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Clinical Severity of Severe Acute Respiratory Syndrome Coronavirus 2 Omicron Variant Relative to Delta in British Columbia, Canada: A Retrospective Analysis of Whole-Genome Sequenced Cases

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Background. In late 2021, the Omicron severe acute respiratory syndrome coronavirus 2 variant emerged and rapidly replaced Delta as the dominant variant. The increased transmissibility of Omicron led to surges in case rates and hospitalizations; however, the true severity of the variant remained unclear. We aimed to provide robust estimates of Omicron severity relative to Delta.

Methods. This retrospective cohort study was conducted with data from the British Columbia COVID-19 Cohort, a large provincial surveillance platform with linkage to administrative datasets. To capture the time of cocirculation with Omicron and Delta, December 2021 was chosen as the study period. Whole-genome sequencing was used to determine Omicron and Delta variants. To assess the severity (hospitalization, intensive care unit [ICU] admission, length of stay), we conducted adjusted Cox proportional hazard models, weighted by inverse probability of treatment weights (IPTW).

Results. The cohort was composed of 13 128 individuals (7729 Omicron and 5399 Delta). There were 419 coronavirus disease 2019 hospitalizations, with 118 (22%) among people diagnosed with Omicron (crude rate = 1.5% Omicron, 5.6% Delta). In multivariable IPTW analysis, Omicron was associated with a 50% lower risk of hospitalization compared with Delta (adjusted hazard ratio [aHR] = 0.50, 95% confidence interval [CI] = 0.43 to 0.59), a 73% lower risk of ICU admission (aHR = 0.27, 95% CI = 0.19 to 0.38), and a 5-day shorter hospital stay (aß = −5.03, 95% CI = −8.01 to −2.05).

Conclusions. Our analysis supports findings from other studies that have demonstrated lower risk of severe outcomes in Omicron-infected individuals relative to Delta.

Keywords. SARS-CoV-2; COVID-19; Omicron; Delta; severity.

Assessing the risk of severe outcomes associated with coronavirus disease 2019 (COVID-19) and identifying characteristics associated with increased risk are critical to inform clinical and public health decision-making. In addition to well-established risk factors such as older age, male sex, comorbidities, and lack of immunization, previous research has identified severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants of concern (VOCs) as an important determinant of infection severity [1–3]. Indeed, each newly dominant VOC has generally been more virulent than the previous (Delta [Pangolin lineages [4] B.1.617.2 and AY.*] > Alpha [B.1.1.7 and Q.*] > wild type).

In late 2021, the Omicron SARS-CoV-2 variant (B.1.1.529 and BA.*) emerged and quickly replaced Delta as the dominant variant globally [5]. The increased transmissibility of Omicron led to a much higher case rate compared with previous COVID-19 waves and was followed by a large increase in hospitalizations. However, it was not clear whether increases in hospitalizations were the result of the sheer number of Omicron cases, increased virulence relative to Delta, and/or increased identification of incidental hospitalizations (ie, infection identified in persons hospitalized for other reasons). Promisingly, laboratory and animal studies suggested attenuated severity of infection with Omicron and reduced ability to replicate in the lower respiratory tract [6, 7]. Early reports also suggested less severe infection

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with Omicron, although these studies were mostly conducted in South Africa, a setting that is very different from North America and Europe with respect to age distribution of infections and underlying pattern of protective immunity from prior infection in previous waves, potentially affecting generalizability of results [8, 9]. Also, most prior studies either lacked individual-level data on VOCs [10, 11] or used reverse-transcription polymerase chain reaction (RT-PCR) S-gene target failure as a proxy for Omicron infection (as opposed to whole-genome sequencing [WGS]), a source of misclassification bias. To date, relatively few peer-reviewed studies with individual-level VOC data have been published on Omicron severity, and those that have been published have identified a relatively wide range of reduced severity estimates relative to Delta (36%–73%) [12–17]. Additional analyses are therefore needed to better understand the severity of a globally dominant variant.

British Columbia (BC) has experienced more than 18 000 COVID-19 hospitalizations and 2800 deaths since the beginning of the pandemic and is well placed to answer questions related to Omicron severity given the extent of WGS and availability of linked population-based registries. Our objective in this study was to determine the clinical severity of WGS-confirmed Omicron relative to Delta during substantial cocirculation of these 2 variants.

