Viral dynamics of the SARS-CoV-2 Omicron Variant among household contacts with 2 or 3 COVID-19 vaccine doses

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SUMMARY

Objectives: SARS-CoV-2 shedding has changed as new variants have emerged. It is important to understand the trajectory of PCR positivity due to Omicron in vaccinated populations.

Methods: Double- or triple-vaccinated adult household contacts of individuals with COVID-19 self-collected oral-nasal swabs for 14 days. A hierarchical linear model estimated viral load trajectories and an exploratory logistic regression model assessed for factors associated with viral detection before symptom onset.

Results: Forty-one participants developed COVID-19 with 37 (90%) symptomatic. Viral load peaked 3 days after symptom onset at a median concentration of 8.83 $\log_{10}$ copies/milliliter (range 5.95–10.32) and the mean difference between participants with two or three COVID-19 vaccine doses was 0.02 $\log_{10}$ copies/milliliter (95% CI -0.13 to 0.16). PCR positivity began with a range of 4 days prior to 3 days after symptom onset and was positive on the day of symptom onset in 76% (28/37). SARS-CoV-2 detection on the day of symptom onset was less likely among those with 2 vaccine doses (OR 0.13, 95%CI 0.02–0.79). 68% (25/37) of infected participants had detectable SARS-CoV-2 with Ct<30 at 7 days after symptom onset.

Conclusions: Peak viral load and duration of PCR positivity were similar in participants with COVID-19 after two versus three COVID-19 vaccine doses. Onset of viral detection relative to symptom onset was variable.

Introduction

The SARS-CoV-2 Omicron variant has rapidly become dominant worldwide. At the outset of the pandemic, individuals infected with SARS-CoV-2 were observed to shed virus prior to the development of symptoms, achieve a peak viral load 2-3 days following symptom onset and remain communicable to others for approximately 9 days.[1–3] As new variants emerged, the viral kinetics changed: the Alpha and Delta variants exhibited a shortened duration of shedding and shorter time to peak shedding.[4] The Omicron variant appears to be more transmissible than earlier variants, which might be due to one or a combination of increased shedding, altered binding affinity, or immune evasion.[5–7] Determining the viral shedding dynamics of Omicron is crucial to understand the reason for enhanced transmissibility and to inform public health interventions.

The kinetics of viral shedding of the Omicron variant are as yet not well understood. Initial reports suggest that viral shedding of Omicron is highly variable, with a tendency to a lower peak concentration and a shorter total duration of shedding as compared to Delta.[6] COVID-19 immunization may be partially responsible for changes in the pattern of viral shedding of the Delta variant as compared to earlier variants, but whether a third vaccine dose alters the viral trajectory is unknown.[4] In addition, existing studies

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of the kinetics of the Omicron variant have not characterized viral detection in relation to symptom onset. We sought to characterize the viral kinetics of the Omicron variant among household contacts of individuals with COVID-19 who received either 2 or 3 COVID-19 vaccine doses in a prospective cohort from Toronto, Ontario.

Methods

Study population

Eligible participants were consecutive adults (18 years or older) who were a household contact of a person with a positive SARS-CoV-2 test between December 19, 2021 and January 23, 2022. Participants were asymptomatic at the time of enrollment, did not have a reported prior episode of COVID-19, had received at least two doses of a Health Canada approved COVID-19 vaccine (one or more of Comirnaty[TM] by Pfizer, Spikevax[TM] by Moderna, or Vaxzevria[TM] by Astra Zeneca) and provided informed consent. The study was approved by the Michael Garron Hospital Research Ethics Board.

Specimen collection

Each participant self-swabbed the back of the tongue, buccal mucosa, and anterior aspect of both nares daily for 14 days .[8,9] Specimens were placed into guanidine thiocyanate-based transport medium (McMaster Molecular Medium, Bay Area Health Trustee Corp, Canada) or viral transport medium (Copan Diagnostics Inc, Murrieta, California), and refrigerated at home until all 14 specimens were collected, which is expected to maintain testing integrity.[10] All specimens from each participant were retrieved by a courier and transported to the study laboratory where aliquots were created then stored frozen at -80 ^{0}C until analyzed.

