Public Health Ontario | Santé publique Ontario

SYNTHESIS

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COVID-19 Real-World Vaccine Effectiveness – What We Know So Far

Introduction

Public Health Ontario (PHO) is actively monitoring, reviewing and assessing relevant information related to Coronavirus Disease 2019 (COVID-19). "What We Know So Far" documents are intended to provide a rapid review of the evidence related to a specific aspect or emerging issue related to COVID-19.

The development of these documents includes a systematic search of the published literature as well as scientific grey literature (e.g., ProMED, CIDRAP, Johns Hopkins Situation Reports) and media reports, where appropriate. Relevant results are reviewed and data extracted for synthesis. All "What We Know So Far" documents are reviewed by PHO subject-matter experts before posting.

As the COVID-19 outbreak continues to evolve and the scientific evidence rapidly expands, the information provided in these documents is only current as of the date of posting.

Key Findings

- All of the COVID-19 vaccines approved for use in Canada are effective at preventing symptomatic SARS-CoV infection and COVID-19 related hospitalizations and death. There are numerous studies on the real-world vaccine effectiveness (VE) of the mRNA vaccines (Pfizer-BioNTech COVID-19 vaccine [BNT162b2] and Moderna COVID-19 vaccine [mRNA-1273]) and a growing amount of VE data for the viral vector vaccines. There are several studies from the United Kingdom (UK) that report VE data for the Oxford/AstraZeneca (AZD1222/ChAdOx1-S) vaccine, however only one study from the United States (US) that reports VE data for the Janssen/Johnson & JohnsonVaccine (JNJ-78436735/Ad26.COV2.S) vaccine.
- In general, VE is about 60-80% for preventing symptomatic COVID-19 infection 3-4 weeks after receiving a single dose of Pfizer or Moderna and 60-70% for preventing symptomatic COVID-19 after a single dose of the AstraZeneca vaccine, although this varies by population (i.e., older adults, long-term care residents and health care workers). VE increases to greater than 85% after a second dose of mRNA vaccine. The VE for the Janssen vaccine is 77%.
- VE for preventing severe disease, and COVID-19-related hospitalization and death ranges from about 70 to 90% for the Pfizer, Moderna and AstraZeneca vaccines 3-4 weeks after the first dose.
- For the general population in Ontario, the VE is 60% for preventing symptomatic disease and 70% for preventing severe outcomes (hospitalization or death) two weeks or more after a first dose of mRNA vaccine, which increases to 91% and 98%, respectively, after a second dose.

- There is evidence that COVID-19 vaccines reduce asymptomatic infection by up to 90% which will have an important role in reducing transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although outbreaks are still possible despite high vaccine coverage, population-wide studies have shown that vaccines can reduce transmission to other individuals, including transmission within households and long-term care homes.
- Studies have shown mixed results with respect to VE for variants of concern (VOCs). Of greatest current interest in Ontario, Canada and globally is the Delta variant. Although early evidence suggests COVID-19 vaccines are less effective against the Delta variant, recent data from Ontario indicate that Pfizer, Moderna, and AstraZeneca vaccines provide a high degree of protection, particularly for prevention hospitalization or death (VE: 78 to 96%) resulting from this VOC.

Background

Vaccine efficacy and vaccine effectiveness measure the proportionate reduction in cases among vaccinated persons compared to those not vaccinated. Vaccine efficacy refers to the reduction in disease incidence when a study is carried out under ideal conditions (e.g., clinical trial), whereas vaccine effectiveness refers to a vaccine's ability to prevent illness in people vaccinated in the real world setting. Both vaccine efficacy and effectiveness are determined by calculating the risk of disease among vaccinated and unvaccinated persons, and determining the percentage reduction in risk of disease among vaccinated persons relative to unvaccinated persons. For example, a VE of 80% translates to an 80% reduction in disease occurrence among the vaccinated group, or an 80% reduction in the number of cases you would have expected if the group had not been vaccinated.[1]

This WWKSF document is a synthesis of available real-world VE data for vaccines authorized by Health Canada as of March 12, 2021. The four COVID-19 vaccines currently in use in Canada are: Pfizer-BioNTech COVID-19 vaccine (BNT162b2), Moderna COVID-19 vaccine (mRNA-1273), Oxford University/AstraZeneca (AZD1222/ChAdOx1-S) and Janssen/Johnson & Johnson COVID-19 vaccine (JNJ-78436735/Ad26.COV2.S). In Canada, the brand names of the Oxford University/AstraZeneca (AZD1222/ChAdOx1-S) vaccine are AstraZeneca COVID-19 vaccine and COVISHIELD, as there are two different manufacturers.[2] See COVID-19- What We Know So Far About…Herd Immunity for information on vaccine efficacy for Pfizer-BioNTech and Moderna vaccines.[3]

Methods

To identify relevant evidence on this topic, systematic searches in MEDLINE and Embase were conducted on March 9, 2021 and updated on May 14, 2021 and August 6, 2021 by PHO Library Services. A grey literature search including pre-prints was also conducted on March 11, 2021 and updated on May 21, 2021 and August 6, 2021 by PHO Library Services. It is recognized that there may be additional information not captured in this document. Relevant results were reviewed and data extracted for synthesis. Additional information was reviewed from the National Advisory Committee on Immunization (NACI) recommendations on the use of COVID-19 vaccines and the Public Health Agency of Canada COVID-19 Vaccine Effectiveness Surveillance Program (VESPa). All data reported for VE refers to vaccine effectiveness, unless otherwise stated.

Results

The majority of VE studies are from Israel, the UK, Europe and North America. All but one study reported VE data for the Pfizer-BioNTech COVID-19 vaccine (herein referred to as Pfizer) (Israel, UK, US, Canada,

Denmark, Sweden), Moderna COVID-19 vaccine (herein referred to as Moderna) (US, Canada) and the Oxford/AstraZeneca COVID-19 vaccine (herein referred to as AstraZeneca) (UK). One study from the US reported VE data for the Janssen/Johnson & Johnson vaccine (herein referred to as Janssen).

SARS-CoV-2 Infection, Symptomatic Disease and Asymptomatic Infection

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, confirmed by positive SARS-CoV-2 polymerase chain reaction (PCR) test may include asymptomatic and/or symptomatic disease depending on the jurisdictional testing strategy and population under consideration. For example, in some jurisdictions, the general population may only be eligible for testing if individuals are symptomatic or have had exposure to a confirmed case, whereas in other jurisdictions, workers and/or patients/residents in healthcare settings may take part in asymptomatic testing often as part of screening efforts. Therefore, in this document, SARS-CoV-2 infection refers to both asymptomatic and symptomatic COVID-19 disease unless otherwise specified. The administration schedule for Pfizer, Moderna and AstraZeneca vaccines are intended to be two doses, 3-12 weeks apart whereas Janssen is a single dose vaccine.[4] As it takes time to develop immunity, vaccines are not expected to offer protection in the first two weeks following administration of the first vaccine dose.[5]

GENERAL POPULATION

Between 2-3 weeks after a single dose of mRNA vaccine (Pfizer or Moderna), studies have reported a VE of approximately 40-60% for SARS-CoV-2 infection overall,[5-9,11] 56% for symptomatic disease and 29% for asymptomatic infection.[5] Although estimates vary, VE appears to increase 3 weeks after the first dose of Pfizer vaccine. Dagan et al. reported a VE of 65% for SARS-CoV-2 infection, 71% for symptomatic disease and 52% for asymptomatic infection between days 21-27, whereas Hunter et al. estimated a VE of 90% for symptomatic and asymptomatic SARS-CoV-2 infection 21 days after a first dose.[5,10,11] An Ontario study reported VE for symptomatic infection reaching 71% by 35-41 days after a first dose of mRNA vaccine.[9] A study in the UK of the general population reported a VE of 61 and 66% for prevention of SARS-CoV-2 infection at 21 days or more following a single dose of Pfizer or AstraZeneca vaccine, respectively. There was no clinically or statistically difference between vaccines.[12]

One to two weeks after the second dose of either Pfizer or Moderna vaccine, studies have reported VE for symptomatic and asymptomatic SARS-CoV-2 infection to be 86-97%.[5,7-9,11,13-15] After the second dose of the AstraZeneca vaccine, estimated VE for was 79%.[12] In a study of over 2000 individuals in the US, the VE of the Janssen vaccine was reported to be 77% for preventing SARS-CoV-2 infection.[16]

ADOLESCENTS

There is currently limited data on the use of COVID-19 vaccines in individuals aged 12-17 years. On May 5, 2021, Health Canada authorized the use of the Pfizer vaccine in adolescents 12-15 years.[17] While some studies of VE in the general population include patients age 16 years or older, they generally do not include stratification of adolescents between 16-19 years of age. Therefore while there is currently a lack of vaccine effectiveness data specific to patients less than 18 years of age, two placebo-controlled, observer-blinded, randomized trials have demonstrated vaccine efficacy of 100% for preventing symptomatic infection in this younger age group.[18,19]

OLDER ADULTS

In an Israeli study of older adults over 60 years of age, VE for SARS-CoV-2 infection was 44% 13-24 days after one dose of the Pfizer vaccine.[6] In another study of individuals over 70 years of age, VE was estimated to be 50% for SARS-CoV-2 infection and 64% for symptomatic disease 21-27 days after the first dose.[5] For this same age group, Chung et al. reported a VE of 40% against symptomatic disease 14 or more days after a first dose of an mRNA vaccine in Ontario; however, it should be noted that while the VE was lower in the initial time period following vaccination, VE for this group was comparable to younger adults at 28 days.[9] A study of community dwelling adults 70 years of age and older in British Columbia reported an overall VE of 65% $\geq$ 21 days after a single dose of an mRNA vaccine.[20] Another study found a VE of 60-75% for prevention of symptomatic disease 28 days after receiving a first dose of either Pfizer or AstraZeneca vaccine.[21]

Studies report high VE following the second dose of vaccine in older adults. Israeli studies of adults over 60 years of age demonstrated a VE of 95-96% for prevention ofSARS-CoV-2 infection and 96-98% for prevention of symptomatic disease 1-2 weeks after a second dose of the Pfizer vaccine.[5,22] A further analysis of adults over 70 years of age found VE to be 92% for prevention of SARS-CoV-2 infection and 92% for symptomatic disease 7-28 days after a second dose.[11] This is consistent with Ontario data which found a VE of 90%, seven days after a second dose of mRNA vaccine.[9] Lopez Bernal et al. reported a VE of 85-90% for prevention of symptomatic disease in those over 70 years of age, 14 days after the second dose of the Pfizer vaccine in the UK.[21] The vast majority of data pertaining to older adults refers to individuals living in the community; however, some studies included those residing in long-term care (LTC) homes or did not specify whether residents of LTC were included.

