be monitored closely and the decisions regarding the second dose will be continuously assessed based on surveillance and effectiveness data and post-implementation study designs. In addition, effectiveness against variants of concern will also be monitored closely. If indicated based on these data, recommendations will be revised to offer earlier second doses to some cohorts or population groups.

As summarized in more detail above, NACI developed its recommendations utilizing multiple sources of evidence in support of an extended interval of up to four months if needed to offer all currently eligible populations rapid vaccination. While studies have not yet accumulated data up to four months after the first dose, the AstraZeneca vaccine modelled one-dose efficacy of 76% up to 90 days from vaccination, and effectiveness data for one dose of mRNA vaccines have extended up to two months. Vaccinology principles support a better immune response with longer intervals between priming and boosting doses. Modelling demonstrated that longer intervals would have substantial population-level benefits. With anticipated vaccine supplies of mRNA vaccines alone, extending the interval to the second dose would allow over 90% of older adults (50 years of age and over) and 75% of younger adults (16 to 49 years of age) to be vaccinated by the middle of June, 2021, with second doses following afterwards. Compared to shorter intervals between doses, extending the interval between doses results in faster direct protection to substantially more of the population, along with the possibility of more rapid indirect and community protection. Second doses should be offered as soon as possible after all eligible populations have been offered first doses. Vaccinated individuals (with one or two doses) should continue to follow public health recommendation regarding COVID-19 prevention measures. Monitoring of VE and efficacy studies is ongoing and recommendations will be adjusted, including offering early vaccinations to some cohorts or population groups if needed.

V. TABLES

Table 1: Summary of efficacy and effectiveness data from the first dose of COVID-19 vaccines

Source	Description	Protection from the first dose of COVID-19 vaccines
Clinical trials		
<p>Polack F.P et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. Published New England Journal of Medicine. December 10, 2020</p> <p>Letter to the editor of the New England Journal of Medicine in response to Polack et al by Skowronski D and De Serres G.</p>	<ul style="list-style-type: none"> Re-analysis of symptomatic illness from the clinical trial of the Pfizer-BioNTech vaccine removing the first 14 days when the vaccine is not expected to have an impact 	<p>The initial analysis by Polack et al. showed the efficacy between the first and second dose to be 52% (95% CI: 29.5 to 68.4)</p> <p>Re-analysis by Skowronski and De Serres used data submitted to the Food and Drug Administration (FDA) to remove the first 14 days when the vaccine is not expected to be protective and found a 92.6% (95% CI: 69.0 to 98.3%) one-dose efficacy from 14 days after dose 1 until dose 2 at approximately 21 days.</p>
<p>Vaccine and Related Biological Products Advisory Committee Meeting FDA briefing document – Moderna COVID-19 – December 17, 2020</p> <p>Baden LR et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. Published New England Journal of Medicine. December 30, 2020</p>	<ul style="list-style-type: none"> Symptomatic illness from the clinical trial of the Moderna vaccine Asymptomatic infection from the clinical trial of the Moderna vaccine based on swab results when receiving the first dose and then again at the time of the second dose 	<p>92.1% (95% CI: 68.8 to 99.1%) for those who only received one dose more than 14 days after that dose – data provided FDA briefing</p> <p>94.3% calculated efficacy based on published data indicating 2 cases in the vaccine group and 35 cases in the placebo group from 14 days after dose 1 until dose 2 at approximately 28 days – data provided in Baden et al.</p> <p>61% reduction based on those who had no initial evidence of infection at the first dose but a positive swab on the day of the second dose (15 people had asymptomatic infection in the group that received one dose of Moderna vaccine, compared to 39 people in the placebo group) – data provided in Baden et al.</p>

Source	Description	Protection from the first dose of COVID-19 vaccines
		Note: The first 14 days when the vaccine is not expected to be protective is included in this estimate, so the result may have been higher if the first 14 days could be removed.
Voysey M et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. Published The Lancet. February 19, 2021	<ul style="list-style-type: none"> Symptomatic illness from clinical trial of the AstraZeneca vaccine 	An exploratory analysis found that a single standard dose of the AstraZeneca vaccines was 76.0% (95% CI: 59.3 to 85.9%) from days 22 to 90 after vaccination. Modelling did not demonstrate waning during that 3-month time period.
Israel – Effectiveness data		
Chodick G et al. The effectiveness of the first dose of BNT162b2 vaccine in reducing SARS-CoV-2 infection 13-24 days after immunization: real-world evidence. Preprint MedRxiv. January 29, 2021 Reanalysis by Hunter PR and Brainard J. Estimating the effectiveness of the Pfizer COVID-19 BNT162b2 vaccine after a single dose. A reanalysis of a study of 'real-world' vaccination outcomes from Israel. Preprint MedRxiv. February 3, 2021	<ul style="list-style-type: none"> Retrospective cohort study from Maccabi Healthcare Services in Israel assessing incidence rates of PCR positive cases by specimen collection date from date of vaccination using Pfizer-BioNTech vaccine. Compared cumulative incidence rates from days 13 to 24 to days 1 to 12 post vaccination in 503,875 people. The data was re-analyzed to determine the incidence rates per day post-vaccination. They calculated the VE per day from days 13 to 24, comparing an actual and expected number of cases per day (with the expected based on the pooled incidence from days 1 to 12). 	<p>Initial analysis showed 51% (95% CI: -7.2 to 78.0%) reduction in laboratory-confirmed infection (regardless of symptoms) in the 13 to 24 day period after vaccination compared to the 1 to 12 day period after vaccination. However, VE was only notable from 18 days post-vaccination so analysis over the entire 13 to 24 days underestimated VE.</p> <p>Re-analysis of the data showed effectiveness as high as 91% (90% credible interval: 83 to 98%) on day 21 post-vaccination with a single dose of Pfizer-BioNTech vaccine.</p>

Source	Description	Protection from the first dose of COVID-19 vaccines
Dagan N et al., BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. Published New England Journal of Medicine. February 24, 2021.	A large prospective cohort study from Clalit Health Services in Israel using the Pfizer-BioNTech vaccine. Matched 596,618 vaccinated individuals to an equal number of unvaccinated individuals on a number of variables including age, sex, sector, neighbourhood, history of influenza vaccine, pregnancy and number of coexisting conditions and assessed various outcomes in three time intervals after vaccination (14 to 20 days after dose one; 21 to 27 days after dose one, with the second dose administered around day 21; and 7 or more days after the second dose).	<p>VE that reflects one dose (14 to 20 days – first bold number) or possibly reflects one dose but also including some second dose effect (21 to 27 days – second bold number) was as follows:</p> <ul style="list-style-type: none"> Asymptomatic infection (exploratory) – 29% (95% CI: 17 to 39%), 52% (95% CI: 41 to 60%) Documented infection (PCR positive – 57% of cases were symptomatic): 46% (95% CI: 40 to 51%), 60% (95% CI: 53 to 66%) Symptomatic illness: 57% (95% CI: 50 to 63%), 66% (95% CI: 57 to 73%) Hospitalization: 74% (95% CI: 56 to 86%), 78% (95% CI: 61 to 91%) Severe disease: 62% (95% CI: 39 to 80%), 80% (95% CI: 59 to 94%) Deaths: 72% (95% CI: 19 to 100%), 84% (95% CI: 44 to 100%) <p>Note: As this analysis is based on dates of specimen collection, this will underestimate the impact in each time period as specimen collection dates are generally later than symptom onset date. For hospitalization and deaths, this analysis used dates of these events, and not date of onset or specimen collection date in those who subsequently had these events. Using dates of these events, the VE in the early period appears higher than would have been expected based on the time required for the vaccine to be protective and prevent subsequent hospitalizations and deaths.</p>
Aran D. Estimating real-world COVID-19 vaccine effectiveness in Israel using aggregated counts. Preprint MedRxiv. February 23, 2021	Using administrative data from the Ministry of Health in Israel, this study assessed the number of vaccinated individuals with the Pfizer-BioNTech vaccine (<60 and > 60 years) for positive cases (symptomatic and asymptomatic), COVID-19 hospitalizations, COVID-19 severe diseases over 5 time periods: 1-13 days after first dose, 14-20 days after first dose,	<p>For all outcomes, effectiveness was mainly noted beginning in the 0-6 days after the second dose (generally given on day 21 from the first dose). Given the delay in the outcomes (laboratory confirmation, hospitalization and severe disease), a portion of the effectiveness in this period is likely attributed to the first dose. This is particularly true for hospitalizations and severe disease (assuming what is reported is the date of these events).</p> <p>Mid-range estimates for 14-20 days after first dose and 0-6 days after second dose were as follows:</p>

