Supplementary Material

Supplementary Methods

Outcomes

SARS-CoV-2 infections were identified using the Integrated COVID-19 database (created by ICES), which combines SARS-CoV-2 testing data from the Ontario Laboratories Information System (OLIS) database, Distributed Lab (which was the network of laboratories responsible for SARS-CoV-2 testing in early 2020), and reportable disease data on confirmed COVID-19 cases in the Public Health Case and Contact Management Solution (CCM) database. CCM contains information on risk factors and the clinical course (including hospitalizations, interventions, and complications) of all confirmed COVID-19 cases who meet the provincial case definition.

Individuals tested for SARS-CoV-2, irrespective of the presence of symptoms, were included in the 'any infection' study population. Symptomatic infection was identified using OLIS. The details regarding how symptom status at the time of SARS-CoV-2 testing was determined and the limitations of these data have been previously described.[1] Individuals with at least one symptom consistent with COVID-19 disease recorded in OLIS when they were tested were included in the 'symptomatic infection' study population. Due to under-reporting of symptom information in OLIS, we assumed that individuals with a severe outcome (COVID-19-related hospitalizations or death) also had symptomatic disease. Severe outcomes were identified using CCM (more below). The test-negative controls for the 'severe outcome' study population were the same as the controls from the 'symptomatic infection' study population.

CCM contains information on confirmed COVID-19 cases that was gathered during the case and contact management process. Deaths were verified with the individual's death certificate (when available) to determine whether COVID-19 was the underlying cause of death or contributed to death. In a sensitivity analysis, we assessed VE using alternative definitions of severe outcomes because misclassification could bias estimates of VE duration.[2] These included definitions that exclusively used health administrative databases to capture severe outcomes among confirmed COVID-19 cases that may not have been reported to the public health units and recorded in CCM. We used the Canadian Institute of Health Information's Discharge Abstract Database (DAD), and Ontario's Registered Persons Database (RPDB) to identify hospitalizations and deaths temporally associated with a recent SARS-CoV-2 diagnosis. For hospitalizations, a positive test result must have occurred within 14 days before or three days after admission. We excluded hospitalizations that were for external injuries and non-urgent elective admissions. For additional specificity, we also restricted to hospitalizations with the International Classification of Diseases Tenth Revision code for COVID-19 virus identified (U07.1) as of the most responsible diagnosis for the encounter to determine whether effectiveness differed between hospitalizations *due to* COVID-19 versus those with incidentally diagnosed SARS-CoV-2 near the time of hospitalization. For deaths, a positive test result must have occurred within 30 days before death or within seven days postmortem. Due to lack of data availability, we were not able to verify the cause of death for deaths identified in RPDB.

The index date was the date of specimen collection for the 'any infection' and 'symptomatic infection' study populations, and the earliest of the specimen collection date or the hospitalization or death date for the 'severe outcomes' study population.

COVID-19 vaccination

We used the COVaxON database to identify receipt of COVID-19 vaccination. This centralized vaccine information system contains documentation of all COVID-19 vaccination events in Ontario (in real-time as they are being administered), including product, date of administration, and dose number. In Ontario, the following products were widely used: Pfizer-BioNTech BNT162b2 (Comirnaty), Moderna mRNA-1273 (Spikevax), AstraZeneca ChAdOx1 (Vaxzevria) and Verity Pharmaceuticals

Inc/Serum Institute of India ChAdOx1 (COVISHIELD). COVaxON also has records of COVID-19 vaccines received outside of Ontario if reported by the recipient to their local Public Health Unit.[3] For these analyses, we used the COVaxON file containing events up to 13 March 2022, which likely captured all vaccination events during our study period (i.e., vaccinations administered up to 21 November 2021).