Laboratory analysis

A 140 μL aliquot of transport medium was extracted on the MGISP-960 automated workstation using the NUCLISENS easyMAG extraction kit (bioMérieux, North Carolina, USA). Detection of the SARS-CoV-2 E-gene and 5′-UTR and the internal control (RNase P) was performed using the Luna Universal Probe One-Step RT-qPCR kit (New England Biolabs, Whitby, Ontario) on the Rotor-Gene Q Real-time PCR detection system (Qiagen, Hilden, Germany) as previously described[8]. Standard curves were used to quantify viral load in $\log_{10}$ copies per milliliter of the E-gene. Whole genome sequencing of specimens was performed as previously described.[11]

Analysis

Demographic information was presented with medians and interquartile ranges for continuous variables and proportions for categorical variables. The primary outcome was the daily $\log_{10}$ SARS-CoV-2 copies per milliliter standardized to the day of self-reported symptom onset as day 0. The viral trajectory from the time of symptom onset was characterized using a hierarchical generalized additive model with Gaussian distribution and a log link along with a smoothing spline placed on time (measured in days) to allow for non-linear effects. This allowed for overall and individual $\log_{10}$ viral trajectories to be modeled. A similar model was used to compare the average trajectories between participants with two versus three COVID-19 vaccine doses by evaluating the interaction between vaccine dose and time. A sensitivity analysis was performed on participants who had at least one negative swab prior to a positive swab with time standardized to the date of the first positive test. Exploratory analyses used logistic regression models to determine if age in decades, sex, an underlying illness or number

Table 1

Characteristics and outcomes of household contacts of individuals with COVID-19 who subsequently test positive for COVID-19 stratified by the number of COVID-19 vaccine doses received.

Characteristic	Number of COVID-19 vaccine doses received		p value
	Two ($n = 19$)	Three ($n = 22$)	
Median age (range)	42 yrs ([19]-60)	41 yrs (32–62)	0.90
Sex (% female)	11 (58%)	13 (59%)	1.00
Any chronic illness[1]	7 (37%)	7 (32%)	0.99
Vaccine received			
Comirnaty[TM]	10 (53%)	9 (41%)	<0.001
Spikevax[TM]	5 (26%)	3 (14%)	
Vaxzevria[TM]	1 (5%)	0 (0%)	
Mixed	3 (16%)	10 (45%)	
Median days since most recent vaccine dose (IQR)	188 (180–194)	27 (14-47)	<0.001
Developed COVID-19			
With any symptom	16 (84%)	21 (96%)	0.50
With febrile illness	0 (0%)	3 (14%)	0.28
Positive PCR on day of symptom onset[2]	9/16 (56%)	19/21 (90%)	0.03
Viral Load characteristics			
Peak concentration in median $\log_{10}$ copies/ml (IQR)	8.7 (8.3–9.2)	8.7 (8.4–9.1)	0.51
Median day of peak concentration (range)	3 (0–8)	3 (0–9)	0.53
Median days of PCR positivity before symptoms[2] (range)	0 (−2–3)	0 (−4–2)	0.04
All specimens on/after day 7 negative	4 (21%)	1 (5%)	0.26

[1] One participant was potentially mildly immunocompromised (systemic lupus erythematosus stable on hydroxychloroquine); other chronic illnesses included one of hypertension, diabetes, inflammatory bowel disease, rheumatoid arthritis, asthma.

[2] Could only be evaluated in the subset ($n = 37$) of participants who developed symptoms.

of vaccine doses were associated with viral detection on the day of symptom onset. All analyses were performed in R version 4.1.2 with the 'mgcv' package used for the generalized additive model.

