COVID-19 Gamma Variant: Risk Analysis and Implications for Practice

07/22/2021

Key Messages

- Since first identified in Brazil in early December 2020, Gamma (PANGO lineage P.1) has remained low in prevalence globally (around 2%).

- Preliminary data suggest that Gamma has increased transmissibility and increased severity compared to non-variants of concern (VOCs).

- Limited evidence from adults at least 60 years old suggests two doses of AstraZeneca COVID-19 vaccine was effective against symptomatic infection and severe outcomes (hospitalization and death). However, mild disease was reported in 14 miners (French Guiana) who were infected with Gamma after two doses of the Pfizer-BioNTech vaccine.

- Gamma is relatively rare in Ontario. Accordingly, the current risk of Gamma transmission in Ontario is low and depends on the number and spread of existing cases and continued introductions into areas of the province.

Issue and Research Question

Despite its low global prevalence of about 2%, high transmissibility leading to local dominance has been reported for the Gamma VOC.\(^1\) In addition, early in-vitro assays raised the potential of reduced vaccine efficacy, and a seroprevalence study using convenience sampling of blood donors in Brazil\(^2\) suggested the risk of reinfection with Gamma. In Canada, Gamma was associated with a large-scale outbreak at a ski resort in British Columbia making it prudent to monitor the trends of this VOC. Given Ontario entered Step Three of Roadmap to Reopen on July 16, 2021,\(^3\) it is important to consider the potential impact of Gamma in Ontario, particularly going into fall.

Methods

From January 17 to July 22, 2021, Public Health Ontario (PHO) Library Services conducted daily searches of primary and preprint literature on VOC and variants of interests (VOI) of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) using the MEDLINE database (search strategies available upon request). In addition, PHO performed daily grey literature searches using news feeds in the Shared Library Services Partnership. English language peer-reviewed and non-peer-reviewed (preprint) records that described COVID-19 variants were included.
Epidemiological Context

Global

- The number of countries reporting cases infected with Gamma increased slightly in July 2021, from 74 countries as of July 6 to 75 as of July 13 and 78 as of July 20.

- Globally, the prevalence of reported cases infected with Gamma has remained at around 2%; South and Central America (primarily Haiti, Brazil, Trinidad and Tobago, and French Guiana) were the areas with the highest reported prevalence.

- In the United States, the percentage (95% confidence interval [CI]) of cases infected with Gamma among circulating lineages increased from 5.3% (3.7%–7.6%) in the biweekly period of April 11–24, 2021 to 11.1% (8.7%–13.9%) in the period of May 23–June 5, 2021. In that span of time, Alpha (B.1.1.7) dropped from 66.3% (62.3%–70.1%) to 59.7% (56.2%–63.1%) while Delta rose from 0.6% (0.4%–0.8%) to 10.3% (7.6%–13.8%). Since then, Gamma decreased to 3.3% (1.5%–5.1%) in the period of July 4–17, 2021, and Alpha further dropped to 8.3% (5.6%–11.1%) while Delta rose rapidly to 83.2% (79.2%–86.8%).

- In Canada, Gamma accounted for about 23% to 28% of all surveillance testing samples sequenced by the National Microbiology Laboratory in May 2021. As of July 12, 2021, 54.8% of the 19,530 Gamma cases in Canada were reported by British Columbia, 24.7% by Ontario, and 14.3% by Alberta. Outbreaks have been reported in a ski resort in British Columbia and workplaces in Alberta.

Ontario

- 105/4,310 (2.4%) Coronavirus Disease 2019 (COVID-19) cases sequenced in Ontario from June 6 to July 3, 2021 were Gamma. Among the 15 public health units where Gamma was sequenced, the highest percentages were noted in Huron Perth (14.3%), Middlesex-London (12.1%), Niagara Region (10.6%), and Southwestern (10.3%). Among 102 cases with information available, 8 (7.8%) were hospitalized and 3 (2.9%) were deceased.