METHODS

Data Sources

We used data from the BC COVID-19 Cohort (BCC19C; Supplementary Table 1). The BCC19C is a surveillance platform that integrates a range of COVID-19 datasets (eg, case surveillance, laboratory tests, vaccinations) with administrative data holdings for the entire BC population (eg, physician billings, hospitalization discharges; Supplementary Table 2). The Behavioural Research Ethics Board at the University of British Columbia reviewed and approved this study.

Sequencing Strategy

In British Columbia, the sequencing strategy of laboratory-confirmed COVID-19 samples has changed over time, including during our study period [18, 19]. Between 1 December and 15 December, the strategy was to sequence all positive COVID-19 samples; during this time, about 80% of laboratory-confirmed positive samples were sequenced. Due to the large case load by 15 December, British Columbia transitioned to sequencing a representative subset of positive samples (Supplementary Table 3) in addition to priority cases (outbreaks, long-term care, vaccine escape, travel-related, and hospitalization), approximately 10%–20% of all cases (Supplementary Figure 1).

Study Population

We included individuals with a laboratory-confirmed first-time infection between 1 December 2021 and 31 December 2021 whose SARS-CoV-2 lineage was confirmed as Delta or Omicron through WGS. We selected our study period to capture the time when Omicron first emerged and there was substantial cocirculation of Delta and Omicron (Supplementary Figure 1). Due to the small number of Delta infections and important changes to the COVID-19 diagnostic testing criteria in January 2022, we selected 31 December 2021 as our study end date [20].

We excluded individuals who resided outside of Canada, were admitted to the hospital more than 2 days prior to their positive laboratory collection date, or had missing information.

Exposure of Interest: SARS-CoV-2 Lineage

Our exposure of interest was SARS-CoV-2 lineage, as determined by WGS. Lineage was defined as Delta (B.1.617.2, AY.*) or Omicron (B.1.1.529, BA.*). Other lineages were excluded from analysis (Supplementary Table 2).

Hospitalization Due to COVID-19

We defined our primary outcome as a hospital admission date within −2 to 14 days of the positive laboratory collection date, as done by others who have assessed SARS-CoV-2 severity [2, 3]. Hospital data sources are described in Supplementary Table 2.

Secondary Outcomes

Definitions and data sources for secondary outcomes (intensive care unit [ICU] admission, length of stay [LOS]) are described in detail in Supplementary Table 2. In brief, if an individual met the criteria of hospitalization in any hospital data source and had a record of ICU admission associated with that hospitalization (from the same data source), then the criteria for ICU admission was met. For individuals who were hospitalized within the −2- to 14-day time window, LOS was calculated as the difference between admission date and discharge date.

Mortality was defined as a death within 30 days of the laboratory collection date; modeling was not conducted due to the small number of deaths during the study period; however, counts are reported.

Analyses

We conducted Cox proportional hazards models weighted by inverse probability of treatment weights (IPTW) to examine the relationship between SARS-CoV-2 lineage and hospitalization. Individuals were followed from 2 days prior to the laboratory collection date to the earliest of 14 days following the laboratory collection date, COVID-19 death, or hospital admission. IPTW were calculated from a logistic regression model with VOC as the outcome and sex, age, geography, comorbidities, neighborhood income quintile, and vaccination status (full model only) as the independent variables. We used a doubly robust approach and adjusted for these same variables in a multivariable IPTW model. Standardized mean differences (SMDs)

were computed using a threshold of 0.1 to assess success of weighting. The same methodology was applied for the secondary outcomes. Cox regression and linear regression were used to model ICU and LOS among hospitalized cases, respectively.

For all analyses, we examined an overall model and models stratified by vaccination status. Unvaccinated was defined as no record of vaccination 14 days prior to the laboratory collection date. Fully vaccinated was defined as a record of 2 or more vaccinations (or 1 dose of Johnson & Johnson) at least 14 days prior to the laboratory collection date. Stratified analyses excluded individuals who were partially vaccinated (only 1 dose 14 days prior to the laboratory collection date) and individuals aged ≤11 years, as no one in this age group was fully vaccinated during the study period.

Covariate Measurement

Age, sex, and geography of residence were extracted from the case surveillance dataset or, if missing, from the client roster of all individuals enrolled in universal health insurance. Comorbidities were assessed using the Elixhauser index [21] and based on physician billing and hospitalization discharge data prior to the laboratory collection date. Neighborhood income was extracted at the level of dissemination area (the smallest standard unit of geography in Canada, equivalent to a street block; see Supplementary Table 2 for more details).