Results

Overall, 91 adult household contacts of an individual with COVID-19 consented to participate, with 91% (83/91) returning self-collected swabs. Of these, 95% (79/83) collected all 14 daily swabs (the remaining 4 collected 13) and 86% (71/83) of the cohort collected specimens in molecular transport media with the remainder using viral transport media. Overall, 54% (45/83) reported developing symptoms, of whom 82% (37/45) had at least one swab with SARS-CoV-2 detected ; 11% (4/38) who were asymptomatic also had at least one positive swab. Of the 41 participants with infection, 15 (37%) had detectable SARS-CoV-2 on their first swab. The median age of the infected cohort was 41 years (range 19–62 years), 59% (24/41) were female, 46% (19/41) had received two COVID-19 vaccine doses and none self-reported a previous infection (Table 1). Sequences were available for 98% (40/41) of participants or their household member with 90% (37/41) of specimens sequenced successfully from the study participants and 7% (3/41) from another infected household member. All specimens were identified as the Omicron variant (12 BA.1 and 28 BA.1.1). In the 7 households with more than one member with detectable SARS-CoV-2 the variants were identical.

Of the 37 infected participants who were symptomatic, 76% (28/37) had a swab positive for SARS-CoV-2 on the day of symptom onset. Initial detection was as early as 4 days prior and as late as 3 days after symptom onset (Fig. 1). No participant received a COVID-19 specific therapy and none were hospitalized in the subsequent 28 days.
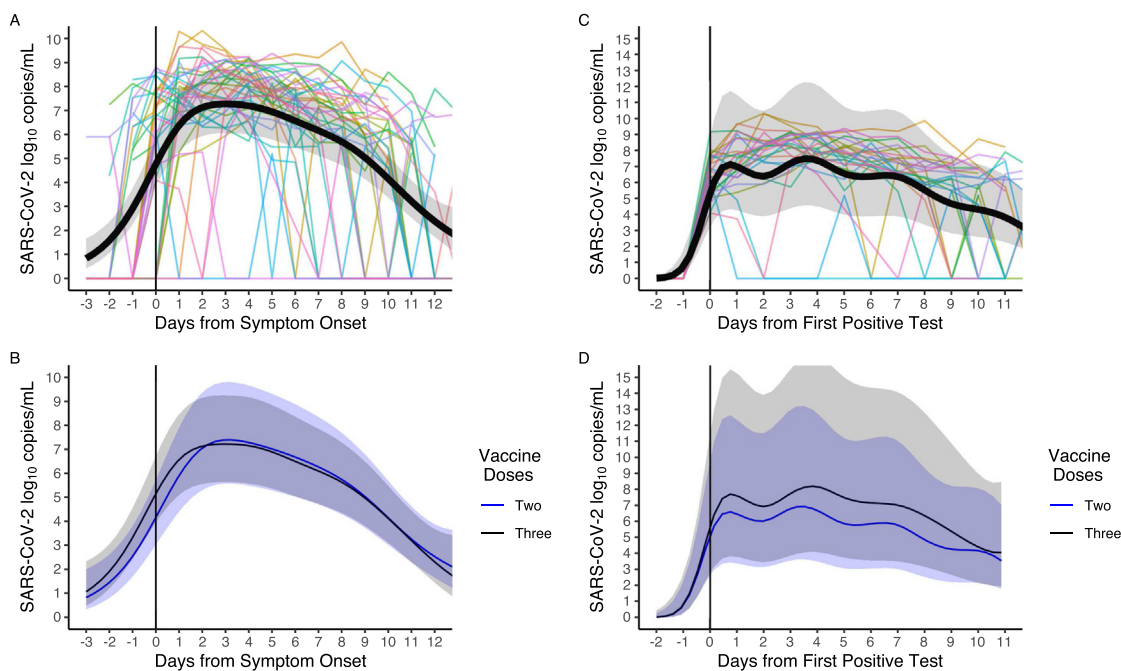
Fig. 1. SARS-CoV-2 viral load trajectories from self-collected oral-nasal swabs standardized to the date of symptom onset for the 37 participants with symptoms (A, B) and from the first positive swab in the 26 participants with at least one preceding negative swab (C, D). Each participant's viral load trajectory is represented along with the modeled trajectory using a generalized additive model with a smoothing spline placed on the time for the overall cohort (A, C). The viral load trajectories of participants with 2 or 3 COVID-19 vaccine doses are also depicted (B, D).

Table 2

Odds ratios for characteristics associated with SARS-CoV-2 detection on the day of symptom onset in 37 symptomatic participants. Multivariable logistic regression adjusted for age per decade, sex at birth, any underlying medical condition and number of vaccine doses was used.

