Australian Government
National Health and Medical Research Council

NHMRC

National COVID-19 Health and Research Advisory Committee*

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Severity of COVID-19 illness in children and young adults

Focus

Children and young adults infected with SAR-CoV-2 tend to present with very mild symptoms or are asymptomatic. An increase has been reported in the number of children and young adults experiencing severe illness and requiring medical intervention and management due to COVID-19.

The rapid review of the evidence is to identify if there is increasing incidence of infection in children and young adults (i.e. up to 30 years of age), and if they are experiencing more severe illness from infection of SARS-CoV-2 due to the variants of concern or other risk factors.

Notes

This report was developed by an NCHRAC working group, chaired by Dr Mike Freelander with members Dr Katie Allen and Professor Jonathan Carapetis, and with the assistance of external experts Professors David Burgner, Nigel Crawford and Kim Mulholland.

Key findings

The key findings represent expert interpretation of relevant evidence as at 10 May 2021. In order to provide timely advice, a full systematic review process was not undertaken. This report is point in time and may need further review as more evidence is available.

- Severe illness continues to be reported far less in children and young adults, compared with older adults.
- There was no documented evidence linking any of the SARS-CoV-2 variants of concern with increased severity of illness in children.
- Children/young adults with certain underlying medical conditions (such as obesity) and infants under 1 year of age may be at increased risk for severe illness from SARS-CoV-2 infection, however the mortality rate remains low compared to the adult population.
- Multisystem Inflammatory Syndrome in Children (MIS-C) associated with COVID-19 (also termed PIMS-TS) is a rare but serious condition that evolves weeks after COVID-19 infection, and commonly presents with fever and gastrointestinal symptoms. Given the severity of MIS-C illness and the lack of well-defined risk factors, children who have tested positive for COVID-19 should be monitored for the warning signs in the weeks following infection.

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* NHMRC is providing secretariat and project support for the Committee, which was established to provide advice to the Commonwealth Chief Medical Officer on Australia's health response to the COVID-19 pandemic. The Committee is not established under the NHMRC Act and does not advise the NHMRC CEO.

Background

It has been observed, particularly in Brazil and India, that more children and young adults are suffering increased severity of symptoms and mortality due to SARS-CoV-2. It is unclear if this observation is due to a particular strain/variant of SARS-CoV-2 or if there are particular risk factors that are unique for increased disease severity/mortality in this age group. It has been established that this age group is at risk of Multisystem Inflammatory Syndrome in Children (MIS-C).

For the purposes of this review infants are defined as 0-1 years, children 2-17 and young adults 18 to 30 years of age. Severe illness, as defined by the National COVID-19 Clinical Evidence taskforce clinical guidelines, is characterised by pneumonia, with hypoxia, dyspnoea, and tachypnoea, usually requiring oxygen therapy and hospitalisation.[i] Critical illness includes severe pneumonia, acute respiratory distress syndrome, septic shock, and/or multiple organ dysfunction requiring hospitalisation in intensive care.

Summary of Evidence

Presentation of COVID-19 in children and young adults

The signs and symptoms of COVID-19 in children are similar to those of other infections and non-infectious processes, including influenza, streptococcal pharyngitis, and allergic rhinitis. The most commonly reported symptoms in children have been similar to those in adults, i.e. fever, cough, shortness of breath, myalgia, fatigue and headache. However, gastrointestinal symptoms are twice as common in children as in adults.[1]

A recent systematic review estimated that 16% of children with SARS-CoV-2 infection are asymptomatic, but evidence suggests that as many as half of paediatric infections may be asymptomatic.[2]

Severe illness

A comprehensive study of paediatric COVID-19 cases found that only 3% of confirmed cases present with severe illness, the remaining being either mild or without symptoms.[3] While many children experience mild or asymptomatic COVID-19 disease, severe COVID-19 in children is serious and can require respiratory support and intensive care admission.[3] Children infected with SARS-CoV-2 are also at risk for developing Multisystem Inflammatory Syndrome in Children (MIS-C) also termed Paediatric Multisystem Inflammatory Syndrome – Temporally Associated with SARS-CoV-2 (PIMS-TS).