Sensitivity Analyses

We performed sensitivity analyses to explore the impact of different potential biases. To account for potential incidental infections, we excluded people hospitalized within the 2 days prior to the laboratory collection date and conducted an additional analysis removing individual diagnosed on the same day as hospitalization. To explore the effect of sampling bias introduced by the change in sequencing strategy in mid-December, we performed an analysis limited to individuals diagnosed between 15 December and 31 December. Last, we also conducted another analysis adjusting for additional vaccination variables (booster within 14 days prior to laboratory collection and time since fully vaccinated).

RESULTS

Study Population

Overall, 41 322 people were diagnosed with laboratory-confirmed SARS-CoV-2 infection between 1 December 2021 and 31 December 2021 (Figure 1). We excluded 27 851 (67.4%) people whose diagnostic specimen was not sequenced during this period. Overall, the sequenced and nonsequenced populations had similar demographic distributions, although there were minor differences in geography and vaccination status (Supplementary Table 3). In addition, a higher percentage of sequenced cases were hospitalized, reflecting the targeted sequencing strategy implemented in mid-December.

Of the remaining 13 470 individuals, we excluded an additional 342 due to incomplete data (Figure 1). Our final study population included 13 128 individuals (5399 Delta and 7729 Omicron; Table 1). Most Omicron infections were BA.1 (77.5%), and the majority of Delta infections were AY.25.1 (69.1%). The majority of the cohort was fully vaccinated (n = 9310; 70.9%), while 3266 (24.9%) were unvaccinated.

Overall, the study population was split evenly by sex (50.9% female), and half (49.1%) of participants were aged between 20 and 50 years (median = 33.0; interquartile range = 25.0). There were several differences in characteristics by VOC, as reflected by the preweighted SMDs in Supplementary Figure 2. Omicron infections were more concentrated in the 20- to 40-year range, and a larger proportion of individuals diagnosed with Delta were aged ≤11 years or ≥60 years. Individuals infected with Omicron were twice as likely to be fully vaccinated (87.6% vs 47.0%). Delta also had a more even geographic distribution, whereas Omicron had a greater proportion of diagnoses in more urban geographic regions (Table 1). During the study period, there were 33 deaths, with a higher case fatality rate found in those diagnosed with Delta (0.5%) compared with Omicron (0.1%).

Crude Hospitalization Rates

Overall, there were 419 hospitalizations in our analysis, with 301 (71.8%) occurring in people with Delta and 118 (28.2%) with Omicron (Table 1). The crude rate of hospitalization was higher for Delta (5.6%) compared with Omicron (1.5%). When stratified by vaccination status, the crude hospitalization rate for the unvaccinated was 15.0% for Delta and 3.8% for Omicron; in the vaccinated stratum, it was 3.0% and 1.4%, respectively. Crude hospitalization rates by sociodemographic and other covariates are presented in Supplementary Table 4.

IPTW and Balance

After weighting by IPTW, there was improved balance between individuals infected with Omicron and Delta across all variables (Supplementary Figure 2). In the full study population, preweighted SMDs were very large for geography (SMD = 1.39), vaccination status (SMD = 1.04), and age (SMD = 0.69). After weighting, all SMDs were <0.1. Similar improvements in balance were found in each of the vaccination status strata as well, however, to a lesser degree in the unvaccinated stratum.

Risk of Hospitalization Among People With Delta and Omicron Infection

Omicron was associated with a 50% lower risk of hospitalization (vs Delta; adjusted hazard ratio [aHR] = 0.50, 95% confidence interval [CI] = .43 to .59; Table 2, Supplementary Table 4). In stratified analyses, a lower risk of hospitalization for Omicron was observed for both vaccinated and unvaccinated individuals (Table 2). However, the strength of association differed by vaccination strata. Among unvaccinated individuals, the risk of hospitalization for Omicron was 62% lower