- Out of the 5,027 Gamma cases identified by mutation profile K417T+/N501Y+/E484K+ or genomic analysis as of July 17, 2021:
  - 3,177 (63.2%) were outbreak-associated or close contact of a confirmed case
  - 60 (1.2%) were travel-related
  - 1,562 (31.1%) had no known epidemiologic link
  - 228 (4.5%) were missing relevant information

Transmissibility

Epidemiological evidence and mathematical modelling estimates from three peer-reviewed and five preprint studies consistently point to higher transmissibility of Gamma relative to other VOCs or non-VOCs. Two preprint cohort studies and two peer-reviewed genomic epidemiological reports described the rapid growth of Gamma incidence within short periods of time in Brazil, even gaining dominance in some regions in Brazil. Two preprint and one peer-reviewed modelling studies
estimated that Gamma could be 2.4 to 2.6 times\textsuperscript{18,19} times, or up to 46\%\textsuperscript{20} more transmissible than regional historical lineages. A peer-reviewed modelling study estimated an effective reproduction number (R\textsubscript{e}) of 2.6 for Gamma with a viral load approximately 10-fold higher than non-Gamma cases.\textsuperscript{16} Another peer-reviewed genomic epidemiological analysis estimated that Gamma’s R\textsubscript{e} was 38\% higher than that of non-VOCs, 10\% higher than that of Alpha and 17\% higher than that of Beta (B.1.351).\textsuperscript{21} As most of the data came from Brazil at times when under 20\% of the population had received at least one dose of COVID-19 vaccine\textsuperscript{22} and before Delta was prevalent (Delta was first reported in Brazil in late April 2021),\textsuperscript{23} the findings may not be generalizable to the current Ontario context where Delta is the dominant strain.\textsuperscript{24}

- Two epidemiological reports estimated R\textsubscript{e} and/or viral load for Gamma.
  - Campbell et al. analyzed 1,722,652 SARS-CoV-2 sequences uploaded to the Global Initiative on Sharing All Influenza Data (GISAID) hCOV-19 database. Using a multinomial logistic model of competitive growth, the R\textsubscript{e} of each VOC or VOI relative to that of the non-VOC virus population for each reporting country was estimated. The pooled mean Re for Gamma showed a statistically significant increase of 38\% (95\% CI: 29\%–48\%) compared to non-VOCs/VOIs, a relative increase of 10\% (95\% CI: 3\%–17\%) compared to Alpha and a relative increase of 17\% (95\% CI: 6\%–30\%) compared to Beta. On the other hand, the pooled mean Re for Delta showed a relative increase of 34\% (95\% CI: 26\%–43\%) compared to Gamma.\textsuperscript{21}
  - Naveca et al. reported that genome sequencing and real-time PCR assays that detect the ΔA106-108 deletion at nsp6 (a genetic signature of Gamma, Alpha, Beta and Iota) showed a sharp increase of Gamma prevalence in the Amazonas state: 0\% in November 2020 (n=0/355); 8.6\% in December 1 to 15, 2020 (n=33/384); 50.8\% in December 16 to 31, 2020 (n=177/348); 73.8\% in January 1 to 15, 2021 (n=487/660). The effective reproductive number of Gamma was estimated at 2.6. Using real-time RT-PCR cycle threshold (Ct) scores as a proxy of viral load in the upper respiratory tract, Gamma samples had approximately 10-fold higher viral load than non-Gamma infections (Ct = 19.8 vs. 23.0; P < 0.0001) when comparing samples collected at similar time from symptom onset.\textsuperscript{16}