LONG-TERM CARE RESIDENTS

Canadian data from Ontario, British Columbia and Quebec demonstrate a VE of 80% for preventing SARS-CoV-2 infections in LTC residents 2-3 weeks following a single dose of either Pfizer or Moderna vaccine.[23-25] In Ontario, VE was 89% for LTC residents 8 weeks after the start of vaccination at which point 92% had received a first dose of either Pfizer or Moderna vaccine, and 67% had received a second dose.[25] European studies have reported a lower first dose VE for mRNA vaccines. In Spain, VE was found to be 40-60% following a first dose of mRNA vaccine in this population; however, this increased to 80-90% after the second dose.[26,27] Additionally, a study from Denmark reported no significant VE between 14 days after the first dose of the Pfizer vaccine to before the second dose, given 24 days after first dose (interquartile range [IQR]: 20-52), and a VE of 52% less than seven days after the first dose which increased to 64% more than seven days after the second dose of vaccine.[28] However, measuring VE less than 14 days after a first vaccine dose likely underestimates its effectiveness, which could account for lower estimates in the Denmark data. In the UK, the VE was approximately 60% 28 days after a first dose of AstraZeneca or Pfizer vaccine.[29]

HEALTHCARE WORKERS

The VE for healthcare workers (HCW) in Israel, England, US, Europe and Canada 2-3 weeks after receiving a single dose of Pfizer or Moderna vaccine is 70-90% for COVID-19 infection and symptomatic disease.[23,30-38] This is in contrast to results from Denmark where a VE of 17% was observed > 14 days after the first dose (before the second dose) of Pfizer vaccine; however, due to a relatively short time frame between doses (median 25 days [IQR: 20-51]), it is difficult to determine the impact of a single dose from this study.[28] The VE less than seven days after the second dose was 46%, this increased to 90% after seven days following the second dose.[28] This is consistent with several other studies that found VE of over 94% for SARS-CoV-2 infection and symptomatic disease more than seven days

following the second dose of mRNA vaccine in HCW.[36,37,39,40] In addition, studies have reported VE of 80-90% for asymptomatic infection after two doses of vaccine in HCW.[30,39,40] In Ontario, the VE for HCW in LTC facilities eight weeks after the start of vaccination was 79%, at which point 55% had received at least one dose of Pfizer or Moderna vaccine and 45% had received two doses of either vaccine.[25]

One US study which included HCW (55%) as well as first responders (22%), and other essential and frontline workers (23%) found a VE of 81% for prevention of SARS-CoV-2 infection more than 14 days after the first dose and before the second dose and 91%, 14 days after the second dose of mRNA vaccine.[41]

(See Table 1 for study details.)

ASYMPTOMATIC COVID-19

Given the challenge in preventing and detecting asymptomatic spread of COVID-19, the impact of vaccines on asymptomatic disease is particularly important. Data from individuals in Israel receiving the Pfizer vaccine indicate that VE for preventing asymptomatic infection 14 to 20 days after the first dose, 21 to 27 days after the first dose, and more than seven days after the second dose is 29%, 52% and 90% to 92%, respectively.[5,14] A US retrospective cohort study of asymptomatic individuals undergoing screening before surgical and medical procedures found a VE of 79% more than 10 days after the first dose (and before the second dose) of Pfizer vaccine and a VE of 80% after the second dose.[42] However, the VE after the second dose was estimated starting at 0 days after the second dose, likely underestimating full VE after two doses since it is known that a minimum of 14 days is required to mount immunity.[42]

In one study of hospital staff where vaccination with a first dose of Pfizer vaccine increased from 8% to 83% over a two month period, a significant reduction in both symptomatic and asymptomatic cases was observed.[43] Data on reduction of asymptomatic infection in HCW also demonstrates very high VE following two doses of vaccine. VE for preventing asymptomatic infection in HCW at least 12 days after the first dose of Pfizer vaccine was 42%, rising to 86-90% after > 7 days after the second dose, further increasing to 94% at > 21 days after the second dose.[39,40] An additional study of HCW demonstrated a VE against preventing asymptomatic infection of 91% > 7 days after a second dose of Pfizer or Moderna vaccine.[44] These data suggest vaccines help in playing a key role in the prevention of COVID-19 transmission by reducing the risk of asymptomatic infection both in the general population and healthcare settings.

Population-Level Vaccine Effectiveness

There is some VE data at the population-level, estimating the impact of the Pfizer and Moderna vaccines on COVID-19 transmission in the community[45-49] and LTC[31] settings in the US and Israel.[34] An analysis of early statewide vaccination efforts in the US found that vaccination was effective in reducing daily COVID-19 case growth rates by 0.124, 0.347, 0.345, 0.464, 0.490, and 0.756 percentage point declines, respectively, in the 1-5, 6-10, 11-15, 16-20, 21-25, and 26 or more days after the start of vaccination (i.e., administration date of first COVID-19 vaccine dose).[47] A separate analysis of vaccination rates and COVID-19 incidence found that the cumulative county-level vaccination rate was significantly associated with a corresponding decline in COVID-19 incidence; that is, higher vaccination rates translated to a decreased county-level COVID-19 incidence.[48] In Israel, where COVID-19 cases and hospitalizations started to decline after implementation of a national vaccine campaign that prioritized vaccination of older individuals, an analysis between early-vaccinated cities and late-vaccinated cities found a larger and earlier decrease in the number of COVID-19 cases and hospitalizations of older individuals (> 60

years) in earlier compared to later-vaccinated cities.[49] While a concurrent lockdown could have influenced results, the study authors note that these same downward trends in older individuals were not observed during previous lockdowns in which clinical measures had similar dynamics across age groups.[49] Another study analyzing the first four months of the national vaccine campaign in Israel found that across all age groups, as vaccine coverage increased, the incidence of SARS-CoV-2 outcomes (symptomatic and asymptomatic infection, COVID-19 related hospitalizations and death) declined.[14] An additional study of 223 communities in Israel identified a strong negative association between community rate of vaccination and risk of infection for unvaccinated individuals (those less than 16 years of age) in the same community.[50]

In the US, a decrease in COVID-19 cases, emergency room visits, hospital admissions and deaths were seen between the periods November/December 2020 (pre-vaccine period) and April/May 2021 (vaccination period) as population-level vaccine coverage increased, with a 40-66% greater decline in older adults which was the cohort with highest vaccination coverage.[46] A recent analysis of the COVID-19 vaccination program in New York City estimated a 30% reduction in COVID-19 cases, 51% reduction in hospitalizations and 48% reduction in deaths compared with expected rates between December 12 2020 and July 1 2021 attributed to immunization. During this timeframe, 69% of adult residents were vaccinated with at least one dose and 64% were fully vaccinated compared with the national average of 59% for complete vaccination.[45]

A study of over 500,000 households in the UK found that the likelihood of household transmission was reduced by about 50% when the index case had been previously vaccinated at least 21 days before, compared to index cases that were unvaccinated.[51] Most received one dose of vaccine (93%) and the VE was similar for the Pfizer and AstraZeneca vaccines.[51] A study of over 65,000 households in Israel reported an estimated VE of 89% against transmission for the Pfizer vaccine.[52]

A study of HCW in the UK also found decreased transmission in households of HCW vaccinated with Pfizer and AstraZeneca when compared with unvaccinated HCW; this translated to a 30% and 54% reduction in documented cases 14 or more days after the first dose and second dose of vaccine, respectively. However, there was uncertainty as to whether this reduction in risk was due to lack of HCW infection or lack of transmission from HCW.[53] A study of HCW in a tertiary centre in India found a reduced secondary attack rate of 4.25% in high risk contacts (persons residing in the same dormitory as confirmed cases) following staff vaccination with the AstraZeneca vaccine (97% coverage) as compared with a secondary attack rate of 20.6% in the pre-vaccination period.[54]

A US study of over 2000 nursing homes in one county found that spread of SARS-CoV-2 infection decreased at a faster rate in homes that held vaccine clinic administering the first dose of Pfizer vaccine compared with homes that did not (although vaccination rates were not reported). While a decreasing trend in new infections was observed prior to the start of the vaccine clinics, three weeks after the vaccine clinic, there was a 48% decline in new resident cases in vaccinated homes compared with a 21% decline in non-vaccinated homes, and a 33% decline in new staff cases in vaccinated homes compared with an 18% decline in new staff cases in non-vaccinated homes.[31] Similarly, Mor et al. found that the incidence of new SARS-CoV-2 infections and hospitalization and/or death among LTC residents with new infection in the prior 30 days was significantly lower in LTCs that held vaccine clinics administering mRNA vaccines earlier than those that held clinics later.[55] Domi et al. also reported decreased spread of SARS-CoV-2 in residents and staff and decreased deaths among residents following vaccine clinics in LTC homes that was associated with timing (5 and 6 weeks) after the clinic date.[56] De Salazar et al. found that 75% of expected infections and 74% of COVID-19-related deaths were prevented in LTC residents once a high level of regional vaccination coverage was achieved in this population (70% fully

vaccinated); detectable transmission among residents was reduced by 69% at 14 days after this level of vaccination was achieved and increased to 90% reduction by 42 days.[57] Additionally, in a study of 299,209 LTC residents where over 90% were fully vaccinated, the estimated indirect protection of unvaccinated residents without previous infection reached 81%.[27]

Several studies in the US and Europe have reported on VE within the context of LTC home outbreaks. In Germany, a single dose of Pfizer vaccine did not prevent symptomatic infection and death (35% case fatality rate) in a LTC home where 96% of residents and 90% of staff had received a first dose within 23 days of the outbreak.[58] Conversely, in the US, partial vaccination with the Pfizer vaccine (> 14 days after first dose but < 7 days after the second dose) had an estimated VE of 63% in preventing new infection in residents of two facilities experiencing COVID-19 outbreaks.[59] One study of an outbreak where over 90% of residents and 50% of staff were vaccinated with two doses of mRNA vaccines found a VE of 66% for prevention of overall infection, 87% for symptomatic infection, 94% for hospitalization and 94% for death in residents.[60] For healthcare workers, the VE was 76% for prevention of infection and 87% for symptomatic infection.[60] A French analysis of an outbreak in a LTC home where the B.1.351 (Beta, 501Y.V2) variant was identified found a VE of 50% for prevention of infection and a lower proportion of residents with severe disease in the vaccinated group (15%), compared with the unvaccinated group (80%).[61] The SARS CoV-2 viral load, estimated by mean cycle threshold value was also significantly lower in vaccinated residents. In this study, vaccination coverage was 80% for residents and 32% for staff (two doses of Pfizer vaccine).[61]

Severe Disease, COVID-19-related Hospitalization and Death

GENERAL POPULATION

In studies of the general population, VE for prevention of severe disease, hospitalization and death is roughly between 70-90%, 3-4 weeks after the first dose of vaccine which increases to over 90% after the second dose.

