Relative Virulence of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Among Vaccinated and Unvaccinated Individuals Hospitalized With SARS-CoV-2

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Background. The rapid development of safe and effective vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been a singular scientific achievement. Confounding due to health-seeking behaviors, circulating variants, and differential testing by vaccination status may bias analyses toward an apparent increase in infection severity following vaccination.

Methods. We used data from the Ontario, Canada, Case and Contact Management Database and a provincial vaccination dataset (COVaxON) to create a time-matched cohort of individuals who were hospitalized with SARS-CoV-2 infection. Vaccinated individuals were matched to up to 5 unvaccinated individuals based on test date. Risk of intensive care unit (ICU) admission and death were evaluated using conditional logistic regression.

Results. In 20 064 individuals (3353 vaccinated and 16 711 unvaccinated) hospitalized with infection due to SARS-CoV-2 between 1 January 2021 and 5 January 2022, vaccination with 1, 2, or 3 doses significantly reduced the risk of ICU admission and death. An inverse dose–response relationship was observed between vaccine doses received and both outcomes (adjusted odds ratio [aOR] per additional dose for ICU admission, 0.66; 95% confidence interval [CI], .62 to .71; aOR for death, 0.78; 95% CI, .72 to .84).

Conclusions. We identified decreased virulence of SARS-CoV-2 infections in vaccinated individuals, even when vaccines failed to prevent infection sufficiently severe to cause hospitalization. Even with diminished efficacy of vaccines against infection with novel variants of concern, vaccines remain an important tool for reduction of ICU admission and mortality.

Keywords. epidemiology; SARS-CoV-2; vaccination; pandemic; outcomes.

The global pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has sickened hundreds of millions of people and killed millions [1]. The rapid development of safe and effective vaccines against the virus has been a singular scientific achievement and has likely prevented many more illnesses and deaths [2–4]. However, the ongoing emergence of novel viral variants remains a challenge, with reduced protection against infection seen with the B.1.529 (Omicron) variant that emerged in fall 2021 [5]; though vaccines seem to continue to prevent severe illness, resulting in reduced hospitalizations, intensive care unit (ICU) admissions, and deaths. Indeed, the effectiveness of vaccination for prevention of severe outcomes reflects 2 effects that may be difficult to disentangle: prevention of infection and prevention of severe outcomes even when vaccination does not prevent infection. Studies may be further complicated by factors such as decreased propensity to test vaccinated individuals with mild symptoms of respiratory illness, which could produce biases that result in increased apparent severity of infection following vaccination.

Previously, we evaluated the effectiveness of SARS-CoV-2 vaccines to prevent infection in the Canadian province of Ontario [6]. However, vaccines that result in attenuation of severity, even among individuals in whom they failed to protect against infection, would be of considerable value to vaccinated individuals and to the wider community by limiting consumption of scarce critical care resources. We sought to study the impact of prior vaccination on severity of illness among individuals admitted to the hospital with SARS-CoV-2 in Ontario, Canada, because a study limited to hospitalized individuals should limit biases introduced by differential testing according to disease severity and vaccination status. As both the propensity to receive vaccination and the dominant viral variant of concern (VOC) has varied over the course of the pandemic in Ontario, we used a time-matched cohort to evaluate the adjusted risk of ICU admission and death in vaccinated and unvaccinated
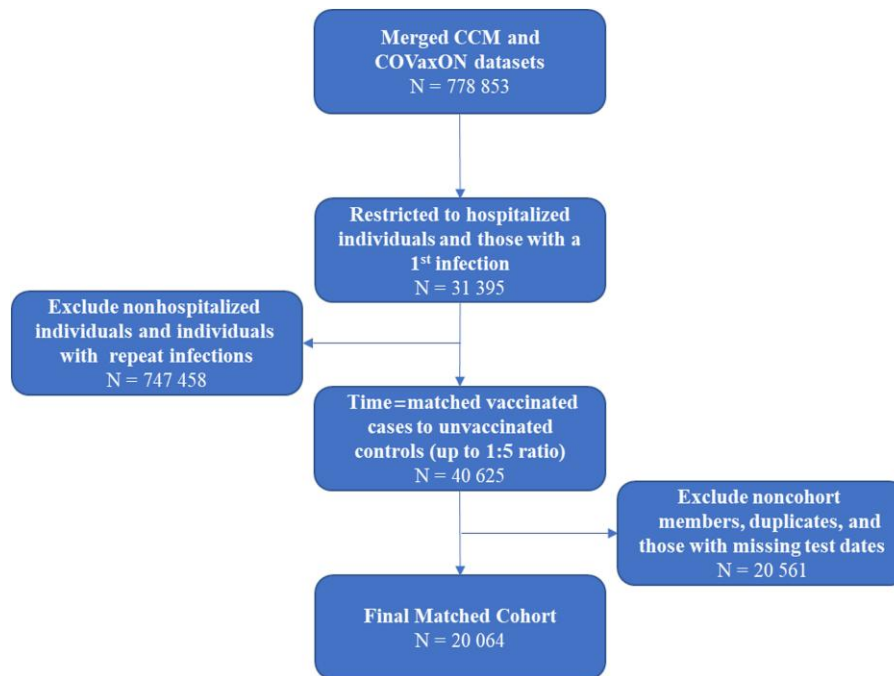
Figure 1. Flow diagram for the creation of the matched cohort. Abbreviations: CCM, Case and Contact Management System (Ontario's line list database); COVaxON, Ontario provincial vaccination database.