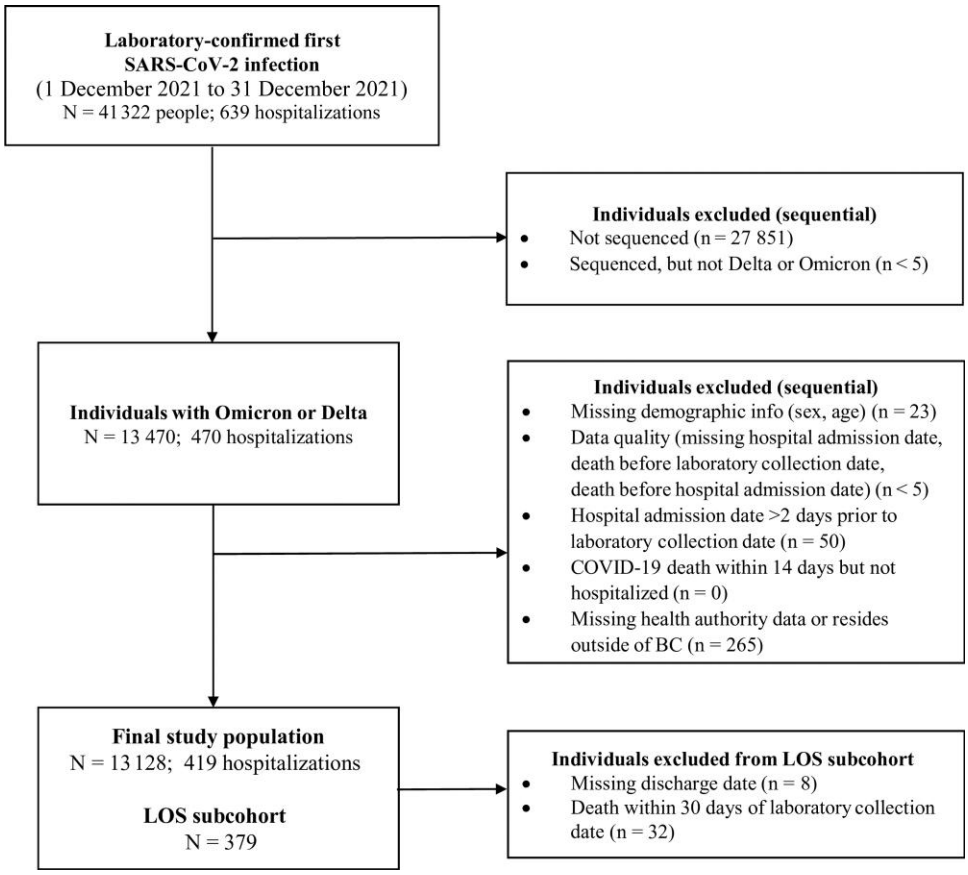

Figure 1. Study flow diagram. Abbreviations: BC, British Columbia; COVID-19, coronavirus disease 2019; LOS, length of stay; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

(vs Delta; aHR = 0.38, 95% CI = .30 to .49), while among vaccinated people the risk was 30% lower (vs Delta; aHR = 0.70, 95% CI = .56 to .87).

Sensitivity Analyses

Model estimates were relatively unchanged in sensitivity analyses accounting for incidental infections (aHR = 0.51, 95% CI = .43 to .60 for a hospitalization window of 0–14 days and aHR = 0.50, 95% CI = .39 to .64 for a hospitalization window of 1–14 days; Supplementary Table 5) and with additional variables to adjust for booster doses and time since vaccination (aHR = 0.47, 95% CI = .40 to .55; Supplementary Table 6). Of note, in the sensitivity analysis accounting for the change in sequencing strategy in mid-December, the lower severity of Omicron relative to Delta was more pronounced (68% reduced risk of hospitalization, 95% CI = 62% to 74%; Supplementary Table 5).

ICU Admission

There were 130 ICU admissions. The crude ICU admission rate was much higher for Delta (2.1%) compared with Omicron (0.2%). When stratified by vaccination status, the crude rates for fully vaccinated individuals were 0.8% for Delta and 0.1% for Omicron and 5.4% and 0.9%, respectively, for the unvaccinated. In the Cox model, Omicron was associated with a 73% reduced risk of ICU admission (vs Delta; aHR = 0.27, 95% CI = .19 to .38; Table 2).

LOS

An additional 8 individuals were excluded due to missing discharge dates; 32 who died within 30 days of the laboratory collection date were excluded. LOS was higher for Delta compared with Omicron. Median LOS was 9 for Delta (25th percentile = 4, 75th percentile = 19) and 4 for Omicron (25th percentile = 2, 75th percentile = 8). In the IPTW multivariable linear regression model, Omicron was associated with an average LOS that was 5 days shorter compared with Delta (β-estimate = −5.03, 95% CI = −8.01 to −2.05). Although weighting by IPTW significantly improved SMD balance across covariates, some SMDs remained high (Supplementary Figure 2).