A study of 1116 patients up to the age of 21 from 66 US hospitals has compared the risk ratios and factors associated with both severe COVID-19 and MIS-C.[4] Their findings indicate that children with MIS-C were more likely to be in the 6-12 year old age group, be of Black (non-Latinx) ethnicity and have no chronic underlying medical conditions, compared to children with severe COVID-19.[4] Table 2 is reproduced from a paper by Feldstein et al. and lists the absolute risk ratios for these characteristics.

[i] https://app.magicapp.org/#/guideline/L4Q5An/section/nV2P3n

Table 2: Significant differences observed in occurrences of MIS-C versus severe COVID-19 disease[4]

Clinical characteristic, lab value or symptom	Risk ratio, % [95% CI]*
Age 6-12	1.51 [1.33 to 1.72]
Underlying medical condition	0.52 [0.45 to 0.60]
Black (non-Hispanic) ethnicity	1.43 [1.17 to 1.76]

* values >1 indicate that the characteristic is more common in MIS-C than severe acute COVID-19

Severe acute COVID-19 in children (not including MIS-C)

Clinical symptoms

Most serious respiratory manifestations observed in children are acute respiratory distress syndrome (ARDS) and pneumonia. Variation in the degrees of severity and presentation compare to that seen in adults and is thought to be attributed to vascular, immunological and molecular mechanisms.[4,5,6]

Children with severe COVID-19 may develop respiratory failure, myocarditis, shock, acute renal failure, coagulopathy, and multi-organ system failure. Some children with COVID-19 have developed other serious problems like intussusception or diabetic ketoacidosis.[5] Other presentations include: vaso-occlusive crises in the setting of sickle cell anaemia, diabetic ketoacidosis, seizures, circulatory collapse and gastrointestinal tract symptoms.[6]

Demographics and risk factors for severe COVID-19

It is well documented that increasing age is associated with a higher risk of severe COVID-19 disease in adults, however the relationship of age and disease severity is more complex for children and young adults.[7] A retrospective cohort study of 454 children and young adults up to 23 years of age revealed that children/young adults in the age groups of 0-3 months and 20-23 had the highest risk of both hospitalisation and requirement of respiratory support.[7] This is in line with evidence that that children with certain underlying medical conditions and infants (age <1 year) might be at increased risk for severe illness from SARS-CoV-2 infection.[8,6]

Of the children who have developed severe illness from COVID-19, most have had underlying medical conditions.[9] Similar to adults, children with obesity, diabetes, asthma or chronic lung disease, sickle cell disease, or immunosuppression might also be at increased risk of severe illness from COVID- 19.[10] Obesity is a major factor in poor prognosis for children as illustrated by a recent systematic review and meta-analysis, which reported that childhood obesity is likely associated with a worsened prognosis of COVID-19 infection. This is in keeping with several adult studies and a meta-analysis that have shown being overweight or obese to be associated with an increased requirement of non-invasive respiratory support as well as mechanical ventilation due to SARS-CoV-2 infection.[11,12]

Clinical risk factors for the requirement of respiratory support include obesity, asthma and a pre-existing respiratory infection at the time of diagnosis.[7] Götzinger et al. explored various risk factors for admission to intensive care. Age below 1 month, male sex, clinical evolution with lower airway infections compromise and a history of co-morbidities showed relevance. They also identified a heterogeneity of pre-existing diseases, including chronic pulmonary diseases, congenital heart disease, malignancy, and neurological disorders.[13]

Pathophysiology

It is still unclear why children generally have milder symptoms and a better prognosis than adults. Several explanations are offered in the literature that warrant further research:

1. Expression of the ACE2 in the nasal epithelium is lowest in young children and increases towards young adulthood.[14] This may be linked with lower acquisition of SARS-CoV-2 infection in children.[15] Reduced levels of ACE2 in the lower respiratory system may be associated with more severe disease and some studies have revealed older adults were more likely to develop severe pneumonia due to decreased expression of ACE2 in that area.[16]
2. Innate immunity is trained to generate immune memory from non-specific immune protection, i.e. secondary to live vaccine and frequent infections.[ii]
3. Protection from other coronavirus infections (adults display a suppressed adaptive immunity and dysfunctional overactive innate immune response).[17]
4. Children have healthier respiratory systems (due to less exposure to cigarettes smoke or pollution) as well as less incidence of risk factors such as comorbidities.[18]
5. Lower seroconversion and less exposure to some sources of transmission, although infection through familial clusters predominates.[19]
6. The differences in airway microbiota in children may decrease colonisation and growth of the virus.[20]

Multisystem inflammatory syndrome (MIS-C).

Severe cases presenting with persistent fever and the involvement of two or more organ systems in have been reported in children and young people with COVID-19, termed MIS-C. MIS-C is a post-infectious manifestation of COVID-19, occurring after acute infection with SARS-CoV-2, which may have been asymptomatic. MIS-C is a rare but very serious complication, a meta-analysis of 660 patients revealed that admission to intensive care was required in 64-80% of cases and a mortality rate of 2-4% has been observed.[24]

Clinical symptoms and public health implications

The symptoms of MIS-C are similar to Kawasaki Disease (KD) and toxic shock syndrome, but it is clinically and immunologically distinct from these conditions.[21] The onset of MIS-C typically occurs within four to six weeks of COVID-19 infection, but is not necessarily associated with severe or even symptomatic COVID-19 disease.[22-23]

MIS-C has varying clinical presentations, however the most common features include fever and gastrointestinal symptoms.[29-27] Other symptoms observed in COVID-19 related MIS-C include dermatologic, mucocutaneous and cardiac abnormalities.[29] Mild symptoms of MIS-C can escalate into severe illness in a few days and critical warning signs of progression (including respiratory distress, tachycardia, haemodynamic instability and left ventricular dysfunction) should be monitored.[24] Respiratory symptoms such as hypoxia, cough and shortness of breath have been observed in MIS-C cases, however, these symptoms are generally not considered to be part of the MIS-C presentation.[29]

[ii]Live vaccination such as BCG vaccination is thought to be protective to children Ref 13, not sure if that is still thought to be correct

A study of 99 children diagnosed with MIS-C in New York State investigated differences in clinical symptoms between age groups.[27] Table 3 summarises the key differences in presentations between infants, children and young adults.

Treatment for MIS-C has been based on those for Kawasaki disease, and is dependent on the organs affected in each case. Common treatments include intravenous immunoglobulin and steroids to treat the inflammation.[30-24] Future treatment options may soon be guided by data from the UK RECOVERY (Randomised Evaluation of COVID-19 Therapy) and BATS (Best Available Treatment Study) for MIS-C trials which has enrolled patients with MIS-C.[25,26]

Table 3: MIS-C symptoms with observed variations across age groups

	Infants and young children	**Adolescents and young adults (up to age 20)***
Myocarditis	Myocarditis observed young children aged 0-5 (39%) and 6-12 (50%).[27]	High rates of myocarditis observed in 13-20 year olds (81%).[27]
Neurological symptoms (headache, altered mental status and confusion)	Neurological symptoms observed young children aged 0-5 (13%) and 6-12 (38%).[27]	Highest rates of neurologic symptoms in young adults (39%)
Presentation with Kawasaki disease criteria	Kawasaki like disease presentation common in children (48% in children aged 0-5 and 43% in children aged 6-12).[27]	Kawasaki like disease presentation much less common in 13-20 year olds (12%).[27]
Dermatologic or muscocutaneous symptoms	Highest in young children aged 0-5 (87%) and 6-12 years (78.6%)[27]	Observed in young adults (61.5%).[27]