- Three epidemiological studies attempted to infer high transmissibility of Gamma from the rapid rise in Gamma incidence.
  - Adamoski et al. reported on the results from voluntary testing of individuals in the community of a university in Curitiba, Brazil, who had no or mild symptoms between October 10, 2020 and May 24, 2021. From 7,249 persons, 12,558 saliva samples were collected for COVID-19 testing by PCR. The percentage of Gamma cases increased rapidly from 9.1\% at first detection on January 21, 2021 to 42.9\% two weeks later.\textsuperscript{14}
  - Moreira et al. analyzed 244 genomic sequences from 278 samples, collected via convenience sampling, out of 1,224 COVID-19 patients evaluated at a COVID-19 diagnostic facility in Rio de Janeiro from December 1, 2020 to May 12, 2021. From the data, the authors reported that P.2 was the predominant SARS-CoV-2 lineage from December 2020 to January 2021. Gamma was first detected in epidemiological week 6 of 2021, and by epidemiological week 12, Gamma had become 100\% of the sampled sequences in the city with little variation in the ensuing weeks.\textsuperscript{15}
  - Barbosa et al. reported that, out of 52 whole genome sequences from nasopharyngeal (NP) samples from 30 patients and 22 HCWs at a university hospital in São Paulo, Brazil, Gamma accounted for 78.6\% and 91.7\% of cases from the first to the second week of March 2021.
The authors stressed that Gamma has spread widely throughout Brazil despite interventions such as public masking, physical distancing, flight travel reductions and lockdown in São Paulo. No difference in mean Ct values was observed compared with those from patients in the first wave (data not reported).  

- Three modelling studies reported higher transmissibility of Gamma compared to local historical lineages.
  - Stefanelli et al. reported that significant co-circulation of Alpha and Gamma was detected based on 2 genomic surveillance surveys on February 18, 2021 (1,296 clinical samples) and on March 18, 2021 (1,938 clinical samples) across Italy. Alpha had a national prevalence of 54% on February 18 and almost completely replaced historical lineages by March 18 with a national prevalence of 87%. Meanwhile, Gamma remained almost exclusively found in Central Italy from February to March with a prevalence of 18%, suggesting the inability of Gamma to outcompete Alpha. Using a susceptible-infectious-recovered (SIR) mathematical model, the authors estimated that Gamma was more transmissible than historical lineages in Italy by 12% to 14% (95% CI: 3%–42%) if Gamma was able to evade immunity from infection and vaccination, or by 39%–46% (95% CI: 26%–63%) in the case of complete cross-protection.  
  - A modelling study by Coutinho et al., using data from the Brazilian national health surveillance of hospitalized individuals and data on Gamma incidence in Manaus from December 2020 to February 2021, estimated that Gamma is 2.6 (95% CI: 2.4–2.8) times more transmissible than strains previously circulating in Brazil.  
  - A modelling study by Faria et al. estimated that Gamma may be 1.4 to 2.4 times more transmissible than non-Gamma lineages. From available data, it could not be determined if Gamma infection was associated with increased viral loads or a longer duration of infection.  

**Disease Severity**

Epidemiological evidence from four studies (three in Brazil and one from 7 European countries) reported increased risk of hospitalization and ICU admission for infections with Gamma compared to non-VOCs. However, the actual risk of disease severity due to Gamma requires further study, preferably linking disease severity to individual variant status, and using data that reflect current levels of vaccination.

- Funk et al. compared Gamma (n=325) to non-VOC cases (n=3,348) reported by seven European countries (Cyprus, Estonia, Finland, Ireland, Italy, Luxembourg, and Portugal) between epidemiological weeks 38 of 2020 and 10 of 2021. Compared to non-VOCs, infection with Gamma was found to have significantly higher risks of hospitalization and intensive care unit (ICU) admission but not mortality. The authors noted that the Gamma cases in the study had higher mean age than non-VOC cases (46 years vs. 40 years; P < 0.05), and fewer Gamma cases had pre-existing conditions compared to non-VOC cases (27.8% vs 89.0%; P < 0.05). However, mortality risk may be underestimated as data collection was discontinued early after the introduction of VOCs into the region.  
  - Adjusted odds ratio for hospitalisation: 2.6 (95% CI: 1.4–4.8)  
  - Adjusted odds ratio for ICU admission: 2.2 (95% CI: 1.7–2.8)
• Adjustment was made for age, sex, week, country, pre-existing condition and health care worker status using logistic regression.

