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SYNTHESIS

Omicron Disease Severity – 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). "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.

Key Findings

- There is strong evidence that infection with the Omicron variant causes less severe disease compared to the Delta variant; however, Omicron infections can still be severe, particularly in older age groups, individuals with comorbidities, and unvaccinated individuals.
- Although there is no evidence that Omicron causes more severe disease in children than previous variants, the evidence base is small, and the increased risk of infection due to community prevalence of a more transmissible variant, coupled with growing evidence of long-term COVID outcomes and limited vaccine eligibility in the pediatric population, suggests children are a vulnerable group.
- Due to increased transmissibility of Omicron, the absolute number of cases with severe outcomes (hospitalizations, ICU admission, deaths) has strained health system capacity and critical infrastructure at the peak of transmission in many jurisdictions, including Ontario.
- At this time, the impact of Omicron on hospitalization outcomes, mortality, and long-term COVID outcomes at the population level remains unclear.

Background

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) lineage Omicron (B.1.1.529, first reported in South Africa) was reported on November 8, 2021 in South Africa,[1] and was designated a variant of concern (VOC) by the World Health Organization (WHO) on November 26, 2021.[2] Since then, Omicron has rapidly displaced Delta as the dominant variant in countries where it emerged. Modelling, in vitro and in-silico analyses support the epidemiological findings of Omicron having higher transmissibility and suggest potential mechanisms, but it remains unclear to what extent the increased transmission of Omicron is due to inherent characteristics of the virus (i.e., enhanced ability to infect cells, tissue tropism) or due to immune evasion.[3]

The high transmissibility of Omicron resulted in record case numbers, which raised concerns about severity and potential impact on health care systems and critical infrastructure. When comparing Omicron to previous SARS-CoV-2 variants, indicators such as emergency department (ED) visits, hospitalization, length of stay in a hospital (LoS), intensive care unit (ICU) admission, and death are used as proxies for disease severity,[4] but have several limitations. COVID-19 hospital admission data are complicated by screening and testing practices and high community prevalence because patients may test positive for SARS-CoV-2 but are hospitalized for a different diagnosis that does not require COVID-19 related care. The studies that do attempt to address this, do so in different ways, making hospitalization rates less comparable across studies and jurisdictions. In addition, the early Omicron severity data is of limited validity due to patients with mild presentations possibly being more likely to be admitted in a hospital as a precaution, insufficient follow-up time for severe outcomes to accumulate, and not enough cases to properly represent entire populations. It should be noted, that severe outcomes are a lagging indicator meaning that severe outcomes often occur after (e.g. days or weeks) cases initially become ill. Severe outcomes trends are reflective of earlier trends in COVID-19 infections.[5] At the other end of the Omicron epidemic wave, degrading data quality from changes to testing strategies in some jurisdictions presents a challenge as the true number of cases is unknown and the case data available are influenced by testing criteria, making comparison of incidence and hospitalization curves more complicated.

Although South Africa was the first country to report Omicron and the Omicron wave in South Africa started earlier than in other countries, South African evidence of Omicron disease severity may not be generalizable to the Ontario context for a few reasons, including: differences in history of previous SARS-CoV-2 infection (i.e., previous infection expected to result in less severe illness), differences in vaccination status and vaccination program, as well as age distribution of the population.

The purpose of this document is to summarize the literature on disease severity and clinical presentation of Omicron (B.1.1.529) cases. Several rodent studies have reported evidence that Omicron is less pathogenic,[6-9] but the synthesis will focus on human studies. Local severity data from Public Health Ontario (PHO) is included.

Methods

This rapid review summarizes available evidence regarding Omicron disease severity from November 2021 to February 24, 2022, relevant to the Ontario context. The evidence in this report was identified using previous PHO COVID-19 Variant of Concern Omicron (B.1.1.529): Risk Assessments released since November 29, 2021.[3,10-19] Please see the corresponding Methods sections for more details. In brief, PHO Library Services conducted daily searches of primary and preprint literature using the MEDLINE database, as well as daily grey literature searches using various news feeds and custom search engines. If more than one publication reported the same disease severity indicators (e.g., routine reports from a public health agency), the most recent publication was used as it usually also contained the larger sample size. The Ontario COVID-19 severity data is based on the most recent available PHO Weekly Epidemiologic Summary: COVID-19 Cases with Severe Outcomes.[5]