Source	Description	Protection from the first dose of COVID-19 vaccines
	0-6 days after second dose (second dose generally administered around day 21 from the first dose), 7-13 days after second dose and 14 and more days after second dose. Expected numbers of positive cases were estimated based on daily vaccination and general incidence rates, adjusting for number of cases that would have occurred without vaccination and across various incidence rates.	<ul style="list-style-type: none"> • Positive cases >60 years of age: 0% and 73% • Positive cases <60 years of age: 12% and 77% • Hospitalization cases >60 years of age: 0% and 81% • Hospitalization cases <60 years of age: 34% and 81% • Severe cases >60 years of age: 1% and 81% • Severe cases <60 years of age: 44% and 85%
Amit S et al. Early rate reductions of SARS-CoV-2 infection and COVID-19 in BNT162b2 vaccine recipients. Published correspondence. February 18, 2021 Supplementary material	Retrospective cohort study from the Sheba Medical Centre in Israel comparing the rates of positive SARS-CoV-2 tests and symptomatic laboratory-confirmed COVID-19 among unvaccinated (1,895) and vaccinated (7214 with at least one dose, of which 6037 received two doses) health care workers. Vaccinated health care workers were within 1 to 14 and 15 to 28 days after first dose of Pfizer-BioNTech vaccine. The later time period was further broken down in the supplementary material into days 15 to 21 and days 22 to 28. Most received a second dose around day 21 or 22.	<p>Reduction in the rate of SARS-CoV-2 infection in vaccinated health care workers (symptomatic and asymptomatic) compared with unvaccinated health care workers was:</p> <ul style="list-style-type: none"> • 65% (95% CI: 43 to 79%) from days 15 to 21 after first vaccination, and • 86% (95 CI: 70 to 94%) from days 22 to 28 after first vaccination (which includes time after second dose) <p>Reduction in the rate of symptomatic COVID-19 in vaccinated health care workers compared with unvaccinated health care workers was:</p> <ul style="list-style-type: none"> • 76% (95% CI: 51 to 88%) from days 15 to 21 after first vaccination, and • 94% (95% CI: 76 to 99%) from days 22 to 28 after first vaccination (which includes time after second dose) <p>Note: It is not clear what date is based on. Likely specimen collection date.</p>

Source	Description	Protection from the first dose of COVID-19 vaccines
Zacay G. et al., BNT162b2 Vaccine Effectiveness in Preventing Asymptomatic Infection with SARS-CoV-2 Virus: A Nationwide Historical Cohort Study. SSRN-Lancet preprint. March 3, 2021.	Prospective cohort study of VE against PCR- confirmed infection in 6,286 individuals who were frequently tested in the Meuhedet Health Maintenance Organization (many of whom may have been health care workers) (2,941 received two doses of the Pfizer-BioNTech vaccine, 1,445 received one dose and 1,900 were not vaccinated). The included individuals had at least two PCR tests during November 2020, at least two PCR tests during December 2020, and at least one PCR test during January 2021, all of which were previously negative	VE against PCR positive SARS-CoV-2 (with or without symptoms) from ≥ 14 days after dose 1 until the receipt of dose 2 was estimated to be 61% (CI 49%-71%) and 82% (71%-89%) for the period from 1 to 6 days after the second dose. Note: The VE per day is not shown in this study and previous studies note that it increases across the time period from ≥ 14 days after vaccination to the second dose. B.1.1.7 was the dominant circulating strain.
Canada – Effectiveness data		
Institut national de santé publique du Québec (INSPQ). Preliminary Data on Vaccine Effectiveness and Supplementary Opinion on the Strategy for Vaccination Against COVID-19 in Quebec in a Context of Shortage. February 12, 2021 and updated, as per Personal Communication Gaston De Serres following presentation to NACI on February 24, 2021.	Analysis of surveillance data from residents in long term care facilities (LTCF) and health care workers (HCWs) in Quebec. In Quebec, about 70% of doses in both target groups were Pfizer-BioNTech and the remainder was Moderna . Vaccinations began on December 14, 2020 and this study used data until February 10, 2021. Following presentation to NACI on February 24, 2021 additional follow-up data were provided, extending to February 15, 2021 (63 days of follow-up), and	VE against SARS-CoV-2 after one dose of mRNA vaccines in vaccinated compared to unvaccinated HCWs increased to almost 80% at the end of the observation period. Using the screening method to compare percentage of health care workers with SARS-CoV-2 who were vaccinated ≥ 2 weeks before to the overall vaccination rates in health care workers, VE against SARS-CoV-2 ranged from 71% to 82% (depending on selected denominator). Compared to the first nine days after vaccination, VE against SARS-CoV-2 in HCWs was 79.6% 28 days or more after one dose of mRNA vaccination. Update following February 24, 2021 NACI presentation: from December 14, VE in HCWs from days 21 to 63 after single-dose