A Scottish study of their national vaccine program reported a VE of 91% (Pfizer vaccine) and 88% (AstraZeneca vaccine) for preventing COVID-19-related hospitalization 28-34 days after a single dose of vaccine in the general population.[62] However, as this study had several important methodological limitations, this data was not used to inform recommendations by the National Advisory Committee on Immunization (NACI) pertaining to the AstraZeneca vaccine for individuals 65 years of age and older in Canada. For example, an unexpectedly high VE for hospitalization 7-13 days after vaccination was biologically implausible since it takes at least 2 weeks for immunity to develop. There was potentially incomplete adjustment of confounders in the statistical analyses, and inclusion of only a small number of individuals vaccinated with AstraZeneca in the period 28 days and more after vaccination.[4] Similarly, in Israel, VE was 65% for prevention of severe disease and 70% for prevention of hospitalization, 14-20 days after first dose of Pfizer vaccine; however, this increased to 77% and 78%, respectively, 21-27 days after the first dose.[11] For this cohort, VE for prevention of death was 84% three weeks after the first dose.[5] In Ontario, VE was 70% for prevention of hospitalization or death associated with SARS-CoV-2 infection 14 or more days after a first dose of mRNA vaccine.[9] In the US, VE was 77% for prevention of hospitalization and 64% for prevention of death 14 days or more after the first dose of an mRNA vaccine which increased for fully-vaccinated to 96% and 99% for prevention of COVID-19 related hospitalization and death, respectively.[63]

One to two weeks after a second dose of Pfizer vaccine, Israeli studies indicate a VE of 94-95% for preventing severe infection, 92-97% for preventing hospitalization, and 94-99% for preventing

death.[11,14,15,22] Pawlowski et al. reported a VE of 89% and 86% for the Pfizer and Moderna vaccines respectively, for preventing COVID-19 related hospitalization 7 days after a second dose; both vaccines were 100% effective in preventing COVID-19 related ICU admission in this American study of community adults.[13] In Ontario, VE after a second dose of mRNA was 98% for prevention of hospitalization or death.[9]

OLDER ADULTS

Most studies of older adults report a VE of 70-80% for hospitalization 2-4 weeks after the first dose of vaccine. A test negative case-control study of individuals over 80 years of age hospitalized for COVID-19 or other acute respiratory disease in the UK found VE to be 71% for Pfizer and 80% for AstraZeneca at least 14 days after the first dose.[64] This is consistent with two other UK studies of this same age group which found VE to be 80% or greater for prevention of hospitalization 28 or more days after a first dose of Pfizer or AstraZeneca vaccine.[62,65] A test negative case-control study of those over 70 years of age in the UK found VE to be 80% for prevention of hospitalization and 85% for prevention of death 28 days after receiving a first dose of either Pfizer or AstraZeneca vaccine.[21] In adults greater than 65 years of age, a US study of partial vaccination with mRNA vaccine defined as a single dose more than 14 days before illness-onset or with a second dose received less than 14 days before illness-onset reported a VE of 65% for prevention of hospitalization.[66]

In studies of older adults, the VE for prevention of severe disease and hospitalization is greater than 90% two weeks or more following the second dose of mRNA or AstraZeneca vaccine. The VE for prevention of hospitalization was 92% for individuals over 80 years of age in the UK and 94% after for adults greater than 65 years of age in the US more than two weeks after receiving two doses of vaccine.[65,66] For adults over 60 years of age in Israel, VE for prevention of severe disease and hospitalization less than 14 days after the second dose was about 79-83%; this increased to 97-98% after 14 or more days following vaccination.[22] In addition, approximately two months after initiation of a national immunization campaign in Israel where 85% of individuals older than 60 years of age were vaccinated with 2 doses, there was a 68% decrease in hospitalization and 67% decrease in hospitalization with severe illness (based on clinical criteria as per the Israeli Ministry of Health and including ventilated and critically ill patients) compared to the peak period when there was no vaccination campaign.[49]

An Ontario study of those over 70 years of age found a VE of 67% for prevention of severe outcomes which was defined as hospitalization or death following a second dose of mRNA vaccine; this increased to 97% after two doses.[9] A study of older adults more than 70 years of age in the UK found a VE of 44-55% for prevention of death 14 or more days after a first dose of Pfizer or AstraZeneca vaccine. This increased to 69% at seven days or more after a second dose of Pfizer vaccine.[67]

LTC RESIDENTS

Data from one LTC home in Quebec demonstrated a VE of 40% for the prevention of serious SARS-CoV-2 infection (not defined) and 50% for prevention of death two weeks following the first dose of Pfizer vaccine.[24] In Ontario, eight weeks after starting the vaccination program among LTC residents with Pfizer or Moderna vaccine, the estimated VE for preventing mortality was 96%.[25] A study of LTC residents in Spain found a VE of 50% for prevention of infection and 50% for prevention of death from the date of the first dose up to the date of the second dose of Pfizer vaccine; this increased to 97% and 98% respectively after the second dose up to two months .[26]

(See Table 2 for study details)

SPECIAL POPULATIONS

There is currently limited VE data on populations who are at increased risk of severe outcomes from COVID-19 and who may mount a suboptimal immune response to vaccines. Several Israeli studies provide data on this cohort of individuals. One study which included patients with immunosuppression (transplant recipients, patients receiving immunosuppressive therapy, asplenia, and chronic renal failure) reported a VE of 44% against SARS-CoV-2 infection and 50% against symptomatic disease 13-24 days after the first dose of Pfizer vaccine; a follow-up study reported a VE of 71% against SARS-CoV-2 infection and 75% against symptomatic infection 7-27 days after the second dose. [6,68] Another study with data on 1,674 immunodeficient individuals including those with a solid organ transplant reported a VE of 90% for prevention of SARS-CoV-2 infection and 85% for prevention of symptomatic disease 7-28 days after a second dose of Pfizer vaccine for this cohort. Although the reported VE was 100% for prevention of serious infection and hospitalization, it should be noted that there were very few events in those categories and none in the vaccinated group.[11]

Several studies of individuals with inflammatory bowel disease (IBD) demonstrate similar VE as compaed to the general population. A Veterans Health Administration study found a VE of 80% against SARS-CoV-2 infection in fully vaccinated individuals with IBD and exposure to immunosuppressive medications.[6] An Israeli study of individuals with IBD found a comparable VE with a similar rate of breakthrough infections (0.14%) as compared to matched controls (0.10%) 14 days after second dose of Pfizer vaccine.[70] (Ref: Ben-Tov) Similarly, Hadi et al found no significant difference in new diagnosis of COVID-19 in those with IBD that received COVID-19 vaccination compared with a matched cohort (RR 0.95 [95% CI: 0.51-1.78).[71]

A US study found reduced VE of 59% (95% CI: 12–81%) against hospitalization in fully vaccinated individuals (Pfizer or Moderna) with immunocompromising conditions compared with a VE of 91% (95% CI: 86-95%) for those without immunocompromising conditions. The VE was 51% (95% CI: -31-82%) for the subset of individuals with solid organ or hematologic malignancy and solid organ transplant recipients (SOTR); however, there was a large confidence interval for this value which limits the precision of this estimate.[66] Another study specific to the SOTR population found an 81% reduction in the incidence of symptomatic COVID-19 infection for those fully vaccinated with an mRNA or Janssen vaccine compared with unvaccinated SOTR.[72]

With respect to pregnancy, a study in Qatar reported a VE of 40% against SARS-CoV-2 infection at least 2 weeks after a first dose of mRNA vaccine and a VE of 68% at least 2 weeks after a second dose. There were no cases of severe or critical disease in vaccinated individuals while there were 9 cases in the unvaccinated group. [73] A study of pregnant women in Israel found a VE of 71% against symptomatic infection 3-4 weeks after a first dose of Pfizer vaccine. Seven to 56 days after the second dose, VE against symptomatic infection increased to 96% and VE against hospitalization was estimated to be 89%.[74]

Heterologus (Combination) Vaccination

A Danish study of 136, 551 individuals who received combination vaccination (AstraZeneca as the first dose and mRNA vaccine as a second dose) found that VE against symptomatic infection was 88% (95% CI: 83-92%) 14 days after the second dose with no COVID-19 related hospitalizations or deaths occurred in any individuals receiving combination vaccination during the study period.[75]

Vaccine Effectiveness and Variants of Concern (VOC)

Several studies discussed VE with respect to the following VOC: B.1.1.7 (Alpha, first identified in the UK), B.1.351 (Beta, first identified in South Africa), P.1 (Gamma, first identified in Brazil) and B.1.617.2 (Delta, first identified in India).

Several studies from the UK concluded that VE was demonstrated by the Pfizer and AstraZeneca vaccines against Alpha, as it was the dominant lineage circulating at the time of these studies; however, VE after a first dose of vaccine may be slightly lower.[12,21,29,32,76,] Estimated VE for the general population in the US was somewhat lower at 59% more than two weeks after the first dose of mRNA vaccine in Andrejko et al. where 69% of sequenced isolates were VOC Alpha, B.1.427, or B.1.429 during the study period.[7] This is consistent with results of a study on breakthrough infections that suggested a decreased VE against Alpha between two weeks after the first dose and one week after the second dose of the Pfizer vaccine.[77] A UK study of healthcare workers vaccinated with Pfizer or AstraZeneca vaccine found no evidence that Alpha changed the extent of protection after the first dose.[78] However, a recent UK study on VOCs reported a VE of 51% for prevention of symptomatic infection caused by the Alpha variant at 21 or more days after a first dose of Pfizer or AstraZeneca vaccine.[79] In Ontario, VE for the Alpha variant was 61% for prevention of symptomatic disease and 59% for prevention of severe outcomes (hospitalization or death) 14 or more days after a single dose of mRNA vaccine.[9]

The VE for fully vaccinated individuals appear to be similar against Alpha as for other non-VOC. In three Israeli studies of the Pfizer vaccine where the Alpha variant was reported to be highly prevalent, two of these studies reported a second dose VE of over 90% on all outcomes (symptomatic and asymptomatic infection, COVID-19 related hospitalization and death) and the third concluded that the vaccine was capable of reducing transmission based on a sharp decline in cases during a period in which the Alpha variant became the dominant circulating lineage.[14,15,80] An Ontario study reported VE of > 90% against this variant for prevention of symptomatic disease and severe outcomes after a second dose of mRNA vaccine.[9]

Studies have shown reduced VE against Beta for those fully vaccinated with the Pfizer vaccine. Abu-Raddad et al. provided VE of the Pfizer vaccine specific to two VOC, VE for the general population in Qatar was 90% against the Alpha variant, whereas it was 75% for the Beta variant more than 14 days after two doses of vaccine.[81] Bailly et al. reported on an LTC outbreak where the Beta variant was identified and estimated a VE of 50% in homes where 80% of residents were vaccinated with two doses of Pfizer vaccine.[61] Kustin et al. found that fully vaccinated individuals who tested positive at least a week after the second dose were disproportionally infected with the Beta variant.[77] However in contrast, a subsequent study in Qatar demonstrated VE of 61% (95% CI: 57-66%) against the Beta variant after the first dose and 96% (95% CI: 92-99%) 14 or more days after the second dose of Moderna vaccine.[82]

