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SYNTHESIS

COVID-19 Vaccine Effectiveness Over Time - What We Know So Far

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Introduction

Public Health Ontario (PHO) is actively monitoring, reviewing and assessing relevant information related to Coronavirus Disease 2019 (COVID-19) which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). "What We Know So Far" documents 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 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 pandemic 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

- Vaccine effectiveness (VE) against severe disease (i.e., hospitalization or death) is well maintained over time from the second dose of Pfizer-BioNTech, Moderna, or Astra-Zeneca/COVISHIELD, including among older adults and in settings where the Delta variant of concern (VOC) is the dominant circulating strain. Evidence indicates slight decreases in protection against hospitalization and death over time, but to a much smaller degree than the waning VE observed for infection.

- VE against any SARS-CoV-2 infection gradually decreases over time from the second dose of Pfizer-BioNTech, Moderna, or Astra-Zeneca/COVISHIELD. VE tends to be slightly lower for older adults compared to younger age groups, however decreases in VE over time appear to occur at similar rates across age groups. VE against infection with the Delta VOC may decline to a greater degree compared to other SARS-CoV-2 strains. The VE of Astra-Zeneca/COVISHIELD may also decline more than the VE of mRNA vaccines (i.e., Pfizer-BioNTech and Moderna). There is some evidence to suggest VE may be lower in those who received their vaccines doses within a shorter interval compared to extended intervals, however more evidence is needed to understand the impact of dose intervals on VE over time.

- Evidence related to waning VE over time is complicated by the concurrent emergence of the more transmissible and severe Delta VOC, relaxation of public health measures in many study jurisdictions and challenges associated with accounting for many factors influencing VE outcomes within and between studies. However, evidence is strengthened by relatively

consistent findings of durable VE against severe disease and waning VE against infection over follow up times up to seven months after second doses.

Background

As of October 24, 2021, 84.6% of Ontario's eligible population (ages ≥12) have been vaccinated with a complete primary series.[1] Ontario has achieved this considerable COVID-19 vaccine coverage among eligible populations following vaccine campaigns which began in late 2020 and continued through 2021. The first phase of vaccination in Ontario began in December 2020 and continued into early 2021, targeting high risk populations including frontline healthcare workers, seniors in congregate living settings, adults ages ≥80, adults in First Nations, Métis and Inuit populations, and chronic home care recipients.[2] The next phase included adults ages ≥55, select essential workers, those living in other congregate settings, COVID-19 hot spot communities and those with select health conditions, before expansion to the general population according to age.[2]

Those eligible for COVID-19 vaccination in Ontario are vaccinated with a complete primary series which involves two doses of Pfizer-BioNTech Comirnaty™ (referred to as Pfizer-BioNTech in this report), Moderna Spikevax™ (referred to as Moderna) or Astra-Zeneca Vaxzevria™/COVISHIELD (referred to as Astra-Zeneca/COVISHIELD). Due to changes in vaccine recommendations over time in response to vaccine safety or vaccine supply considerations, some Ontarians have received mixed product schedules, such as Astra-Zeneca/COVISHIELD followed by an mRNA product (i.e., Moderna or Pfizer-BioNTech), or a schedule consisting of two different mRNA products. Those vaccinated earliest in the campaign have now been vaccinated up to approximately nine months, and many received their vaccine doses using the manufacturer recommended interval (i.e., 21 days for Pfizer-BioNTech, 28 days for Moderna).[3] In early March in the context of disrupted vaccine supply, an updated recommendation by Canada's National Advisory Committee Immunization (NACI) extended the second dose interval to up to 16 weeks.[4] Finally, upon the return of adequate vaccine supply, Ontario began offering accelerated second doses using the manufacturer recommended intervals again in the summer of 2021.[5]

Vaccine effectiveness (VE) measures the proportionate reduction in cases of infection or severe disease among vaccinated persons compared to unvaccinated persons.[6] Real-world evidence of VE following a complete primary vaccine series indicates substantial protection against SARS-CoV-2 infection, and especially against severe COVID-19 disease and hospitalization.[6] However, there is emerging evidence of possible waning VE over time. The United States (US) Centers for Disease Control and Prevention (CDC) have presented data from the US where second doses were administered according to manufacturers' recommendations, suggesting that VE against infection may gradually decline over time, but VE against severe disease appears to be well maintained.[7-9] A recent NACI statement has noted waning VE may be a consideration particularly for older adults who may produce weaker immune responses than younger individuals due to immunosenescence.[3]

It is important to understand if and to what extent the protection against severe disease and infection, provided by vaccination changes over time. It is also important to understand the factors that may influence VE over time, such as age, interval between vaccine doses, vaccine product(s) received, comorbidities, immune-compromising conditions, and the impact of VOCs, such as the currently dominant strain in Ontario, Delta (B.1.617.2, first identified in India).[10] Several jurisdictions are exploring, planning or have launched campaigns to administer "booster" doses to those vaccinated earliest in the pandemic and are assumed to have responded adequately to their primary vaccine series.[11] Third doses as part of an extended primary vaccine series are differentiated from booster doses and are administered to specific populations with weakened immune systems who do not mount an adequate immune response to the two dose series. There remain many uncertainties and considerations related to booster dose programs, though Ontario's ethical framework for vaccine

distribution outlines key goals of the COVID-19 vaccine program overall.[11,12] The objectives of Ontario's vaccine program are first to prevent death, then to prevent illness, hospitalization, and intensive care unit (ICU) admission; and finally to reduce transmission of infection.[12]

This WWKSF document is a synthesis of available data related to VE against any SARS-CoV-2 infection, symptomatic disease and severe disease (i.e., hospitalization or death) over time.

Methods and Scope

To identify relevant published and pre-print evidence on this topic, systematic searches in Medline and Embase were conducted on September 20, 2021, and in National Institutes of Health (NIH) COVID-19 Portfolio on September 22, 2021 by Public Health Ontario (PHO) Library Services. Additionally, relevant records identified by PHO subject matter experts up to October 15, 2021 were screened for inclusion in this synthesis. It is recognized that there may be additional information not captured in this document. Relevant results were reviewed and data extracted for synthesis.