Findings

Ontario Context

In terms of severity studies in Ontario, a matched cohort study of hospitalization and death associated with Omicron (11,622 cases) compared to Delta (14,181 cases) reported that Omicron cases had 59 (0.51%) hospitalizations and 3 (0.03%) deaths, compared to 221 (1.56%) hospitalizations and 17 (0.12%) deaths among matched Delta cases.[20] The hospitalization or death risk was 65% lower (hazard ratio, HR=0.35, 95% confidence interval [CI]: 0.26–0.46,) for Omicron cases, compared to Delta cases, and the ICU admission or death risk was 83% lower (HR=0.17, 95% CI: 0.08–0.37). To help address the possibility of incidental COVID-19 cases being counted in the severity data due to routine screening testing at hospitals, a sensitivity analysis excluded cases with a first positive specimen collection on the day of or the day prior to hospitalization and still found reduced severity of Omicron relative to Delta (HR=0.25, 95% CI: 0.16–0.41). Stratification by age, gender, and vaccination status all indicated reduced severity of Omicron.

Based on information available from CCM as of February 23, 2022:[5]

- Between December 12, 2021 and February 19, 2022, 10,502 cases of COVID-19 in Ontario had a severe outcome (hospitalized or in the ICU or died because of COVID-19), 9,531 cases were admitted to hospital, 1,380 cases were admitted to an ICU, and 2,227 cases died. A case can be counted in more than one of these categories.

- In terms of trajectory among COVID-19 cases with severe outcomes, from January 16, 2022 to February 12, 2022: weekly hospitalizations decreased from 1,649 to 624, weekly ICU admissions decreased from 240 to 90, and weekly deaths decreased from 451 to 197.

Severity

Most of the evidence suggests that Omicron causes less severe disease than other VOCs, with the comparator usually being the Delta variant, with the rare exception.[21] The evidence for pediatric cases and older individuals are highlighted due unique characteristics of these groups (e.g., vaccine eligibility, quality of immune response, additional risk due to congregate living for older people). Disease severity by vaccination status is included if it was reported. Of note, data from other jurisdictions will have varying levels of generalizability to the Ontario context due to differences in history of previous SARS-CoV-2 infection and vaccine programme, as well as age distribution of the population.

UNITED STATES (US)

- The US Centers for Disease Prevention and Control (CDC) used three surveillance systems and a large health care database to compare severity indicators across three periods: winter 2020–21, Delta predominance, and Omicron predominance.[4] In the study, the Omicron period showed lower disease severity than previous periods of high transmission, which the authors suggest is likely related to higher vaccination coverage reducing disease severity, lower virulence of Omicron, and immunity from previous infections. Although Omicron disease was less severe, the authors note it can cause higher volume healthcare utilization due to the number of cases. The highest daily 7-day moving average cases (798,976 daily cases during January 9–15, 2022), ED visits (48,238), and admissions (21,586) were reported during the Omicron period; however, the highest daily 7-day moving average of deaths (1,854) was lower during the Omicron period than during previous periods. The ratio of peak ED visits to cases (event-to-case ratios) (87 per 1,000

cases), hospital admissions (27 per 1,000 cases), and deaths (nine per 1,000 cases) during the Omicron period were lower than during winter 2020–21 (92, 68, and 16 respectively) and the Delta period (167, 78, and 13, respectively). The mean LoS (5.5 days), percentages admitted to an ICU (13.0%) or received invasive mechanical ventilation (3.5%) or died while in the hospital (7.1%) were significantly lower during the Omicron period than previous periods (Delta: 7.6 days, 17.5%, 6.6%, 12.3%, respectively).

- A retrospective cohort study examined electronic health record data of 577,938 first-time SARS-CoV-2 infected patients from a multicenter, nationwide database in the US between September 1 to December 15, 2021 (n=563,884, Delta cohort)[22] and between December 15 to 24, 2021 (n=14,054, Omicron cohort). After propensity-score matching for demographics, socio-economic determinants of health, comorbidities, medications and vaccination status, the risk of severe outcomes in the three days following infection in the Omicron cohort were less than half those in the Delta cohort: ED visit: 4.55% vs. 15.22% (risk ratio [RR]: 0.30, 95%CI: 0.28–0.33); hospitalization: 1.75% vs. 3.95% (RR: 0.44, 95% CI: 0.38–0.52]); ICU admission: 0.26% vs. 0.78% (RR: 0.33, 95% CI:0.23–0.48); mechanical ventilation: 0.07% vs. 0.43% (RR: 0.16, 95% CI: 0.08–0.32). First time SARS-CoV-2 infections that occurred during the Omicron period were associated with significantly less severe outcomes than first-time infections during the Delta period.