There are several Canadian studies that provide VE data on VOCs. An Ontario study that included a subgroup analysis for E484K+ variants (which included Beta and Gamma variants) reported a VE of 43% for prevention of symptomatic disease and 56% for severe outcomes, 14 or more days after a first dose of mRNA vaccine; this increased to 88% and 100% respectively after two doses.[9] A study in British Columbia found that VE against symptomatic disease at $\geq$ 21 days after a single dose was 72% (95% CI: 58-81%) for non-VOC, 67% (95% CI: 57-75%) for the Alpha variant and 61% (95% CI: 45-72%) for the Gamma variant. [20] A study of HCW in Quebec found that VE against symptomatic disease was higher for non-VOC (77%, 95% CI: 73-81%) than VOC (majority were Alpha) (63%, 95% CI: 57-67%) after one dose of mRNA vaccine. However, after two doses of vaccine, VE did not differ significantly between non-VOC

(87%, 95% CI: 57-96%) and VOC (94%, 95% CI: 89-96%).[30] In an outbreak of the Gamma variant in an Ontario LTCH, VE against SARS-CoV-2 infection was 53% (95% CI: 27-69%) and 79% (95% CI: 48-91%) against severe disease in fully vaccinated residents. For staff, VE against infection was 66% (95% CI: 2-88%) in fully vaccinated staff.[83]

DELTA VARIANT

The Delta variant has increased transmissibility and increased severity after controlling for other variables with large scale outbreaks having been reported, especially for susceptible populations including partially vaccinated individuals Several studies indicate a reduced VE for symptomatic disease after one dose of vaccine but high protection against hospitalization and similar VE for symptomatic disease after 2 doses.[84]

A study in the UK found an absolute reduction of approximately 20% in VE for preventing symptomatic infection after a first dose of Pfizer or AstraZeneca vaccine for the Delta variant compared to the Alpha variant[79] The estimated VE three weeks after a first dose of either vaccine against the Delta variant was 31% (95% CI: 25-36%) compared with 49% (95% CI: 46-52%) for the Alpha variant. The estimated VE against the Delta variant was 88% (95% CI: 85-90%) at two weeks after the second dose of Pfizer and 67% (95% CI: 61-72%) at two weeks after the second dose of AstraZeneca whereas, the VE against the Alpha variant was 94% (95% CI: 92-95%) and 75% (95%CI: 68-79%) for Pfizer and AstraZeneca respectively. During this study which included data up to May 16 2021, the Delta variant accounted for 22% of total cases.[79] An additional analysis found that VE against hospitalization with the Delta variant to be very high for both the Pfizer and AstraZeneca vaccines, and similar to the Alpha variant. For the Pfizer vaccine, it was 94% (95% CI: 46-99%) after the first dose and 96% (95% CI: 86-99%) after the second dose. For the AstraZeneca vaccine, it was 71% (95% CI: 51-83%) after the first dose and 92% (95% CI: 75-97%) after the second dose.[85]

A Scottish study also found both the Pfizer and AstraZeneca vaccines to be effective in reducing SARS-CoV-2 infection and COVID-19 hospitalization with respect to the Delta variant; however, in this study, VE was generally lower for the Delta variant than with the Alpha variant. The estimated VE was 79% (95% CI: 75-82%) for preventing SARS-CoV-2 infection after 2 doses of Pfizer vaccine for the Delta variant compared with 92% (95% CI: 90-93%) for the Alpha variant. For the AstraZeneca vaccine, the estimated VE was 60% (95% CI: 53-66%) for the Delta variant compared with 73% (95% CI: 66-78%) for the Alpha variant.[86]

In Ontario, there was lower VE against symptomatic infection with the Delta variant following partial vaccination ($\geq$ 14 days after first dose) compared to the Alpha variant for Pfizer (56% vs 66%) and Moderna (72% vs 83%) vaccines. However, similar VE for the Delta variant was observed for the AstraZeneca vaccine (67%) as was for the Alpha variant. Vaccine effectiveness against hospitalization or death after partial vaccination ranged between 78-96% against the Delta variant depending on whether the vaccine was Pfizer, Moderna or AstraZeneca . For fully vaccinated individuals ($\geq$ 7 days after second dose) with the Pfizer vaccine, VE against symptomatic infection was similar against the Delta variant (87%, [95% CI: 64-95%]) as for the Alpha (89% [95% CI: 86-91%) and Beta/Gamma (84% [95% CI: 69-92%) variants.[87]

However, recent data from England and Israel may be signaling reduced VE against SARS-CoV-2 infection even after two doses of vaccine. The REACT-1 study in England which analyzed prevalence trends between May 20 and June 7, 2021 during which time the Delta variant had completely replaced the Alpha variant, estimated a lower VE of 49-58% against SARS-CoV-2 infection and 59% against symptomatic infection after 2 doses of vaccine.[88] Israeli data from June 20 to July 17, 2021 during which

time the Delta variant became dominant, also indicated a lower VE of 39% for SARS-CoV-2 infection and 41% for symptomatic infection in fully vaccinated individuals.[89]

DELTA VARIANT & BREAKTHROUGH INFECTIONS

Since the COVID-19 vaccines authorized for use in Canada are highly effective, breakthrough infections in fully vaccinated individuals are generally rare with most being asymptomatic and occurring within 14 days of a first dose when an individual is not yet considered full vaccinated.[90] However, there is emerging evidence that the Delta variant is associated with an increased rate of breakthrough infections including recent reports of outbreaks of the Delta Variant involving fully vaccinated individuals:

- An analysis of HCW in several facilities in India found that the Delta variant dominated vaccine breakthrough infections and that it was associated with greater transmissions to other HCW compared with non-Delta variants.[91]

- An analysis of patients in a US hospital system found that Delta variants caused a significantly higher rate of vaccine breakthrough cases compared with other VOC.[92]

- In April 2021, six breakthrough cases involving the Delta variant were identified in fully vaccinated individuals who had attended wedding events in Texas which took place outdoors and required all 92 guests to be fully vaccinated. All 6 individuals were symptomatic; two of whom were hospitalized and with one COVID-19 related death.[93]

- In May 2021, an outbreak of the Delta variant in a hospital in Finland resulted in SARS-CoV-2 infections in 45 healthcare workers; 18 (40%) of whom were vaccinated with 2 doses of Pfizer vaccine. There was evidence of secondary transmission from fully vaccinated, symptomatic HCW to patients despite universal masking.[94]

- In July 2021, 469 COVID-19 cases associated with multiple large public gatherings in a town located in Barnstable County, Massachusetts were identified; 346 (74%) occurred in fully vaccinated persons and of these, 274 (79%) were symptomatic. Of the five patients hospitalized, four were vaccinated; no deaths were reported. The Delta variant was identified in 90% of specimens tested (n=133 patients). Cycle threshold (Ct) values in specimens from breakthrough cases were similar to those who were not fully vaccinated. This led to changes in CDC recommendations that individuals including those that are fully vaccinated continue to wear masks in indoor settings where COVID-19 transmission is high.[95]

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Appendix

Table 1: Vaccine Effectiveness (VE) for Prevention SARS-CoV-2 Infection, Symptomatic Disease and Asymptomatic infection

Population	Study (Country) Study Period	Vaccine	Study Outcomes	Timeframe	VE for Prevention of SARS-CoV-2 infection
General Population (<60 y) (N=2,992,441)	Aran[22] (Israel) 12/20/2020-01/23/2021	Pfizer	SARS-CoV-2 infection (PCR positive)	0-13 days after 2nd dose	77-81%
General Population (< 60 y) (N=2,992,441)	Aran[22] (Israel) 12/20/2020-01/23/2021	Pfizer	SARS-CoV-2 infection (PCR positive)	≥ 14 days after 2nd dose	94%
General Population (> 16 y, no upper age limit, N=503,875) Mean age = 59.7 y (SD = 14.7)	Chodick[6] (Israel) 12/19/2020-01/17/2021	Pfizer	SARS-CoV-2 infection (PCR confirmed)	13-24 days after 1st dose	51% (95% CI: 16-72) Symptomatic: 54% (95% CI: 21-74)
General Population (≥ 16 y, no upper age limit, N=693,814) Median age = 45 (IQR: 35-62)	Dagan[3] (Israel) 12/20/2020-02/14/2021	Pfizer	Estimated vaccine effectiveness for SARS-CoV-2 infection (PCR confirmed), symptomatic disease and asymptomatic illness	14-20 days after 1st dose	48% (95% CI: 42-52) Symptomatic: 56% (95% CI: 51-61) Asymptomatic: 29% (95% CI: 17-39)
General Population (≥ 16 y, no upper age limit, N=480,438) Median age = 45 (IQR: 35-62)	Dagan[3] (Israel) 12/20/2020-02/14/2021	Pfizer	Estimated vaccine effectiveness for SARS-CoV-2 infection (PCR confirmed), symptomatic disease and asymptomatic illness	21-27 days after 1st dose	65% (95% CI: 60-69) Symptomatic: 71% (95% CI: 66-75) Asymptomatic: 52% (95% CI: 41-60)
General Population (≥ 16 y, no upper age limit, N=310,696) Median age = 45 (IQR: 35-62)	Dagan[3] (Israel) 12/20/2020-02/14/2021	Pfizer	Estimated vaccine effectiveness for SARS-CoV-2 infection (PCR confirmed), symptomatic disease and asymptomatic illness	> 7 days after 2nd dose	93% (95% CI: 91-94) Symptomatic: 96% (95% CI: 94-97) Asymptomatic: 90% (95% CI: 83-94)
General Population (> 16 y, no upper age limit, N=503,875) Mean age = 59.7 y (SD = 14.7)	Hunter[10] (Israel) 12/19/2020-01/17/2021	Pfizer	SARS-CoV-2 infection (PCR confirmed)	> 21 days after 1st dose	90%