This synthesis included English language peer-reviewed and non-peer-reviewed records published after January 1, 2021. Study populations must have included fully vaccinated individuals (i.e., received a complete primary series), with no restriction on vaccine dose intervals used in the study population. The term vaccination throughout this report is in reference to a complete primary vaccine series with two doses. Included vaccine products are those authorized by Health Canada and have been used in vaccine campaigns in Canada: Pfizer-BioNTech, Moderna and Astra-Zeneca/COVISHIELD. Studies needed to provide evidence related to VE against severe disease (i.e., hospitalization or death) or infection (i.e., any SARS-CoV-2 infection regardless of symptoms) over time since the second vaccine dose, with data available for a minimum follow up time of three months. Finally, this synthesis included real-world VE outcomes, real-world evidence related to changing protection over time not measured by VE (e.g., odds of infection), and vaccine efficacy outcomes in the context of clinical trials.

This synthesis excluded studies related to several specific immune compromised populations: transplant recipients (including solid organ and hematopoietic stem cell transplants), patients with hematological cancers (e.g., lymphoma, myeloma, leukemia) on active treatment (e.g., chemotherapy, targeted therapies, immunotherapy), and recipients of an anti-CD20 agent (e.g. rituximab, ocrelizumab, ofatumumab). Studies investigating waning immunity assessed only through immunogenicity outcomes (e.g., antibody levels) after vaccination were also excluded.

Findings

Database searches by PHO Library Services returned a total of 2,195 published and pre-print records. In addition, PHO subject matter experts provided relevant literature not captured in the search. After screening for eligibility, a total of 24 records relevant to VE assessed by time since vaccination were included in this synthesis.

Results are organized first by outcome, with VE against severe disease followed by VE against infection. Within each outcome, studies are categorized by their sample population, with studies providing evidence related to older adults presented first, followed by studies without age-based results.

VE Against Severe COVID-19 Disease

OLDER ADULTS

We included eight studies with evidence related to VE against severe disease over time with age-stratified results that included older adults ages $\geq$55.[13-20] Seven studies provide real-world evidence

related to VE over time[13-15,17-20] and one study provides relevant efficacy data from a clinical vaccine trial.[16] Studies were conducted in the UK,[13] US,[14-16] Israel,[17] Qatar,[18] Netherlands,[19] and Portugal.[20] All studies were conducted over time periods when Delta became the dominant strain. Severe disease was defined in studies as: COVID-19 clinical presentation requiring hospitalization, requiring ICU admission, and/or death.

VE against severe disease was largely found to be sustained at high levels over time. Evidence indicates slight decreases in VE over time, initial VE is lower in older adults compared to younger ages, but slight deceases in VE occur at a similar rate across age groups. In most studies changes in VE over time were not statistically significant. Details of all studies assessing this outcome are described below.

REAL-WORLD VE EVIDENCE

- Andrews et al. (2021) (preprint) conducted a test-negative study conducted in the UK with data from a total of 1,475,391 individuals ages ≥16 who reported COVID-19 symptoms and had PCR testing within 10 days of symptom onset between December 8, 2020 and September 3, 2021 (Delta dominant during second half of study period).[13] The authors considered severe disease as hospitalization within 14 days of PCR confirmation and death within 28 days of PCR confirmation. Dose intervals for vaccines in the UK were extended to 12 weeks in early January of 2021, and in June intervals were reduced to eight weeks. Individuals with prior SARS-CoV-2 infections were excluded. Overall, protection against hospitalization and death remained more stable over time for those vaccinated with Pfizer-BioNTech compared to Astra-Zeneca/COVISHIELD. VE estimates for older age groups were overall lower compared to younger age groups, but appear to decline over time at a similar rate.
    - Pfizer-BioNTech VE against Delta hospitalization (2-9 weeks versus 20+ weeks):
        - Ages ≥16: 98.4% (95% CI: 97.9, 98.8) versus 92.7% (95% CI: 90.3, 94.6)
        - Ages ≥65**:** 97.9% (95% CI: 95.9, 99.0) versus 90.7% (95% CI: 86.0, 93.8).
    - Astra-Zeneca/COVISHIELD VE against Delta hospitalization (2-9 weeks versus 20+ weeks):
        - Ages ≥16: 95.2% (95% CI: 94.6, 95.6) versus 77.0% (95% CI: 70.3, 82.3)
        - Ages ≥65**:** 92.2% (95% CI: 89.4, 94.3) versus 76.3% (95% CI: 65.3, 83.8).
    - Pfizer-BioNTech VE against Delta death (2-9 weeks versus 20+ weeks):
        - Ages ≥16: 98.2% (95% CI: 95.9, 99.2) versus 90.4% (95% CI: 85.1, 93.8)
        - Ages ≥65: 97.0% (95% CI: 91.2, 99.0) versus 91.0% (95% CI: 85.3, 94.5).
    - Astra-Zeneca/COVISHIELD VE against Delta death (2-9 weeks versus 20+ weeks):
        - Ages ≥16: 94.1% (95% CI: 91.8, 95.8) versus 78.7% (95% CI: 52.7, 90.4)
        - Ages ≥65**:** 92.8% (95% CI: 87.4, 95.9) versus 79.1% (95% CI: 51.6, 91.0).[13]
- Tartof et al. (2021) conducted a retrospective cohort study in the US with data from 3,436,957 individuals ages ≥12 who are members of a large integrated health system in Southern California.[14] Data were collected for individuals vaccinated with two doses of Pfizer-BioNTech (dose interval not reported). Severe disease was defined as a positive PCR test conducted 14

days prior to three days after the date of hospital admission.[14] Dose intervals were not reported. Overall, VE against hospitalization did not significantly wane over time.

