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.

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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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.

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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.

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See **Online** for appendix

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Applying prospective genomic surveillance to support investigation of hospital-onset COVID-19

Here, we provide an update on our previous Article,[1] which described the use of rapid SARS-CoV-2 genome sequencing to investigate hospital-acquired infections (HAIs) at Cambridge University Hospitals NHS Foundation Trust (CUH), Cambridge, UK. CUH experienced a substantial second wave of COVID-19 (figure). Between Nov 2, 2020, and Feb 7, 2021, 162 (14%) of 1178 patients with COVID-19 at CUH had a suspected or definite HAI (as previously defined[1]), and 465 infected health-care workers (HCWs) were identified via the staff screening programme.[2] Nanopore sequencing was attempted for 513 (44%) of 1178 patients, prioritising those with hospital-onset infections, and 324 (70%) of 465 HCWs; 252 (21%) of 1178 patients and 317 (68%) of 465 HCWs had SARS-CoV-2 genomes available after quality control filtering (as previously described[1]). Patient coverage was lower than in our previous study[1] and for HCWs, reflecting different diagnostic testing methods and limitations on sequencing capacity. The frequency of the B.1.1.7 PANGO-lineage[3] increased from 8% (nine of 109) in November, 2020, to 83% (257 of 311) in January, 2021.

As in the first wave, outbreaks of hospital-onset COVID-19 occurred on wards intended for patients without COVID-19, termed green wards. Where genomics were available, cases on these wards were often phylogenetically clustered (virus genomes with zero to one single nucleotide polymorphism differences), consistent with ward-based transmission.[1] This transmission occurred despite substantial efforts to reduce HAIs, including universal surgical mask wearing by staff, SARS-CoV-2 screening of all patients at hospital admission and regularly thereafter, cohorting of patients to green, amber, and red wards, and a comprehensive staff screening programme. Continued hospital-based transmission despite these efforts emphasises how challenging it is to limit SARS-CoV-2 transmission in hospitals with limited side-room capacity, given the high infectivity of SARS-CoV-2 and potential for asymptomatic transmission. Genomic data were presented at seven of 11 clinical HAI review meetings and at infection-control meetings, informing decision-making. Staff vaccinations began in January, 2021, and have already had a substantial impact on reducing COVID-19 incidence.[4]

Our experience from the first and second epidemic waves of COVID-19 at CUH identified several challenges to applying prospective genomic surveillance to infection control. First, close and efficient working between clinical, infection-control, sequencing, and bioinformatic-analysis teams is crucial. Second, changes in SARS-CoV-2 diagnostic methods resulted in technical difficulties in obtaining sufficient good-quality genetic material for sequencing. Third, the speed from sampling to sequencing to analysis is crucial; for maximum impact, genomic data should be available to inform real-time decision-making. Finally, sustained funding and human resource capacity are essential for consistent service delivery. Nevertheless, we have shown that introducing rapid genomic sequencing and data analysis into hospital outbreak investigations is both feasible and beneficial; the challenge is to translate this from an emergency response into routine clinical practice.

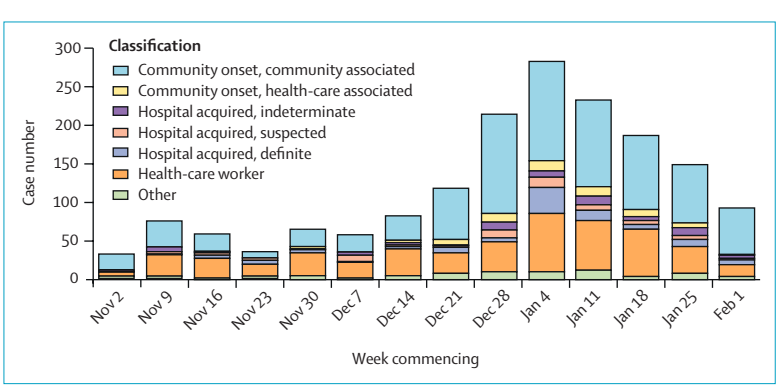

***Figure*: Hospital-acquired SARS-CoV-2 infections in Cambridge University Hospitals during the second wave**

Epidemic curve showing weekly case numbers for new diagnoses of COVID-19 at Cambridge University Hospitals (positive SARS-CoV-2 PCR tests) from Nov 2, 2020, to Feb 7, 2021, coloured by infection classification (appendix).

See **Online** for appendix

CJRI, CJ, and DDA report funding to their institution from MRC. MPW reports grants from Wellcome. SJP reports receiving consulting fees for participating on the Pfizer Coronavirus External Advisory Board and honoraria from SVB Leerink. IG reports grants from Wellcome and MRC. MET reports grants from Academy of Medical Sciences and The Health Foundation, non-financial