Source	Description	Protection from the first dose of COVID-19 vaccines
	restricting to HCWs 20 to 64 years of age and LTCF residents 65 years of age and over. Additional sensitivity analysis was also undertaken, restricting the analysis period from January 3 to February 15, 2021 (43 days of follow-up) to address potential variation over the holiday period.	<p>vaccination was 80% (95% CI: 77 to 82%) and from January 3 VE in HCWs from days 21 to 43 after single-dose vaccination was 83% (95%CI: 79 to 86%).</p> <p>Compared to the first nine days after vaccination, VE against SARS-CoV-2 was 80.3% 21 to 27 days after vaccination with one dose of mRNA vaccine in LTCF residents. Update following February 24, 2021 NACI presentation: from December 14, VE in LTCF residents from days 21 to 63 after single-dose vaccination was 88% (95% CI: 85 to 90%) and from January 3 VE in LTCF residents from days 21 to 43 after single-dose vaccination was 90% (95%CI: 87 to 93%)</p> <p>Note: SARS-CoV-2 rates were declining in the general population as well but to a lesser extent than among HCWs or LTCF residents.</p>
Personal Communication, as per Danuta M Skowronski, Lead for Influenza & Emerging Respiratory Pathogens, BC Centre for Disease Control following presentation to NACI on February 24, 2021	<ul style="list-style-type: none"> Following presentation to NACI on February 24, 2021 updated analysis of surveillance data from health care workers (HCWs) 20 to 64 years of age and long term care facility (LTCF) residents 65 years of age and over were shared from British Columbia (BC). Vaccination of HCWs began December 15 and of LTCF residents began December 23, 2020 in BC. In BC, first doses among HCWs and LTCF residents included in cohort analyses of VE were compromised of about 80% and 60% Pfizer-BioNTech, respectively and the remainder was Moderna. Follow-up extended to February 15, 2021 (62 and 54 days of follow-up for 	<p>Using the screening method to compare percentage of HCWs SARS-CoV-2 cases who were vaccinated ≥ 2 weeks before to the overall vaccination rates in HCWs, VE against SARS-CoV-2 ranged from 74 to 79% (depending on selected denominator) when second dose recipients were excluded.</p> <p>Compared to the first nine days after vaccination, from December 15, VE against SARS-CoV-2 in HCWs from days 21 to 62 after single-dose vaccination was 81% (95% CI: 73 to 86%) and from January 3 VE in HCWs from days 21 to 43 after single-dose vaccination was 89% (95%CI: 82 to 93%).</p> <p>Compared to the first nine days after vaccination, from December 23, VE against SARS-CoV-2 in LTCF residents from days 21 to 54 after single-dose vaccination was 87% (95%CI: 79 to 92%) and from January 3 VE in LTCF residents from days 21 to 43 after single-dose vaccination was 80% (95%CI: 65 to 88%).</p> <p>Note: SARS-CoV-2 rates were declining in the general population as well but to a lesser extent than among HCWs or LTCF residents.</p>

Source	Description	Protection from the first dose of COVID-19 vaccines
	HCWs and LTCF residents, respectively). Additional sensitivity analysis was also undertaken, restricting the analysis period from January 3 to February 15, 2021 (43 days of follow-up) to address potential variation over the holiday period.	
United States – Effectiveness data		
Pawlowski C et al. FDA-approved COVID-19 vaccines are effective per real-world evidence synthesized across a multi-state health system. Preprint MedRxiv. February 27, 2021.	Retrospective cohort study of vaccinated (31,069) and propensity matched non-vaccinated (31,069) members of the Mayo clinic health system in the United States where the Pfizer-BioNTech and Moderna vaccines are available, assessing PCR positive specimens. Propensity matching was based on geography, demographics and record of previous PCR testing.	VE based on a positive SARS-CoV-2 PCR test at time periods that are likely to represent the effect of one dose ranged from 69.2% (95% CI: 54.1 to 79.8%) from days 15 to 21 after vaccination to 74.2% (95% CI: 58.4 to 84.7%) from days 22 to 28 after vaccination.
Tande et al., Impact of the COVID-19 Vaccine on Asymptomatic Infection Among Patients Undergoing Pre-Procedural COVID-19 Molecular Screening. Clinical Infectious Diseases. March 10, 2021.	Retrospective cohort study of consecutive asymptomatic patients (39,156) undergoing pre-symptomatic screening before surgical and select medical procedures (48 to 72 hours before the procedure) from December 17, 2020 to February 8 2021 using electronic health records to capture vaccination, test results, demographics from Mayo clinic associated sites in the United States. Participants were not symptomatic at time of screening but were not followed for future symptoms. The Pfizer-BioNTech and Moderna vaccines were used and the analysis was	<p>Compared to unvaccinated, the VE against asymptomatic disease for Pfizer and Moderna combined in the adjusted analysis was:</p> <ul style="list-style-type: none"> • 79% (95% CI: 63 to 88%) from >10 days after dose one to before dose 2 • 80% (95% CI: 56 to 91%) after dose 2 <p>Results for Pfizer-BioNTech alone were similar.</p> <p>Note: It is possible that there is unmeasured confounding despite adjustments that contributed to the lower rate of test positivity within the vaccinated group.</p>

Source	Description	Protection from the first dose of COVID-19 vaccines
	adjusted for age, sex, race/ethnicity, residence, and repeat screening. The VE was assessed by number of doses and time period from vaccination.	
Britton A et al. Effectiveness of the Pfizer-BioNTech COVID-19 Vaccine Among Residents of Two Skilled Nursing Facilities Experiencing COVID-19 Outbreaks — Connecticut, December 2020–February 2021 MMWR. March 15, 2021	Investigation of outbreaks in two skilled nursing homes in Connecticut, United States (142 residents and 321 residents) where the Pfizer-BioNTech vaccine was in use. Weekly surveillance testing was done to identify the outbreak and then once or twice weekly testing of residents and staff, as well as testing of symptomatic residents and staff and exposed residents. Test information, vaccination information and co-morbidities determined for residents, and time since vaccination determined. Case date was symptom onset date or SARS-CoV-2 test result, whichever came first. Person years were determined from vaccination date or admission date, whichever came later. Time to event analysis was necessary to adjust for change in risk due to the dynamics of the outbreak	Vaccination >14 days after first dose to 7 days after second dose resulted in a vaccine effectiveness of 63% (95% CI: 33 to 79%) against SARS-CoV-2, regardless of symptoms. Sensitivity analysis showed that VE was 66% (95% CI: 29 to 83%) >14 days after the first dose to the time of the second dose.
United Kingdom – Effectiveness data		
Hall VJ et al., Effectiveness of BNT162b2 mRNA Vaccine Against Infection and COVID-19 Vaccine Coverage in Healthcare Workers in England, Multicentre Prospective Cohort Study (the	Analysis of vaccinated (with the Pfizer-BioNTech vaccine) and unvaccinated health care workers who underwent regular screening for SARS-CoV-2 in the UK, including every other week PCR testing and some who had twice weekly	In those without past COVID-19 and assessing SARS-CoV-2 infection rates by PCR (with or without symptoms), a single dose of Pfizer-BioNTech vaccine was 72% (95% CI: 58 to 86%) effective at ≥21 days after vaccination. The effect was first noted on day 10 and plateaued after 21 days.