Population	Study (Country) Study Period	Vaccine	Study Outcomes	Timeframe	VE for Prevention of SARS-CoV-2 infection
General Population (≥ 16 y, N=6,352,000)	Goldberg[15] (Israel) 03/01/2020-03/20/2021	Pfizer	SARS-CoV-2 infection (PCR confirmed)	> 7 days after 2nd dose	92.8% (95% CI: 92.6-93.0) B.1.1.7 was most prevalent variant during study period
General Population (≥ 16 y, N= 6,538,911)	Haas[14] (Israel) 01/24/2021-04/03/2021	Pfizer	SARS-CoV-2 infection (PCR confirmed)	> 7 days after 2nd dose	95% (95% CI: 95-96) Symptomatic: 97% (95% CI: 97-97) Asymptomatic: 92% (95% CI: 91-92) During the observation period, SARS-CoV-2 B.1.1.7 prevalence was 94.5%.
General Population (18-64 y) (N=805,741)	Bjork[8] (Sweden) 12/27/2020-02/28/2021	Pfizer	SARS-CoV-2 infection (PCR or antigen positive)	≥ 14 days after 1st dose 0-6 days after 2nd dose (likely first dose effect)	42% (95% CI: 14-63) 60% (95% CI: 27-81)
General Population (18-64 y) (N=805,741)	Bjork[8] (Sweden) 12/27/2020-02/28/2021	Pfizer	SARS-CoV-2 infection (PCR or antigen positive)	≥ 7 days after 2nd dose	86% (95% CI: 72-94)
General Population (≥ 18 y, N=48,000) Asymptomatic individuals undergoing pre-procedural tests	Tande[42] (US) 12/17/2020-02/08/2021	Pfizer	SARS-CoV-2 infection (PCR positive)	> 10 days after 1st dose	Asymptomatic: 79% (95% CI: 63-88)
General Population (N=213,749)	Abu-Raddad[81] (Qatar) 02/01/2021-03/31/2021	Pfizer	SARS-CoV-2 infection (PCR confirmed)	≥ 14 days after 2nd dose	B.1.1.7: 90% (95% CI: 86-92) B.1.351: 75% (95% CI: 71-79)
General Population (≥ 18 y, no upper age limit, N =136,532)	Pawlowski[13] (US) 12/01/2020-04/20/2021	Pfizer	SARS-CoV-2 infection (PCR positive)	≥ 7 days after 2nd dose	86% (95% CI: 82-89)

Population	Study (Country) Study Period	Vaccine	Study Outcomes	Timeframe	VE for Prevention of SARS-CoV-2 infection
General Population (≥ 18 y, no upper age limit, N =136,532)	Pawlowski[13] (US) 12/01/2020-04/20/2021	Moderna	SARS-CoV-2 infection (PCR positive)	≥ 7 days after 2nd dose	93% (95% CI: 86-97)
General Population (≥ 18 y, N=645)	Andrejko[7] (US) 02/24/2021-04/07/2021	Pfizer, Moderna	SARS-CoV-2 infection (PCR confirmed)	≥ 15 days after 1st dose	59% (95% CI: -10-84)
General Population (≥ 18 y, N=645)	Andrejko[7] (US) 02/24/2021-04/07/2021	Pfizer, Moderna	SARS-CoV-2 infection (PCR confirmed)	≥ 15 days after 2nd dose	86% (95% CI: 67-94)
General Population (≥ 16 y, community dwelling, N = 324,033) 6.6% received ≥ 1 dose	Chung[9] (Canada) 12/14/2020-04/19/2021	Pfizer, Moderna	SARS-CoV-2 infection (PCR confirmed) and symptomatic	≥ 14 days after 1st dose	Symptomatic: 60% (95% CI: 57-64) B.1.1.7: 61% E484K+ (B.1.351/P.1): 43%
General Population (≥ 16 y, community dwelling, N = 324,033) 6.6% received ≥ 1 dose	Chung[9] (Canada) 12/14/2020-04/19/2021	Pfizer, Moderna	SARS-CoV-2 infection (PCR confirmed) and symptomatic	≥ 7 days after 2nd dose	Symptomatic: 91% (95%CI: 89-93) B.1.1.7: 90% E484K+ (B.1.351/P.1): 88%
General Population (≥ 16 y, N=2,183,939)	Glampson[76] (UK) 12/08/2020-02/24/2021	Pfizer	SARS-CoV-2 infection (PCR confirmed)	22-28 days after 1st dose	74% (95% CI: 65-81) B.1.1.7 was likely dominant variant during study period
General Population (≥ 16 y, N=2,183,939)	Glampson[76] (UK) 12/08/2020-02/24/2021	AstraZeneca	SARS-CoV-2 infection (PCR confirmed)	22-28 days after 1st dose	78% (95% CI: 73-82) B.1.1.7 was likely dominant variant during study period
General Population (≥ 16 y, N=383,812)	Pritchard[12] (UK) 12/01/2020-05/08/2021	Pfizer	SARS-CoV-2 infection (PCR confirmed)	≥ 21 days after first dose, no second dose	66% (95% CI: 60-71)

Population	Study (Country) Study Period	Vaccine	Study Outcomes	Timeframe	VE for Prevention of SARS-CoV-2 infection
General Population (≥ 16 y, N=383,812)	Pritchard[12] (UK) 12/01/2020-05/08/2021	AstraZeneca	SARS-CoV-2 infection (PCR confirmed)	≥ 21 days after first dose, no second dose	61% (95% CI : 54-68)
General Population (≥ 16 y, N=383.812)	Pritchard[12] (UK) 12/01/2020-05/08/2021	Pfizer	SARS-CoV-2 infection (PCR confirmed)	After 2nd dose (after second vaccination, ≥21 days following first vaccination)	80% (95% CI: 73-85)
General Population (≥ 16 y, N=383,812)	Pritchard[12] (UK) 12/01/2020-05/08/2021	AstraZeneca	SARS-CoV-2 infection (PCR confirmed)	After 2nd dose (after second vaccination, ≥21 days following first vaccination)	79% (95% CI : 65-88)
General Population (≥ 16 y, N = 12,675)	Lopez Bernal[21](UK) 10/26/2020-05/16/2021	Pfizer, AstraZeneca	SARS-CoV-2 infection (PCR confirmed)	≥ 21 days after 1st dose	B.1.1.7: 51% (95% CI : 47-55) B.1.617.2 : 34% (95% CI :90-96)
General Population (≥ 16 y, N = 12,675)	Lopez Bernal[21] (UK) 10/26/2020-05/16/2021	Pfizer	SARS-CoV-2 infection (PCR confirmed)	≥ 14 days after 2nd dose	B.1.1.7: 93% (95% CI : 90-95) B.1.617.2 : 88% (95% CI :78-93)
General Population (≥ 16 y, N = 12,675)	Lopez Bernal[21] (UK) 10/26/2020-05/16/2021	AstraZeneca	SARS-CoV-2 infection (PCR confirmed)	≥ 14 days after 2nd dose	B.1.1.7: 66% (95% CI : 54-75) B.1.617.2: 60% (95% CI :29-77
General Population (> 18 y, N=2,195 vaccinated compared to N=21,950 unvaccinated))	Corchado-Garcia[16] (US) 02/27/2021-04/14/2021	Janssen	SARS-CoV-2 infection (PCR positive)	> 14 days after 1st dose	77% (95% CI: 30-95)
Older Adults (> 60 y) (N=1,303,244)	Aran[22] (Israel) 12/20/2020-01/23/2021	Pfizer	SARS-CoV-2 infection (PCR positive)	0-13 days after 2nd dose	73%
Older Adults (> 60 y) (N=1,303,244)	Aran[22] (Israel) 12/20/2020-01/23/2021	Pfizer	SARS-CoV-2 infection (PCR positive)	≥ 14 days after 2nd dose	96%
Older Adults (> 60 y)	Chodick[6] (Israel) 12/19/2020-01/17/2021	Pfizer	SARS-CoV-2 infection (PCR positive)	13-24 days after 1st dose	44%

Population	Study (Country) Study Period	Vaccine	Study Outcomes	Timeframe	VE for Prevention of SARS-CoV-2 infection
Older Adults (≥ 70 y) LTC residents were excluded	Dagan[3] (Israel) 12/20/2020-02/01/2021	Pfizer	SARS-CoV-2 infection (PCR positive) and symptomatic disease	14-20 days after 1st dose	22% (95% CI:–9-44) Symptomatic: 44% (95% CI: 19-64)
Older Adults (≥ 70 y) LTC residents were excluded	Dagan[3] (Israel) 12/20/2020-02/01/2021	Pfizer	SARS-CoV-2 infection (PCR positive) and symptomatic disease	21-27 days after 1st dose	50% (95% CI: 19-72) Symptomatic: 64% (95% CI: 37-83)
Older Adults (≥ 70 y, N=28,318) LTC residents were excluded	Dagan[3] (Israel) 12/20/2020-02/14/2021	Pfizer	SARS-CoV-2 infection (PCR positive) and symptomatic disease	7-28 days after 2nd dose	91% (95% CI: 86-95) Symptomatic: 92% (95% CI: 83-97)
Older Adults (≥ 70 y, N= 7.5 million) LTC residents were included	Lopez Bernal[21] (England) 12/08/2020-02/19/2021	Pfizer	Symptomatic disease (PCR positive)	28-35 days after 1st dose	Symptomatic: 61-70%
Older Adults (≥ 70 y, N= 7.5 million) LTC residents were included	Lopez Bernal[21] (England) 12/08/2020-02/19/2021	Pfizer	Symptomatic disease (PCR positive)	14 days after 2nd dose	Symptomatic: 89%
Older Adults (≥ 70 y, N= 7.5 million) LTC residents were included	Lopez Bernal [21](England) 12/08/2020-02/19/2021	AstraZeneca	Symptomatic disease (PCR positive)	28-35 days after 1st dose	Symptomatic: 60-73%
Older Adults (≥ 70 y, community dwelling, N = 28,448)	Chung[9] (Canada) 12/14/2020-04/19/2021	Pfizer, Moderna	SARS-CoV-2 infection (PCR confirmed) and symptomatic	≥ 14 days after 1st dose	Symptomatic: 40%
Older Adults (≥ 70 y, community dwelling, N = 28,488)	Chung[9] (Canada) 12/14/2020-04/19/2021	Pfizer, Moderna	SARS-CoV-2 infection (PCR confirmed) and symptomatic	≥ 7 days after 2nd dose	Symptomatic: 94%
Older Adults (≥ 70 y, community dwelling, N = 16,993)	Skowronski[20] (Canada) 04/04/2021-	Pfizer, Moderna	SARS-CoV-2 infection (PCR confirmed)	≥ 21 days after 1st dose	Overall: 65% (95% CI: 58-71) Non-VOC: 72% (95% CI: 58-81) Alpha: 67% (95% CI: 57-75)

