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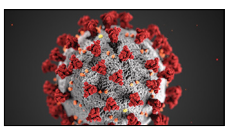
# Understanding COVID-19: what does viral RNA load really mean?



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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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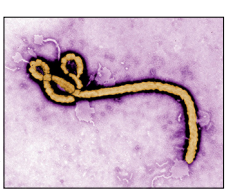
# Chimpanzee adenovirus type 3 vectored Ebola vaccine: expanding the field



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Two phase 2 randomised clinical trials evaluating ChAd3-EBO-Z administered to healthy adults in Cameroon, Mali, Nigeria, and Senegal[1] and healthy children in Mali and Senegal[2] are reported by Milagritos Tapia and colleagues in *The Lancet Infectious Diseases*. No vaccine-related serious adverse events were observed and adverse events were minimal. No clinically meaningful haematological abnormalities or thrombocytopenia were reported. The ChAd3-EBO-Z vaccine was therefore considered well tolerated in adults and children.

In 2019, Ervebo, the rVSV-ZEBOV vaccine[3] for the prevention of Ebola virus disease in individuals aged 18 years and older was approved by regulators in the USA and Europe. The question of how dozens of Ebola vaccines using various platforms (eg, vectored, DNA, RNA, antigen presentation vaccines)[4] will be implemented in the wake of rVSV-ZEBOV approval needs to be further considered as most vaccines are not expected to show equivalence or superiority to rVSV-ZEBOV. The PREVAIL study revealed anti-glycoprotein Ebola virus immunoglobulin (Ig)G concentrations were higher 1 month post vaccination with rVSV-ZEBOV compared with ChAd3-EBO-Z.[5] Although rVSV-ZEBOV, was safe and immunogenic in children and adolescents, shedding of the vaccine was observed in saliva and urine. The present outbreak in the Democratic Republic of the Congo, in which approximately 29% of cases are in children aged younger than 18 years, has a case fatality rate of up to 80%. The current reports support the potential use of ChAd3-EBO-Z in individuals aged younger than 18 years.

The ChAd3-EBO-Z vaccine was protective in a non-human primate model, which is the most direct evidence of vaccine efficacy.[6] Predictive comparisons between non-human primate observations and human responses to vaccines are essential but limited because of the high viral titre in the non-human primate challenge and variations in the T-cell receptor subtypes. Phase 1 studies indicated acceptable safety and reactogenicity, but transient decreases in thrombocyte counts were regarded as a potential safety signal requiring further assessment in these phase 2 studies. The secondary endpoint in each trial included evaluation of anti-glycoprotein antibody titres before and 30 days after vaccination. A control with ChAd3 empty vector rather than phosphate buffered saline versus ChAd3-EBO-Z would be more appropriate, but it is understandable that trials should be streamlined so that the number of different cohorts is as small as possible. Determination of pre-existing immunity to the ChAd3 component might have been helpful in the interpretation of observations. Vaccine associated T-cell responses were of low amplitude and neutralising antibody responses are a small proportion of total IgG to