Source	Description	Protection from the first dose of COVID-19 vaccines
SIREN Study). Preprint The Lancet February 22, 2021.	rapid tests confirmed by PCR. 23,324 health care workers met inclusion criteria from 104 hospitals.	Note that updated data was published by Public Health England showing no evidence of a decline in effectiveness with good protection out to the period between 58 and 81 days ⁽²⁶⁾ .
Vasileiou E et al., Effectiveness of First Dose of COVID-19 Vaccines Against Hospital Admissions in Scotland: National Prospective Cohort Study of 5.4 Million People. SSRN-Lancet preprint. February 19, 2021.	Prospective cohort study using national linked administrative data from Scotland (5.4 million people) to assess COVID-19 hospitalizations comparing unvaccinated and vaccinated individuals by time from vaccination after a single dose of either the Pfizer- BioNTech or AstraZeneca vaccine. Hospital admission was defined as: COVID-19 as the main cause of admission or hospitalization within 28 days of a positive PCR SARS-CoV-2 test. Covariates were controlled for using a number of analyses.	<p>VE against hospitalization using Pfizer-BioNTech peaked at:</p> <ul style="list-style-type: none"> • 85% (95% CI: 76 to 91%) 28 to 34 days after one dose. <p>VE against hospitalization using AstraZeneca peaked at:</p> <ul style="list-style-type: none"> • 94% (95% CI: 73 to 99%) 28 to 34 days after one dose <p>Note: For the AstraZeneca vaccine, the VE against hospitalization was high (70%, 95% CI: 63 to 76%) even within 7 to 13 days after one dose, which would be too early to have an impact on hospitalization, making the results challenging to interpret.</p>
Lopez Bernal J. et al., Early effectiveness of COVID-19 vaccination with BNT162b2 mRNA vaccine and ChAdOx1 adenovirus vector vaccine on symptomatic disease, hospitalisations and mortality in older adults in the UK: a test negative case control study. Preprint. March 1, 2021 and Public Health England. Vaccine effectiveness report. March 17, 2021 Public Health England. Vaccine effectiveness report. March 17, 2021 Public Health	Test negative-case control study using linked surveillance data in the UK. Assessed the Pfizer-BioNTech and AstraZeneca vaccines in those ≥70 years of age (over 7.5 million). PCR tests were within 10 days of onset of symptoms. For those who were vaccinated, cases (PCR positive) and controls (PCR negative) were assessed by time since vaccination to onset of symptoms. Controlled for covariates such as age, gender, deprivation and ethnicity, geography, period of time and care home status. A post-hoc analysis using days 4-9 post-vaccination as the baseline was conducted. The impact of vaccination on	<p>For the Pfizer-BioNTech vaccine in those ≥80 years of age, with vaccination before January 4, 2021 VE against symptomatic COVID-19 was:</p> <ul style="list-style-type: none"> • 61% (95% CI: 45 to 71%) 42 or more days (maximum ~75 days) after vaccination using the test negative design • 72% (95% CI: 60 to 80%) 42 or more days (maximum ~75 days) after one dose of vaccine compared to the 4-9 days post-vaccination <p>For the Pfizer-BioNTech vaccine in those ≥70 years of age, with vaccination from January 4, 2021 to February 21, 2021, VE against symptomatic COVID-19 was:</p> <ul style="list-style-type: none"> • 61% (95% CI: 51 to 69%) 28 to 34 days and 57% (95% CI: 36 to 71%) 35 or more days (maximum ~48 days) after vaccination using the test negative design

Source	Description	Protection from the first dose of COVID-19 vaccines
England. Vaccine effectiveness report. March 17, 2021	hospitalization and deaths for cases was assessed.	<p>For the AstraZeneca vaccine in those ≥70 years of age, with vaccination from January 4, 2021 to February 21, 2021 VE was:</p> <ul style="list-style-type: none"> • 60% (95% CI: 41% to 73%) 28 to 34 days and 73% (95% CI: 27 to 90%) 35 or more days (maximum ~48 days) after vaccination using the test negative design; Note: the latter estimate is based on small numbers of cases <p>Hospitalization within 14 days of a positive test and death within 21 days of a positive test for those ≥80 years of age:</p> <ul style="list-style-type: none"> • For those who did get symptomatic disease and tested positive 14 or more days after vaccination, there was an additional 43% and 37% protection against hospitalization with the Pfizer-BioNTech and AstraZeneca vaccines, respectively. • For those who did get symptomatic disease and tested positive 14 or more days after vaccination, there was an additional 51% protection against death with the Pfizer-BioNTech vaccine (data not available for AstraZeneca). <p>The report from Public Health England covering the same period noted VE against symptomatic disease in those ≥70 years of age of:</p> <ul style="list-style-type: none"> • 58% (95% CI: 49 to 65%) for Pfizer-BioNTech from 28 days post-vaccination; and • 58% (95% CI: 38 to 72%) for AstraZeneca from 35 days after vaccination <p>For those ≥80 years of age, hospitalizations were reduced by 80% for both vaccines combined and deaths were reduced by 85% for the Pfizer-BioNTech vaccine (not assessed for AstraZeneca).</p>
Weekes M et al., Single-dose BNT162b2 vaccine protects against asymptomatic SARS-CoV-2 infection. Preprint Authorea . February 24, 2021.	A prospective cohort studies of health care workers in Cambridge University hospitals in the UK assessing the Pfizer-BioNTech vaccine. Health care workers were screened weekly for SARS-CoV-2 and percent positivity and cycle threshold	Comparing unvaccinated, vaccinated < 12 days and vaccinated >12 days, percent positivity for asymptomatic workers was 0.8%, 0.37% and 0.20% - representing a four-fold decrease in risk from unvaccinated to >12 days after vaccination and a calculated VE of 75%.

Source	Description	Protection from the first dose of COVID-19 vaccines
	values over two consecutive week periods were reported based on unvaccinated workers and those vaccinated <12 days or >12 days before a PCR positive test.	Assessing both symptomatic and asymptomatic workers, percent positivity was 1.71% in unvaccinated and 0.40% those vaccinated >12 days previously – representing a 4.3- fold reduction in risk and a calculated VE of 76.6%. Note: Study does not indicate if they excluded previously positive health care workers and VE calculated from rates provided in the study.
Hyams C, et al. Assessing the Effectiveness of BNT162b2 and ChAdOx1nCoV-19 COVID-19 Vaccination in Prevention of Hospitalisations in Elderly and Frail Adults: A Single Centre Test Negative Case-Control Study. Preprint – The Lancet. March 3, 2021	Test-negative case control study of 466 hospitalized people ≥80 years of age (many of whom were frail with comorbidities) in two hospitals in Bristol, UK. Patients admitted with two or more signs of respiratory illness, or a confirmed clinical or radiological diagnosis of acute lower respiratory disease were selected for inclusion (466 eligible people ≥80 years of age). Cases were PCR positive and controls were PCR negative. Vaccination was determined by record linkage. VE was assessed for the Pfizer-BioNTech and AstraZeneca in those who had been vaccinated ≥14 days before symptom onset.	For Pfizer-BioNTech the VE for hospitalization with a positive laboratory test and symptom onset ≥14 days after vaccination (maximum 80 days): <ul style="list-style-type: none"> • 71.4% (95% CI: 43.1 to 86.2%) for the entire time period from December 8, 2020 • 79.3% (95% CI: 47.0 to 92.5%) for a later time period beginning January 4, 2021, which covers the same period as the AstraZeneca distribution For AstraZeneca the VE for hospitalization with a positive laboratory test and symptom onset ≥14 days after vaccination (maximum 53 days): <ul style="list-style-type: none"> • 80.4% (95% CI: 36.4 to 94.5%) for the later time period beginning January 4, 2021 Note: Separate analyses seemed to have been conducted for AstraZeneca and Pfizer-BioNTech but it is unclear how the study subjects for each analysis were assigned.
Menni C et al. Vaccine after Effects and Post-Vaccine Infection in a Real World Setting: Results from the COVID Symptom Study App. SSRN-Lancet Preprint. March 4, 2021.	Prospective cohort study of people using an app to report vaccination status and details (date of vaccination, Pfizer-BioNTech or AstraZeneca), adverse events post-vaccination, symptoms, testing and test results on a daily basis in the UK. 42,866 people vaccinated with Pfizer-BioNTech and 16,773 people vaccinated with AstraZeneca who had at	For the Pfizer-BioNTech vaccine, VE based on self-reported test results and vaccination status with one dose was: <ul style="list-style-type: none"> • 57% (95% CI: 38 to 71%) 12 to 21 days after vaccination • 68% (95% CI: 47 to 81%) 21 to 30 days after vaccination • 70% (95% CI: 57 to 100%) more than 30 days after vaccination For the AstraZeneca vaccine, VE based on self-reported test results and vaccination status was: <ul style="list-style-type: none"> • 42% (95% CI: 17 to 71%) 12 to 21 days after vaccination