- A prospective cohort study conducted in California reported that over 288,534 person-days of follow-up after an outpatient positive test, 88 patients with Omicron variant infections were admitted to hospital, whereas 189 patients with Delta variant infections over 264,408 person-days of follow-up.[23] Compared to cases with a Delta infection, the unadjusted hazard ratios of ICU admission and mortality associated with Omicron variant infection were 0.26 (95% CI: 0.10–0.73) and 0.09 (95% CI: 0.01–0.75), respectively, among cases with infections first ascertained in the outpatient setting. The daily risk of mechanical ventilation for Delta patients was significantly higher compared to Omicron patients (0.04 vs 0 per 1000 person days at risk following a positive outpatient test; $p<0.001$). The estimated median LoS for symptomatic Omicron patients was 1.5 (1.3–1.6) days, with 90% of patients expected to complete hospitalizations within 3.1 (2.7–3.6) days. Among symptomatic hospitalized Delta patients, the median LoS was 4.9 (4.3–5.6) days.

- In a cohort of COVID-19 infections in a Houston, Texas hospital system, of 862 Omicron infections, 15% of cases were admitted and 0.9% of cases died. Of 15,639 Delta infections, 43% were admitted, and 5.3% died.[24] Of note, Omicron cases were much younger and much more likely to have received at least two vaccinations.

- Using COVID-19 surveillance and immunization registry data, the Los Angeles County Department of Public Health explored COVID-19 hospitalization rates by COVID-19 vaccination status and variant predominance.[25] In the last week of Delta predominance, the hospitalization rates among unvaccinated persons were 83.0 times that of fully vaccinated persons with a booster and 12.9 times that of fully vaccinated persons without a booster. During the Omicron period, unvaccinated persons had a hospitalization rate 23.0 times that of fully vaccinated persons with a booster and 5.3 times that of fully vaccinated persons without a booster.

- Using remnant clinical specimens from Johns Hopkins Medical System, an evaluation was conducted of clinical outcomes between Delta and Omicron infections during the period when both variants were co-circulating. The study revealed that Omicron cases (N=1,121) were less likely than Delta cases (N=910) to be admitted to hospital (3 % vs 13.8 %, $p < 0.00001$), require ICU care (0.5% vs 3.5%, $p < 0.00001$), or die as a result of their infection (0.1 vs 1.1, $p = 0.004$),

regardless of vaccination status.[26] Of note, Omicron cases were younger (median age 32 years vs 197 35, $p < 0.001$) and significantly more likely to be vaccinated than Delta cases ($p < 0.00001$)

EUROPE

- Preliminary analysis of case-based data submitted by 15 European Union (EU)/European Economic Area countries to The European Surveillance System (TESSy) between week 46 2021 and week 2 2022 reported that Omicron infection was less likely to be reported with admission to hospital compared to Delta infections (aOR 0.41; 95% CI: 0.37–0.46).[27] Among Omicron cases with known outcomes reported into TESSy as of January 19, 2022, 884 (1.14%) were hospitalized, 120 (0.16%) required ICU admission/respiratory support, and 48 (0.06%) died.

- A retrospective cohort study in France investigated 149,064 COVID-19 cases, of which 497 had a serious hospital event (447 Delta, 50 Omicron), which was defined as admission to the ICU or admission to a critical care unit or death.[28] The risk of a serious event was lower among Omicron cases compared to Delta cases (adjusted HR [aHR] = 0.13 95% CI 0.09–0.18 in 18 to 79 year olds, aHR=0.30 95% CI 0.17–0.54 in 80 years and older; risk adjusted for age, sex, vaccination status, presence of comorbidity and region of residence). Risk increased with age, and was higher in cases with comorbidities (aHR = 3.70, 95% CI 2.66–5.13 fort 18-79 year olds with very-high-risk comorbidity versus no comorbidity) and in males.

    - Risk was lower in vaccinated compared to unvaccinated cases, without interaction between variant and vaccination status (aHR=0.15 95% CI 0.11–0.19 for 18-79 year olds with primary vaccination versus unvaccinated).

