Is COVID-19 disease severity correlated with initial viral exposure / inoculation dose?

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Key findings:

- There does not appear to be published data on the direct correlation between the initial inoculating dose ("dose dependent") of SARS-CoV-2 and severity of symptoms. The scant number of studies addressing a possible correlation between viral load (VL) and symptom severity in COVID-19 are conflicting.
- Some evidence exists for a positive correlation between viral load and symptom severity in MERS and SARS; there is conflicting data on whether this correlation is also present for COVID-19.
- Studies on MERS and SARS support the notion that viral load is a good proxy for initial inoculating dose, but this has not yet been observed in COVID-19.
- We are not aware of any published data or other documentation on the relative severity of COVID-19 symptoms experienced by healthcare workers and caregivers of individuals with COVID-19. While indirect evidence suggests that healthcare workers and caregivers of individuals with COVID-19 may be at risk for disproportionately severe cases of COVID-19, due to likely exposure to a relatively high initial inoculating dose of SARS-CoV-2, it remains unclear whether that is the case.

Related topics: Viral shedding

Summary of information:

No direct data for "dose-dependent" severity for COVID-19, but there is some data that supports correlation between viral load (VL) and symptom severity in COVID-19:

- Serial VL comparison of patients with mild vs severe symptoms in China. More severe patients had higher viral loads. Study clearly defined "mild" vs "severe" and longitudinal data is a plus to follow "mild" patients and ensure they don't develop severe disease later.[1]
- Viral load study of symptomatic and (at the time of study) asymptomatic patients in Lombardy: No difference in VL between symptomatic and asymptomatic patients (unclear whether asymptomatic patients went on to develop disease).[2]
- Serial viral load testing in Hong Kong did not demonstrate a correlation between viral load and severity of symptoms, but interestingly found that higher viral load correlated with older age[3] (This raises the question of whether viral load is a good proxy for initial inoculating dose. See below.)

- Serial viral load testing in 18 patients that required ICU care and their contacts (with and without symptoms) showed no difference in VL dynamics between the patients, but did not look at age.[4]

There is better evidence for a positive correlation of viral load and symptom severity in MERS and SARS, including one study that adjusted for age and comorbid conditions[3]:

- Serial tracheal aspirate/sputum and nasopharyngeal viral load correlated with severe symptoms in the MERS outbreak in South Korea[5]
- A retrospective study of SARS patients with higher VL correlated to worse symptoms. The study also looked at specific symptoms and site-specific viral load (ie higher viral load in feces correlates with more GI symptoms, and higher viral load in urine correlated with urinary symptoms.)[6]
- Higher VL was correlated with more severe disease for patients hospitalized with MERS in Saudi Arabia. Interestingly, this holds even when adjusted for age and comorbid conditions.[7]

Regarding the issue of whether viral load is a good proxy for initial inoculating dose; it appears that in well-controlled conditions viral load is a good proxy, as shown in mice for both MERS and SARS.[8]

A report from the SARS outbreak in Hong Kong tracked viral load as a function of geographic distance from an index case in a dense highrise complex. They found viral load to be correlated with how far away residents lived from the index case. It was hypothesized that the virus spread via air currents, common plumbing systems, and/or fomites. This report suggests that viral load is correlated to initial infectious dose - i.e. those who were farther away geographically were exposed to a lower initial dose - but this was not proved.[8]

Revision log:

Date	Editor	Action/Comments

References:

1. Liu Y, Yan L-M, Wan L, et al. Viral dynamics in mild and severe cases of COVID-19. *Lancet Infect Dis*. March 2020. doi:10.1016/S1473-3099(20)30232-2
2. Cereda D, Tirani M, Rovida F, et al. The early phase of the COVID-19 outbreak in

Lombardy, Italy. *ArXiv200309320 Q-Bio*. March 2020. http://arxiv.org/abs/2003.09320. Accessed April 19, 2020.
3. To KK-W, Tsang OT-Y, Leung W-S, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. *Lancet Infect Dis*. March 2020. doi:10.1016/S1473-3099(20)30196-1
4. Zou L, Ruan F, Huang M, et al. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. *N Engl J Med*. 2020;382(12):1177-1179. doi:10.1056/NEJMc2001737
5. Oh M-D, Park WB, Choe PG, et al. Viral Load Kinetics of MERS Coronavirus Infection. *N Engl J Med*. 2016;375(13):1303-1305. doi:10.1056/NEJMc1511695
6. Hung IFN, Cheng VCC, Wu AKL, et al. Viral loads in clinical specimens and SARS manifestations. *Emerg Infect Dis*. 2004;10(9):1550-1557. doi:10.3201/eid1009.040058
7. Feikin DR, Alraddadi B, Qutub M, et al. Association of Higher MERS-CoV Virus Load with Severe Disease and Death, Saudi Arabia, 2014. *Emerg Infect Dis*. 2015;21(11):2029-2035. doi:10.3201/eid2111.150764
8. Chu C-M, Cheng VCC, Hung IFN, et al. Viral load distribution in SARS outbreak. *Emerg Infect Dis*. 2005;11(12):1882-1886. doi:10.3201/eid1112.040949