Source	Description	Protection from the first dose of COVID-19 vaccines
	least one test (PCR or lateral flow rapid test) were included in this part of the analysis. Rates of positive tests were compared among vaccinated people (by date since first vaccination) and unvaccinated people who had a test on the same day. Rates were adjusted for age, sex, body mass index, smoking, race/ethnicity, health care status and the presence of comorbidities. Information was available for 42,866 people who received the Pfizer-BioNTech vaccine and 16,773 people who received the AstraZeneca vaccine.	Note: Data is self-reported which may affect validity.
Lumley SF et al. An observational cohort study on the incidence of SARS-CoV-2 infection and B.1.1.7 variant infection in healthcare workers by antibody and vaccination status. MedRxiv. March 12, 2021	A longitudinal cohort study of 13,109 healthcare workers (HCWs) in four hospitals and associated facilities in Oxfordshire, UK who received Pfizer-BioNTech or AstraZeneca vaccine (8,285 received the Pfizer-BioNTech vaccine [1,407 two doses] and 2,738 the Oxford-AstraZeneca vaccine [49 two doses]). Asymptomatic swabbing was offered every two weeks and serology every two months. VE against symptomatic and asymptomatic PCR-confirmed SARS-CoV-2 infection was estimated using Poisson regression adjusted for age, sex and temporal changes in incidence and role.	At >14 days following vaccination in previously seronegative HCWs compared to unvaccinated seronegative HCWs: <ul style="list-style-type: none"> • PCR-confirmed symptomatic infection was 67% (95% CI: 48 to 79%) lower • any PCR-positive result (with or without symptoms) was 64% (95% CI: 50 to 74%) lower

Source	Description	Protection from the first dose of COVID-19 vaccines
Shah ASV et al., Effect of vaccination on transmission of COVID-19: an observational study in healthcare workers and their households. medRxiv. March 21, 2021.	A cohort study using record linkage from multiple national data sets of 144,525 healthcare workers (HCWs) and 194,362 household members in Scotland. 78.3% of healthcare workers received at least one dose of the Pfizer-BioNTech or AstraZeneca vaccine and 25.1% received two doses. Cox regression models were used to estimate hazard ratios for the effect of vaccination (≥ 14 days) on SARS-CoV-2 PCR positive cases and hospitalization (within 28 days of a positive PCR test or PCR positive while in hospital). Co-variables included age, sex, deprivation index, ethnicity, comorbidities, health care worker roles, occupation and part-time status.	Compared to unvaccinated health care workers, VE against PCR positive SARS-CoV-2 ≥ 14 days after vaccination was 55% (95% CI: 51 to 58%) and against hospitalization was 84% (95% CI: 73 to 91%).
Azamgarhi et al., Experience of COVID-19 Vaccination of Healthcare Workers in a Hospital Setting. ResearchSquare Preprint. March 9, 2021.	Single centre hospital in the UK assessing VE against PCR positive disease in health care worker who were screened every two weeks. 1,373 out of 2,257 health care workers were vaccinated using the Pfizer-BioNTech vaccine. Health care workers were classified as unvaccinated, vaccinated between days 0 and 13 and vaccinated 14 or more days in the past. Outcome was time to symptoms or to PCR positive test if asymptomatic. Adjusted for age, sex, staff group and ethnicity.	VE against PCR positive disease comparing those vaccinated 14 or more days previously and unvaccinated health care workers was 80% (95% CI: 21 to 95%). Based on 45 new cases and follow-up to 42 days post vaccination.
Denmark – Effectiveness data		

Source	Description	Protection from the first dose of COVID-19 vaccines
Moustsen-Helms et al., Vaccine effectiveness after 1st and 2nd dose of the BNT162b2 mRNA Covid-19 Vaccine in long-term care facility residents and healthcare workers – a Danish cohort study. medRxiv. March 9, 2021.	Registry- and population-based observational cohort study using linkages to vaccination and laboratory data bases. Studied all long term care facility residents (39,040) and all frontline health care workers (331,039) using PCR-confirmed outcomes (symptomatic and asymptomatic). Compared rates in unvaccinated to those vaccinated at various intervals related to first and second dose of the Pfizer-BioNTech vaccine in Denmark. Days between first and second doses were 24 (IQR 20 to 52) and 25 (IQR 20 to 51) for long-term care home residents and health care workers, respectively.	<p>VE for nursing home residents (adjusted for calendar time and unadjusted):</p> <ul style="list-style-type: none"> • 21% (95% CI: - 0.11 to 44%) and 60% (95% CI: 46 to 71%) >14 days after vaccination to dose 2 • 52% (95% CI: 27 to 69%) and 80% (95% CI: 70 to 88%) 0-7 days after dose 2 • 64% (95% CI: 14 to 84%) and 96% (95% CI: 91 to 98%) >7 days after dose 2 <p>VE for health care workers (adjusted for calendar time and unadjusted):</p> <ul style="list-style-type: none"> • 17% (95% CI: 4 to 28%) and 50% (95% CI: 29 to 66%) >14 days after vaccination to dose 2 • 46% (95% CI: 28 to 59%) and 77% (95% CI: 57 to 90%) 0-7 days after dose 2 • 90% (95% CI: 82 to 95%) and 97% (95% CI: 90 to 100%) >7 days after dose 2 <p>Note: The VE was negative in the first time period after vaccination (0-14 days) which was made worse by adjusting for calendar time, indicating potential methodologic bias which may underestimate the vaccine effectiveness.</p>

Abbreviations: CI: confidence interval, LTCF: long-term care facility, mRNA: messenger ribonucleic acid, NACI: National Advisory Committee on Immunization, PCR: polymerase chain reaction, VE: vaccine effectiveness

Additional studies that assessed one-dose of a COVID-19 vaccine were reviewed but were not included in the analysis because they did not provide a definitive VE estimate ⁽⁵⁶⁻⁶⁰⁾.

Table 2. Strength of NACI Recommendations

Strength of NACI Recommendation <i>based on factors not isolated to strength of evidence</i> (e.g., public health need)	STRONG	DISCRETIONARY
Wording	<i>“should/should not be offered”</i>	<i>“may/may not be offered”</i>
Rationale	Known/anticipated advantages outweigh known/anticipated disadvantages (“should”), OR Known/Anticipated disadvantages outweigh known/anticipated advantages (“should not”)	Known/anticipated advantages are closely balanced with known/anticipated disadvantages, OR uncertainty in the evidence of advantages and disadvantages exists
Implication	A strong recommendation applies to most populations/individuals and should be followed unless a clear and compelling rationale for an alternative approach is present.	A discretionary recommendation may/may not be offered for some populations/individuals in some circumstances. Alternative approaches may be reasonable.