Characteristic	OR (95% CI)	p value
Age (per decade)	1.21 (0.39–3.69)	0.74
Sex: Female	Ref	0.96
Male	1.05 (0.18–6.19)	
Chronic underlying illness:	Ref	0.75
None	1.41(0.17–11.61)	
Present		
Previous COVID-19 vaccine:	Ref	0.03
Three doses	0.13(0.02–0.79)	
Two doses		

There was variability in the SARS-CoV-2 viral trajectories (Fig. 2). Overall, the proliferation phase of SARS-CoV-2 PCR positivity was steeper than the clearance phase. Peak viral load occurred at a mean of 2.97 days following symptom onset with a median viral load of 8.83 $\log_{10}$ copies per milliliter (range 5.95–10.32 $\log_{10}$ copies per milliliter). When time was standardized to the first positive test among participants with at least one preceding negative swab, peak viral load occurred at a mean of 2.89 days after first positive test with a viral load of 9.02 $\log_{10}$ copies per milliliter (range 6.17–10.32 $\log_{10}$ copies per milliliter). The viral trajectories between participants with two COVID-19 vaccine doses and those with three doses were similar with a mean difference in daily viral load of 0.02 $\log_{10}$ copies per milliliter (95% CI −0.13 to 0.16 $\log_{10}$ copies per milliliter). There was no difference in time to peak viral load between those with two or three COVID-19 doses when restricting the analyses to participants with at least one negative swab prior to a positive (Fig. 1).

In exploratory multivariable analyses, having received 2 vaccine doses was associated with a lower likelihood of SARS-CoV-2 PCR positivity on the day of symptom onset with an odds ratio (OR) of 0.13 (95% CI 0.02–0.79, $p = 0.03$) (Table 2). When evaluating only

the 24 symptomatic participants with at least one negative swab preceding the first positive swab, the odds of SARS-CoV-2 PCR positivity prior to symptom onset was lower with 2 vaccine doses (OR 0.09, 95% CI 0.01–0.95, $p = 0.04$).

Overall, 85% (35/41) of participants had a positive test on day 7 from the first positive test with 66% (27/41) having a cycle threshold of less than 30 (Fig. 3). Among those with symptoms, 68% (25/37) had detectable SARS-CoV-2 with a cycle threshold below 30 at 7 days after symptom onset.

Discussion

Our study demonstrated substantial variability in SARS-CoV-2 PCR positivity among vaccinated participants infected with the Omicron variant: peak concentrations varied over 4 logs, virus was first detectable by PCR from 4 days before until 3 days after the onset of symptoms and 85% of participants continued to be PCR positive after day 7 of symptoms. The main difference in SARS-CoV-2 PCR positivity between participants with two versus three COVID-19 vaccine doses was that it started earlier in relation to symptoms in the latter group. In contrast, when evaluating the timing of PCR positivity among those with at least one negative swab prior to viral detection, no difference in the trajectories were observed.