individuals with identically timed infection admitted to Ontario hospitals. Our primary objective was to determine whether the risks of ICU admission and death were diminished significantly by vaccination among individuals whose vaccination failed to prevent hospitalization. We also performed exploratory analyses to determine whether protective effects were modified by an individual's characteristics or by infecting viral variant.

METHODS

Data Sources

We created a time-matched cohort of individuals who were hospitalized due to SARS-CoV-2 infection between 1 January 2021 and 5 January 2022. Individuals who had received 1, 2, or 3 doses of a SARS-CoV-2 vaccine were included as exposed and were matched to unvaccinated individuals based on the test date for SARS-CoV-2. Each vaccinated individual was matched with up to 5 unvaccinated individuals who acted as controls [7]. We identified vaccinated and unvaccinated SARS-CoV-2 cases in the province's Case and Contact Management (CCM) System, as described elsewhere [8, 9].

We included only cases with a unique "pseudo-health card number," permitting linkage with the provincial vaccination COVaxON database [9], which provided information on dose administration, dates, and vaccines used. We considered individuals to be vaccinated 14 days or more after vaccine dose administration [10]. We used the date of positive testing as a surrogate for onset of infection; when individuals had a test date <14 days from a dose of vaccine, they were considered to be not protected by that dose. For example, an individual tested for infection 2 days after their second dose of vaccine would be considered single-dose vaccinated. While information on third vaccine doses was available in COVaxON, third doses were not widely available at the time of the analysis, and a small number of hospitalized individuals had received a third dose of vaccine. Consequently, we evaluated individuals based on the number of vaccine doses received and by classifying them as unvaccinated, single-dose vaccinated, double-dose vaccinated, or triple-dose vaccinated.

There have been several waves of the SARS-CoV-2 pandemic in Ontario, with different infecting variants prevalent for each. Initial waves were driven by the Wuhan variant, then waves were driven by Alpha in spring 2021, Delta in summer and fall 2021 [9], and finally Omicron in December 2021 [11]. As such, infecting viral variants in our analysis were classified as non-VOC, N501Y+ variant (including the Alpha, Beta, and Gamma variants) or Delta variant, as described elsewhere [9]. Individuals were considered infected with the Omicron variant (B.1.1.529) if they had been identified as such through whole-genome sequencing or if they were infected on or after 10 November 2021 with a strain with S-gene target failure or the N501Y mutation. Individuals were also considered infected with the Omicron variant if they had been classed as infected with an unknown VOC after 13 December 2022. A flow diagram outlining creation of the cohort is presented in Figure 1.