Population	Study (Country) Study Period	Vaccine	Study Outcomes	Timeframe	VE for Prevention of SARS-CoV-2 infection
	05/01/2021				Gamma: 61% (95% CI: 45-72)
Immunosuppressed patients (N=38,482)	Chodick[6] (Israel) 12/19/2020-01/17/2021	Pfizer	SARS-CoV-2 infection (PCR confirmed)	13-24 days after 1st dose	45% (95% CI: 2-69) Symptomatic: 50% (95% CI: 9-72)
Immunosuppressed patients (N=27,822)	Chodick[6](Israel) 12/19/2020-03/03/2021	Pfizer	SARS-CoV-2 infection (PCR confirmed)	7-27 days after 2nd dose	71% (95% CI 37-87) Symptomatic: 75% (95% CI: 44-88)
Immunodeficient patients (N=1,674) Includes solid organ transplant	Dagan[3] (Israel) 12/20/2020-02/14/2021	Pfizer	SARS-CoV-2 infection (PCR positive) and symptomatic disease	7-28 days after 2nd dose	90% (95% CI: 49-100) Symptomatic: 84% (95% CI: 19-100)
Solid Organ Transplant Recipient (SOTR) (N=2,151)	Aslam[72] (US) 01/01/2021-06/02/2021	Pfizer (41%), Moderna (69%)	Symptomatic disease (PCR positive)	≥ 14 days after 2nd dose	Symptomatic: 80% compared with unvaccinated SOTR
Individuals with Inflammatory Bowel Disease (IBD) (N=14,697)	Khan[69] (US) 12/18/2020-04/20/2021	Pfizer (45%), Moderna (55%)	SARS-CoV-2 infection (PCR positive)	≥ 7 days after 2nd dose	80%
Pregnant Individuals (≥ 16 y) (N=10,861)	Balicer[74] (Israel) 12/20/2021-06/03/2021	Pfizer	SARS-CoV-2 infection (PCR positive) and symptomatic disease	14-20 days after 1st dose	67% (95% CI: 40-84) Symptomatic: 66% (95% CI: 32-86)
Pregnant Individuals (≥ 16 y) (N=10,861)	Balicer[74] (Israel) 12/20/2021-06/03/2021	Pfizer	SARS-CoV-2 infection (PCR positive) and symptomatic disease	21-27 days after 1st dose	71% (95% CI: 33-94) Symptomatic: 76% (95% CI: 30-100)
Pregnant Individuals (≥ 16 y) (N=10,861)	Balicer[74] (Israel) 12/20/2021-06/03/2021	Pfizer	SARS-CoV-2 infection (PCR positive) and symptomatic disease	7-56 days after 2nd dose	96% (86-100) Symptomatic: 96% (95% CI: 89-100)
Pregnant Individuals (N=2,020)	Butt[73] (Qatar) 12/20/2021-06/30/2021	Pfizer, Moderna	SARS-CoV-2 infection (PCR positive)	≥ 14 days after 1st dose	40% (95% CI: 0-80)
Pregnant Individuals (N=2,020)	Butt[73] (Qatar) 12/20/2021-06/30/2021	Pfizer, Moderna	SARS-CoV-2 infection (PCR positive)	≥ 14 days after 2nd dose	68% (95% CI: 31-87)

Population	Study (Country) Study Period	Vaccine	Study Outcomes	Timeframe	VE for Prevention of SARS-CoV-2 infection
LTC Residents (> 65 y)	BCCDC[23] (Canada) 12/2020-02/2021	mRNA vaccine (not specified)	SARS-CoV-2 infection	≥ 14 days after 1st dose	> 80%
CHSLD Residents (N=33,331) 78% vaccinated with single dose	INSPQ[24] (Canada) 12/14/2020-02/10/2021	Pfizer (75%), Moderna	SARS-CoV-2 infection	10-13 days after first dose	15%
CHSLD Residents (N=33,331) 78% vaccinated with single dose	INSPQ[24] (Canada) 12/14/2020-02/10/2021	Pfizer (75%), Moderna	SARS-CoV-2 infection	14-20 days after 1st dose	49%
CHSLD Residents (N=33,331) 78% vaccinated with single dose	INSPQ[24] (Canada) 12/14/2020-02/10/2021	Pfizer (75%), Moderna	SARS-CoV-2 infection	21-27 days after 1st dose	80%
LTC Residents (N=69,799) 92% received 1st dose, 67% received 2 doses	Brown[25] (Canada) 12/14/2020-02/23/2021	Pfizer, Moderna	SARS-CoV-2 infection	8 weeks after start of vaccination program	89% (95% CI: 85-93)
LTC Residents	Moustsen-Helms[28] (Denmark) 12/27/2020-02/18/2021	Pfizer	SARS-CoV-2 infection (PCR positive)	> 14 days after first dose to before 2nd dose	No significant VE
LTC Residents	Moustsen-Helms[28] (Denmark) 12/27/2020-02/18/2021	Pfizer	SARS-CoV-2 infection (PCR positive)	0-7 days after 2nd dose	52% (95% CI: 27-69)
LTC Residents	Moustsen-Helms[28] (Denmark) 12/27/2020-02/18/2021	Pfizer	SARS-CoV-2 infection (PCR positive)	> 7 days after 2nd dose	64% (95% CI: 14-84)

Population	Study (Country) Study Period	Vaccine	Study Outcomes	Timeframe	VE for Prevention of SARS-CoV-2 infection
LTC Residents (N=28,594)	Cabezas[26] (Spain) 12/27/2020-03/05/2021	Pfizer	SARS-CoV-2 infection (PCR confirmed or lateral flow test)	Follow-up from date of second dose up to 2 months	92% (95% CI: 91-93)
LTC Residents (N = 299,209)	Monge[27] (Spain) 12/27/2020-03/10/2021	Pfizer	SARS-CoV-2 infection (PCR or antigen test positive)	22-28 days after 1st dose	No prior infection: 63% (95% CI: 62-64) Prior infection: 35% (95% CI: 25-44)
LTC Residents (N = 299,209)	Monge[27] (Spain) 12/27/2020-03/10/2021	Pfizer	SARS-CoV-2 infection (PCR or antigen test positive)	≥ 7 days after 2nd dose	No prior infection: 82% (95% CI: 81-83) Prior infection: 57% (95% CI: 47-68)
LTC Residents (N=10,412)	Shrotri[29] (UK) 12/08/2020-03/15/2021	Pfizer (33%), AstraZeneca (67%)	SARS-CoV-2 infection (PCR confirmed)	28-34 days after 1st dose	56% (95% CI 19-76) Similar effect sizes seen for Pfizer and AstraZeneca vaccines Significantly higher PCR cycle (Ct) values in infections occurring at ≥ 28 days post vaccination compared to unvaccinated period. Rapid emergence of B.1.1.7 during study
LTC Residents (N=10,412)	Shrotri[29] (UK) 12/08/2020-03/15/2021	Pfizer (33%), AstraZeneca (67%)	SARS-CoV-2 infection (PCR confirmed)	35-48 days after 1st dose	62% (95% CI 23-81) Similar effect sizes seen for Pfizer and AstraZeneca vaccines Significantly higher PCR cycle (Ct) values in infections occurring at ≥ 28 days post vaccination compared to unvaccinated period. Rapid emergence of B.1.1.7 during study

Population	Study (Country) Study Period	Vaccine	Study Outcomes	Timeframe	VE for Prevention of SARS-CoV-2 infection
HCW (hospital, N=9109) 79% received 1st dose, 66% received 2 doses (21-22 days after 1st dose)	Amit[35] (Israel) 12/19/2020-01/25/2021	Pfizer	SARS-CoV-2 infection (exposed and symptomatic, PCR positive) and symptomatic disease adjusted for community exposure	1-14 days after 1st dose	30% (95% CI:2-50) Symptomatic: 47% (95% CI: 12-64)
HCW (hospital, N=9109) 79% received 1st dose, 66% received 2 doses (21-22 days after 1st dose)	Amit[35] (Israel) 12/19/2020-01/25/2021	Pfizer	SARS-CoV-2 infection (exposed and symptomatic, PCR positive) and symptomatic disease adjusted for community exposure	15-28 days after 1st dose	75% (95% CI: 72-84) Symptomatic: 85% (95% CI: 71-92)
HCW	BCCDC[23] (Canada) 12/2020-02/2021	Pfizer, Moderna	SARS-CoV-2 infection	≥ 14 days after 1st dose	> 80%
HCW (N=325,000) (53% vaccinated with single dose)	INSPQ[24] (Canada) 12/14/2020-02/10/2021	Pfizer (75%), Moderna	SARS-CoV-2 infection	About 8 weeks after start of vaccination program	80%
HCW (N=325,000) (53% vaccinated with single dose)	INSPQ[24] (Canada) 12/14/2020-02/10/2021	Pfizer (75%), Moderna	SARS-CoV-2 infection	10-13 days after 1st dose	38%
HCW (N=325,000) (53% vaccinated with single dose)	INSPQ[24] (Canada) 12/14/2020-02/10/2021	Pfizer (75%), Moderna	SARS-CoV-2 infection	14 to 27 days after 1st dose	74-79%
HCW (N=325,000) (53% vaccinated with single dose)	INSPQ[24] (Canada) 12/14/2020-02/10/2021	Pfizer (75%), Moderna	SARS-CoV-2 infection	≥ 28 days after 1st dose	80%
HCW (LTC, N = 100,000) 55% received 1st dose, 45% received 2 doses	Brown[25] (Canada) 12/14/2020-02/23/2021	Pfizer, Moderna	SARS-CoV-2 infection	8 weeks after start of vaccination program	79% (95% CI: 71-85)

Population	Study (Country) Study Period	Vaccine	Study Outcomes	Timeframe	VE for Prevention of SARS-CoV-2 infection
HCW (hospital)	Dunbar[33] (US) 11/14/2020-01/19/2021	Pfizer, Moderna	SARS-CoV-2 infection (symptomatic, PCR positive)	14-28 days after 1st dose	Symptomatic: 74.6%
HCW (hospital)	Dunbar[33] (US) 11/14/2020-01/19/2021	Pfizer, Moderna	SARS-CoV-2 infection (symptomatic, PCR positive)	> 28 days after 1st dose	Symptomatic: ~100%
HCW (hospital, N= 23,324) 89% received 1st dose; 8% received 2 doses	Hall[32] (England) 12/07/2020-02/05/2021	Pfizer	SARS-CoV-2 infection (PCR positive) in antibody-negative cohort	21 days after 1st dose	72% (95% CI: 58-86)
HCW (hospital, N= 23,324) 89% received 1st dose; 8% received 2 doses	Hall[32] (England) 12/07/2020-02/05/2021	Pfizer	SARS-CoV-2 infection (PCR positive) in antibody-negative cohort	7 days after 2nd dose	86% (95% CI: 76-97)
HCW (hospital, N = 2,235)	Azamgarhi[34] (England) 01/15/2021-02/26/2021	Pfizer	SARS-CoV-2 Infection (PCR positive)	≥ 14 days after 1st dose	70% (95% CI: 6-91)
HCW	Moustsen-Helms[28] (Denmark) 12/27/2020-02/18/2021	Pfizer	SARS-CoV-2 infection (PCR positive)	> 14 days after first dose, before 2nd dose	17% (95% CI: 4-28)
HCW	Moustsen-Helms[28] (Denmark) 12/27/2020-02/18/2021	Pfizer	SARS-CoV-2 infection (PCR positive)	0-7 days after 2nd dose	46% (95% CI: 28-59)
HCW	Moustsen-Helms[28] (Denmark) 12/27/2020-	Pfizer	SARS-CoV-2 infection (PCR positive)	> 7 days after 2nd dose	90% (95% CI: 82-95)

