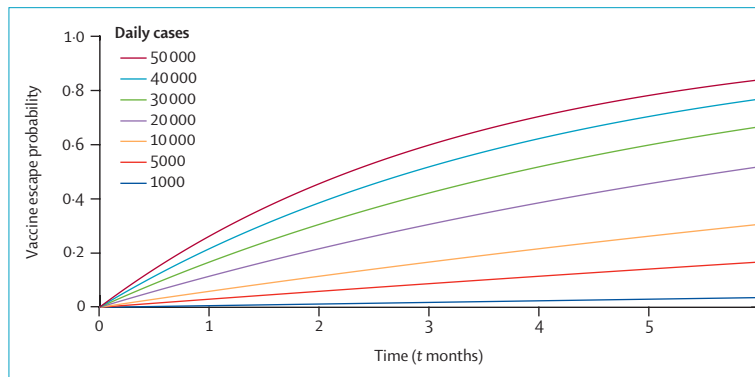**Figure:** Risk that at least one vaccine escape variant arises in a time period of length *t*, for different daily numbers of cases
The per-infection probability of vaccine escape is $p=2 \times 10^{-7}$ (for details, see the appendix).

For more on **JUNIPER** see
https://maths.org/juniper/

vaccines to lower incidence. When considering vaccines that do not prevent transmission entirely, there is an interplay between reduced cases at the population-level and the potential for selection for vaccine escape variants in infected vaccinated hosts.[2–4] A related question is whether it is most beneficial to vaccinate many individuals using single vaccine doses or fewer individuals twice. Dose-sparing strategies could in theory lead to selection for vaccine escape variants.[5] However, evidence suggests tentatively that the net vaccine escape risk is lower when more hosts are vaccinated with single doses than when fewer hosts are vaccinated twice due to reduced cases.[2]

Despite its simplicity, our quantitative illustration demonstrates that strategies for mitigating the vaccine escape risk should be explored. Reducing case numbers locally should be only one element of these strategies. Travel restrictions to reduce the risk of importing novel variants should be considered. We recognise that assessing the escape variant emergence risk not only requires the variant to arise via mutation as considered here, but also to grow to appreciable frequencies. This is a stochastic process, depending on the availability of hosts to infect and the escape variant's fitness. A reduction in cases leads to both a reduction in the risk of escape variants appearing and a reduction in their subsequent

establishment via transmission in the population. Acquisition of additional mutations that are beneficial for the virus is also more likely to be suppressed if incidence is reduced.

In summary, high SARS-CoV-2 incidence rates act to increase the vaccine escape risk. Maintaining low case numbers using NPIs and vaccines is crucial at this time.

*Robin N Thompson, Edward M Hill, Julia R Gog
robin.n.thompson@warwick.ac.uk

Mathematics Institute (RNT, EMH), Zeeman Institute for Systems Biology and Infectious Disease Epidemiology Research (RNT, EMH), and School of Life Sciences (EMH), University of Warwick, Coventry, UK; Department of Applied Mathematics and Theoretical Physics, University of Cambridge, Cambridge, UK (JRG)

1   The Lancet Infectious Diseases. An exceptional vaccination policy in exceptional circumstances. *Lancet Infect Dis* 2021; **21:** 149.
2   Cobey S, Larremore DB, Grad YH, Lipsitch M. Concerns about SARS-CoV-2 evolution should not hold back efforts to expand vaccination. 2021. https://nrs.harvard.edu/URN-3:HUL.INSTREPOS:37366988 (accessed March 12, 2021).
3   Saad-Roy CM, Morris SE, Metcalf CJE, et al. Epidemiological and evolutionary considerations of SARS-CoV-2 vaccine dosing regimes. *Science* 2021; published online March 9. https://doi.org/10.1126/science.abg8663.
4   Gog JR, Hill EM, Danon L, Thompson RN. Vaccine escape in heterogeneous populations: insights for SARS-CoV-2 from a simple model. *medRxiv* 2021; published online March 17. https://doi.org/10.1101/2021.03.14.21253544 (preprint).
5   Bieniasz PD. The case against delaying severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccine boosting doses. *Clin Infect Dis* 2021; published online Jan 27. https://doi.org/10.1093/cid/ciab070.

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.

*Mattia Trunfio, Andrea Calcagno, Stefano Bonora, Giovanni Di Perri
mattia.trunfio@edu.unito.it

University of Torino, Department of Medical Sciences at the Unit of Infectious Diseases, Amedeo di Savoia Hospital, Torino, Italy (MT, AC, SB, GDP); Clinica Universitaria I Piano, Ospedale Amedeo di Savoia, 10149 Torino, Italy (MT)

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.

Authors' reply

We thank Mattia Trunfio and colleagues for their interest in our Personal View regarding the impact of non-pharmaceutical interventions (NPIs) on the viral inoculum of SARS-CoV-2.[1] We agree that increasing evidence supports that NPIs are expected to lower the viral inoculum, potentially contributing to lower transmission. We acknowledge Trunfio and colleagues' point that the evidence supporting the impact of reduced inoculum on COVID-19 severity is less strong than that on infection; we had, therefore, presented this idea as a hypothesis and suggested potential experimental approaches. Of note, human challenge trials have since started in the UK, which will provide more direct evidence on the relationship between viral inoculum and both infection and disease.

We agree that the young age of the participants in Bielecki and colleagues' study is a limitation,[2] although it is not clear how non-airborne routes of transmission would bias the results. The study by Marks and colleagues supports the importance of the index viral load, regardless of symptom status, in forward transmission risk.[3] Although Marks and colleagues did not find a statistically significant association between the index cases' viral loads and the first positive viral loads of the secondary cases (p=0·10), the timing of presentation for symptoms influenced the timing of measurement.[3] Temporal, longitudinal dynamics of PCR cycle thresholds should be accounted for in this type of analysis, given the potential for cycle thresholds to peak before symptoms. Moreover, shedding of viral fragments might not reflect the true inoculum, with additional viral culture studies needed.

We disagree that the referenced challenge study in rhesus macaques[4] provides conflicting results on the dose–response relationship. A single dosage (nCoV-WA1-2020 isolate) was provided in this animal study and was not systematically varied in a controlled manner. Therefore, information on the dose–response relationship cannot be inferred from this study. In our Personal View, we suggest experimental approaches in animal models that could explore this hypothesis further—ie, systematically varying the inoculum dose, confirming successful infection using viral culture or molecular methods, and then presenting data on clinical outcomes among animals that were successfully infected.

We agree that host factors such as age and chronic medical conditions are key factors in SARS-CoV-2 susceptibility.[1] However, as these factors are generally not modifiable, we argue that further research is needed to explore the relationship between NPIs and the viral inoculum. Such exploration could provide additional evidence supporting the use of NPIs in COVID-19 mitigation. Given the need to protect unvaccinated individuals and reduce transmission while vaccination distribution continues, this research hypothesis merits continued focus.

Matthew A Spinelli, George Rutherford, *Monica Gandhi
monica.gandhi@ucsf.edu

Division of HIV, Infectious Diseases and Global Medicine (MAS, MD), and Department of Epidemiology (GR), University of California, San Francisco, CA 94110, USA