Analysis

We used our matched cohort to calculate the risk of ICU admission and death among those hospitalized due to SARS-CoV-2 using conditional logistic regression models. The models were specified a priori to adjust for age category (treated as a 9-level ordinal variable), sex, healthcare worker status, long-term care residence, comorbidity, and infecting variant. Vaccine status was treated as a 4-level nominal variable (0, 1, 2, or 3 doses) where 0 doses was used as the referent. Due to the rarity of deaths in healthcare workers, healthcare worker status was not included in models used to evaluate risk of death.

We also performed exploratory restriction analyses in which vaccinated and unvaccinated cases were limited to a single infecting variant (non-VOC, N501Y+ VOC, Delta VOC, or Omicron VOC) and additional exploratory analyses were conducted in which unvaccinated individuals were compared with individuals vaccinated exclusively with viral vector vaccines or to individuals vaccinated exclusively with messenger RNA (mRNA) vaccines. As conditional logistic regression models failed to converge for some of these models, we modeled the effect of vaccination using unmatched logistic regression models, with time trend modeled as a cubic trend function. We investigated heterogeneity in the adjusted odds ratios (aORs) for ICU admission and death according to infecting variant or vaccine product used using meta-analytic techniques (ie, graphically using forest plots, statistically using the meta-analytic Q statistic, and through construction of meta-regression models). The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology Guidelines for observational research [12] and received ethics approval from the University of Toronto Research Ethics Board.

Table 1.   Baseline Characteristics of the Matched Cohort

Characteristic	Vaccinated	(%)	Unvaccinated Controls	(%)	Total	(%)	P Value
N	3353		16 711		20 064		
Outcome							
Intensive care unit admission	467	13.93	3819	22.85	4286	21.36	<.001
Death	517	15.42	1849	11.06	2366	11.79	<.001
Age group, y							
0–9 or 10–19[a]	32	0.95	1038	6.21	1070	5.33	<.001
20–29	52	1.55	905	5.42	957	4.77	
30–39	96	2.86	1665	9.96	1761	8.78	
40–49	142	4.24	2195	13.14	2337	11.65	
50–59	281	8.38	3108	18.60	3389	16.89	
60–69	576	17.18	3376	20.20	3952	19.70	
70–79	798	23.80	2669	15.97	3467	17.28	
80+	1376	41.04	1754	10.50	3130	15.60	
Male	1838	54.82	8935	53.47	10 773	53.69	.135
Healthcare worker	16	0.48	88	0.53	104	0.52	.716
Long-term care	102	3.04	93	0.56	195	0.97	<.001
Comorbidity							
Any significant comorbidity	1088	32.45	3242	19.40	4330	21.58	<.001
Asthma	79	2.36	344	2.06	423	2.11	.274
Hematological disease	47	1.40	136	0.81	183	0.91	.001
Cardiac disease	578	17.24	1662	9.95	2240	11.16	<.001
Chronic obstructive pulmonary disease	142	4.24	276	1.65	418	2.08	.628
Diabetes	344	10.26	1110	6.64	1454	7.25	<.001
Renal disease	138	4.12	226	1.35	364	1.81	<.001
Neurological disease	90	2.68	186	1.11	276	1.38	<.001
Obesity	49	1.46	244	1.46	293	1.46	.996
Liver disease	35	1.04	73	0.44	108	0.54	<.001
Immune compromise	215	6.41	448	2.68	663	3.30	<.001
Infecting variant of concern							
Not detected	69	2.06	432	2.59	501	2.50	<.001
N501Y+	1056	31.49	5648	33.80	6704	33.41	
Delta	954	28.45	5362	32.09	6316	31.48	
Presumptive Omicron	645	19.24	2917	17.46	404	2.01	
Other	49	1.46	207	1.24	256	1.28	
Unknown	580	17.30	2145	12.84	5883	29.32	

[a]Age groups combined due to small cells (≤5).

RESULTS

The final matched cohort consisted of 3353 vaccinated individuals and 16 711 unvaccinated individuals. Most cohort members were aged ≥50 years (69.47%), and most were infected with the N501Y+ VOC (33.41%). The majority of the cohort were male (53.69%), and 21.58% of individuals had a recorded major medical comorbidity. In univariable analyses, vaccinated and unvaccinated individuals differed significantly according to age group, residence in long-term care, comorbidity status, and infecting variant (Table 1). Among vaccinated individuals, 51.12% had received 1 dose, 44.23% had received 2 doses, and only 4.65% had received 3 doses.