DISCUSSION

In this large retrospective analysis of 7729 and 5399 individuals with WGS-confirmed Omicron and Delta SARS-CoV-2

Table 1. Characteristics by the Study Population, Overall and by Variant of Concern, 1 December to 31 December 2022

Characteristic	Delta (N = 5399)	Omicron (N = 7729)	Overall (N = 13 128)
Sex			
Female	2746 (50.9%)	3939 (51.0%)	6685 (50.9%)
Male	2653 (49.1%)	3790 (49.0%)	6443 (49.1%)
Age, years			
Mean (standard deviation.)	34.4 (20.7)	35.0 (16.3)	34.8 (18.2)
Median (interquartile range)	35.0 (35.0)	32.0 (23.0)	33.0 (25.0)
Age group, years			
0–4	225 (4.2%)	131 (1.7%)	356 (2.7%)
5–11	844 (15.6%)	233 (3.0%)	1077 (8.2%)
12–19	342 (6.3%)	549 (7.1%)	891 (6.8%)
20–29	618 (11.4%)	2390 (30.9%)	3008 (22.9%)
30–39	982 (18.2%)	1671 (21.6%)	2653 (20.2%)
40–49	934 (17.3%)	1143 (14.8%)	2077 (15.8%)
50–59	592 (11.0%)	870 (11.3%)	1462 (11.1%)
60–69	446 (8.3%)	459 (5.9%)	905 (6.9%)
70–79	179 (3.3%)	134 (1.7%)	313 (2.4%)
80+	237 (4.4%)	149 (1.9%)	386 (2.9%)
Health authority			
Fraser	1421 (26.3%)	3297 (42.7%)	4718 (35.9%)
Interior	1458 (27.0%)	798 (10.3%)	2256 (17.2%)
Northern	472 (8.7%)	132 (1.7%)	604 (4.6%)
Vancouver Coastal	826 (15.3%)	2383 (30.8%)	3209 (24.4%)
Vancouver Island	1222 (22.6%)	1119 (14.5%)	2341 (17.8%)
Vaccination status[a]			
Not vaccinated	2535 (47.0%)	731 (9.5%)	3266 (24.9%)
Partially vaccinated	327 (6.1%)	225 (2.9%)	552 (4.2%)
Fully vaccinated	2537 (47.0%)	6773 (87.6%)	9310 (70.9%)
Elixhauser comorbidity index			
0	2285 (42.3%)	3337 (43.2%)	5622 (42.8%)
1	1376 (25.5%)	2176 (28.2%)	3552 (27.1%)
2	782 (14.5%)	1120 (14.5%)	1902 (14.5%)
3+	956 (17.7%)	1096 (14.2%)	2052 (15.6%)
Neighborhood income quintile			
1	981 (18.2%)	1012 (13.1%)	1993 (15.2%)
2	885 (16.4%)	1172 (15.2%)	2057 (15.7%)
3	1094 (20.3%)	1413 (18.3%)	2507 (19.1%)
4	1019 (18.9%)	1685 (21.8%)	2704 (20.6%)
5 (wealthiest)	1025 (19.0%)	1750 (22.6%)	2775 (21.1%)
Missing	395 (7.3%)	697 (9.0%)	1092 (8.3%)
Hospitalization			
No	5098 (94.4%)	7611 (98.5%)	12 709 (96.8%)
Yes	301 (5.6%)	118 (1.5%)	419 (3.2%)
Intensive care unit admission			
No	5284 (97.9%)	7714 (99.8%)	12 998 (99.0%)
Yes	115 (2.1%)	15 (0.2%)	130 (1.0%)
Death			
No	5371 (99.5%)	7724 (99.9%)	13 095 (99.7%)
Yes	28 (0.5%)	<5 (0.1%)	33 (0.3%)

[a]Fully vaccinated: received second dose (or first dose of Johnson & Johnson) at least 14 days prior to laboratory collection date. Unvaccinated: received no dose of any vaccine 14 days prior to laboratory collection date.

infection, respectively, we identified less severe outcomes among individuals diagnosed with Omicron. In multivariable IPTW analysis, Omicron was associated with a statistically significant 50% lower risk of hospitalization relative to Delta after adjustment for age, sex, comorbidities, vaccination status, geography, and neighborhood income. When stratified by vaccination status, the lower risk of hospitalization with Omicron relative to Delta was less pronounced in vaccinated individuals