- A single-centre retrospective cohort study in France characterized the first 1,119 cases of Omicron at a hospital, and compared them to 3,075 Delta cases occurring at the same time period.[29] Among Omicron cases, most (63.55%) of the patients were symptomatic. The hospitalization rate was low (1.9%), and the median age of hospitalized patients was 49 years. One patient required intensive care. In contrast to Omicron cases, Delta cases during the same time period were significantly older, more likely to be symptomatic (77.6%), and the hospitalization rate was 6.2 times higher, transfer to ICU was 31 times more frequent, and mortality rate was 13 times higher. Of note, the Omicron cases were significantly younger.

    - Of the 826 Omicron cases with known vaccination status, 46.4% were vaccinated (7.8% having one dose, 67.1% two doses, 24.8% three doses, and 0.3% four doses). Compared to Omicron cases, the Delta cases were significantly less likely to be vaccinated (40.4%).

- A cohort study (N=15,978) in Portugal compared the risk of severe disease among patients infected with Omicron (N=6,581) or Delta (N=9,397), in the same time period, adjusting for sex, age, previous infection, and vaccination status.[30] In the Delta group, 148 (1.6%) were hospitalized, and in the Omicron group, 16 (0.2%) were hospitalized. From the 26 total deaths, all were in the Delta group. Adjusted HR for hospitalization for the Omicron group compared with Delta was 0.25 (95% CI 0.15–0.43). The LoS for Omicron patients was significantly shorter than for Delta (confounding-adjusted difference -4.0 days [95% CI -7.2 to -0.8]). The odds of death were 0.14 (95% CI 0.00–1.12), which translates to a reduced risk of death of 86% for the Omicron group, compared with Delta. The authors concluded that Omicron was associated with a 75% risk reduction of hospitalization compared with Delta and reduced LoS.

SCANDANAVIA

- A Swedish study of Omicron disease severity in risk groups defined by sex, age, comorbidities, and vaccination status was conducted using three calendar periods (55,269 cases): i) Delta dominant, ii) transition to Omicron period, and iii) Omicron dominant (74% sample prevalence week 52 of 2021, 88% sample prevalence week 1 of 2022).[31] After adjusting for age, sex, comorbidities, prior infection, booster dose, and time since last dose among the vaccinated, the odds of severe COVID-19 was 40% lower (95% CI 18–56% lower) among unvaccinated and 71% lower (95% CI 54–82% lower) among vaccinated individuals during the Omicron period compared to the Delta period.
    - Vaccine effectiveness (VE) against severe COVID-19 was estimated monthly, and remained stable around 90% across all periods.
- Individual-level data from the Norwegian Preparedness Registry was used to estimate the risk of hospitalization for Omicron cases (39,524) compared with Delta cases (51,481), as well as the LoS, risk of admission to an ICU and deaths.[32] Of the Omicron cases, 91 (0.2%) were hospitalized, whereas 552 (1.1%) of Delta cases were hospitalized. Omicron was associated with an overall 73% reduced risk of hospitalization (aHR = 0.27; 95% CI: 0.20–0.36) compared with Delta. The crude median LoS for Omicron patients was 2.8 days (interquartile range [IQR]: 1.6–6.8) compared with 6.5 (IQR: 3.2–12.3) among Delta patients. Seven Omicron patients (7.7%) were admitted to an ICU, compared with 135 (24%) Delta patients. The aHR for discharge for Omicron patients compared with Delta patients was 1.44 (95% CI: 0.99–2.07), which represents an expected 31% shorter LoS (95% CI: 1% longer–52% shorter). The aHR for the risk of ICU admission for Omicron patients compared with Delta patients was 0.51 (95% CI: 0.20–1.29).
    - The reduced risk of hospitalization for Omicron as compared to Delta was smaller among cases who completed a primary vaccination schedule 7–179 days before their positive test, as compared with unvaccinated cases (66% for Omicron vs 93% for Delta with CI that did not overlap). Having a third vaccine dose yielded a similar reduction in hospitalization risk for Omicron and Delta cases, compared to unvaccinated cases (86% and 88% respectively with overlapping CI). Of note, Omicron cases who had partially completed a primary vaccination series or who had completed primary vaccination with maximum two doses ≥ 180 days before positive test had no significant decrease in risk compared with unvaccinated.