We fit 2 conditional logistic regression models to assess the risk of being admitted to the ICU and the risk of death in hospitalized individuals (Table 2). Compared with no vaccination, vaccination with a single dose of vaccine (aOR, 0.57; 95% confidence interval [CI], .49 to .66), with 2 doses (aOR, 0.51; 95% CI, .44 to .60), or with 3 doses (aOR, 0.56; 95% CI, .34 to .93) significantly reduced

ICU admission risk. When vaccination status was treated as a 4-level ordinal variable, we identified a significant inverse dose–response relationship between vaccine doses received and ICU admission risk (aOR per additional dose, 0.66; 95% CI, .62 to .71).

Vaccination also significantly decreased the risk of death conditional on hospitalization for SARS-CoV-2 (aOR for a single vaccine dose, 0.5; 95% CI, .44 to .59; aOR for 2 doses, 0.48; 95% CI, .40 to .56; and aOR for 3 doses, 0.52; 95% CI, .31 to .86). We identified a significant inverse dose–response relationship between the number of vaccine doses received and risk of death (aOR per additional dose, 0.78; 95% CI, .72 to .84).

We also performed an exploratory subgroup analysis on the odds of ICU admission and death stratified by the infecting variant. Heterogeneity in the aORs for ICU admission and death is shown in Figure 2. There was no significant heterogeneity between variants within each outcome. However, there was significant heterogeneity in vaccine effects based on the outcome used, with greater protection against ICU admission

Table 2. Odds Ratios and 95% Confidence Intervals from Conditional Logistic Regression on Intensive Care Unit Admission and Death Due to Severe Acute Respiratory Syndrome Coronavirus 2

Covariate	Crude OR	Lower CI	Upper CI	P Value	Adjusted OR[a]	Lower CI	Upper CI	P Value
Intensive care unit admission								
Vaccinations received								
Unvaccinated (referent)	1.00				1.00			
1 dose	0.57	.49	.66	<.001	0.51	.44	.59	<.001
2 doses	0.51	.44	.60	<.001	0.48	.40	.56	<.001
3 doses	0.56	.34	.93	.024	0.52	.31	.86	.011
Age group (per 10-year increase)	1.03	1.01	1.05	.001	1.07	1.05	1.09	<.001
Male	1.42	1.32	1.53	<.001	1.43	1.33	1.55	<.001
Healthcare worker	0.67	.38	1.18	.164	0.76	.43	1.35	.348
Long-term care	0.39	.23	.69	.001	0.43	.25	.75	.003
Any significant comorbidity	1.08	.98	1.18	.104	1.12	1.02	1.22	.019
Infecting VOC								
Non-VOC, unknown Other (referent)	1.00				1.00			
N501Y+	1.01	.89	1.15	.831	1.16	1.01	1.33	.040
Delta	1.80	1.61	2.01	<.001	1.78	1.56	2.04	<.001
Presumptive Omicron	0.50	.39	.65	<.001	1.04	.77	1.39	.816
Death								
Vaccinations received								
Unvaccinated (Referent)	1.00				1.00			
1 dose	1.52	1.32	1.75	<.001	0.68	.58	.80	<.001
2 doses	1.38	1.17	1.63	<.001	0.62	.51	.74	<.001
3 doses	1.98	1.05	3.73	.034	0.83	.42	1.61	.575
Age group (per 10-year increase)	1.69	1.63	1.75	<.001	1.77	1.70	1.84	<.001
Male	1.55	1.41	1.71	<.001	1.75	1.58	1.95	<.001
Long-term care	3.39	2.22	5.17	<.001	1.67	1.05	2.66	.029
Any significant comorbidity	1.66	1.50	1.85	<.001	1.40	1.25	1.57	<.001
Infecting VOC								
Non-VOC, unknown Other (referent)	1.00				1.00			
N501Y+	1.09	.93	1.27	.301	1.06	.89	1.27	.517
Delta	1.33	1.15	1.54	<.001	1.47	1.22	1.77	<.001
Presumptive Omicron	1.31	.89	1.93	.172	2.71	1.69	4.33	<.001

Abbreviations: CI, confidence interval; OR, odds ratio; VOC, variant of concern.