Table 2. Multivariable Inverse Probability of Treatment Weight Regression Models Assessing Association Between the Variant of Concern and Severity Outcomes

Stratification[a]	Variant	(n/N)	Crude Rate (%)	aHR[b] (95% CI)
Hospitalization				
Full	Delta	301/5399	5.6%	
	Omicron	118/7729	1.5%	0.50 (.43 to .59)
Fully vaccinated[c]	Delta	75/2537	3.0%	
	Omicron	93/6772	1.4%	0.70 (.56 to .87)
Unvaccinated[c]	Delta	216/1438	15%	
	Omicron	17/445	3.8%	0.38 (.30 to .49)
Intensive care unit admission				
Full	Delta	115/5399	2.1%	…
	Omicron	15/7729	0.2%	0.27 (.19 to .38)
Fully vaccinated	Delta	21/2537	0.8%	…
	Omicron	9/6772	0.1%	0.24 (.13 to .44)
Unvaccinated	Delta	90/1438	6.3%	…
	Omicron	5/445	1.1%	0.43 (.29 to .63)
Length of stay[d]				
Stratification	Variant	N	Mean (standard deviation), median (interquartile range)	Multivariable estimate (95% CI)
Full	Delta	269	14.7 (15.9); 9 (15.0)	…
	Omicron	110	8.4 (11.0); 4 (6.0)	−5.03 (−8.01 to −2.05)

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval.

[a]Partially vaccinated individuals removed from stratified analysis. Only those aged ≥12 years were kept in stratified analysis.

[b]All models are adjusted for age, sex, geography, Elixhauser index (comorbidities), and sociodemographic status (neighborhood income quintile). The unstratified full model also adjusts for vaccination status.

[c]Vaccination status: received second dose (or first dose of Johnson & Johnson) at least 14 days prior to laboratory collection date. Unvaccinated: received no dose of any vaccine 14 days prior to laboratory collection date.

[d]Linear regression model.

(30% lower risk vs 62% among unvaccinated), potentially reflecting greater vaccine protection against hospitalization for Delta with 2 messenger RNA (mRNA) doses [22–25]. However, fully vaccinated individuals remained at much lower risk of severe outcomes overall, and crude hospitalization rates were 5 times higher for the unvaccinated compared with those fully vaccinated. Further, studies demonstrate that booster doses can increase vaccine protection against hospitalization to similarly high levels for both Omicron and Delta [15, 23–26], emphasizing the continued importance of vaccination.

Our findings are similar to those from studies published elsewhere. Analyses from the United States, United Kingdom, Norway, Denmark, and Ontario, Canada, have identified a 36%–73% reduced risk of hospitalization with Omicron relative to Delta [12–17, 23]. Estimates from our primary (50%) and sensitivity analyses (49%–68%) fall within this range. Variability between studies may be explained by differences in jurisdictional policies (eg, diagnostic testing and sequencing strategies) and analytic approaches (eg, outcome definitions, confounder adjustment). Unlike other studies, we included only WGS-confirmed cases, and a relatively large proportion (33%) of positive SARS-CoV-2 samples were sequenced during our study period. The extent of WGS is a key strength of our study, which likely reduced the potential for misclassification that may arise from using RT-PCR S-gene target failure as a proxy for Omicron infection. Overall, our findings suggest that the sheer number of Omicron cases led to higher numbers of hospitalizations than observed in the previous COVID-19 waves dominated by the Alpha, Gamma, and Delta variants, highlighting the importance of both transmissibility and severity from a public health perspective. Further, given that new VOCs may emerge, timely WGS of hospitalized cases may help inform prioritization of care for individuals infected with variants that are more virulent.

With respect to the impact of vaccination on disease severity, we report a lower risk of hospitalization with Omicron among both vaccinated and unvaccinated individuals, suggesting that lower Omicron severity is related to viral evolution. The lower severity of Omicron relative to Delta was less evident among vaccinated individuals, similar to findings from other studies [12, 15, 16]. A potential explanation is that vaccination provides more protection against severe outcomes for Delta, leading to a smaller difference in severity. Indeed, analyses of vaccine effectiveness suggest that 2 mRNA doses provide less protection against hospitalization for Omicron but that this protection increases to similarly high levels as for Delta following a booster dose [22, 24–26]. While our analytic approach is not optimal compared with other designs (eg, test-negative; randomized, controlled trials) for assessing vaccine

effectiveness, we identified a much higher risk of hospitalization overall among unvaccinated individuals in our analysis. These findings highlight the importance of booster doses to further reduce the severity of Omicron infection.