- All ages ≥12: VE against hospitalization was 87% (95% CI: 82, 91) <1 month after second dose, and 88% (95% CI: 82, 92) ≥5 months after second dose.
- Ages ≥65: VE against hospitalization was 84% (95% CI: 74, 90) <1 month after second dose, and 83% (95% CI: 69, 90) ≥5 months after second dose.[14]

- Tenforde et al. (2021) conducted a case-control study in the US with 3,089 hospitalized adults ages ≥18 during the study period March 11 to July 14, 2021.[15] Alpha was the dominant strain in March to May, and Delta was the dominant strain from June to July. Participants were vaccinated with two doses of Pfizer-BioNTech or Moderna (dose intervals not reported). Hospitalized cases included those with COVID-19 like illness and a positive PCR or antigen test result. Controls had COVID-19 like illness and a negative PCR test result, or no COVID-19 symptoms and negative PCR test result. VE for hospitalization was not found to wane significantly over time:
  - VE 2-12 weeks after vaccination: 86% (95% CI: 82, 90)
  - VE 13-24 weeks after vaccination: 84% (95% CI: 77, 90).
  - There was no significant change in VE over time since vaccination for three sub-groups: ages ≥65, immunocompromised patients, or patients with multiple comorbidities ($p>0.05$ for all).[15]

- Goldberg et al. (2021) (preprint) conducted a retrospective cohort study in Israel with data from 4,785,245 vaccinated adults from the general population ages ≥16.[17] Participants were vaccinated with two doses of Pfizer-BioNTech, 21 days apart. Severe disease was defined as COVID-19 associated hospitalization, severe illness or death during the study period of July 11 to July 31, 2021 when Delta was the dominant strain. VE against severe disease is estimated for those vaccinated in March (approximately four months since second dose) versus January (approximately seven months since second dose):
  - Ages 16-39: Not reported
  - Ages 40-59: 98% (95% CI: 94, 99) versus 94% (95% CI: 87, 97)
  - Ages ≥60: 91% (95% CI: 85, 95) versus 86% (95% CI: 82, 90).[17]

- Chemaitelly et al. (2021) conducted a test-negative, case-control study in Qatar with national data from 907,763 individuals vaccinated with two doses of Pfizer-BioNTech 21 days apart, and with PCR test results recorded within the study period from December 21, 2020 to September 5, 2021.[18] This period included times when Alpha and Beta were dominant (January to June) and when Delta became dominant (June to September). The exact age range of all participants is not reported; ages are reported in 10 year ranges, anchored by <20 and ≥70 (median age: 31). Severe disease was defined as acute case hospitalization, ICU hospitalization or death. Of note, sample sizes for were smaller for longer follow up periods resulting in wide CIs. VE appears to persist for approximately six months. VE against severe disease over time since vaccination by age (<60 versus ≥60):
  - Month 1: 71.9% (95% CI: 62.3, 79.1) versus 44.4% (95% CI: 13.2, 64.4)
  - Month 3: 97.0% (95% CI: 90.6, 99.1) versus 90.4% (95% CI: 79.2, 95.6)

- Month 6: 93.3% (95% CI: 49.5, 99.1) versus 66.7% (-95% CI: 220.5, 96.5)
- Month 7+: 57.1% (95% CI: -65.7, 88.9) versus 50.0% (95% CI: -451.4, 95.5).[18]

- de Gier et al. (2021) (preprint) conducted a retrospective cohort study in the Netherlands with 15,571 individuals ages ≥15 hospitalized with COVID-19 during the study period April 4 to August 29, 2021.[19] The dominant strain during April to July was Alpha, and from July to August was Delta. At the time of hospitalization, 5.7% of all participants were vaccinated with Pfizer-BioNTech, Moderna, Astra-Zeneca/COVISHIELD or Johnson & Johnson. The median dose interval for Pfizer-BioNTech and Moderna is five weeks, and for Astra-Zeneca/COVISHIELD is 11 weeks. COVID-19 hospitalization and ICU admissions were defined by admission with a positive SARS-CoV-2 test (test not specified) or CT-confirmed COVID-19.
    - VE against hospitalization by time since vaccination (0-4 weeks versus 20+ weeks):
        - Ages 15-49: 99% (95% CI: 97, 99) versus 97% (95% CI: 87, 99)
        - Ages 50-69: 98% (95% CI: 97, 98) versus 98% (95% CI: 94, 99)
        - Ages ≥70: 90% (95% CI: 85, 93) versus 91% (95% CI: 87, 94).
    - VE against ICU admission by time since vaccination (0-4 weeks versus 20+ weeks):
        - Ages 15-49: 100% (0 cases) versus 100% (0 cases)
        - Ages 50-69: 99% (95% CI: 98, 99) versus 100% (0 cases)
        - Ages ≥70: 99% (95% CI: 93, 100) versus 90% (95% CI: 57, 98).[19]
- Nunes et al. (2021) (preprint) conducted a cohort study in Portugal with community dwelling adults ages ≥65 with data collected from the Ministry of Health database from February 2 to August 13, 2021.[20] The dominant strain shifted from Alpha to Delta in May of 2021. A total of 1,409,831 people ages 65 to 79, and 470,820 people ages ≥80 were enrolled. COVID-19 hospitalization was defined as admission for at least 24 hours with COVID-19 as the primary diagnosis and a positive PCR test. COVID-19 associated death was an all-cause death accompanied by a positive PCR result within the last 30 days. Vaccinated participants were recipients of Pfizer-BioNTech or Moderna (dose intervals not reported). VE by time since vaccination was analyzed for ages ≥80, and results suggest sustained protection against hospitalization and a slight non-significant decline in protection against death:
    - VE against hospitalization 14-41 days versus ≥98 days after vaccination:
      82% (95% CI: 64, 91) versus 89% (95% CI: 71, 96).
    - VE against death 14-41 days versus ≥98 days after vaccination:
      86% (95% CI: 68, 93) versus 74% (95% CI: 60, 83).[20]

CLINICAL TRIAL EVIDENCE

- Baden at al. (2021) (preprint) report on a Moderna vaccine trial conducted in the US with participants ages >18 and data collected during the study period July 1 to August 27, 2021 when Delta was dominant.16 A total of 14,746 participants were vaccinated early in the trial (July 27 to December 16, 2020), and 11,431 were vaccinated later (December 29, 2020 to April 30, 2021). Two doses were administered 28 days apart. Severe COVID-19 disease was defined as confirmed COVID-19 via PCR test and one or more of the following: clinical signs indicative of

severe systemic illness; evidence of shock; significant acute renal, hepatic or neurologic dysfunction; admission to ICU; or death. Incidence rates for severe COVID-19 cases during the study period are analyzed by age and by late versus early vaccination. There is a slight and statistically non-significant (very wide CIs which include zero) increase in severe disease incidence in the early compared to late vaccinated group:

- All ages: There were 13 severe cases (6.2/1000 person-years) in the early vaccinated group and 6 severe cases (3.3/1000 person-years) in the late vaccinated group, for a 46.0% (95% CI: -52.4, 83.2) reduction in severe COVID-19 disease incidence in the late compared to early vaccination group.