Population	Study (Country) Study Period	Vaccine	Study Outcomes	Timeframe	VE for Prevention of SARS-CoV-2 infection
	02/18/2021				
HCW (LTC, N=26,238)	Cabezas[26] (Spain) 12/27/2020-03/05/2021	Pfizer	SARS-CoV-2 infection (PCR confirmed or lateral flow test)	Date of second dose up to 2 months	88% (95% CI: 85-90)
HCW (N=61,951)	Cabezas[26] (Spain) 12/27/2020-03/05/2021	Pfizer	SARS-CoV-2 infection (PCR confirmed or lateral flow test)	Date of second dose up to 2 months	95% (95% CI: 93-96)
HCW (N=6,423)	Fabiani[38] (Italy) 12/27/2020-03/24/2021	Pfizer	SARS-CoV-2 infection (PCR confirmed)	14-21 days after 1st dose	84% (95% CI: 40-96) Symptomatic: 83% (95% CI: 15-97)
HCW (N=6,423)	Fabiani[38] (Italy) 12/27/2020-03/24/2021	Pfizer	SARS-CoV-2 infection (PCR confirmed)	≥ 7 days after 2nd dose	95% (95% CI: 62-99) Symptomatic: 94% (95% CI: 51-99)
HCW (N=41,171 received 2 doses N=2,757 received 1 dose)	Swift[36] (US) 01/01/2021-03/31/2021	Pfizer	SARS-CoV-2 infection (PCR positive)	≥ 14 days after 1st dose, ≤ 14 days after 2nd dose	78% (95% CI: 71-82)
HCW (N=41,171 received 2 doses N=2,757 received 1 dose)	Swift[36] (US) 01/01/2021-03/31/2021	Pfizer	SARS-CoV-2 infection (PCR positive)	> 14 days after 2nd dose	97% (95% CI: 95-98)
HCW (N=3,421 received 2 doses N=1,301 received 1 dose)	Swift[36] (US) 01/01/2021-03/31/2021	Moderna	SARS-CoV-2 infection (PCR positive)	≥ 14 days after 1st dose, ≤ 14 days after 2nd dose	91% (95% CI: 81-96)
HCW (N=3,421 received 2 doses N=1,301 received 1 dose)	Swift[36] (US) 01/01/2021-03/31/2021	Moderna	SARS-CoV-2 infection (PCR positive)	> 14 days after 2nd dose	99% (95% CI: 90-100)
HCW (N=623 positive cases compared to 1,220 controls)	Pilishvili[37] (US) 01/01/2021-03/31/2021	Pfizer (76%), Moderna (24%)	SARS-CoV-2 infection (PCR or antigen test positive)	≥ 14 days after 1st dose, < 6 days after second dose	82% (95% CI: 74-87)
HCW (N=623 positive cases compared to 1,220 controls)	Pilishvili[37] (US) 01/01/2021-03/31/2021	Pfizer (76%), Moderna (24%)	SARS-CoV-2 infection (PCR or antigen test positive)	≥ 7 days after 2nd dose	94% (95% CI: 87-97)

Population	Study (Country) Study Period	Vaccine	Study Outcomes	Timeframe	VE for Prevention of SARS-CoV-2 infection
HCW, first responders, frontline and essential workers (N=3,975)	Thompson[41] (US) 12/14/2020-04/10/2021	Pfizer (63%), Moderna (30%), not reported (8%)	SARS-CoV-2 infection (PCR confirmed)	≥ 14 days after 1st dose but before 2nd dose	81% (95% CI: 64-90)
HCW, first responders, frontline and essential workers (N=3,975)	Thompson[41] (US) 12/14/2020-04/10/2021	Pfizer (63%), Moderna (30%), not reported (8%)	SARS-CoV-2 infection (PCR confirmed)	≥ 14 days after 2nd dose	91% (95% CI: 76-97)
HCW (N=6,710)	Angel[39] (Israel) 12/20/2020-02/25/2021	Pfizer	SARS-CoV-2 infection (PCR confirmed)	7-28 days after 1st dose	Symptomatic: 89% (95% CI: 83-94)
HCW (N=6,710)	Angel[39] (Israel) 12/20/2020-02/25/2021	Pfizer	SARS-CoV-2 infection (PCR confirmed)	> 7 days after 2nd dose	Symptomatic: 97% (95% CI: 94-99) Asymptomatic: 86% (95% CI 69-93)
HCW (N=6,710)	Angel[39] (Israel) 12/20/2020-02/25/2021	Pfizer	SARS-CoV-2 infection (PCR confirmed)	> 21 days after 2nd dose	Symptomatic: 98% (95% CI 94-100) Asymptomatic: 94% (95% CI: 78-98)
HCW (hospital, N = 5,217)	Tang[40] (US) 12/17/2020-03/20/2021	Pfizer	SARS-CoV-2 infection (PCR confirmed)	≥ 12 days after 1st, before 2nd dose	58% (95% CI: 30-74) Asymptomatic: 42% (95% CI -13 - 70)
HCW (hospital, N = 5,217)	Tang[40] (US) 12/17/2020-03/20/2021	Pfizer	SARS-CoV-2 infection (PCR confirmed)	≥ 7 days after 2nd dose	96% (95% CI: 91-98) Asymptomatic: 90% (95% CI 78-96)
HCW (N=13,109)	Lumley[78] (UK) 04/23/2020-02/28/2021	Pfizer (n=8285), AstraZeneca (n=2738)	SARS-CoV-2 infection (PCR confirmed)	> 14 days after 1st dose	64% (95% CI: 50-74) Symptomatic: 67% (95% CI: 48-79)
HCW (N=13,109)	Lumley[78] (UK) 04/23/2020-02/28/2021	Pfizer (n=1407), AstraZeneca (n=49)	SARS-CoV-2 infection (PCR confirmed)	> 14 days after 2nd dose	90% (95% CI: 72-98) Symptomatic: no cases

Population	Study (Country) Study Period	Vaccine	Study Outcomes	Timeframe	VE for Prevention of SARS-CoV-2 infection
HCW (front-line hospital, N=2,462)	Knobel[44] (Spain) 12/01/2020-04/20/2021	Pfizer (74%), Moderna (26%)	SARS-CoV-2 infection (PCR confirmed)	> 7 days after 2nd dose	Asymptomatic: 91%

HCW: healthcare workers, CHSLDs (centres d'hébergement de soins et de longue durée -residential and long-term care centres in Quebec), LTC: long-term care, Pfizer: Pfizer-BioNTech BNT162b2, Moderna: Moderna mRNA-1273, AstraZeneca: Oxford/ AstraZeneca AZD1222/ChAdOx1-S, Janssen: J&J/AD26.COV2.S, PCR: polymerase chain reaction; CI: confidence interval, SARS-CoV-2 infection refers to both asymptomatic and symptomatic disease unless otherwise specified; PCR positive shown only if specifically indicated in study criteria

Table 2: Vaccine Effectiveness (VE) for Prevention of Severe Disease, Hospitalization and Death due to COVID-19

Population	Study (Country) Study Period	Vaccine	Study Outcomes	Timeframe	VE for Prevention of Severe Disease, Hospitalization & Death
General Population (< 60 y) (N=2,992,441)	Aran[22] (Israel) 12/20/2020-01/23/2021	Pfizer	Severe disease and COVID-19 hospitalization (as per Israeli Ministry of Health)	≥ 14 days after 2nd dose	Severe disease: 94% Hospitalization: 93%
General Population (≥ 16 y, no upper age limit, N= 693,814) Median age = 45 (IQR: 35-62)	Dagan[3] (Israel) 12/20/2020-02/14/2021	Pfizer	COVID-19–related hospitalization, severe illness (as per National Institutes of Health criteria), death	14-20 days after 1st dose	Severe disease: 65% (95% CI: 45–80) Hospitalization: 70% (95% CI: 52–82) Death: 72% (95% CI: 19–100)
General Population (≥ 16 y, no upper age limit, N= 480,438) Median age = 45 (IQR: 35-62)	Dagan[3] (Israel) 12/20/2020-02/14/2021	Pfizer	COVID-19–related hospitalization, severe illness (as per National Institutes of Health criteria), death	21-27 days after 1st dose	Severe disease: 77% (95% CI: 56-91) Hospitalization: 78% (95% CI: 61–90) Death: 84% (95% CI: 44–100)
General Population (≥ 16 y, no upper age limit, N= 310,696) Median age = 45 (IQR: 35-62)	Dagan[3] (Israel) 12/20/2020-02/14/2021	Pfizer	COVID-19–related hospitalization, severe illness (as per National Institutes of Health criteria)	7-28 days after 2nd dose	Severe disease: 95% (95% CI: 89-99) Hospitalization: 92% (95% CI: 85-97)
General Population (≥ 16 y, N=6,352,000)	Goldberg[15] (Israel) 03/01/2020-03/20/2021	Pfizer	COVID-19-related hospitalization, severe illness (as per international recommendations), death due to COVID-19	> 7 days after 2nd dose	Hospitalization : 94% (95% CI: 94-95) Severe Illness: 94% (95% CI: 94-95) Death: 94% (95% CI: 92-95) B.1.1.7 was most prevalent variant during study period.
General Population (≥ 16 y, N= 6,538,911)	Haas[14] (Israel)	Pfizer	COVID-19-related hospitalization, severe and critical hospitalization (as per international recommendations), death due to COVID-19	> 7 days after 2nd dose	Hospitalizaton: 97 (95% CI: 97-98) Severe or Critical Hosptialization: 98% (95% CI :97-98) Death: 97% (95% CI : 96-97)