LIST OF ABBREVIATIONS

Abbreviation	Term
CI	Confidence interval
EEFA	Ethics, equity, feasibility, and acceptability
HCW	Health care worker
LTCF	Long-term care facility
mRNA	Messenger ribonucleic acid
NACI	National Advisory Committee on Immunization
PCR	Polymerase chain reaction
PHAC	Public Health Agency of Canada
VE	Vaccine effectiveness

ACKNOWLEDGEMENTS

This statement was prepared by: B Warshawsky, M Salvadori, O Baclic, A Nam, MW Yeung, R Ximenes, K Farrah, YE Chung, M Tunis, S Deeks, and C Quach on behalf of NACI.

NACI gratefully acknowledges the contribution of: Dr. N Andrews, Dr. G De Serres, V Ferrante, Dr. A Iorio, Dr. S Ismail, Dr. L Linkins, Dr. J Little, Dr. T Piggott, K Ramotar, Dr. D Skowronski, E Wong, K Young, and the NACI Secretariat.

NACI

Members: C Quach (Chair), S Deeks (Vice-Chair), J Bettinger, P De Wals, E Dubé, V Dubey, R Harrison, K Hildebrand, K Klein, J Papenburg, C Rotstein, B Sander, S Smith, and S Wilson.

Liaison representatives: LM Bucci (Canadian Public Health Association), E Castillo (Society of Obstetricians and Gynaecologists of Canada), A Cohn (Centers for Disease Control and Prevention, United States), L Dupuis (Canadian Nurses Association), J Emili (College of Family Physicians of Canada), D Fell (Canadian Association for Immunization Research and Evaluation), M Lavoie (Council of Chief Medical Officers of Health), D Moore (Canadian Paediatric Society), M Naus (Canadian Immunization Committee), and A Pham-Huy (Association of Medical Microbiology and Infectious Disease Canada).

Ex-officio representatives: D Danoff (Marketed Health Products Directorate, HC), E Henry (Centre for Immunization and Respiratory Infectious Diseases [CIRID], PHAC), M Lacroix (Public Health Ethics Consultative Group, PHAC), J Pennock (CIRID, PHAC), R Pless (Biologic and Radiopharmaceutical Drugs Directorate, Health Canada), G Poliquin (National Microbiology Laboratory, PHAC), V Beswick-Escanlar (National Defence and the Canadian Armed Forces), and T Wong (First Nations and Inuit Health Branch, Indigenous Services Canada).

NACI High Consequence Infectious Disease Working Group

Members: C Quach (Chair), Dr. S Deeks (Vice-Chair), Y-G Bui, Dr. K Dooling, R Harrison, K Hildebrand, M Murti, J Papenburg, R Pless, N Stall, and S Vaughan, M Miller, S Ramanathan.

PHAC Participants: N Abraham, O. Baclic, YE Chung, L Coward, P Doyon-Plourde, K Farrah, V Ferrante, N Forbes, SJ Ismail, C. Jensen, A Killikelly, R Krishnan, A Nam, M Patel, M Salvadori, A Sinilaite, R Stirling, E Tice, M Tunis, Ms. E Wong, MW Yeung, K Young, J Zafack, and B Warshawsky.

REFERENCES

1. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med*. 2020 Dec 31;383(27):2603,2615. doi: 10.1056/NEJMoa2034577.
2. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2021 Feb 4;384(5):403,416. doi: 10.1056/NEJMoa2035389.
3. Skowronski DM, De Serres G. Safety and efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med*. 2021 Feb 17;384(11):10.1056/NEJMc2036242#sa1. doi: 10.1056/NEJMc2036242.
4. Moderna. Vaccines and Related Biological Products Advisory Committee Meeting December 17, 2020. FDA Briefing Document. Moderna COVID-19 Vaccine [Internet].; 2020 Dec [cited 2020 Dec 23]. Available from: <https://www.fda.gov/media/144434/download>.
5. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet*. 2021 Jan 9;397(10269):99,111. doi: 10.1016/S0140-6736(20)32661-1.
6. Amit S, Regev-Yochay G, Afek A, Kreiss Y, Leshem E. Early rate reductions of SARS-CoV-2 infection and COVID-19 in BNT162b2 vaccine recipients. *The Lancet*. 2021 Mar 6;397(10277):875,877. doi: 10.1016/S0140-6736(21)00448-7.
7. Aran D. Estimating real-world COVID-19 vaccine effectiveness in Israel using aggregated counts. *medRxiv*. 2021 Feb 23. doi: <https://doi.org/10.1101/2021.02.05.21251139>.
8. Chodick G, Tene L, Patalon T, Gazit S, Tov AB, Cohen D, et al. The effectiveness of the first dose of BNT162b2 vaccine in reducing SARS-CoV-2 infection 13-24 days after immunization: real-world evidence. *medRxiv*. 2021 Jan 29. doi: <https://doi.org/10.1101/2021.01.27.21250612>.
9. Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA Covid-19 Vaccine in a nationwide mass vaccination setting. *N Engl J Med*. 2021 Feb 24. doi: 10.1056/NEJMoa2101765.
10. Zacay G, Shasha D, Bareket R, Kadim I, Sikron FH, Tsamir J, et al. BNT162b2 vaccine effectiveness in preventing asymptomatic infection with SARS-CoV-2 virus: A nationwide historical cohort study. SSRN- Lancet prepublication. 2021 Mar 3. <https://dx.doi.org/10.2139/ssrn.3796868>.
11. Hunter PR, Brainard J. Estimating the effectiveness of the Pfizer COVID-19 BNT162b2 vaccine after a single dose. A reanalysis of a study of 'real-world' vaccination outcomes from Israel. *medRxiv*. 2021 Feb 3. doi: <https://doi.org/10.1101/2021.02.01.21250957>.
12. Comité sur l'immunisation du Québec. Preliminary data on vaccine effectiveness and supplementary opinion on the strategy for vaccination against COVID-19 in Quebec in a context

of shortage [Internet]. Québec (QC): Institut national de santé publique du Québec (INSPQ) [updated 2021 Mar 18; cited 2021 Mar 18]. Available from: <https://www.inspq.qc.ca/en/publications/3111-vaccine-effectiveness-strategy-vaccination-shortage-covid19>.

13. Personal communication, as per Danuta M Skowronski, Lead for Influenza & Emerging Respiratory Pathogens, BC Centre for Disease Control following presentation to NACI on February 24, 2021.

14. Personal communication, as per Gaston De Serres (l'Institut national de santé publique du Québec) following presentation to NACI on February 24, 2021.

15. Britton A, Jacobs Slifka KM, Edens C, Nanduri SA, Bart SM, Shang N, et al. Effectiveness of the Pfizer-BioNTech COVID-19 Vaccine among residents of two skilled nursing facilities experiencing COVID-19 outbreaks - Connecticut, December 2020-February 2021. *MMWR Morb Mortal Wkly Rep*. 2021 Mar 19;70(11):396,401. doi: 10.15585/mmwr.mm7011e3.