Categorization of variants of concern (VOC)

During the study period, whole genome sequencing (WGS) was performed on SARS-CoV-2-positive specimens that had cycle threshold values ≤30 and specific mutations detected on mutation screening VOC polymerase chain reaction (PCR) tests. In addition, samples from confirmed COVID-19 cases associated with airport screening/travel, outbreaks, and suspected breakthrough infections or re-infections underwent WGS. Mutations included N501Y (starting 3 February 2021) and E484K (starting 22 March 2021). Selected laboratories were also screening for L452R. WGS was also performed on a random sample of SARS-CoV-2-positive specimens that did not have any mutations detected on VOC PCR. Based on the fluctuating incidence of COVID-19 cases in Ontario and the laboratory resource capacity to perform WGS, the proportion of mutation-positive specimens that were sequenced changed over the study period; from 100% up to 1 May 2021, 10% to 29 May 2021, 50% to 13 June 2021, 100% to 26 August 2021, and then to 50% until the end of the study period.[4-7]

For the main analyses, to understand whether trends in vaccine effectiveness (VE) by time since second dose was due to waning protection or because of a predominant strain that evaded the vaccine's immune response, we assessed VE restricted to periods when one VOC was predominant (e.g., 28 June 2021 to 21 November 2021 when all cases were assumed to be Delta [B.1.617] because ~97% of sequenced cases were identified as this lineage). However, analyses that rely solely on dates are subject to misclassification since some cases might be another lineage. In a sensitivity analysis for the last subperiod, we restricted to cases that were confirmed to be Delta by WGS, negative for both N501Y and E484K (N501Y-/E484K-) mutations, or positive for the L452R mutation.

Supplementary Results

Characteristics of the study populations

We included 3,045,059 unique subjects (261,360 cases) in the SARS-CoV-2 infection study population, 648,767 subjects (87,280 cases) in the symptomatic infection study population, and 624,906 subjects (13,737 cases) in the severe outcomes study population (**Supplementary Figure 1**). Among test-negative controls in the infection study population, 20% were included in >1 subperiod. Similarly, among test-negative controls in the symptomatic infection and severe outcomes study population, 8% were included in >1 subperiod. In the infection study population, across all subperiods, test-positive cases were younger, less likely to have a comorbidity, and more likely to have no SARS-CoV-2 tests prior to vaccine availability. Cases were also more likely to live in neighbourhoods with low income, higher proportions of visible minorities and non-health essential workers, and larger households, but these socio-demographic differences were not consistently observed across all subperiods (**Supplementary Table 2**). In the symptomatic infection study population, cases were collectively older and had no difference in the prevalence of comorbidities compared to symptomatic test-negative controls. Further, some of the differences in socio-demographic characteristics were consistent with those observed in the infection cohort, however the magnitude and the subperiods differed (**Supplementary Table 3**). In the severe outcomes study population, cases were notably older and more likely to be male and have comorbidities (**Supplementary Table 4**).

In our tested study population (i.e., the SARS-CoV-2 infection ['any infection'] study population, which includes all study subjects), 41% of subjects aged 16-69 years and 57% of aged ≥70 years received two doses by their testing date. For subjects aged 16-69 years, 1,013,271 (91%) received two mRNA vaccines (of whom 66% received BNT162b2 for both doses, 19% mRNA-1273 for both, and 15% received a heterologous mRNA schedule) and 98,636 (9%) received ChAdOx1 for at least 1 dose (of whom 27% received ChAdOx1 for both doses, 33% ChAdOx1/BNT162b2, and 40% ChAdOx1/mRNA-1273). The mean dosing interval was 53.8 days (standard deviation [SD] = 22.9 days) for mRNA recipients and 70.0 days (SD=13.3 days) for those who received at least 1 ChAdOx1 vaccine. For subjects aged ≥70 years, 187,942 (98%) received two mRNA vaccines (of whom 70% received BNT162b2 for both doses, 21% mRNA-1273 for both, and 9% received a heterologous mRNA schedule) and 4,165 (2%) received ChAdOx1 vaccine regimen (50% received ChAdOx1 for both doses, 30% ChAdOx1/BNT162b2, and 20% ChAdOx1/mRNA-1273). The mean dosing interval was 66.8 days (SD=27.8 days) for mRNA recipients and 76.7 days (SD=14.9 days) for ChAdOx1 recipients.

We created a comparison group of all community-dwelling individuals aged ≥16 years in Ontario who were not included in our tested study population. We used the distribution of index dates in the tested study population and assigned pseudo-index dates to the comparison group to determine the vaccination status as of the pseudo-index date. Among individuals who completed their two-dose primary series ≥7 days before their pseudo-index date, the proportions of each vaccine schedule were similar to the vaccinated tested study population. However, the intervals between doses were longer for the comparison group, except among individuals aged ≥70 years who received a ChAdOx1-containing schedule (**Supplementary Figure 1, Supplementary Table 5**).

References

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