UNITED KINGDOM (UK)

- An UK Health Security Agency (UKHSA) report found that the risk of presentation to emergency care or hospital admission with Omicron was roughly half of that for Delta (HR 0.53, 95% CI: 0.50–0.57).[33] The risk of hospital admission from ED for Omicron was approximately one-third of that for Delta (HR 0.33, 95% CI: 0.30–0.37). The analyses were adjusted for age, sex, ethnicity, local area deprivation, international travel, vaccination status, and whether the current infection was a known reinfection.
    - The UKHSA report that the risk of hospitalization is lower for Omicron cases after two and three doses of vaccine, with an 81% (77 to 85%) reduction in the risk of hospitalization after three doses as compared to unvaccinated Omicron cases.
- Imperial College examined UKHSA and National Health Service data in England for cases with specimen collection dates between December 1 and 14, 2021 and indicated a reduction in the risk of hospitalization for infection with Omicron relative to the Delta variant.[34] Omicron cases were estimated to have a 20-25% reduced risk of any hospitalization (including Accident and Emergency departments) and a 41% (95% CI: 37%–45%) reduced risk of a hospitalization resulting in a stay of one or more nights. Since COVID-19 reinfections are associated with milder disease, the study assumed 33% of true reinfections were correctly identified as such. The corrected estimates resulted in a lower reduction in Omicron hospitalization compared to Delta (from 0-30%), and a higher reduction in the risk of hospitalization associated with reinfection (of approximately 55-70%).
    - Stratification by vaccination status revealed that cases vaccinated with two doses of Pfizer or Moderna had a similar or higher risk of hospitalization with Omicron as compared to Delta, but cases with AstraZeneca as their primary series vaccination tended to have a lower risk of hospitalization relative to Delta.
- A national nested test negative study in Scotland analyzed 119,100 non-S-gene target failure (SGTF) cases (surrogate for Delta) and 22,205 SGTF cases (surrogate for Omicron) between November 1 and December 19, 2021. There were 15 hospital admissions in the SGTF group, which translated to SGTF case hospitalizations being 0.32 times (95% CI 0.19–0.52) the expected hospitalizations compared to non-SGTF cases.[35] Of note, 10 times more SGTF cases were possible reinfections compared to the non-SGTF cases (7.6% versus 0.7%).
    - A third vaccine dose was associated with a 57% (95% CI 55–60) reduced risk of symptomatic SGTF infection as compared to ≥25 weeks post-second dose.
- A study of sentinel hospitals in the Greater Manchester area found that the proportion of Omicron in hospital samples followed a similar trajectory to the SGTF proportion in cases, but with a two-day offset, which is consistent with the lag between testing positive to hospital admission, suggesting a similar proportion of Omicron cases were becoming hospital admissions as was the case for Delta.[21] Of note, these analyses were conducted early in the Omicron wave during exponential case growth in Manchester, which could impact the representativeness of the cases being identified.

SOUTH AFRICA

Due to notable differences in history of previous SARS-CoV-2 infection and vaccine programme, as well as age distribution of the population in South Africa as compared to Ontario, select studies are highlighted below based on their sample size, or progress through an Omicron wave, or if they adjusted severity analyses for previous infection and vaccination. Additional studies of Omicron severity in South Africa can be found in the PHO COVID-19 Variant of Concern Omicron (B.1.1.529): Risk Assessments.[36-39]

- A South African study comparing SGTF (surrogate for Omicron cases), non-SGTF, and Delta cases reported that after controlling for factors associated with hospitalization, SGTF cases had significantly lower odds of admission than non-SGTF cases (256/10,547 [2.4%] vs 121/948 [12.8%]; adjusted odds ratio [aOR] 0.2, 95% CI 0.1–0.3),[40] which is an 80% lower odds of being admitted to hospital compared to non-SGTF infections. Differences in severity of disease among hospitalized SGTF and non-SGTF cases was less clear potentially because of the low numbers of individuals in the analysis. After controlling for disease severity factors, the odds of severe disease were comparable between hospitalized SGTF versus non-SGTF infections (42/204 [21%] vs 45/113 [40%]; aOR 0.7, 95% CI 0.3–1.4), and SGTF-infected individuals had significantly lower odds of severe disease (496/793 [62.5%] vs 57/244 [23.4%]; aOR 0.3, 95% CI 0.2–0.5), as compared to individuals with earlier Delta variant infections.

- A cohort study in South Africa of 5,144 patients from wave four (Omicron) and 11,609 from prior waves used Cox regression analysis to compare the risk between waves for death and severe outcomes ≤ 14 days after diagnosis.[41] After adjusting for age, sex, comorbidities and sub-district there was a substantially reduced hazard of death in the Omicron wave compared to the previous wave (aHR 0.27; 95% CI: 0.19–0.38), which was attenuated (0.41; 95% CI 0.29–0.59) when adjusted for prior infections and vaccination. The hazard of reduced severity showed a similar pattern to severe hospitalization and death.