16. Pawlowski C, Lenehan P, Puranik A, Agarwal V, Venkatakrishnan AJ, Niesen MJM, et al. FDA-authorized COVID-19 vaccines are effective per real-world evidence synthesized across a multi-state health system. *medRxiv*. 2021 Feb 27. doi: <https://doi.org/10.1101/2021.02.15.21251623>.

17. Tande AJ, Pollock BD, Shah ND, Farrugia G, Virk A, Swift M, et al. Impact of the COVID-19 vaccine on asymptomatic infection among patients undergoing pre-procedural COVID-19 molecular screening. *Clin Infect Dis*. 2021 Mar 10;ciab229. doi: 10.1093/cid/ciab229.

18. Weekes M, Jones NK, Rivett L, Workman C, Ferris M, Shaw A, et al. Single-dose BNT162b2 vaccine protects against asymptomatic SARS-CoV-2 infection. *Authorea*. 2021 Feb 24. doi: 10.22541/au.161420511.12987747/v1.

19. Vasileiou E, Simpson CR, Robertson C, Shi T, Kerr S, Agrawal U, et al. Effectiveness of first dose of COVID-19 vaccines against hospital admissions in Scotland: national prospective cohort study of 5.4 million people. *SSRN- Lancet prepublication*. 2021 Feb 19. <https://dx.doi.org/10.2139/ssrn.3789264>.

20. Shah ASV, Gribben C, Bishop J, Hanlon P, Caldwell D, Wood R, et al. Effect of vaccination on transmission of COVID-19: an observational study in healthcare workers and their households. *medRxiv*. 2021 Mar 21. doi: 10.1101/2021.03.11.21253275.

21. Menni C, Klaser K, May A, Polidori L, Capdevila J, Louca P, et al. Vaccine after effects and post-vaccine infection in a real world setting: Results from the COVID Symptom Study App. *SSRN- Lancet prepublication*. 2021 Mar 4. <https://dx.doi.org/10.2139/ssrn.3795344>.

22. Lumley SF, Rodger G, Constantinides B, Sanderson N, Chau KK, Street TL, et al. An observational cohort study on the incidence of SARS-CoV-2 infection and B.1.1.7 variant infection in healthcare workers by antibody and vaccination status. *medRxiv*. 2021 Mar 12. doi: 10.1101/2021.03.09.21253218.

23. Hyams C, Marlow R, Maseko Z, King J, Ward L, Fox K, et al. Assessing the effectiveness of BNT162b2 and ChAdOx1nCoV-19 COVID-19 vaccination in prevention of hospitalisations in elderly and frail adults: A single centre test negative case-control study. SSRN- Lancet prepublication. 2021 Mar 3. doi: <https://dx.doi.org/10.2139/ssrn.3796835>.
24. Hall VJ, Foulkes S, Saei A, Andrews N, Oguti B, Charlett A, et al. Effectiveness of BNT162b2 mRNA vaccine against infection and COVID-19 vaccine coverage in healthcare workers in England, multicentre prospective cohort study (the SIREN Study). SSRN- Lancet prepublication. 2021 Mar 9. doi: 10.21203/rs.3.rs-257937/v1.
25. Lopez Bernal J, Andrews N, Gower C, Stowe J, Robertson C, Tessier E, et al. Early effectiveness of COVID-19 vaccination with BNT162b2 mRNA vaccine and ChAdOx1 adenovirus vector vaccine on symptomatic disease, hospitalisations and mortality in older adults in England. medRxiv. 2021 Mar 2. doi: <https://doi.org/10.1101/2021.03.01.21252652>.
26. Public Health England vaccine effectiveness report [Internet]. London (UK): Public Health England; 2021 March 17 [cited 2021 March 18]. Available from: [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/971017/SP PH VE report 20210317 CC JLB.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/971017/SP_PH_VE_report_20210317_CC_JLB.pdf).
27. Azamgarhi T, Hodgkinson M, Shah A, Skinner J, Briggs T, Hauptmannova I, et al. Experience of COVID-19 vaccination of healthcare workers in a hospital setting. Research Square preprint. 2021 Mar 9. doi: 10.21203/rs.3.rs-257937/v1.
28. Moustsen-Helms I, Emborg H, Nielsen J, Nielsen KF, Krause TG, Mølbak K, et al. Vaccine effectiveness after 1st and 2nd dose of the BNT162b2 mRNA Covid-19 Vaccine in long-term care facility residents and healthcare workers – a Danish cohort study. medRxiv. 2021 Mar 9. doi: 10.1101/2021.03.08.21252200.
29. Guijarro C, Galán I, Martínez-Ponce D, Pérez-Fernández E, José Goyanes M, Castilla V, et al. Dramatic drop of new SARS-CoV-2 infections among health care workers after the first dose of the BNT162b2 mRNA Covid-19 Vaccine. medRxiv. 2021 Cold Spring Harbor Laboratory Press:2021.03.24.21254238.
30. Thompson MG, Burgess JL, Naleway AL, Tyner HL, Yoon SK, Meece J, et al. Interim estimates of vaccine effectiveness of BNT162b2 and mRNA-1273 COVID-19 vaccines in preventing SARS-CoV-2 infection among health care personnel, first responders, and other essential and frontline workers — eight U.S. locations, December 2020–March 2021. MMWR Morb Mortal Wkly Rep. ePub: 29 March 2021. doi: <http://dx.doi.org/10.15585/mmwr.mm7013e3>.
31. Haas EJ, Angulo FJ, McLaughlin JM, Anis E, Singer SR, Khan F, et al. Nationwide vaccination campaign with BNT162b2 in Israel demonstrates high vaccine effectiveness and marked declines in incidence of SARS-CoV-2 infections and COVID-19 cases, hospitalizations, and deaths. SSRN- Lancet prepublication. 2021 Mar 24. <https://ssrn.com/abstract=381138>.
32. Plotkin SA, Halsey N. Accelerate coronavirus disease 2019 (COVID-19) vaccine rollout by delaying the second dose of mRNA vaccines. Clin Infect Dis. 2021 Jan 27;ciab068. doi: 10.1093/cid/ciab068.