- Ages ≥65: There were 6 severe cases (11.0/1000 person-years) in the early vaccinated group and 2 severe cases (3.9/1000 person-years) in the late vaccinated group, for a 64.2% (95% CI: -100.2, 96.5) reduction in severe COVID-19 disease incidence in the late compared to early vaccination group.[16]

STUDIES WITHOUT AGE-BASED RESULTS

We included four studies with evidence related to VE against severe disease over time without results analyzed by age, and all four provide real-world VE evidence.[21-24] Studies were conducted in British Columbia,[24] Quebec,[23] and the US.[21,22] All studies were conducted over time periods when Delta became the dominant strain. Severe disease was defined in studies as: COVID-19 clinical presentation requiring hospitalization, and/or death.

Similar to the age-based results above, VE against COVID-19 hospitalization and death was found to be well maintained over time across included studies. Details of all studies assessing this outcome are described below.

- Skowronski et al. (2021) (grey literature) and the British Columbia Centre for Disease Control (BCCDC) report on a test-negative study conducted with 246,656 individuals ages ≥18 during the study period May 30 to September 11, 2021.[24] The Delta VOC became dominant during this period. Participants were vaccinated with two doses of Pfizer-BioNTech (67%), Moderna (16%), Astra-Zeneca/COVISHIELD (3%) or a mix of vaccine products (13%). Overall, VE against hospitalization was maintained at >90% from 2-7 weeks after vaccination through ≥4 months after vaccination (CIs not reported). While not analyzed by time since second dose, mixed schedules consisting of one dose of Astra-Zeneca/COVISHIELD followed by a dose of either Pfizer-BioNTech or Moderna vaccine provided slightly higher VE than two doses of Astra-Zeneca/COVISHIELD for protection against any hospitalization (99% versus 93%) and Delta hospitalization (99% versus 93%).[24]

- De Serres et al. (2021) (grey literature) and the Institut national de santé publique du Québec (INSPQ) provide a report on VE over time since vaccination among adults ≥18.[23] The study period was March 14 to September 11, 2021, during which time Delta became dominant. Participants were vaccinated with Pfizer-BioNTech, Moderna or Astra-Zeneca/COVISHIELD (dose intervals not reported). VE for hospitalization was stable over time: at one month after vaccination VE was 96%, and at ≥5 months after vaccination VE was 90% (CIs not reported).[23]

- Bajema et al. (2021) conducted a test-negative study in the US with 1,175 US veterans ages ≥18 (388 cases, 787 controls) who were vaccinated with two doses of Pfizer-BioNTech or Moderna (dose intervals not reported).[22] The study period was February 1 to August 6, 2021, during which time Delta became the dominant strain. Hospitalization was defined as COVID-19 like illness and positive test result (PCR or isothermal nucleic acid amplification test) within 14 days before admission or during the first 72 hours after admission. VE against hospitalization over time was

assessed, and no significant difference in VE was found for individuals vaccinated <90 days versus ≥90 days before hospitalization: 86.1% (95% CI: 76.5, 91.8) versus 87.2% (95% CI: 8, 92.5).[22]

- Self et al. (2021) conducted a case-control study in the US with 3,689 hospitalized adults ages ≥18.[21] Hospitalizations with COVID-19 like illness and a positive PCR or antigen test result were assessed during the study period March 11 to August 15, 2021 during which time Delta became the dominant strain. Vaccinated participants had received Pfizer-BioNTech (20.0%), Moderna (12.9%) or Johnson & Johnson (3.1%). Intervals between doses were 3 weeks for Pfizer-BioNTech and 4 weeks for Moderna. VE against hospitalization analyzed for Pfizer-BioNTech and Moderna are based on time since second dose (14-120 days versus ≥120 days):
    - Pfizer-BioNTech: 91% (95% CI: 88, 93) versus 77% (95% CI: 67, 84)
    - Moderna: 93% (95% CI: 90, 95) versus 92% (95% CI: 87, 96).
    - Study authors suggest higher mRNA content in the Moderna vaccine as a possible cause for the difference in VE results from Pfizer-BioNTech, and also note the difference in dose intervals or other differences between groups not accounted for in analysis could impact this outcome.[21]

VE Against SARS-CoV-2 Infection

OLDER ADULTS

We identified nine studies with evidence related to VE against infection over time with age-stratified results that included older adults ages ≥55.[13,14,16-18,25-28] Six studies provide real-world evidence related to VE over time,[13,14,17,18,25,26] two studies present outcomes related to potential changing vaccine protection over time but not measured by VE (e.g., odds ratios [ORs]),[27,28] and one study provides relevant evidence from a clinical vaccine trial.[16] Studies were conducted in the United Kingdom (UK),[13,25] US,[14,16,26] Israel[17,27,28] and Qatar,[18] and all studies were conducted during a time period when Delta became the dominant strain. Most investigated VE for any SARS-CoV-2 infection confirmed by polymerase chain reaction (PCR) test,[14,16-18,25-28] whereas one study specifically assessed VE for symptomatic SARS-CoV-2 infection.[13]

Overall, results consistently indicated that VE against infection gradually decreases over time. Most studies found initial VE to be lower for older age groups compared to younger age groups, but decreased over time at a similar rate. The degree to which VE decreased, and the measures by which changes in VE were reported varied between studies. These studies investigated factors such as age group, dose interval and infection with VOCs and their impact on VE. Details of each study assessing this outcome are described below.