*MIS-C observed in children and young adults up to age 20. Similar illness has been reported in adults aged over 21 years but is termed multisystem inflammatory syndrome in adults (MIS-A).[28]

Demographics and risk factors for MIS-C

The reported median age of children diagnosed with MIS-C ranges from 7 to 10 years, although cases have been reported in children as young as 7 months and young adults up to age 20.[29] There is evidence that children of Hispanic, African/Afro Caribbean backgrounds are disproportionally affected by MIS-C following COVID-19 infection.[29]

There is not yet firm agreement on the pathogenesis of COVID-19 associated with MIS-C in children. The illness may be associated with SARS-CoV-2 viral infection in the gastrointestinal tract, however the delay in onset suggests post-infectious immune activation is a more likely mechanism.[30] Further, the occurrence of positive antibody results, or family exposure without PCR COVID-19 diagnosis, suggest that MIS-C illness is antibody-mediated rather than the result of acute COVID-19 infection.[29-31]

Unfortunately, the risk factors associated with MIS-C are not well defined yet, although it has been suggested that lacking common (i.e. non-SARS-COV-2) coronavirus antibodies may leave children vulnerable to MIS-C.[32] On 3 September 2020, Safer Care Victoria issued an alert to paediatricians and ED physicians raising awareness of MIS-C.[33] Given the severity of MIS-C illness and the lack of well-defined risk factors, clinicians and parents should be aware of possible signs of MIS-C when caring for

children who have tested positive for COVID-19 or those living in a family cluster for several weeks following infection/exposure.[34]

Social determinants

The US COVID-19 data on infections in children and young adults is influenced by racial/ethnic groups that are disproportionately represented among essential and direct service workers. The inability to work from homes for such workers results in higher risk of exposure to SARS-CoV-2, with potential secondary transmission among household members, including infants, children, adolescents, and young adults.

In addition, disparities in social determinants of health, such as crowded living conditions, food and housing insecurity, wealth and educational gaps, and racial discrimination, likely contribute to racial and ethnic disparities in COVID-19 and MIS-C incidence and outcomes.[35]

Public health advice

COVID-19 prevention messages (e.g. mask wearing, physical distancing, hand hygiene) for children, young adults and their caregivers need to be clear, consistent, and developmentally and culturally appropriate.[Error! Bookmark not defined.] Particular focus should be placed on those from racial and ethnic minority groups at higher risk, and those with underlying medical conditions.

Although rare, cases of MIS-C in children can be very serious and occur weeks following COVID-19 infection or exposure. Health professionals and caregivers should be made aware of warning signs and monitor recovering children for possible MIS-C symptoms.[34]

Prevalence/ epidemiology

- The exact number of children infected with SAR-CoV-2 is unknown due to incomplete reporting and testing in a number of countries. One Chinese study of laboratory confirmed cases found that that children accounted for less than 2% of total cases.[36, 37]
- The majority of reports reveal that children develop less severe symptoms and hospitalisation rates are significantly lower in children with COVID-19 compared with adults.[38,39]
- Younger children, especially infants, are more susceptible to severe symptoms (10.6% <1-year-old vs. 3%=16 years old). One potential explanation is the immaturity of the immune system in younger children.[40]
- There was no evidence linking severity of disease in children with infection with any of the SARS-CoV-2 variants of concern. However, this may be because countries experiencing high rates of SARS-CoV-2 community transmission lack the capacity to perform serology or genotyping on a large proportion of reported cases.

Australia

- The prevalence of COVID-19 has been low in Australia, compared with other countries. The table below shows the case numbers across different age groups from children through to middle aged adults.
- Children accounted for 5% of COVID-19 cases in Australia and there were no deaths (Table 1).
- There has been one death recorded in Australia in the 20-29 age group and 2 deaths recorded in the 30-39 age group, however no deaths have been recorded in people under the age of 20.[41]

- There was no evidence to suggest severity of illness in children is linked to infection with a variant of concern.