The relatively rapid increase in viral load followed by a more gradual decline in our cohort is similar to that reported by a study from the National Basketball Association.[6] Our study extends these findings by recruiting exposed household contacts, which permitted an assessment of the degree of heterogeneity in viral load prior to symptom onset. We found that approximately one-quarter of cases do not have detectable virus by PCR on the day symptoms begin, which may explain why negative tests (either lateral flow or PCR) early in illness are relatively common.[12] The variability in the onset of SARS-CoV-2 PCR positivity related to the timing of symptom onset among individuals who are vaccinated is unexpected. It may reflect differences in mucosal immune response to viral
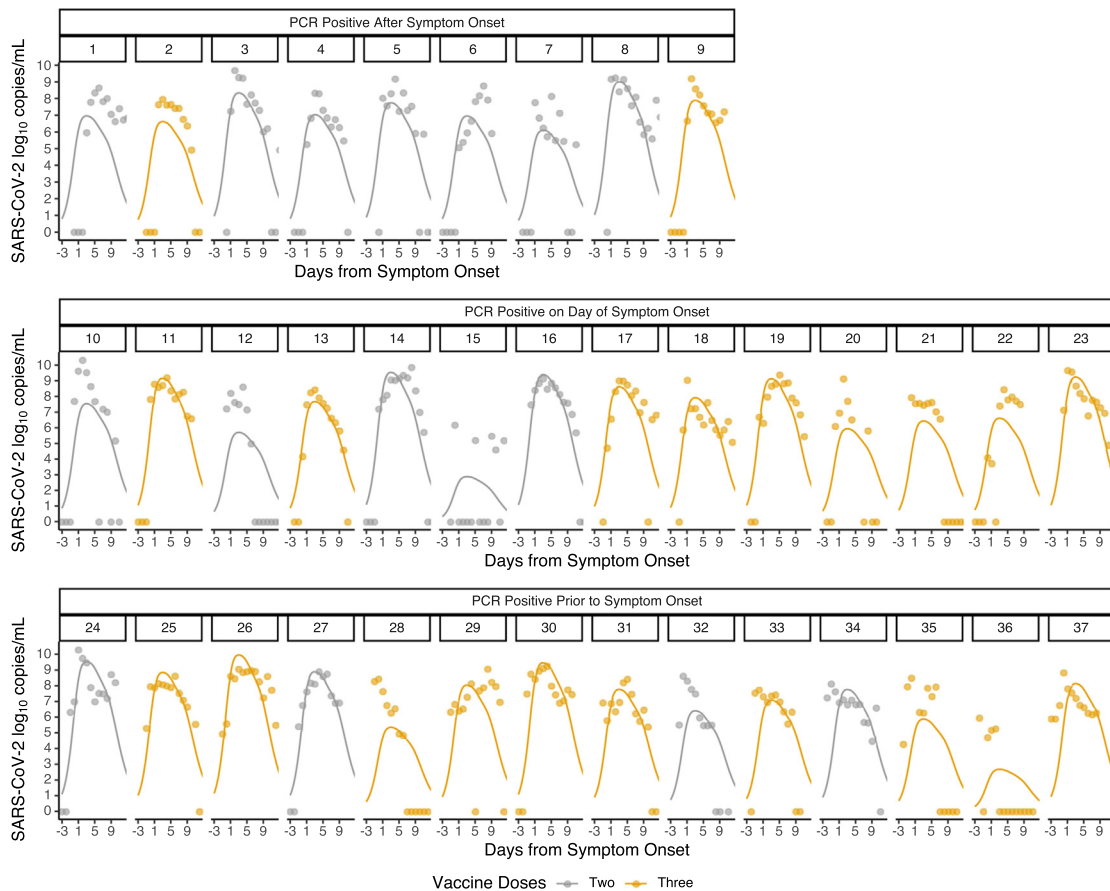
Fig. 2. Daily SARS-CoV-2 viral load with their trajectory modeled using a hierarchical generalized additive model with a smoothing spline placed on the day from symptom onset (day 0) for each individual with symptoms. Rows are grouped by timing of SARS-CoV-2 detection in relation to symptom onset; yellow lines/dots represent participants who had received 3 doses of a COVID-9 vaccine, and gray lines/dots those who had received 2 doses.
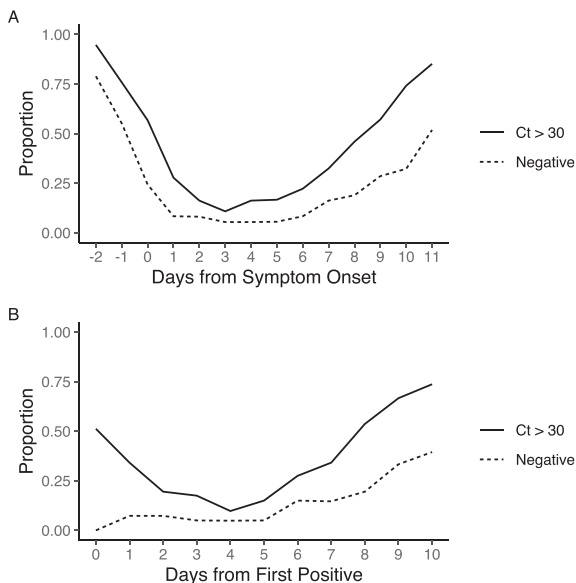
Fig. 3. The proportion of participants with an E-gene cycle threshold above 30 and a negative swab standardized to the day of symptom onset (A) and day of first positive test (B).

pathogens, but may also occur because of difficulty distinguishing normal variability in sensation from mild symptoms of upper respiratory tract infection, particularly in people who are aware of being exposed and at risk.[13] In our cohort 18% (8/45) of household contacts developed symptoms and never tested positive, a similar

proportion to that observed in a study assessing household transmission of influenza.[14] Larger studies are needed to identify characteristics of individuals associated with differing patterns of SARS-CoV-2 PCR positivity relative to symptom onset.