REAL-WORLD VE EVIDENCE

- Pouwels et al. (2021) conducted a community-based survey of randomly selected households in the UK and collected data from 743,526 adults ages ≥18 who had COVID-19 PCR tests performed between December 1, 2020 and August 1, 2021.[25] Study participants had PCR tests performed on a pre-determined schedule (weekly for one month, then monthly) regardless of symptoms or prior infection. The Alpha VOC was dominant until May, at which point Delta became dominant. Vaccinated participants had received two doses of either Pfizer-BioNTech (median dose interval: 74 days) or Astra-Zeneca/COVISHIELD (median dose interval: 76 days). VE against infection was based on any new positive PCR test result. VE for Pfizer-BioNTech decreased over time more than Astra-Zeneca, however the initial Pfizer-BioNTech VE was much higher and remained

higher than Astra-Zeneca/COVISHIELD at 90 days after vaccination. VE results for all ages by days since second dose (30 days versus 90 days) are summarized as follows:

- Pfizer-BioNTech: 83% (95% CI: 78, 88) versus 75% (95% CI: 70, 80).
  Relative reduction in VE per month from second dose: 22% (95% CI: 6, 41).

- Astra-Zeneca/COVISHIELD: 66% (95% CI: 61, 71) versus 61% (95% CI: 53, 68).
  Relative reduction in VE per month from second dose: 7% (95% CI: -18, 2).[25]

- The reduction in VE was greater in ages 35-64 versus ages 18-34 for both vaccine products, but there was insufficient data to estimate VE in ages ≥65. There was no significant difference in overall VE when comparing dose intervals <6 weeks to ≥6 weeks for Pfizer-BioNTech.

- Andrews et al. (2021) (preprint) conducted a test-negative study in the UK, with data from a total of 1,475,391 individuals ages ≥16 who reported COVID-19 symptoms and had PCR testing within 10 days of symptom onset between December 8, 2020 and September 3, 2021 (Delta dominant during second half of study period).[13] Dose intervals for vaccines in the UK were extended to 12 weeks early January of 2021, and in June intervals were reduced to eight weeks. Individuals with prior SARS-CoV-2 infections were excluded. Age stratified VE for symptomatic Delta infection from time since vaccination (2-9 weeks versus 20+ weeks) was:

  - Pfizer-BioNTech:
    All ages ≥16: 89.8% (95% CI: 89.6, 90.0) versus 69.7% (95% CI: 68.7, 70.5).
    Ages ≥65: 80.1% (95% CI: 77.5, 82.4) versus 55.3% (95% CI: 50.2, 60.0).

  - Astra-Zeneca/COVISHIELD:
    All ages ≥16: 66.7% (95% CI: 66.3, 67.0) versus 47.3% (95% CI: 45.0, 49.6).
    Ages ≥65: 58.9% (95% CI: 54.8, 62.6) versus 36.6% (95% CI: 28.7, 43.7).

  - An analysis restricted to ages ≥80 who received Pfizer-BioNTech before January 4, 2021 found lower VE among those with a short (<4 weeks) versus extended (≥8 weeks) dose intervals at 20+ weeks since vaccination, however CIs were wide and overlapping.[13]

- Tartof et al. (2021) conducted a retrospective cohort study in the US with data from 3,436,957 individuals ages ≥12 who are members of a large integrated health system in Southern California.[14] Data were collected for individuals vaccinated with two doses of Pfizer-BioNTech (dose interval not reported) and who had a PCR test performed between December 14, 2020 and August 8, 2021 (Delta dominant during second half of study period). This study included PCR tests performed in any clinical setting regardless of symptoms.

  - All ages ≥12: VE against any infection decreased from 88% (95% CI: 86, 89) during the first month after vaccination to 47% (95% CI: 43, 51) after ≥5 months.

  - Ages ≥65: VE against any infection was overall lower in this age group than for younger ages, but declined at a similar rate. VE during the first month after vaccination was 80% (95% CI: 73, 85), and after ≥5 months was 43% (95% CI: 30, 54).

  - Analysis by VOC among all ages ≥12: Within one month of vaccination, VE against any Delta infection was 93% (95% CI: 85, 97) and at ≥ 4 months after vaccination VE against Delta was 53% (95% CI: 39%, 65%). Within one month versus ≥ 4 months after vaccination, VE against infection with other variants was 97% (95% CI: 95, 99) versus 67% (95% CI: 45, 80).[14]

- Bruxvoort et al. (2021) (preprint) conducted a test-negative case-control study in the US with a total of 8,153 cases and their matched controls with PCR tests conducted between March 1 and July 17, 2021.[26] This study included PCR tests performed at any clinical setting within a large integrated health network in Southern California, regardless of the presence or absence of symptoms. Participants were adults ages ≥18 who were vaccinated with two doses of the Moderna vaccine, administered ≥24 days apart. VE against any infection with the Delta VOC was assessed by time since vaccination, which found VE gradually declined over time:[26]

    - All ages ≥18:
      14-60 days since vaccination: 94.1% (95% CI: 90.5, 96.3)
      151-180 days since vaccination: 80.0% (95% CI: 70.2, 86.6).

    - Ages 18-64:
      14-60 days since vaccination: 95.1% (95% CI: 91.8, 97.1%)
      151-180 days since vaccination: 79.4% (95% CI: 68.8, 86.3).

