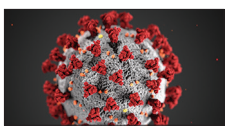
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Understanding COVID-19: what does viral RNA load really mean?



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In *The Lancet Infectious Diseases*, Francois-Xavier Lescure and colleagues[1] describe the first cases of coronavirus disease 2019 (COVID-19) in Europe, which were reported in France. The detailed clinical features of five patients with COVID-19 are aligned with the quantitative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral RNA load from nasopharyngeal and other selected sampling sites. Previous studies in patients with SARS, Middle East respiratory syndrome (MERS), and COVID-19 generally provide insufficient detail to allow examination of the relationship between individual patient clinical course and viral RNA load.[2–4] Although patient numbers are small, the authors provide the first COVID-19 time series correlating viral RNA load and detailed clinical manifestations.[1] Importantly, the dataset is provided in sufficient detail so it could be readily combined with future similar studies for deeper analysis.

Although the authors make a case for COVID-19 presenting as three distinct clinical patterns, we believe a distinction based on such small numbers is highly speculative. Nevertheless, based on the assumption that viral RNA load correlates with high levels of viral replication,[5] there are important insights to be gained from this time-course analysis. Currently, our understanding of the relationship between viral RNA load kinetics and disease severity in patients with COVID-19 remains fragmented. Zou and colleagues reported that patients with COVID-19 with more severe disease requiring intensive care unit admission had high viral RNA loads at 10 days and beyond, after symptom onset.[4] Unfortunately, it is unknown when in the course of their disease these patients deteriorated. By contrast, Lescure and colleagues report the viral RNA kinetics of two patients who developed late respiratory deterioration despite the disappearance of nasopharyngeal viral RNA. It would be interesting to know whether viral RNA load in lung tissue, or a surrogate sample such as tracheal aspirate, mirrors the decline in nasopharyngeal shedding. Nevertheless, this observation suggests that these late, severe manifestations might be immunologically mediated and has obvious implications for the potential to use immune-modulatory therapies for this subset of patients. This finding is consistent with recent reports that corticosteroids were beneficial for acute respiratory distress syndrome,[6] and possibly those with COVID-19.[7] With more detailed data such as those provided by Lescure and colleagues, the use of viral RNA load to suggest potential clinical strategies to treat COVID-19 could be exploited.

In a pandemic, prevention of disease transmission is key. Lescure and colleagues wisely note the implications for transmission from patients with few symptoms but high viral RNA load in the nasopharynx early in the course of disease. Individuals within the community, policy makers, and frontline health-care providers, especially general and emergency room practitioners, should be alert and prepared to manage this risk. Equally worrying is the persistently high nasopharyngeal viral RNA load, and the detection of viral RNA in blood and pleural fluid, of the older patient (aged 80 years) with severe multi-organ dysfunction. This finding broadly correlates with the severely ill group data reported by Zou and colleagues,[4] and has important implications for therapy and infection control. Development and effective administration of antiviral therapy to critically ill patients throughout the course of disease is likely to remain important. Vigilance regarding the strict implementation of transmission precautions is required throughout the prolonged course of COVID-19 in patients who are critically ill, and ancillary staff responsible for collecting and disposing of bodily fluids or waste, who are at high risk during an outbreak,[8] should be properly protected and trained.[9]

It is noteworthy that the presence of viral RNA in specimens does not always correlate with viral transmissibility. In a ferret model of H1N1 infection, the loss of viral culture positivity but not the absence of viral RNA coincided with the end of the infectious period. In fact, real-time reverse transcriptase PCR results remained positive 6–8 days after the loss of transmissibility.[10] For SARS coronavirus, viral RNA is detectable in the respiratory secretions and stools of some patients after onset of illness for more than 1 month, but live virus could not be detected by culture after week 3.[11] The

inability to differentiate between infective and non-infective (dead or antibody-neutralised) viruses remains a major limitation of nucleic acid detection. Despite this limitation, given the difficulties in culturing live virus from clinical specimens during a pandemic, using viral RNA load as a surrogate remains plausible for generating clinical hypotheses.

We declare no competing interests.

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