    - Protection by vaccination against outcomes was similar in the Omicron wave compared to previous wave: protection against death from full vaccination aHR (95% CI) was 0.24 (0.10–0.58) during Omicron and 0.35 (0.22–0.54) near the end of the previous wave. Protection by prior infection against hospitalization or death was aHR (95% CI) of 0.32 (0.20–0.52) in late wave three and 0.13 (0.06–0.27) during Omicron. Even after accounting for previous infections, there was a 25% reduction in severe hospitalization or death in the Omicron wave compared to the previous wave. Of note, for all outcomes, the reduced risk during the Omicron wave was attenuated with adjustment for prior diagnosed infection and vaccination.

- A study in South Africa reported that Omicron cases (identified using a surrogate marker from the PCR platform used)(n=1,486) had a lower hazard of hospital admission (aHR of 0.56, 95% CI 0.34–0.91), than Delta cases (n=150).[42] Adjustments were made for vaccination status, prior infection, and comorbidities. Of note, age and proportion of cases fully vaccinated were similar between Omicron and Delta cases.

    - Complete vaccination was protective of admission for Omicron and Delta cases, with an aHR of 0.45 (95%CI 0.26–0.77).

OMICRON SEVERITY IN PEDIATRIC CASES

Several of the reports in this synthesis described Omicron cases as younger than other VOC cases (usually Delta), but it is unclear how increased transmissibility, vaccine programming and coverage, and the school year might have influenced these findings. Children comprising a larger proportion of Omicron cases than other VOC cases does not necessarily mean that Omicron causes more severe disease in children.[43]

- A retrospective cohort study examined electronic health record data of 577,938 first-time SARS-CoV-2 infected patients from a multicenter, nationwide database in the US between September 1, 2021 and December 24, 2021, including 14,054 infected between December 15 to 24, 2021 (Omicron cohort) and 563,884 infected between September 1 and December 15, 2021 (Delta cohort).[22] Among the children under 5 years old (unvaccinated), the overall risks of ED visits and hospitalization in the Omicron cohort were 3.89% and 0.96% respectively, significantly lower than 21.01% and 2.65% in the matched Delta cohort (RR for ED visit: 0.19, 95% CI:0.14–0.25; RR for hospitalization: 0.36, 95% CI: 0.19–0.68). Similar trends were observed for other pediatric age groups, adults (18-64 years) and older adults.

- A retrospective analysis of health administrative data from an ED in the US compared reports of croup from the Delta dominant period (N=401) and the initial phase of the Omicron surge (N=107).[44] Patients who presented with croup during the Omicron surge were more likely to test positive for COVID-19 (48.2% vs 2.8%, $p<0.0001$), and the incidence of croup almost doubled as compared to the rate in previous months. No differences were observed in presenting age, rate of admission, rate of return to the ED within 72 hours, or admission among those who returned within 72 hours, between the Delta and Omicron periods. Of note, at the same time, there was a decreased in the number of cases of parainfluenza virus.

- The UKHSA reported that the number of pediatric admissions with any COVID-19 infection (>90% of UK samples were Omicron at end of November 2021) began increasing from December 26, 2021, from an average of 40 admissions per day to 120 per day, which is a 3-fold rise in 2 weeks.[45] The increase was most rapid among children under 5 years old, and was highest in infants aged under 1 year. The most common three symptoms were consistent with respiratory infection (not specified). However, The Royal College of Pediatrics and Child Health issued a statement that pediatricians are not reporting Omicron to be a more serious or severe disease in children and young people in the UK.

- Data from South Africa's largest private health insurer reported that during the first half of the Omicron wave, children had a low test-positivity rate compared to adults, and low number of COVID-19 admissions, but appeared to be at 20% greater risk of hospitalization relative to the D614G wave.[38]

- In a cohort of 6,287 pediatric COVID-19 cases in Tshwane District, South Africa, 183 were hospitalized (newborn to 13 years old). Detailed clinical information was available for 139 (76%) of the 183 children hospitalized.[46] Most of the admissions were in the <1 year age group (35%), and 62% of children in the 0-4 years category. For those hospitalized, mean length of hospital stay was 3.2 days. Of 6,287 pediatric (≤19 years) cases, 462 (7.2%) were hospitalized which was an unexpected rise from the first three waves.