    - Ages ≥65: Authors report wide CIs due to low sample size, making trends in VE less apparent.[26]

- Goldberg et al. (2021) (preprint) conducted a retrospective cohort study in Israel with national data from 4,785,245 vaccinated adults from the general population ages ≥16, collected between July 11 and July 31, 2021 when Delta was the dominant strain.[17] Data was collected for all positive SARS-CoV-2 results recorded in the Ministry of Health database during the study period, and for all participants vaccinated with two doses of Pfizer-BioNTech 21 days apart. VE against any SARS-CoV-2 infection is estimated for those vaccinated in May (approximately two months since second dose) versus January (approximately seven months since second dose):[17]

    - Ages 16-39: 73% (95% CI: 67, 78) versus 50% (95% CI: 45, 55)

    - Ages 40-59: 80% (95% CI: 71, 86) versus 58% (95% CI: 54, 62)

    - Ages ≥60: 75% (95% CI: 58, 85) versus 57% (95% CI: 52, 62).[17]

- Chemaitelly et al. (2021) conducted a test-negative, case-control study in Qatar with national data from 907,763 individuals vaccinated with two doses of Pfizer-BioNTech 21 days apart, and with PCR test results recorded within the study period from December 21, 2020 to September 5, 2021.[18] This period included times when Alpha and Beta were dominant (January to June) and when Delta became dominant (June to September). The exact age range of all participants is not reported; ages are reported in 10 year ranges, anchored by <20 and ≥70 (median age: 31). Results showed VE for any SARS-CoV-2 infection declined over time. Note, sample sizes were smaller in later follow up months, resulting in wider CIs.[18] VE against infection over month since vaccination by age group (<60 versus ≥60):

    - Month 1: 77.8% (95% CI: 76.7, 78.9) versus 71.1% (95% CI: 64.8, 76.3)

    - Month 3: 69.9% (95% CI: 66.8, 72.8) versus 67.4% (95% CI: 57.4, 75.1)

    - Month 6: 17.4% (95% CI: 1.9, 30.5) versus 15.4% (95% CI: -88.8, 62.1)

    - Month 7+: 24.5% (95% CI: -0.9, 43.5) versus 6.6% (95% CI: -93.4, 54.9).[18]

REAL-WORLD EVIDENCE NOT MEASURED BY VE

- Israel et al. (2021) (preprint) conducted a retrospective cohort study in Israel using data from 33,933 individuals ages ≥18 who were vaccinated with two doses of Pfizer-BioNTech 21 days apart.[27] Study participants had no prior SARS-CoV-2 infection and had a PCR test result recorded in a national health organization's database during the study period of May 15 to July 26, 2021 when Delta was the dominant strain. VE against any SARS-CoV-2 infection was analyzed by a cut-off time from vaccination of ≥146 days or <146 days since vaccination. Results showed the odds of a positive PCR test result (adjusted for sex, ethnicity and comorbidity factors) were greater ≥146 days since vaccination compared to <146 days since vaccination. Adjusted odds of infection after this cut-off time increased with age:
    - All ages ≥18: AOR=2.06 (95% CI: 1.69, 2.51)
    - Ages 18-39: AOR=1.67 (95% CI: 1.21, 2.29)
    - Ages 40-59: AOR=2.22 (95% CI: 1.62, 3.08)
    - Ages ≥60: AOR=2.76 (95% CI: 1.62, 3.08).[27]
- Mizrahi et al. (2021) (preprint) conduced a retrospective cohort study in Israel with data from 1,352,444 individuals ages ≥16 who received the second dose of the Pfizer-BioNTech vaccine between January and April of 2021.[28] The interval between vaccine doses was 21 to 28 days. Data related to SARS-CoV-2 infection (i.e., positive PCR test result) were collected in the study period June 1 to July 17, 2021, when Delta was the dominant strain. Time of vaccination was categorized as "early" for those vaccinated in January or February, and "late" for those vaccinated in March or April. Overall, those vaccinated early had greater odds of SARS-CoV-2 infection compared to those vaccinated late:
    - All ages ≥16: OR=1.53 (95% CI: 1.40, 1.68)
    - Ages 16-39: OR=1.53 (95% CI: 1.37, 1.71)
    - Ages 40-59: OR=1.49 (95% CI: 1.24, 1.79)
    - Ages ≥60: OR=1.54 (95% CI: 1.03, 2.32).[28]

CLINICAL TRIAL EVIDENCE

- Baden at al. (2021) (preprint) report on a Moderna vaccine trial conducted in the US with participants ages ≥18 and data collected from July 1 to August 27, 2021 when Delta was the dominant strain.[16] A total of 14,746 participants were vaccinated early in the trial (July 27 to December 16, 2020), and 11,431 were vaccinated later (December 29, 2020 to April 30, 2021). Two doses were administered 28 days apart. Incidence rates for SARS-CoV-2 infections confirmed by PCR test during the study period were analyzed by age and by late versus early vaccination. Results indicate a trend of decreasing protection over time, though CIs are wide especially for the analysis of ages ≥65:
    - All ages: There were 162 infections (77.1/1000 person-years) in the early vaccinated group and 88 infections (49.0/person-years) in the late vaccinated group, for a 36.4% (95% CI: 17.1, 51.5) reduction in SARS-CoV-2 incidence in the late compared to early vaccination group.

- Ages ≥65: There were 26 infections (47.8/1000 person-years) in the early vaccinated group and 20 infections (39.5/person-years) in the late vaccinated group, for a 17.4% (95% CI: -53.9, 56.3) reduction in SARS-CoV-2 incidence in the late compared to early vaccination group.[16]

STUDIES WITHOUT AGE-BASED RESULTS

We included 10 studies with evidence related to VE for SARS-CoV-2 infection over time without results analyzed by age.[23,24,29-36] Five studies provide real-world evidence related to VE over time,[23,24,30,31,33] three studies present outcomes related to changing protection over time but not measured by VE (e.g., ORs, attack rates [ARs]),[32,34,35] one study provides relevant evidence from a clinical vaccine trial[36] and one study specifically investigated VE against transmission of SARS-CoV-2 infection over time.[29] Studies were conducted in British Columbia,[24] Quebec,[23] UK,[29,30] US,[31-34] Israel,[35] and in multiple countries.[36] Most studies were conducted in time periods when the Delta VOC became dominant,[23,24,29-35] the international vaccine trial included evidence up to March 2021, before Delta became dominant.[36] Most studies investigated VE for any SARS-CoV-2 infection confirmed by PCR test regardless of symptoms,[23,24,29-31,34-36] two studies from the US specifically assessed VE for symptomatic infection.[32,33]

All studies reported some level of decrease in VE against any SARS-CoV-2 infection or symptomatic infection over time, though the degree of waning varied between studies. These studies investigated factors such as vaccine products and infection with VOCs and their impact on VE. Details of all studies assessing this outcome are provided below.