Table 1. Number of cases of COVID-19 reported in Australia as of 6 May 2021

0-9	10-19	20-29	30-39	40-49
1609	2515	6624	5342	3840

- Preliminary Paediatric Active Enhanced Disease Surveillance (PAEDS) Network surveillance data[42] from eight tertiary hospitals across five states as of 31 December 2020 revealed:
    - Most Australian children (<19yo) with COVID-19 had mild disease.
    - Fewer than one in ten required hospitalisation, two required intensive care.
    - Post-infective multi-system inflammatory syndromes occurred at a lower COVID-19 case-rate than reported in high prevalence settings, but were still associated with the need for intensive care.
    - Kawasaki disease incidence rates remained stable compared to the pre-pandemic surveillance period.
    - No deaths were reported.

International trend analysis

Obtaining full datasets for a global picture of the prevalence comparison between adults and children is difficult due to data collection variances.

United States

- The Centers for Disease Control and Prevention have noted that the number and rate of cases in children in the United States have been steadily increasing since March 2020.[43]
- In the United States (US), which has had one of the highest incidence rates of COVID-19 in the world, only 13.8% of cumulative cases were children.[44]
- Paediatric hospitalisation rates for COVID-19 in a selection of US states was found to have increased from around 1% of cumulative hospitalisations to around 3% over the period May to November 2020.[45]
- Studies of hospitalised children have found that obesity was the most prevalent underlying condition.[43]
- An increase in cases was observed in those aged 18-22 years, which was attributed to college students returning to campus along with increased testing rates.[46] The transmission profile in this age group starts to change with social and employment activities thus reinforcing the need for messaging on preventative measures such as social distancing, mask use and hand hygiene.

Analysis of US data from 12 Feb 2020- 31 July 2020 on COVID-19 related death under 21 years of age showed[47]:

- Hospitalisation rates in the US are higher among Hispanic/Latino children and non-Hispanic Black children compared with non-Hispanic White children. Hispanic, Black, and American Indian/Alaskan Native persons represented 41% of the US population aged <21 years, these groups accounted for approximately 75% of deaths in persons aged <21 years.

- Deaths were more prevalent among males and among persons aged 10–20 years.
- Young adults aged 18–20 years accounted for nearly half of all deaths in this population.
- 75% had at least one underlying condition, and 45% had two or more underlying conditions.

United Kingdom

- The impact of the second wave on children in the United Kingdom (which has had high prevalence of the B.1.1.7 variant) has been a matter of media attention. Analysis of preliminary data from children admitted to hospital showed an increase in the incidence, but not the severity of disease in the second wave. It is thought the increase in admissions could be due to the higher prevalence of SARS-CoV-2 in the community overall.[48]
- Two deaths out of 52,020 cases were recorded in the under 5 age group and three deaths out of 160,620 cases in the 5-15 year group.

Brazil

- A second wave of COVID-19 in Brazil, which commenced in November 2020, has been attributed to several factors including waning immunity due to reduced antibody titres in the general population following the first wave of infection, as well as potential immune escape and increased transmissibility of new SARS-CoV-2 lineages P.1 and P.2.[49]
- A change in the age demographic of COVID-19 hospitalisation in Brazil has been observed and the Brazilian Association of Intensive Care Medicine reported that the number of 18-45 year olds requiring intensive care for COVID-19 in February to March this year was three times greater than in September to November 2020, and coronavirus related deaths in that age group have almost doubled.[50]
- It has been suggested that increased hospitalisations of young people could be directly linked to the emergence of the P.1 variant.[51] Alternative explanations have been proposed, including social factors that prevent young people in poverty from maintaining physical distancing and young age structure of the population in Brazil.[52]

India

- The cause of the rapid surge of the second wave in India is not known and there is very little evidence available in regards to any changes in demographics or severity. Links to the emergence of particularly infectious variants, an increase in unrestricted social interactions and low vaccine coverage have been suggested.[53]
- The World Health Organisation has now designated B.1.617 as a variant of concern, but unfortunately clinical evidence of the impact of this variant is limited. While this variant may be a contributing factor to the second wave in India, there is no evidence yet that variants are linked to any changes to the impact of the disease in children and young people.[54]

Case studies of Brazil and India are provided at Attachment 1.