Population	Study (Country) Study Period	Vaccine	Study Outcomes	Timeframe	VE for Prevention of Severe Disease, Hospitalization & Death
General Population (N=5.4 million) 35% received first dose of vaccine.	Vasileiou[62] (Scotland) 12/08/2020-02/22/2021	Pfizer	Hospitalization (COVID-19 as the main cause of admission, or within 28 days of a positive PCR)	28-34 days after 1st dose	Hospitalization: 91% (95% CI: 85-94)
General Population (N=5.4 million) 35% received first dose of vaccine.	Vasileiou[62] (Scotland) 12/08/2020-02/22/2021	AstraZeneca	Hospitalization (COVID-19 as the main cause of admission, or within 28 days of a positive PCR)	28-34 days after 1st dose	Hospitalization: 88% (95% CI: 75-94)
General Population (≥ 18 y, no upper age limit, N =136,532)	Pawlowski[13] (US) 12/01/2020-04/20/2021	Pfizer	COVID-19 associated hospitalization, COVID-19 associated ICU admission	≥ 7 days after 2nd dose	Hospitalization: 89% (95% CI: 76-96)% ICU admission: 100%
General Population (≥ 18 y, no upper age limit, N =136,532)	Pawlowski[13] (US) 12/01/2020-04/20/2021	Moderna	COVID-19 associated hospitalization, COVID-19 associated ICU admission	≥ 7 days after 2nd dose	Hospitalization: 86% (95% CI: 72-94) ICU admission: 100%
General Population (N=91,134)	Vahidy[63] (US) 12/15/2020-04/04/2021	Pfizer, Moderna	Covid-19 associated hospitalizations and deaths among these hospitalizations.	> 14 days after 1st dose	Hospitalization: 77% (95% CI: 71-82) Death: 64% (95% CI: 13-85)
General Population (N=91,134)	Vahidy[63] (US) 12/15/2020-04/04/2021	Pfizer, Moderna	Covid-19 associated hospitalizations and deaths among these hospitalizations.	> 7 days after 2nd dose	Hospitalization: 96% (95% CI: 95-99) Death: 99% (95% CI: 91-100)
General Population (≥ 16 y, community dwelling, N = 324,033) 6.6% received ≥ 1 dose	Chung[9] (Canada) 12/14/2020-04/19/2021	Pfizer, Moderna	Severe Outcomes (hospitalization or death associated with SARS-CoV-2 infection)	≥ 14 days after 1st dose	Severe Outcomes: 70% (95% CI: 60-77) B.1.1.7: 59% E484K+ (B.1.351/P.1): 56%
General Population (≥ 16 y, community	Chung[9] (Canada) 12/14/2020-04/19/2021	Pfizer, Moderna	Severe Outcomes (hospitalization or death associated with SARS-CoV-2 infection)	≥ 0 days after 2nd dose	Severe Outcomes: 98% (95% CI: 88-100) B.1.1.7: 94%

Population	Study (Country) Study Period	Vaccine	Study Outcomes	Timeframe	VE for Prevention of Severe Disease, Hospitalization & Death
dwelling, N = 324,033) 6.6% received ≥ 1 dose					E484K+ (B.1.351/P.1): 100%
General Population (N=213,749)	Abu-Raddad[81] (Qatar) 02/01/2021-03/31/2021	Pfizer	Combined outcome: severe, critical, or fatal COVID-19 disease (as per WHO criteria)	≥ 14 days after 2nd dose	B.1.1.7: 100% (95% CI: 82-100) B.1.351: 100% (95% CI: 74-100)
Older Adults (> 60 y) (N=1,303,244)	Aran[22] (Israel) 12/20/2020-01/23/2021	Pfizer	Severe disease and COVID-19 hospitalization (as per Israeli Ministry of Health)	0-13 days after 2nd dose	Severe disease: 81-83% Hospitalization: 79-81%
Older Adults (> 60 y) (N=1,303,244)	Aran[22] (Israel) 12/20/2020-01/23/2021	Pfizer	Severe disease and COVID-19 hospitalization (as per Israeli Ministry of Health)	≥ 14 days after 2nd dose	Severe disease: 98% Hospitalization: 97%
Older Adults (> 60 y)	Rossman[49] (Israel) 03/20/2020-02/24/2021	Pfizer	Time dependent changes in COVID-19 hospitalization (includes mild, moderate, severe or ventilated/critical illness) and severe hospitalization (includes severe and ventilated/critical illness) as per Israeli Ministry of Health	2 months after start of vaccination campaign (85% of individuals > 60 vaccinated with 2 doses)	Hospitalization: 68% decrease compared to peak period. Severe hospitalization: 67% decrease compared to peak period
Older Adults (≥ 70 y, N=28,318) LTC residents were excluded	Dagan[3] (Israel) 12/20/2020-02/14/2021	Pfizer	COVID-19–related hospitalization, severe illness (as per National Institutes of Health criteria)	7-28 days after 2nd dose	Severe Disease: 86% (95% CI: 63-97) Hospitalization: 81% (95% CI: 57-94)
Older Adults (≥ 70 y, community dwelling, N = 28,448)	Chung[9] (Canada) 12/14/2020-04/19/2021	Pfizer, Moderna	Severe Outcomes (hospitalization or death associated with SARS-CoV-2 infection	≥ 14 days after 1st dose	Severe outcomes: 67%
Older Adults (≥ 70 y, community dwelling, N = 28,488)	Chung[9] (Canada) 12/14/2020-04/19/2021	Pfizer, Moderna	Severe Outcomes (hospitalization or death associated with SARS-CoV-2 infection	≥ 0 days after 2nd dose	Severe Outcomes: 97%
Older Adults (≥ 70 y, N= 7.5 million)	Lopez Bernal[21] (England) 12/08/2020-02/19/2021	Pfizer	Hospitalization within 14 days of positive PCR, death within 21 days of positive PCR	Test date > 14 days after 1st dose	Hospitalization: 80% Death: 85%
Older Adults (≥ 70 y,	Lopez Bernal[21] (England)	AstraZeneca	Hospitalization within 14 days of positive PCR	Test date > 14 days after 1st dose	Hospitalization: 80%

Population	Study (Country) Study Period	Vaccine	Study Outcomes	Timeframe	VE for Prevention of Severe Disease, Hospitalization & Death
N= 7.5 million)	12/08/2020-02/19/2021				
Older Adults (≥ 70 y, N = 48,096)	Lopez Bernal[21] (England) 12/08/2020-04/06/2021	Pfizer	Death within 28 days of a positive PCR	≥ 21 days after first dose	Death: 44% (95% CI: 32-53)
Older Adults (≥ 70 y, N = 48,096)	Lopez Bernal[21] (England) 12/08/2020-04/06/2021	AstraZeneca	Death within 28 days of a positive PCR	≥ 21 days after first dose	Death: 55% (95% CI: 41-66)
Older Adults (≥ 70 y, N = 48,096)	Lopez Bernal[21] (England) 12/08/2020-04/06/2021	Pfizer	Death within 28 days of a positive PCR	≥ 7 days after second dose	Death: 69% (95% CI: 31-86)
Older Adults (≥ 80 y) LTC residents were included.	Vasileiou[62] (Scotland) 12/08/2020-02/22/2021	Pfizer	Hospitalization (COVID-19 as the main cause of admission, or within 28 days of a positive PCR)	28-34 days after 1st dose	Hospitalization: 88% (95% CI: 76-94)
Older Adults (≥ 80 y) LTC residents were included.	Vasileiou[62] (Scotland) 12/08/2020-02/22/2021	AstraZeneca	Hospitalization (COVID-19 as the main cause of admission, or within 28 days of a positive PCR)	28-34 days after 1st dose	Hospitalization: 81% (95% CI: 60-91)
Older Adults (≥ 80 y, hospitalized, N= 168)	Hyams [64] (England) 12/18/2020-02/26/2021	Pfizer (n=108)	Hospitalization (symptomatic respiratory disease, positive PCR on admission)	≥ 14 days after 1st dose	Hospitalization: 71% (95% CI: 47-91)
Older Adults (≥ 80 y, hospitalized, N= 168)	Hyams[64] (England) 12/18/2020-02/26/2021	AstraZeneca (n=60)	Hospitalization (symptomatic respiratory disease, PCR positive on admission)	≥ 14 days after 1st dose	Hospitalization: 80% (95% CI 36-95)
Older Adults (> 80 y, hospitalized, N= 13,907)	Ismail[65] (England) 12/08/2020-04/18/2021	Pfizer, AstraZeneca	Hospitalization (symptomatic respiratory disease, PCR positive)	≥ 28 days after 1st dose	80% (95% CI: 74-85)
Older Adults (> 80 y, hospitalized, N= 13,907)	Ismail[65] (England) 12/08/2020-04/18/2021	Pfizer, AstraZeneca	Hospitalization (symptomatic respiratory disease, PCR positive)	≥ 14 days after 2nd dose	92% (95% CI: 87-95)
Older Adults (> 80 y, hospitalized, N= 13,907)	Ismail[65] (England) 12/08/2020-04/18/2021	Pfizer	Hospitalization (symptomatic respiratory disease, PCR positive)	≥ 28 days after 1st dose	81% (95% CI: 76-85)
Older Adults (> 80 y, hospitalized, N= 13,907)	Ismail[65] (England) 12/08/2020-04/18/2021	Pfizer	Hospitalization (symptomatic respiratory disease, PCR positive)	> 7 days after 2nd dose	93% (95% CI: 89-95)

Population	Study (Country) Study Period	Vaccine	Study Outcomes	Timeframe	VE for Prevention of Severe Disease, Hospitalization & Death
Older Adults (> 80 y, hospitalized, N= 13,907)	Ismail[65] (England) 12/08/2020-04/18/2021	AstraZeneca	Hospitalization (symptomatic respiratory disease, PCR positive)	≥ 28 days after 1st dose	73% (95% CI: 60-81)
Immunodeficient patients (N=1,674) Includes solid organ transplant	Dagan[3] (Israel) 12/20/2020-02/14/2021	Pfizer	COVID-19–related hospitalization, severe illness (as per National Institutes of Health criteria)	7-28 days after 2nd dose	Severe Disease: 100% (1 event in unvaccinated, 0 in vaccinated) Hospitalization: 100% (2 events in unvaccinated, 1 in vaccinated)
Individuals with immunocompromising conditions (N=248)	Tenforde[96] (US) 03/11/2021-05/05/2021	Pfizer, Moderna	COVID-19-related hospitalization	≥ 14 days after 2nd dose	59% (95% CI: 12-81)
Pregnant Individuals (≥ 16 y) (N=10,861)	Balicer[74] (Israel) 12/20/2021-06/03/2021	Pfizer	COVID-19–related hospitalization	7-56 days after 2nd dose	Hospitalization: 89% (95% CI: 43-100)
CHSLD Residents at one site (age range not reported) (N=221) 82% vaccinated with single dose	INSPQ[24] (Canada) 12/14/2020-02/10/2021	Pfizer	Serious infection (not defined), death	≥ 14 days after 1st dose	Serious infection: 40% Death: 50%
LTC Residents (N=69,799) Mean = 85 y 92% received first dose, 67% received two doses	Brown[25] (Canada) 12/14/2020-02/23/2021	Pfizer, Moderna	Death	8 weeks after start of vaccination program	Death: 96% (95% CI 92-98)
LTC Residents (N=28,594)	Cabezas[26] (Spain) 12/27/2020-03/05/2021	Pfizer	COVID-19 hospital admission, COVID-19 cause of death	Date of second dose up to 2 months	Hospitalization: 97% (95% CI: 95-98) Death: 98% (95% CI: 97-99)

HCW: healthcare workers, CHSLDs (centres d'hébergement de soins et de longue durée -residential and long-term care centres in Quebec), LTC: long-term care, Pfizer: Pfizer/ BioNTech BNT162b2, Moderna: Moderna mRNA-1273, AstraZeneca: Oxford/ AstraZeneca AZD1222/ChAdOx1-S, PCR: polymerase chain reaction; CI: confidence interval; ICU: intensive care unit

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