REAL-WORLD VE EVIDENCE

- Skowronski et al. (2021) (grey literature) and the BCCDC report on a test-negative study conducted with 246,656 individuals ages ≥18 during the study period of May 30 to September 11, 2021.[24] The Delta VOC became dominant during this period. Participants were vaccinated with two doses of Pfizer-BioNTech (67%), Moderna (16%), Astra-Zeneca/COVISHIELD (3%) or a mix of vaccine products (13%). Overall, VE against infection was >90% 2-7 weeks after vaccination, and VE was maintained in the range of 80-90% ≥4 months after vaccination (CIs not reported). While not analyzed by time since second dose, VE against infection was found to be higher among people who received their second dose at longer intervals (≥7 weeks) as compared to shorter intervals (3-6 weeks), among people who received the Pfizer-BioNTech vaccine. Finally, mixed schedules consisting of one dose of Astra-Zeneca/COVISHIELD followed by a dose of either Pfizer-BioNTech or Moderna vaccine provided higher VE than two doses of Astra-Zeneca/COVISHIELD for protection against any infection (91% versus 72%) and Delta infection (91% versus 70%).[24]

- De Serres et al. (2021) (grey literature) and the INSPQ report on VE over time among adults ≥18.[23] The study period was March 14 to September 11, 2021, during which time Delta became dominant. Participants were vaccinated with Pfizer-BioNTech, Moderna or Astra-Zeneca/COVISHIELD (dose intervals not reported). VE for any infection was stable over time: at one month after vaccination VE was 91%, and at ≥5 months after vaccination VE was 86% (CIs not reported).[23]

- The ZOE COVID Study (2021) (grey literature) is an ongoing observational study involving crowd-sourced data collection being conducted in the UK, with results reported online.[30] Approximately 1.2 million individuals (ages not reported) recorded COVID-19 vaccinations (dose intervals not reported) through the online study application between December 8, 2020 and July 31, 2021, and subsequently reported a positive COVID-19 test result. COVID-19 infections

recorded between May 26 and July 31, 2021, when the Delta VOC was dominant, were used to estimate VE over time.

  - VE for Pfizer-BioNTech one month after vaccination was 88%, and five to six months after vaccination was 74%.
  - VE for Astra-Zeneca/COVISHIELD one month after vaccination was 77%, and five to six months after vaccination was 67% (CIs not reported).[30]

- Fowlkes, et al. (2021) conducted a cohort study in the US with 3,483 vaccinated healthcare workers, first responders and essential frontline worker (ages not reported).[31] Participants were vaccinated with Pfizer-BioNTech, Moderna or Johnson & Johnson (dose intervals not reported). VE against SARS-CoV-2 infection is based on weekly PCR tests conducted regardless of symptoms during the study period of December 2020 to August 2021. Results showed a trend but no statistically significant change in VE against infection based on time since vaccination:
  - 14-119 days after vaccination: 85% (95% CI: 69, 93)
  - 120–149 days after vaccination: 81% (95% CI: 34-95)
  - ≥150 days after vaccination: 73% (95% CI: 49, 86).[31]
- Keehner et al. (2021) describe a cohort study conducted in the US. The study included health care workers with no previous SARS-CoV-2 infection who were vaccinated with Pfizer-BioNTech or Moderna (dose intervals not reported).[33] Authors collected data for symptomatic infections confirmed by PCR test results recorded during the study period March 1 to July 31, 2021, during which time Delta became the dominant strain.
  - Overall VE is estimated for each month within the study period: VE exceeded 90% from March through June but fell to 65.5% (95% CI: 48.9, 76.9) in July.
  - Authors note the change in VE may be attributed to a combination of the emergence of Delta, potential waning VE, and the end of masking requirements in California during the study period.[33]

REAL-WORLD EVIDENCE NOT MEASURED BY VE

- Puranik et al. (2021) (preprint) conducted a test-negative case-control study in the US with 652 cases ages ≥18 who had a positive symptomatic test after vaccination with Pfizer-BioNTech, and 5,946 controls with at least one negative symptomatic test after vaccination.[32] Participants received two vaccine doses 18 to 28 days apart. Test results were assessed during the study period February 1 to August 22, 2021, during which time Delta became the dominant strain. Odds (adjusted for sex, age, comorbidities, race and ethnicity) of symptomatic infection increased with increased days since vaccination (relative to date of vaccination, i.e., 0 days):
  - 30 days: AOR=1.81 (95% CI: 0.68, 4.82)
  - 60 days: AOR=2.32 (95% CI: 0.97, 5.52)
  - 90 days: AOR=3.5 (95% CI: 1.47, 8.35)
  - 120 days: AOR=3.21 (95% CI: 1.33, 7.74).[32]

- Hagan et al. (2021) conducted an outbreak investigation for a COVID-19 outbreak among 172 incarcerated individuals in a US federal prison population of 233 individuals.[34] The outbreak occurred in July to August of 2021, and genomic sequencing was conducted on specimens from 58 cases, all of which were identified as the Delta VOC. Of the population of 233, 185 were vaccinated with two doses of Pfizer-BioNTech (66%), Moderna (27%) or one dose of the Johnson & Johnson vaccine (7%). Dose intervals were not reported. Outbreak attack rates (AR) were estimated by time since vaccination and results showed attack rates were higher among those vaccinated ≥4 months before the outbreak (AR: 89%) compared to those vaccinated between 2 weeks and 2 months before the outbreak (AR: 61%; p<0.001).[34]

- Kertes et al. (2021) (preprint) conducted a retrospective cohort study in Israel with 1,423,098 individuals ages ≥16 who were eligible for vaccination with two doses of Pfizer-BioNTech administered 21 days apart, and had a PCR test conducted in the study period of June to July of 2021.[35] Delta was dominant during this study period. SARS-CoV-2 infection rates were compared by early or late vaccination. Individuals vaccinated early in January or February had greater odds of SARS-CoV-2 infection relative to those vaccinated in March to May, OR: 1.61 (95% CI: 1.45, 1.79).[35]

