RESEARCH ARTICLE SUMMARY

CORONAVIRUS

Estimating infectiousness throughout SARS-CoV-2 infection course

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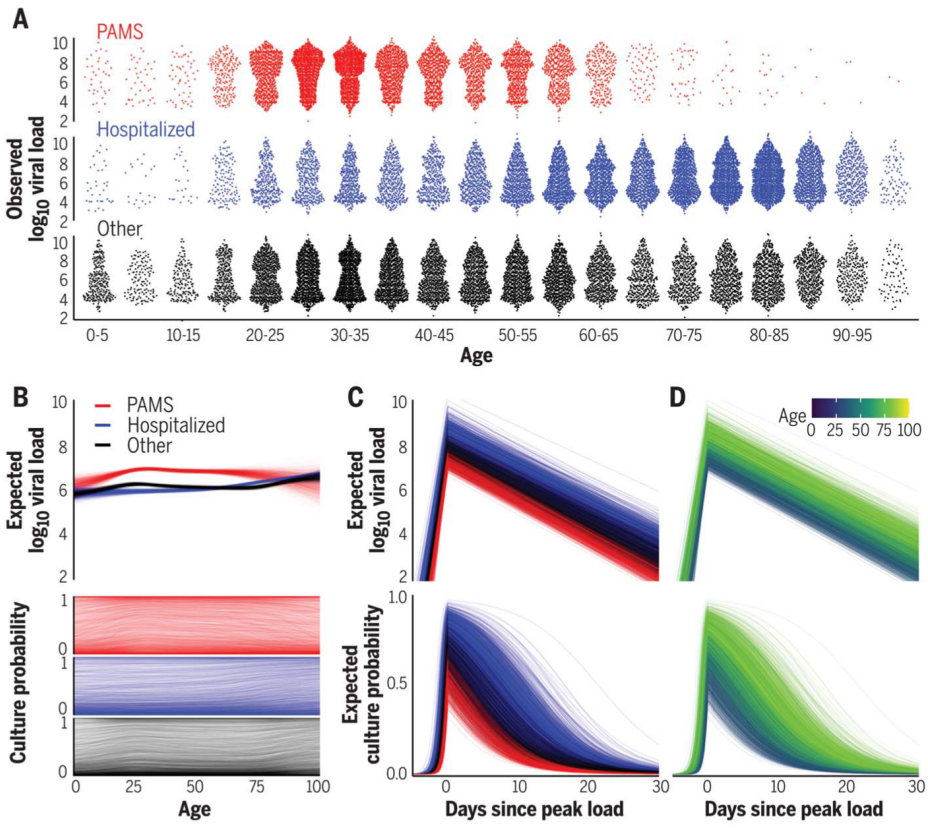
INTRODUCTION: Although post facto studies have revealed the importance of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission from presymptomatic, asymptomatic, and mildly symptomatic (PAMS) cases, the virological basis of their infectiousness remains largely unquantified. The reasons for the rapid spread of variant lineages of concern, such as B.1.1.7, have yet to be fully determined.

RATIONALE: Viral load (viral RNA concentration) in patient samples and the rate of isolation success of virus from clinical specimens in cell culture are the clinical parameters most directly relevant to infectiousness and hence to transmission. To increase our understanding of the infectiousness of SARS-CoV-2, especially in PAMS cases and those infected with the B.1.1.7 variant, we analyzed viral load data from 25,381 German cases, including 9519 hospitalized patients, 6110 PAMS cases from walk-in test centers, 1533 B.1.1.7 variant infections, and the viral load time series of 4434 (mainly hospitalized) patients. Viral load results were then combined with estimated cell culture isolation probabilities, producing a clinical proxy estimate of infectiousness.

RESULTS: PAMS subjects had, at the first positive test, viral loads and estimated infectiousness only slightly less than hospitalized patients. Similarly, children were found to have mean viral loads only slightly lower (0.5 $\log_{10}$ units or less) than those of adults and ~78% of the adult peak cell culture isolation probability. Eight percent of first-positive viral loads were 10^9 copies per swab or higher, across a wide age range (mean 37.6 years, standard deviation 13.4 years), representing a likely highly infectious minority, one-third of whom were PAMS. Relative to non-B.1.1.7 cases, patients with the B.1.1.7 variant had viral loads that were higher by a factor of 10 and estimated cell culture infectivity that was higher by a factor of 2.6. Similar ranges of viral loads from B.1.1.7 and B.1.177 samples were shown to be capable of causing infection in Caco-2 cell culture. A time-course analysis estimates that a peak viral load of $10^{8.1}$ copies per swab is reached 4.3 days after onset of shedding and shows that, across the course of infection, hospitalized patients have slightly higher viral loads than nonhospitalized cases, who in turn have viral loads slightly higher than PAMS cases. Higher viral loads are observed in first-positive tests of PAMS subjects, likely as a result of systematic earlier testing. Mean culture isolation probability declines to 0.5 at 5 days after peak viral load and to 0.3 at 10 days after peak viral load. We estimate a rate of viral load decline of 0.17 $\log_{10}$ units per day, which, combined with reported estimates of incubation time and time to loss of successful cell culture isolation, suggests that viral load peaks 1 to 3 days before onset of symptoms (in symptomatic cases).

CONCLUSION: PAMS subjects who test positive at walk-in test centers can be expected to be approximately as infectious as hospitalized patients. The level of expected infectious viral shedding of PAMS people is of high importance because they are circulating in the community at the time of detection of infection. Although viral load and cell culture infectivity cannot be translated directly to transmission probability, it is likely that the rapid spread of the B.1.1.7 variant is partly attributable to higher viral load in these cases. Easily measured virological parameters can be used, for example, to estimate transmission risk from different groups (by age, gender, clinical status, etc.), to quantify variance, to show differences in virus variants, to highlight and quantify overdispersion, and to inform quarantine, containment, and elimination strategies. ■



Viral load and cell culture infectivity in 25,381 SARS-CoV-2 infections. (**A**) Viral loads in presymptomatic, asymptomatic, and mildly symptomatic cases (PAMS; red), hospitalized patients (blue), and other subjects (black). (**B**) Expected first-positive viral load and cell culture isolation probability, colored as in (A). (**C**) Temporal estimation with lines representing patients, colored as in (A). (**D**) As in (C), but colored by age.

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