Limitations with data on children and young adults

- The true incidence of SARS-CoV-2 infection in children is not known due to the lack of widespread testing and the prioritisation of testing for adults and those with severe illness.[43]
    - The lack of specificity of signs or symptoms and the significant proportion of asymptomatic infections make symptom-based screening for identification of SARS-CoV-2 in children particularly challenging.[55, 56]

    - Case series published in the initial phase of the pandemic potentially suffer from decreased testing of mildly infected individuals thereby leading to a potentially low rate of documented asymptomatic infections.[3]
    - Systematic sero-surveillance, which complements case based reporting which often misses mild or asymptomatic cases, is more challenging to achieve for children.[57,58]
- Children are less often tested for COVID-19 and, in most cases, they have had physical contact with a confirmed case with the exposure normally being at home, differing from adults.
- Lower infection rate among children may be due to the closure of schools and kindergartens consequently reducing the exposure of children to the virus.
- The use of indicators such as the need for hospitalisation and ICU admission are not internationally consistent indicators for disease severity.

Areas for further research

Possible areas for further research suggested by this review include:

- Evaluating the link between comorbidities (such as obesity) and increased rates of hospitalisation and mortality in children
- Further large multisite studies to explore the reasons for disparities in COVID-19-associated hospitalisation rates by race and ethnicity
- Risk factors for the development of MIS-C disease in children and young adults
- Investigation of long COVID-19 in children and young adults (including subclinical disease).

Other considerations

In the course of developing this advice, NCHRAC identified the following considerations that were out of scope for this advice, but are important and related considerations:

- Vaccination of children
- Impacts of COVID-19 during pregnancy on newborn health
- Routes of transmission and the impact of closing educational and day care facilities.

Approach

The searches of Pubmed and medRxiv for pre-print articles was undertaken with the following parameters:

Population: children and young adults
Exposure: SARS-CoV-2 [including search for variants of concern]
Comparator: SARS-CoV-2 infection in adults
Outcome: severe and critical illness [ie respiratory involvement, pneumonia, MIS-C]
Publication type: [Epidemiology] [risk factors] systematic reviews, meta analyses, observational studies, case series
Grey literature was identified via newsletters, internet searches and email alerts and led to the identification of additional references.

Out of Scope:

- Childhood vaccination
- Testing, diagnosis and treatment for COVID-19 in children and young adults.

Attachments

Attachment 1: Case Studies for Brazil and India

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Case study 1 – India

- The second wave in India commenced in mid-February 2021 and is expected to peak in mid-May 2021.[2] The cause of the rapid surge of the second wave in India is not known but there have been suggestions it is linked to several factors including the emergence of particularly infectious variants, a rise in unrestricted social interactions, and low vaccine coverage. Another possibility is that the first wave mainly impacted the urban poor and the virus is now impacting wealthier urban communities that were able to/forced to isolate previously.[1]
- Genomic sequencing is limited, but the main two variants are B.1.1.7 and B.1.617, which were first identified in India and contain two mutations that have been linked to increased transmissibility and an ability to evade immune protection.[1]
- Given the nature of the public health crisis in India, evidence regarding changes to the demographic and severity of cases is not yet available. Media and anecdotal reporting has emerged of increased severity and/or caseloads in younger adults and children.
    - https://www.abc.net.au/news/2021-04-24/how-did-indias-covid-disaster-unfold/100089732
    - https://timesofindia.indiatimes.com/india/covid-19-percentage-of-young-infected-in-second-wave-same-but-more-serious/articleshow/82153956.cms
    - https://www.hindustantimes.com/india-news/young-need-to-be-more-careful-suggests-doctor-amid-raging-covid-19-second-wave-101619431570219.html
- On Wed 21 April, the Indian Ministry of Health held a press conference and Union Health Secretary Rajesh Bhushan reported that the severity and demography of COVID-19 cases is the same in both the first and second waves. [no official source, press conference reported in media]
    - https://science.thewire.in/politics/government/covid-19-severity-demography-of-victims-in-second-wave-same-as-first-claims-health-ministry/
    - https://www.thehindu.com/news/national/government-releases-covid-19-data-showing-severity-of-victims-in-second-wave-same-as-first/article34376496.ece
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1 Mallapaty, S. India's massive COVID surge puzzles scientists. *Nature NEWS*, doi:https://doi.org/10.1038/d41586-021-01059-y (2021).