• Freitas et al. compared the proportion of severe COVID-19 cases, case fatality rates (CFR) and hospital CFR between the first wave (epidemiological weeks 45 to 53 of 2020; n=124,882) and the second wave (epidemiological weeks 5 to 8 of 2021; n=80,912) in Rio Grande do Sul, Brazil when Gamma was considered predominant. Data from March 2021 was excluded as occupancy of ICU beds reached 100% and may impact on the risk of death. Severe COVID-19 cases were those requiring hospitalization associated with dyspnea, difficulty breathing, oxygen saturation < 95% in ambient air or cyanosis, plus nasal wing beats, intercostal circulation, dehydration or lack of appetite for children cases. An increase in the risk ratio (RR) of severe disease and death in the second wave was observed. However, individual-level variant status was not reported.25

• RR of severe disease in the second wave compared to the first:
  - All patients: 1.7 (95% CI: 1.64–1.76); P < 0.0001
  - In patients without underlying conditions: 2.18 (95% CI: 2.01–2.35); P < 0.0001

• RR of death in the second wave compared to the first:
  - All patients: 2.06 (95% CI: 1.94–2.19); P < 0.0001
  - In patients without underlying conditions: 3.55 (95% CI: 2.99–4.2); P < 0.0001

• Martins et al. reported exponential growth of severe COVID-19 that occurred in Rio Grande do Sul, Southern Brazil, in February 2021. Whole genome sequencing (WGS) revealed that Gamma accounted for 88.9% (24/27) specimens collected from patients at a referral COVID-19 hospital in February 2021 compared to 6.7% (1/15) in January 2021. These findings raise concerns regarding a possible association between Gamma and rapid growth in cases and hospitalizations.26

• de Oliveira et al. reported that, despite declining or stabilizing CFRs in all age groups from September 2020 to January 2021 in the state of Parana, Brazil, and a drop in newly diagnosed cases in January and February 2021, CFRs in young adults increased up to 3-fold in February 2021. The actual CFR may be underestimated as mortality in those diagnosed in February may fall outside the study period. Meanwhile, the prevalence of Gamma in Parana rose to 70.4% of tested specimens by March 3 despite its first detection in the state on February 16, 2021. However, the authors noted that epidemiological data alone could not fully inform the reasons for the increase in CFRs in young adults, as the sharp rise in Gamma prevalence may suggest circulation weeks prior to the official first detection date. Significant increase in CFR from January to February 2021 and the RRs for young adults were as follow:27
  - 20–29 years of age: from 0.04% to 0.13%; RR = 3.15 (95% CI: 1.52–6.53); P < 0.01
  - 30-39 years of age: from 0.17% to 0.32%; RR = 1.93 (95% CI: 1.31–2.85); P < 0.01
  - 40–49 years of age: from 0.43% to 0.90%; RR = 2.10 (95% CI: 1.62–2.72); P < 0.01
  - 50–59 years of age: from 1.17% to 2.10%; RR = 1.80 (95% CI: 1.50–2.16); P < 0.01
Reinfection

While reinfection with Gamma has been suggested based on blood donor-based seroprevalence data from within Brazil, only two reports of reinfection with Gamma were identified, both from Brazil.

- Naveca F et al. reported the first documented case of reinfection with Gamma which was in a 29-year-old immunocompetent female in Manaus, Brazil, with no history of immunosuppression, 9 months after the first episode of COVID-19 infection with a B.1 lineage in March 2020. Both episodes were moderate in severity; higher viral load (Ct values <25) in NP and pharyngeal samples were obtained at reinfection compared with the first episode.29

- Goes et al. reported on two reinfections (see Breakthrough Infections below for detail).

Vaccine Effectiveness

Two studies explored VE against COVID-19 infections using a test-negative case-control design. The Canada-based study estimated similar VE against infection with Gamma and Alpha after one dose of mRNA vaccine but lacked clinical information on the cases. The Brazil-based study found substantial protection by the AstraZeneca vaccine against symptomatic infection and severe disease (hospitalization and death) with COVID-19 in the context of high Gamma prevalence. Further studies are required to investigate the VE against infection and severe outcomes due to infection with Gamma over time. Meanwhile, two reports of breakthrough infection with Gamma are included. Both reports came from countries with high Gamma prevalence, and there were no severe diseases among the cases.