[a]Intensive care unit admission adjusted for age group, sex, healthcare worker, long-term care, comorbidity, and infecting variant. Death adjusted for age group, sex, long-term care, comorbidity, and infecting variant.
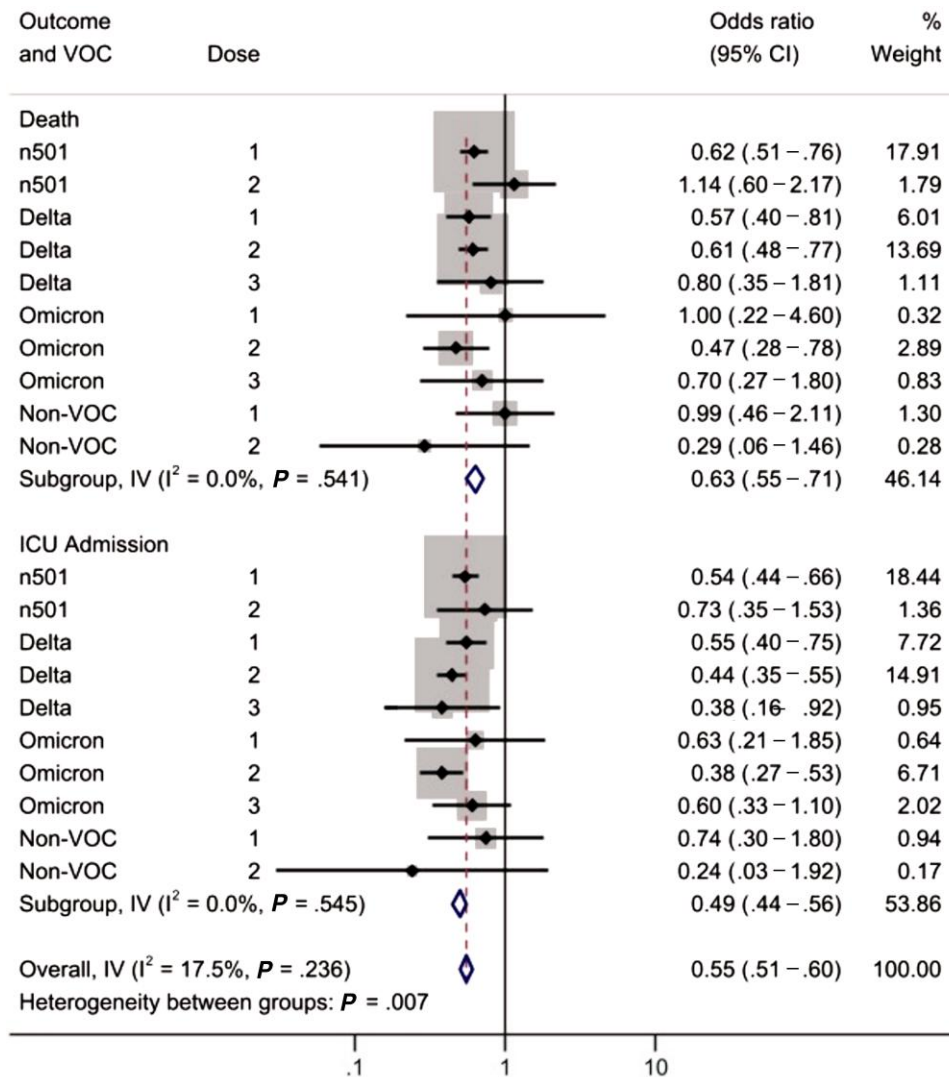
Figure 2. Forest plot to evaluate heterogeneity between estimates by infecting variant and outcome. The analysis is stratified by outcome, with results for death in the upper rows and ICU admission below. Abbreviations: CI, confidence interval; ICU, intensive care unit; IV, contribution of within-stratum variance to overall variance; n501, N501Y-positive variant; VOC, variant of concern.

than death ($P < .05$). When we created a meta-regression model that included vaccine type (mRNA vs viral vector vaccine), dose number, and outcome (death vs ICU), we found that vaccination was more protective against ICU admission than against death (27% relative reduction in risk; 95% CI, 12% to 39%), and mRNA vaccines were more protective against ICU admission and death than viral vector vaccines (36% relative reduction in risk; 95% CI, 10% to 55%). Results of stratified models and meta-regression are presented in detail in Supplementary Tables 1–3.