The peak viral load of 8.83 $\log_{10}$ copies per milliliter from the first positive test is similar to that found in another study of Omicron kinetics.[6] This peak concentration was lower than that reported in studies of other variants, which suggests the rapid spread of the Omicron variant is unlikely to be due to increased oral-pharyngeal shedding.[4] Other explanations such as immune evasion and altered binding affinity are more likely to be responsible for increased transmissibility. Although two studies have suggested that the total duration of shedding is shorter for Omicron as compared to Delta, with at least half of patients with cycle thresholds below 30 five days after the first positive test,[6,9] a third study found that participants infected with Omicron exhibited peak viral shedding 3–6 days after symptom onset, with viable virus cultured until day 10.[15] Our results are consistent with this latter study and suggest that people with COVID-19 who wish to limit transmission should continue with measures to limit transmission for 10 days following symptom onset.

We measured viral RNA concentration rather than infectious virus. While the absence of detectable virus presumptively means that transmission will not occur, the converse is not necessarily true. Three studies have found that the correlation between SARS-CoV-2 viral load and infectious viral titres is low.[9,16,17] As a result, a threshold concentration of viral RNA that demarcates whether an individual remains contagious remains undefined. To date, only older age and severe immune compromise have been identified as factors associated with prolonged durations of viral shedding.[3] Ad-

ditional studies are needed to define whether there are groups of individuals who clear SARS-CoV-2 quickly and for whom a shorter isolation period is warranted.

Unvaccinated individuals are more likely than those who are vaccinated to transmit SARS-CoV-2 to household contacts.[18,19] There are likely a number of reasons for this, but one explanation is the amount and duration of viral shedding, which seems to be longer for people who are unvaccinated.[4,17] Our study demonstrates, however, that there is little difference in SARS-CoV-2 PCR positivity among participants who had and had not recently received a third COVID-19 vaccine dose. Unless infectious virus titers are shown to be lower in those who have received three versus two doses of vaccine, receipt of a third vaccine dose should not influence recommended isolation durations and may not translate into reduced risk of onward transmission among individuals who are infected.

Our study has limitations. Study participants were predominantly young and healthy adults; results may not be applicable to adolescents or more frail populations. We did not serially test study participants until consecutive negative tests were observed so we could not reliably estimate clearance time. We used self-collected oral-nasal swabs, which might be less sensitive than nasopharyngeal swabs; although, specimens from the oropharynx might be more sensitive than the nasopharynx for detection of Omicron.[20] Self-collected swabs are reliable for the detection of SARS-CoV-2, but may result in slightly higher Ct values.[8] We assessed SARS-CoV-2 PCR trajectories in infections due to the BA.1 and BA1.1 variants and at short intervals after a third dose of mRNA vaccines and longer intervals after second doses; viral shedding in infections with other variants and at different durations from last vaccine dose received may be different. With waning of vaccine efficacy over time there may be an additional impact on viral shedding as the time from the most recent vaccine dose increases and among those with a prior episode of COVID-19. Finally, because more than one-third of participants had detectable virus by PCR on their first study swab, our overall results will underestimate the proportion of patients who shed virus before the onset of symptoms.

In summary, our findings suggest that there is individual variability in viral detection relative to symptom onset and that the increased transmissibility of Omicron compared to other variants is not explained by changes in viral shedding. The overall trajectory of SARS-CoV-2 viral loads did not differ based upon the number of COVID-19 vaccine doses. This information is critical for understanding transmission of SARS-CoV-2 and should guide strategies to mitigate onward transmission.

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Declaration of Competing Interest

All authors have no conflicts to declare.

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