OMICRON SEVERITY IN OLDER INDIVIDUALS

- A cohort study of long-term care facility residents in England compared the risk of hospital admission or death in residents who tested positive for SARS-CoV-2 in the period shortly before Omicron emerged (Delta dominant) and the Omicron-dominant period, with adjustments for age, sex, vaccine type, and booster vaccination.[47] The risk of hospital admission was substantially higher in 398 residents infected in the Delta-dominant period (10.8% hospitalized, 95% CI: 8.13–14.29) compared to 1,241 residents infected in the Omicron-period (4.01% hospitalized, 95% CI: 2.87–5.59, adjusted HR 0.50, 95% CI: 0.29–0.87, p=0.014). No residents with previous infection were hospitalized in either period. Overall, mortality was lower in the Omicron versus the pre-Omicron period, (p<0.0001).
    - Reduced risk of hospital admission in the Omicron versus pre-Omicron period was also reported in residents irrespective of whether they had a primary course of AstraZeneca or Pfizer COVID-19 vaccine, or remained unvaccinated.
- A Swedish study (N=55,269) investigated COVID-19 disease severity by comparing the Delta dominant period, the transition to Omicron period, and the Omicron dominant period.[31] The risk for severe COVID-19 remained high among unvaccinated, first-time infected cases of both sexes during the Omicron period in individuals over 65 years old and among males in the age group 40-64 years with two or more comorbidities. The risk of severe COVID-19 for vaccinated cases below 65 years was low for both sexes during Omicron, even with comorbidities, but risk of severe COVID-19 remained high for vaccinated cases over 65 years old during Omicron only in the presence of at least one comorbidity (males) or at least two comorbidities (females).
- A retrospective cohort study from France (described earlier, serious hospital events: 447 Delta, 50 Omicron), reported that the risk of a serious event was lower among Omicron cases compared to Delta cases and increased with age (aHR=0.13 95% CI 0.09–0.18 in 18 to 79 year olds, aHR=0.30 95% CI 0.17–0.54 in 80 years and older; risk adjusted for age, sex, vaccination status, presence of comorbidity and region of residence).[28] Risk was higher in cases with comorbidities (aHR=3.70, 95% CI 2.66–5.13 for 18-79 year olds with very-high-risk comorbidity versus no comorbidity) and in males.
    - Risk was lower in vaccinated compared to unvaccinated cases, without interaction between variant and vaccination status (aHR=0.15 95% CI 0.11–0.19 for 18-79 year olds with primary vaccination versus unvaccinated).

Symptoms and clinical presentation

In general, Omicron cases have reported sore throat and fatigue more often than cases infected with other VOCs. Reports of loss of sense of smell or taste are less common than previous strains. As a result, symptom-based screening tools and algorithms used previously for COVID-19 are less likely to identify those infected with the Omicron VOC. Select studies are reviewed below.

- The UK Covid-19 Infection Survey reported that individuals with Omicron-compatible infections were significantly less likely to report loss of taste or loss of smell than people with Delta-compatible infections.[48-50] In December 2021, which was an Omicron-dominant period, 58% (95% CI: 57%–59%) of people testing positive for COVID-19 reported symptoms, which was a decrease from November 2021 (pre-Omicron), when 65% (95% CI: 63%–67%) of people testing positive reported symptoms. Omicron infections were associated with fewer lower respiratory tract symptoms and more upper respiratory tract symptoms, and increases in sore throat. The authors note, however, that the percentage of people reporting a sore throat who tested negative for COVID-19 had also increased at the time, suggesting the higher frequency of sore throat in Omicron cases could be due to other infections, such as the common cold or flu. A UKHSA analysis of NHS Test and Trace data found that loss of smell or taste was reported less often by Omicron cases than Delta cases (13% of Omicron cases, as compared to 34% of Delta cases, resulting in an aOR: 0.22 (95% CI: 0.21–0.23), but sore throat was reported more often by Omicron cases (53% of Omicron cases, 34% of Delta cases, aOR: 1.93, 95% CI: 1.88–1.98).[45]