2 Ranjan, R., Sharma, A. & Verma, M. K. Characterization of the Second Wave of COVID-19 in India. *medRxiv [preprint]*, 2021.2004.2017.21255665, doi:10.1101/2021.04.17.21255665 (2021).

Case study 2- Brazil second wave/increased hospitalisation in young people/possible link to P.1

- Since the identification of the P.1 variant in Brazil, there has been increased case fatality rates for all adult (20+) age groups in Brazil. The most significant increase has been observed for middle aged adults ("*Patients aged 20-29 years experienced a tripling of their CFR from 0.04% in January 2021 to 0.13% in February 2021*"). There was no observed change in children and adolescents. A summary table summarising the case fatality rates and death risk ratios is reproduced from a paper by de Oliveira et al. (2021).[1]

Table 1: Case fatality rates and death risk ratios for SARS-CoV-2 in Parana, Brazil (Jan 2021 – Feb 2021) [1]

Age Group	Case Fatality Rate		Death Risk Ratio [95% CI]
	Jan 2021	Feb 2021	
0-5	0.01%	0.12%	1.27 [0.18-9.01]
6-9	0.00%	0.00%	-
10-19	0.04%	0.04%	0.88 [0.20-3.94]
20-29	0.04%	0.13%	3.15 [1.52-6.53]
30-39	0.17%	0.32%	1.93 [1.31-2.85]
40-49	0.43%	0.90%	2.10 [1.62-2.72]
50-59	1.17%	2.10%	1.80 [1.50-2.16]
60-69	4.44%	5.16%	1.16 [1.02-1.32]
70-79	9.18%	12.10%	1.32 [1.17-1.48]
80+	20.33%	23.91%	1.18 1.04-1.32]

- The Indigenous population had a younger median age for hospitalised patients.[2] Black/brown, Indigenous, and mixed race adults showed more severe disease and higher in-hospital mortality than white patients[2,3]
- In-hospital mortality is associated with demographic factors, social inequality, and differences in the structure of services and quality of health care (February to June 2020)[3]
- Possible association of P.1 with increased hospital admissions (P.1 accounting for 9/10 admissions to a COVID-19 referral hospital). Suggestion of increased impact of younger age group due to P.1 variant[4].
- Since the start of the second wave (8-14 Nov 2020) health services have observed more younger people presenting with symptoms.[5] Between the first and second waves the hospitalised fatality rate was 2.7 times higher for the 20-39 year old age group.[6]
- There has been a significant increase in the rate of COVID-19 cases in the 30-39, 40-49 and 50-59 age groups by 565%, 626% and 525% respectively (January to mid-March 2021). Increases in mortality for the in the 30-39, 40-49 and 50-59 age groups are 352%, 419% and 317% respectively.[5]
- It is possible that higher mortality rates in the second wave are due to an increased strain on hospitals, however "*If overload was the reason for the increase in the case fatality rate, it would be reasonable to expect that the increase would be similar for different ages and genders*," said André Ricardo, epidemiologist at the Leopoldo Mandic School of Medicine in São Paulo and one of the study's authors. "*P.1 appears to be more lethal among young men and women than the original strain*."[7]

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