DISCUSSION

In a cohort of vaccinated and unvaccinated individuals matched on infection timing and hospitalization with SARS-CoV-2 infection in Ontario, Canada, vaccination was associated with a decreased risk of ICU admission and death after adjustment for confounding factors such as age, sex, health-care worker status, long-term care residence, comorbidity status, and infecting variant. A reduced risk of severe outcomes with increased number of vaccine doses received was also seen. The time-matched nature of our design suggests that our findings are unlikely to be due to changes in vaccine prioritization or dominant circulating variants over time. Restriction to hospitalized individuals makes it less likely that our findings are biased by differential testing in vaccinated and unvaccinated individuals. We postulate that this might result in confounding and selection bias, inasmuch as vaccinated individuals may be less likely to be tested for mild symptoms of infection but may be more likely to be tested overall.

The significant protective effects of vaccination against ICU admission and death were seen for both the N501Y+ and Delta variants in exploratory restriction analyses. While we did not identify significant protection against the Omicron variant in restriction analyses, this likely reflects low statistical power due to recent Omicron emergence. We found no evidence for heterogeneity in effect according to infecting variant. We did, however, identify greater protection against ICU admission than against death with vaccines. It is possible that this relates to residual confounding by long term care residence status, which independently reduced the likelihood of ICU admission while increasing the risk of death.

Protection against infection and symptomatic infection has declined with the emergence of novel VOCs, most notably the Omicron variant [5, 13–16]. While recent data suggest that booster doses of mRNA vaccines substantially restore vaccine efficacy [15, 16], our analysis shows that prior partial vaccination can provide benefits to individuals and health systems even when vaccines fail to prevent infection, or even hospitalization, and remains an important pillar of the public health response to the SARS-CoV-2 pandemic.

Our approach to this analysis emphasized adjustment for confounding both in the design (via matching) and analysis (via multivariable regression). The importance of adjustment for confounding when evaluating vaccine efficacy against SARS-CoV-2 relates to the differential risk profiles of vaccinated and unvaccinated individuals. For example, in Ontario, older individuals and those with medical comorbidities who are expected to have worse outcomes if infected with SARS-CoV-2 have been prioritized for vaccination. This so-called confounding by indication is likely to diminish the apparent crude efficacy of vaccines, as is seen in our unadjusted analyses, simply because those who are more likely to be vaccinated are also more likely to experience adverse outcomes of infection, independent of vaccination status. While confounding by age and comorbidity might be expected, we also adjusted by other factors, including biological sex. As in this analysis, we previously identified male sex as an independent risk factor for poor outcomes in individuals with SARS-CoV-2 infection [17, 18].

The effects we demonstrate here are not unique to SARS-CoV-2, and we have previously identified similar effects with prior pneumococcal and influenza vaccination [19, 20]. As with that earlier work, an important limitation here is the inability to ensure that the effects we observe are not at least in part due to residual confounding. This is a potential limitation of any cohort study and is one that will be the focus of future work. The relatively recent emergence of the Omicron variant and the lags associated with critical illness and death result in the lack of statistical power to estimate Omicron-specific protections, as noted above. Unfortunately, ongoing high rates of SARS-CoV-2 hospitalizations, critical illnesses, and deaths in

Ontario mean that we will be able to address this potential limitation in the months ahead.

In summary, we identified a decrease in the risk of ICU admission and death in hospitalized, vaccinated individuals compared with hospitalized, unvaccinated individuals, matched for infection timing, in Ontario, Canada. Our analysis further emphasizes the critical importance of high rates of vaccination for protection of community health and reduction of the impacts of SARS-CoV-2 on ICU capacity during the pandemic.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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