Lowering SARS-CoV-2 viral load might affect transmission but not disease severity in secondary cases

We read with interest the Personal View by Matthew A Spinelli and colleagues.[1] We agree with the authors on the evident advantage provided by non-pharmaceutical interventions (facial masking, social distancing, and improved ventilation) in lowering SARS-CoV-2 inoculum, thereby reducing viral transmission. Nevertheless, we call for caution before asserting that such measures could make a substantial difference in reducing COVID-19 severity.

Animal models examining a potential dose–response relationship reported conflicting results, and experimental inoculation might inaccurately mimic real-life infection dynamics,[2] including inoculum doses. Two studies are cited to support Spinelli and colleagues' hypothesis.[3,4] Bielecki and colleagues observed no symptomatic SARS-CoV-2 infections in a military company where protective measures were rigorously implemented, whereas 47% of all infections were symptomatic in an identical company where such measures were less strict.[3] This finding is hardly applicable to the general population as the study was in young (median age 20 years), healthy individuals.[3] Bias due to sampling and testing based on self-reported symptoms could not be ruled out, non-airborne routes of transmission could have prevailed, and the primary study aim was not to assess the potential relationship of viral inoculum with disease severity.

The second study cited by Spinelli and colleagues investigated the relationship of viral load with several characteristics of index and secondary cases, as well as with transmission risk in outpatient clusters.[4] The study did not observe any dose–response relationship between index viral load and the probability of symptomatic infections in contacts, nor did it identify any correlation between the index cases' viral amount and COVID-19 incubation length or first viral load in incident secondary cases,[4] by contrast with what was stated by Spinelli and colleagues.[1]

We recently observed no difference in occurrence of symptomatic infections, hospitalisation, and death in household secondary cases when stratified by viral load of their linked index source cases.[5] As previously detailed,[5] it seems that host permissiveness (eg, age, sex, receptor density, genetic and epigenetic factors, host immunological features, comorbidities, comedications) is the key factor in allowing subsequent viral replication and triggering of inflammatory and immune-pathological processes rather than viral amount at exposure.

While reducing the amount of virus circulating in and between individuals might be a key strategy to limit SARS-CoV-2 spread, on the basis of the existing evidence (appendix), it seems unlikely that the inoculum size has any major role in determining disease severity of secondary cases.

We declare no competing interests.

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1 Spinelli MA, Glidden DV, Gennatas ED, et al. Importance of non-pharmaceutical interventions in lowering the viral inoculum to reduce susceptibility to infection by SARS-CoV-2 and potentially disease severity. *Lancet Infect Dis* 2021; published online Feb 22. https://doi.org/10.1016/s1473-3099(20)30982-8.

2 Brosseau LM, Roy CJ, Osterholm MT. Facial masking for covid-19. *N Engl J Med* 2020; **383:** 2092–93.

3 Bielecki M, Züst R, Siegrist D, et al. Social distancing alters the clinical course of COVID-19 in young adults: a comparative cohort study. *Clin Infect Dis* 2021; **72:** 598–603.

4 Marks M, Millat-Martinez P, Ouchi D, et al. Transmission of COVID-19 in 282 clusters in Catalonia, Spain: a cohort study. *Lancet Infect Dis* 2021; published online Feb 2. https://doi.org/10.1016/S1473-3099(20)30985-3.

5 Trunfio M, Longo BM, Alladio F, et al. On the SARS-CoV-2 "variolation hypothesis": no association between viral load of index cases and COVID-19 severity of secondary cases. *Front Microbiol* 2021; published online March 16. https://doi.org/10.3389/fmicb.2021.646679.

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See **Online** for appendix