CLINICAL TRIAL EVIDENCE

- Thomas et al. (2021) conducted an international Pfizer-BioNTech vaccine randomized controlled trial with 42,094 individuals ages ≥12 from the US, Argentina, Brazil, South Africa, Germany and Turkey.[36] Individuals with a previous SARS-CoV-2 infection were excluded from analysis of VE over time, and all received two doses of Pfizer-BioNTech, approximately 21 days apart. Cases of SARS-CoV-2 infections were recorded during the study period October 15, 2020 to March 13, 2021. Vaccine efficacy against SARS-CoV-2 infection was assessed by time since vaccination, and was found to gradually decline:

    - 7 days to <2 months: 96.2% (95% CI: 93.3, 98.1)
    - 2 months to <4 months: 90.1% (95% CI: 86.6, 92.9)
    - ≥4 months: 83.7% (95% CI: 74.7, 89.9).[36]

EVIDENCE FOR VE AGAINST TRANSMISSION

- Eyre et al. (2021) (preprint) conducted a retrospective observational cohort study in the UK with 139,164 contacts of 95,716 COVID-19 index cases, all ages ≥18.[29] Contacts were considered those living in the same household or in close contact (within 1 metre for ≥1 minute or within 2m for ≥15 minutes) with confirmed COVID-19 index cases. Contacts who accessed PCR testing 1-10 days after the index case's PCR test, and within the study period from January 2 to August 2, 2021 (which includes Alpha and Delta dominant periods) were eligible for inclusion. Index cases and contacts who were vaccinated received two doses of Pfizer-BioNTech or Astra-Zeneca/COVISHIELD, most with a dose interval of >6 weeks (98% and 89% for Pfizer-BioNTech and Astra-Zeneca/COVISHIELD, respectively). Pfizer-BioNTech protection waned to a greater degree than Astra-Zeneca/COVISHIELD, but contacts vaccinated with Pfizer-BioNTech still had lower risk of testing positive than those vaccinated with Astra-Zeneca/COVISHIELD up to 14 weeks after vaccination. Vaccination of index cases reduced onward transmission to contacts, but reductions declined over time (2 weeks versus 12 weeks after vaccination):

    - Reduction in transmission of Alpha VOC:
      Pfizer-BioNTech: 68% (95% CI: 52, 79) versus 52% (95% CI: 29, 67)
      Astra-Zeneca/COVISHIELD: 52% (95% CI: 22, 70) versus 38% (95% CI: -1, 62).

- Reduction in transmission of Delta VOC:
  Pfizer-BioNTech: 50% (95% CI: 35, 61) versus 24% (95% CI: 20, 28)
  Astra-Zeneca/COVISHIELD: 24% (95% CI: 18, 30) versus 2% (95% CI: -2, 6).[29]

Discussion and Limitations

- Of the 24 studies included in this synthesis, 10 are pre-print studies and three are grey literature records, therefore are not peer-reviewed. In some cases studies do not report key pieces of information such as CIs or dose intervals.

- The time period of most included studies overlapped with the emergence of the Delta VOC, known to be more transmissible and associated with more severe disease outcomes.[11] Delineating the impact of changes in VE over time from the impact of the Delta VOC becoming the dominant strain is challenging in real-world studies. However, despite these challenges in interpretation of waning of VE against infection, it is important to note that VE against severe disease has remained relatively stable over time across studies conducted during periods when the Delta VOC became dominant. A further consideration for interpretation of the VE estimates summarized in this synthesis, is the lifting of many public health measures in most jurisdictions and the associated changes in the general public's behaviour during study periods, and consequently, the impact on rates of infection on VE estimates.

- Additional confounding factors are challenging to fully account for within and between heterogeneous studies. These factors may include: study design and population, reporting of time interval between doses, vaccine products administered, timing of vaccine campaigns across different jurisdictions where studies were conducted, type of outcomes assessed and reported outcome measures (e.g., VE versus OR). Further, the characteristics of individuals for whom the longest follow-up time is available is an important consideration. As individuals most at risk of exposure or severe outcomes may have been prioritized earlier in the campaign, the generalizability of the long-term VE data to the general population is not yet well understood.

- Investigation of booster doses is out of scope for this product, as the landscape of scientific literature and jurisdictional approaches to third dosing is currently very rapidly evolving and will require careful consideration. The European Centre for Disease Prevention and Control has produced interim considerations for additional COVID-19 vaccine doses.[11] Considerations include: maintaining priority on ensuring all eligible individuals receive the primary vaccine series; clearly differentiating policies for booster doses versus third doses in a primary vaccine series for immune-compromised individuals; considering implications of waning VE against infection versus severe disease; ensuring decisions are evidence-based and knowledge gaps related to waning VE are addressed; and considering vaccine equity on a global scale and the consequences associated with initiating booster doses in select jurisdictions.[11]

Conclusions

Currently available evidence related to VE over time is fairly consistent for several outcomes. VE against severe disease is stable and maintains high levels of protection, including for older adults and in settings where Delta is the dominant strain. This is an important finding, as Ontario's original vaccine program goals emphasize the importance of the prevention of COVID-19 associated deaths and hospitalizations. VE against any SARS-CoV-2 infection appears to be less durable and may gradually decrease over time. Measures of VE before any changes over time show that certain populations may be subject to lower initial VE, including older adults, those who received their doses in the manufacturer recommended (i.e., shorter) time interval, those exposed to the Delta VOC, and those vaccinated with Astra-

Zeneca/COVISHIELD. Some evidence indicates greater waning of VE against the Delta VOC compared to other strains, and greater waning of VE among those vaccinated with Astra-Zeneca/COVIDSHIELD compared to those vaccinated with mRNA products. Of note, analysis by age groups shows declines in VE over time appear to occur at similar rates among older adults and younger age groups. More evidence is needed to understand the impact of longer dose intervals on waning VE over time.

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