The reduced severity of Omicron was also apparent when we assessed ICU admission and LOS, further emphasizing the lower virulence associated with this VOC. Here, Omicron was associated with a 73% lower risk of ICU admission and 5-day shorter hospital stay, on average, compared with Delta. While few deaths (n = 33) were observed during our study follow-up, the crude case fatality rate was higher for Delta (0.5%) compared with Omicron (0.1%), and rates were higher in the unvaccinated compared with vaccinated. The greater reduction in risk for more severe outcomes (ICU admission, mechanical ventilation) has also been observed in other analyses [12]. Others have also identified a similar reduction in LOS (3–5 days) with Omicron [12, 27].

Our study had several strengths and limitations. Strengths include the use of individual-level VOC data as opposed to time period as a proxy, the exhaustive extent of high-quality whole-genome sequences at the population-level during the study period, the focus on a time period of VOC cocirculation to minimize temporal biases, the extensive data linkage to various health and data registries to measure potential confounders, and the rigorous adjustment for confounding and selection bias using IPTW. The association between Omicron and severe outcomes in our analysis is subject to some potential biases [28, 29]. The population infected with Omicron was significantly different from those infected with Delta (eg, younger age, geography), partly due to the different stages of these respective epidemics (ie, Delta was well established and declining, while Omicron was emerging). However, we controlled for differences between populations using IPTW, although some residual confounding likely remains. Limiting this investigation to a short period when there was cocirculation of lineages enabled the control for potential temporal effects by limiting differential exposure risks that influence transmission and could bias comparisons. The sequencing strategy changed on 15 December from sequencing the vast majority (approximately 80%) of samples to sequencing a representative random sample and prioritizing hospitalized cases (approximately 10%–20% of cases). This led to a minority (33%) of laboratory-confirmed cases being sequenced during our study period and therefore included in our analysis. Since Omicron was dominant by 15 December and there were few Delta infections, Omicron was more subject to potential selection bias. In particular, prioritization of hospitalized cases likely artificially elevated the percentage of Omicron cases who were hospitalized and overestimated the severity of Omicron (thereby underestimating the extent to which Omicron severity is lower than Delta; a conservative bias toward the null). Indeed, the lower risk of hospitalization with Omicron was more pronounced (68%) in our sensitivity analysis that was limited to the period after the change in sequencing strategy, although this analysis significantly reduced Delta sample size and may have introduced other biases (such as exclusion and survivorship biases) in addition to partial sampling bias. Estimates of severity are sensitive to changes in case-finding (eg, percent of all cases identified). Therefore, changes in diagnostic testing behaviors/policies/availability during the emergence of Omicron may have introduced bias. For example, less Omicron testing given the reduced availability of testing due to high demand and introduction of rapid antigen testing (not included as these were deployed at the end of the study period) would have lowered Omicron case-finding and biased results toward the null. Analyses suggest that a higher proportion of Omicron hospitalizations are incidental [30], another potential source of bias toward the null. Removal of individuals hospitalized on the day of testing or in the 2 days prior to the laboratory collection date in sensitivity analyses to account for potential incidental hospitalizations had minimal impact on our results, consistent with other studies [13, 14, 17]. Lack of information on undetected prior infection remains an additional limitation. In a study that attempted to adjust for underascertainment of prior infection, the reduction of risk of hospitalization with Omicron (vs Delta) changed from 45% to 35% [13].

In conclusion, our analysis supports that the large numbers of incident Omicron cases rather than increased virulence primarily drove the upsurge in hospitalizations during British Columbia's fifth wave. Our study is an important contribution to the relatively small evidence base of peer-reviewed studies that have assessed Omicron severity relative to Delta, which have produced a relatively wide range of estimates.

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

Author contributions. S. P. H., J. W., H. S., and N. Z. J. developed the study concept and design. C. R. and M. C. contributed to the methodology. S. P. H. conducted the analysis. J. W. wrote the first draft of the manuscript. Y. A. and H. V. G. provided statistical expertise. M. K., N. P., L. H., and J. T. are responsible for the laboratory-related data collection including whole-genome sequencing (WGS). C. R., S. M., B. S., H. V. G., and M. T. supported the data interpretation. All authors contributed to writing and reviewing the article, have approved it for submission, and agree to being accountable for its content.

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