Effectiveness Against Infection or Severe Outcomes

- In a test-negative case-control study based in British Columbia, Canada, Skowronski et al. estimated the effectiveness a single dose of mRNA COVID-19 vaccine (Pfizer-BioNTech or Moderna) against PCR-confirmed COVID-19 infection in community-dwelling elderly aged ≥ 70 years old who were tested for SARS-CoV-2 between April 4 and May 1, 2021. Gamma cases were those with N501Y+/E484K+/K417T+ mutation profile or identified by WGS (n = 314). On the other hand, Alpha cases were either identified by WGS or inferred from the N501Y+/E484K- profile. However, the clinical status of the cases was not available. After adjusting for age group, sex, epidemiological week and health authority of residence, similar VE against COVID-19 infection at ≥ 21 days after a single dose of mRNA vaccine were reported:30

  - Gamma: 61% (95% CI: 45%–72%)
  - Alpha: 67% (95% CI: 57%–75%)

- In another test-negative case-control study in São Paulo, Brazil, where Gamma accounted for 80% of the sequenced isolates from March to May 2021, Hitchings et al. estimated the VE of AstraZeneca vaccine (ChAdOx1) against symptomatic infection, hospitalization, and death due to Gamma. Included in the study were adults ≥ 60 years of age, who had acute respiratory infection symptoms and were tested for SARS-CoV-2 between January 17 and July 2, 2021. The authors reported that two doses of AstraZeneca vaccine provided significantly increased protection over one dose against symptomatic infection, hospitalization and death in older adults in the context of high prevalence of Gamma. However, the authors also noted that VE may have been underestimated as a proportion of the population was likely seropositive. On the other hand, VE may have been overestimated due to the inclusion of controls with mild acute respiratory
symptoms who may have had better access to health care services compared to the unvaccinated.\textsuperscript{31}

- **Adjusted VE (95% CI) against symptomatic COVID-19:**
  - 14–27 days after dose 1: 17.8% (8.0% to 26.5%); \(P = 0.001\)
  - \(\geq 28\) days after dose 1: 33.4% (26.4% to 39.7%); \(P < 0.001\)
  - 0–13 days after dose 2: 38.1% (11.9% to 56.5%); \(P = 0.01\)
  - \(\geq 14\) days after dose 2: 77.9% (69.2% to 84.2%); \(P < 0.001\)

- **Adjusted VE (95% CI) against hospitalization:**
  - 14–27 days after dose 1: 33.6% (19.9% to 45.0%); \(P < 0.001\)
  - \(\geq 28\) days after dose 1: 55.1% (46.6% to 62.2%); \(P < 0.001\)
  - 0–13 days after dose 2: 59.2% (32.4% to 75.4%); \(P = 0.001\)
  - \(\geq 14\) days after dose 2: 87.6% (78.2% to 92.9%); \(P < 0.001\)

- **Adjusted VE (95% CI) against COVID-19–related death:**
  - 14–27 days after dose 1: 37.5% (15.2% to 54.0%); \(P = 0.003\)
  - \(\geq 28\) days after dose 1: 61.8% (48.9% to 71.4%); \(P < 0.001\)
  - 0–13 days after dose 2: 77.8% (49.1% to 90.3%); \(P < 0.001\)
  - \(\geq 14\) days after dose 2: 93.6% (81.9% to 97.7%); \(P < 0.001\)

**Breakthrough Infections**

- Vignier et al. reported an outbreak of non-severe breakthrough infection with Gamma at a gold mine in French Guiana with 24 employee cases from a total of 44 employees. The mean age of these cases was 54.5 years; no cases had a history of previous COVID-19. Eleven cases had hypertension, four had diabetes, four were obese, and three had cardiac insufficiency. The authors noted that the high breakthrough rate was unexpected but dysfunctions of conservation or administration of vaccines was deemed unlikely as there was no evidence of cold-chain interruption and different batches of vaccine were used. The cases included:\textsuperscript{32}
  - 15/25 (60%) of those fully vaccinated with Pfizer-BioNTech vaccine, of which
    - 14 of these cases occurred > 14 days after their second vaccine dose, and
    - 12 of these cases had viral load inferred from Ct value <28;
  - 6/9 (66.7%) of those vaccinated with 1 dose;
  - 3/4 (75%) of those unvaccinated.