- There were a few analyses of health app data and internet searches, comparing the Omicron period to periods dominated by other VOCs. The Zoe COVID Study app is a symptom tracking app based in London, England that was launched at the end of March 2020 by health science company ZOE with scientific analysis provided by King's College London.[51] Analysts compared reported COVID-19 symptoms from the Delta-dominant wave and part way into the Omicron-dominant wave and found no clear difference in symptom profile of the top five symptoms in both VOC (runny nose, headache, fatigue, sneezing, and sore throat).[52-54] The analysis identified only 50% of Omicron cases experience the classic three COVID-19 symptoms of fever, cough, and loss of sense of smell/taste. Though not the most prevalent symptoms reported, new symptoms of Omicron include loss of appetite and brain fog (e.g. memory problems, difficulty concentrating, and not being able to think clearly).[55] A Google Trends analysis investigating COVID-19 signs and symptoms during a period when Omicron represented >80% of cases in the UK compared to a period when the Alpha variant was dominant, found that conjunctivitis, chills, cough, aches, fever, nausea and sore throat were more searched in the Omicron period compared to the Alpha period (>15% increase).[56] In contrast, tiredness, loss of taste or smell, sneezing and shortness of breath were less searched in during Omicron compared to Alpha periods (>15% decrease). The number of Google searches for headache, diarrhea and runny nose were nearly comparable between the two periods (i.e., <15% variation).

- In addition to the more common symptoms for Omicron: runny nose, headache, fatigue (both mild and severe), sneezing, sore throat, as well as loss of appetite and brain fog (more common in those who were fully vaccinated and boosted), a media outlet reported night sweats as a symptom based on information from a UK physician and a US physician.[57]

- An analysis in Norway of the immune recall responses to Omicron and Delta in whole blood in 51 vaccinated individuals infected with Omicron, in 14 infected with Delta, and in 18 healthy controls, using 7 and 14 days after symptom onset for sample collection reported that patients had mild symptoms and few differences in symptoms were observed between Omicron and Delta infected patients. However, smell/taste symptoms were frequent in Delta patients (72%), but infrequent in Omicron patients (15%, $p<0.001$).[58] A larger proportion of Delta patients experienced concentration difficulties ("brain fog", 33%) as compared to Omicron patients (10%, $p=0.017$).

Limitations & Conclusions

- The studies reviewed used different methods to identify Omicron cases, including whole genome sequencing, local estimates of VOC epidemiology over time; i.e., Delta-dominant period vs Omicron-dominant period, and SGTF. The latter two are less precise that WGS and could therefore incorrectly classify a SARS-CoV-2 case as Omicron.

- Pre-existing immunity likely accounts for some of the perceived milder severity of Omicron. As a result, the studies that compared Delta and Omicron case severity at the same time period would best address this. Otherwise differences in severity are likely confounded by vaccination status (e.g., doses, time since last dose) or previous infections.

- The studies varied in how they defined a COVID-19 ED visit or hospitalization in terms of how long before or after did the case tested positive for COVID-19. This is particularly relevant in settings where COVID-19 prevalence was high and screening was routine in hospitals, resulting in individuals presenting for a non-COVID-19 concern and not receiving COVID-19 care, but possibly being counted as a case.[43] The situation is more nuanced than hospitalized COVID-19 cases possibly being overestimated because more evidence is emerging that COVID-19 can trigger existing health issues or cause new ones, which do not present with typical COVID-19 symptoms.

- Early Omicron severity data may have limited validity due to patients with mild presentations being more likely to be admitted to hospital as a precaution, insufficient follow-up time for severe outcomes to accumulate, and not enough cases to properly represent entire populations. In fact, there is data to suggest older age groups experienced an Omicron peak later than younger age groups suggesting Omicron peaks may be age differential.[59,60] As a result, severity studies conducted before the completion of a pandemic wave may misrepresent the true burden and risk for some age groups.

- There is strong evidence that infection with the Omicron variant causes less severe disease compared to the Delta variant, but can still cause severe disease in unvaccinated individuals. There is moderate evidence that Omicron infections can still be severe in older age groups and individuals with comorbidities. Community-based public health measures therefore remain important to protect vulnerable groups who are at highest risk of severe outcomes.[61] Although there is no evidence that Omicron causes more severe disease in children than previous variants, the evidence base is small, and the increased risk of infection due to community prevalence of a more transmissible variant, coupled with growing evidence of long-term COVID outcomes and limited vaccine eligibility in the pediatric population,[62] suggests children are a vulnerable group. When Omicron waves subside in more jurisdictions and time passes, a more complete picture of Omicron severity, including hospitalization outcomes, mortality and long-COVID outcomes, will emerge.

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