33. Public Health Agency of Canada (PHAC). Canadian Immunization Guide [Internet]. Ottawa (ON): PHAC [updated 2021 Mar 26; cited 2021 Mar 31]. Available from: <https://www.canada.ca/en/public-health/services/canadian-immunization-guide.html>.
34. Plotkin SA, Orenstein WA, Offit PA. Plotkin's vaccines. 7th ed. ed. Philadelphia, PA: Elsevier; 2018.
35. FDA Briefing Document. Janssen Ad26.COVS.2 Vaccine for the prevention of COVID-19. Vaccines and Related Biological Products Advisory Committee Meeting February 26, 2021. [Internet]. Silver Spring (MD): U.S. Food and Drug Administration; 2021 [cited 2021 March 17]. Available from: <https://www.fda.gov/media/146217/download>.
36. Emary KRW, Golubchik T, Aley PK, Ariani CV, Angus B, Bibi S, et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): an exploratory analysis of a randomised controlled trial. Lancet. 2021 Mar 30. doi:[https://doi.org/10.1016/S0140-6736\(21\)00628-0](https://doi.org/10.1016/S0140-6736(21)00628-0).
37. Moghadas SM, Vilches TN, Zhang K, Nourbakhsh S, Sah P, Fitzpatrick MC, et al. Evaluation of COVID-19 vaccination strategies with a delayed second dose. medRxiv. 2021 Jan 29. doi: <https://doi.org/10.1101/2021.01.27.21250619>.
38. Matrajt L, Eaton J, Leung T, Dimitrov D, Schiffer JT, Swan DA, et al. Optimizing vaccine allocation for COVID-19 vaccines: critical role of single-dose vaccination. medRxiv. 2021 Mar 3. doi: <https://doi.org/10.1101/2020.12.31.20249099>.
39. Paltiel AD, Zheng A, Schwartz JL. Speed versus efficacy: Quantifying potential tradeoffs in COVID-19 vaccine deployment. Ann Intern Med. 2021 Jan 5;M20-7866. doi: 10.7326/M20-7866.
40. Tuite AR, Zhu L, Fisman DN, Salomon JA. Alternative dose allocation strategies to increase benefits from constrained COVID-19 vaccine supply. Ann Intern Med. 2021 Jan 5;M20-8137. doi: 10.7326/M20-8137.
41. Graham J. Modelling decay of population immunity with proposed second dose deferral strategy. medRxiv. 2021 Jan 6. doi: <https://doi.org/10.1101/2021.01.05.21249293>.
42. Cobey S, Larremore DB, Grad YH, Lipsitch M. Concerns about SARS-CoV-2 evolution should not hold back efforts to expand vaccination. Nature Reviews Immunology. 2021 04/01.
43. Madhi SA, Baillie V, Cutland CL, Voysey M, Koen AL, Fairlie L, et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant. N Engl J Med. 2021 Mar 16. doi: 10.1056/NEJMoa2102214.
44. Shrotri M, Krutikov M, Palmer T, Giddings R, Azmi B, Subbarao S, et al. Vaccine effectiveness of the first dose of ChAdOx1 nCoV-19 and BNT162b2 against SARS-CoV-2 infection in residents of Long-Term Care Facilities (VIVALDI study). medRxiv. 2021 Mar 26. doi: <https://doi.org/10.1101/2021.03.26.21254391>.

45. Ward H, Cooke G, Whitaker M, Redd R, Eales O, Brown JC, et al. REACT-2 Round 5: increasing prevalence of SARS-CoV-2 antibodies demonstrate impact of the second wave and of vaccine roll-out in England. medRxiv. 2021 Mar 1. doi: 10.1101/2021.02.26.21252512.
46. Brockman MA, Mwimanzi F, Sang Y, Ng K, Agafitei O, Ennis S, et al. Weak humoral immune reactivity among residents of long-term care facilities following one dose of the BNT162b2 mRNA COVID-19 vaccine. medRxiv. 2021 Mar 24. doi: <https://doi.org/10.1101/2021.03.17.21253773>.
47. Müller L, Andrée M, Moskorz W, Drexler I, Walotka L, Grothmann R, et al. Age-dependent immune response to the Biontech/Pfizer BNT162b2 COVID-19 vaccination. medRxiv. 2021 Cold Spring Harbor Laboratory Press:2021.03.03.21251066.
48. Whitaker H, Elgohari S, Rowe C, Otter A, Brooks T, Linley E, et al. Impact of COVID-19 vaccination program on seroprevalence in blood donors in England, 2021. SSRN. 2021 Mar 16. <https://papers.ssrn.com/abstract=3803380>.
49. Subbarao S, Warrener LA, Hoschler K, Perry KR, Shute J, Whitaker H, et al. Robust antibody responses in 70–80-year-olds 3 weeks after the first or second doses of Pfizer/BioNTech COVID-19 vaccine, United Kingdom, January to February 2021. Euro Surveill. 2021 Mar 25. doi: 10.2807/1560-7917.ES.2021.26.12.2100329.
50. Boyarsky BJ, Werbel WA, Avery RK, Tobian AAR, Massie AB, Segev DL, et al. Immunogenicity of a single dose of SARS-CoV-2 messenger RNA vaccine in solid organ transplant recipients. JAMA. 2021 Mar 15. doi: 10.1001/jama.2021.4385.
51. Monin-Aldama L, Laing AG, Muñoz-Ruiz M, McKenzie DR, Barrio IdMd, Alaguthurai T, et al. Interim results of the safety and immune-efficacy of 1 versus 2 doses of COVID-19 vaccine BNT162b2 for cancer patients in the context of the UK vaccine priority guidelines. medRxiv. 2021 Mar 17. doi: 10.1101/2021.03.17.21253131.
52. Benotmane I, Gautier-Vargas G, Cognard N, Olagne J, Heibel F, Braun-Parvez L, et al. Weak anti-SARS-CoV-2 antibody response after the first injection of an mRNA COVID-19 vaccine in kidney transplant recipients. medRxiv. 2021 Cold Spring Harbor Laboratory Press:2021.03.08.21252741.
53. Ismail SJ, Hardy K, Tunis MC, Young K, Sicard N, Quach C. A framework for the systematic consideration of ethics, equity, feasibility, and acceptability in vaccine program recommendations. Vaccine. 2020 Aug 10;38(36):5861,5876. doi: 10.1016/j.vaccine.2020.05.051.
54. Collier DA, Ferreira IA, Datir R, Meng B, Bergamaschi L, Collaboration C, et al. Age-related heterogeneity in neutralising antibody responses to SARS-CoV-2 following BNT162b2 vaccination. The Lancet Preprint. 2021 Feb 11.
55. Janssen Inc. Product monograph including patient medication information. Janssen COVID-19 Vaccine. SARS-CoV-2 Vaccine [Ad26.COVS.S, recombinant]. Suspension for intramuscular injection [Internet]. Ottawa (ON): Health Canada; 2021 Mar 5 [cited 2021 Mar 30]. Available from: <https://covid-vaccine.canada.ca/info/pdf/janssen-covid-19-vaccine-pm-en.pdf>.

56. Benenson S, Oster Y, Cohen MJ, Nir-Paz R. BNT162b2 mRNA Covid-19 vaccine effectiveness among health care workers. *N Engl J Med*. 2021 Mar 23. doi: 10.1056/NEJMc2101951.
57. Hollinghurst J, North L, Perry M, Akbari A, Gravenor MB, Lyons RA, et al. COVID-19 infection risk amongst 14,104 vaccinated care home residents: A national observational longitudinal cohort study in Wales, United Kingdom, December 2020 to March 2021. *medRxiv*. 2021 Mar 24. doi: 10.1101/2021.03.19.21253940.
58. Daniel W, Nivet M, Warner J, Podolsky DK. Early evidence of the effect of SARS-CoV-2 vaccine at one medical center. *N Engl J Med*. 2021 Mar 23. doi: 10.1056/NEJMc2102153.
59. Keehner J, Horton LE, Pfeffer MA, Longhurst CA, Schooley RT, Currier JS, et al. SARS-CoV-2 infection after vaccination in health care workers in California. *N Engl J Med*. 2021 Mar 23. doi: 10.1056/NEJMc2101927.
60. Yelin I, Katz R, Herzel E, Berman-Zilberstein T, Ben-Tov A, Kuint J, et al. Associations of the BNT162b2 COVID-19 vaccine effectiveness with patient age and comorbidities. *medRxiv*. 2021 Mar 17. doi: 10.1101/2021.03.16.21253686.