- Goes et al. reported four mild Gamma infections among the 72 COVID-19 patients at a cancer facility in Rio de Janeiro, Brazil between mid-January and March 2021. All four patients with
Gamma had high viral load inferred from Ct values < 30 despite having received at least one dose of COVID-19 vaccine (range from > 1 month after first dose to > 5 months after second dose); two were previously infected.33

### Ontario Risk Assessment

- **Overall, the risk of Gamma transmission in Ontario is low. It is a relatively rare variant and transmission will depend on the number and spread of existing cases and continued introductions into areas of the province.**
- **The overall risk assessment may change as new evidence emerges (Table 1).**

#### Table 1. Risk Assessment for Gamma

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<thead>
<tr>
<th>Issue</th>
<th>Risk Level</th>
<th>Degree of Uncertainty</th>
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<tbody>
<tr>
<td>Increased Transmissibility</td>
<td>Low</td>
<td>High</td>
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<td></td>
<td>Current prevalence of Gamma is low in Ontario.</td>
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<td>Global genomic data suggest Gamma is 10% more transmissible than Alpha.</td>
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<td>Modelling based on Brazilian data suggests Gamma is 1.4 to 2.6 times more transmissible than non-Gamma strains.</td>
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<td>Disease Severity</td>
<td>Moderate</td>
<td>High</td>
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<td></td>
<td>In the context of under-vaccinated populations: higher risks of hospitalization and ICU admission but not mortality were reported in Europe; increased hospitalization and case fatality rates were reported in Brazil.</td>
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<tr>
<td>Re-infection</td>
<td>Low</td>
<td>High</td>
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<td></td>
<td>There have been small number of documented cases of re-infection with Gamma.</td>
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<tr>
<td>Lowered Vaccine Effectiveness</td>
<td>Low</td>
<td>High</td>
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<td>At least in those over 60 years of age with two doses of the AstraZeneca vaccine in Brazil, there is no evidence of lowered VE. However, mild disease was reported in 14 miners (French Guiana) who were infected with Gamma after two doses of the Pfizer-BioNTech vaccine received more than 14 days prior.</td>
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<tr>
<td>Impacts on Testing/ Surveillance</td>
<td>Low</td>
<td>Low</td>
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The province has testing and surveillance sequencing capacity to detect and manage Gamma.

### Practice Implications

- Vaccination remains one of the most effective layers of protection against SARS-CoV-2 including the potentially more severe and transmissible Gamma variant. Vaccination program rollout should continue to target those who have not had a first dose and continue with second doses promptly, particularly in areas and settings that have seen high incidence of SARS-CoV-2 overall including Gamma and other VOC strains detected in Ontario. Further, based on projected approvals for vaccines for those < 12 years old by approximately September 2021, planning should start for rapid rollout of vaccination in younger age groups in the fall to increase overall coverage in the population before winter. Timely administration of second doses may represent a balance between increased VE afforded by a two-dose vaccine schedule and the possibility of a longer duration of protection afforded by longer intervals between doses. The interval between doses in a COVID-19 vaccine series that provides the most optimal duration of protection is currently unknown, but an area of emerging evidence.

- Along with vaccination, a multiple-layer approach for COVID-19 prevention (including cleaning hands, masking, physical distancing, ventilation, staying home when sick) should continue to be promoted, as no single intervention on its own is perfect at preventing COVID-19 spread.

- Sufficient time for assessment of sustained response to reopening stages by appropriate epidemiologic, vaccination and health system indicators will be important to understand how Gamma among other VOCs is/will be spreading in Ontario. It is anticipated that some public health measures, such as community masking, may be required to maintain disease control in the context of the potentially more transmissible Gamma strain.
References


25. Freitas ARR, Lemos DRQ, Beckedorff OA, Cavalcante LPG, Siqueira AM, Mello RCS, et al. The increase in the risk of severity and fatality rate of covid-19 in southern Brazil after the emergence of the Variant of Concern (VOC) SARS-CoV-2 P.1 was greater among young adults without pre-existing risk conditions. medRxiv 21255281 [Preprint]. 2021 Apr 19 [cited 2021 Apr 20]. Available from: https://doi.org/10.1101/2021.04.13.21255281


