Title: Author's reply to correspondence regarding the article ‘Prolonged persistence of SARS-CoV-2 in the upper respiratory tract of asymptomatic infected individuals’

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We appreciate the interest shown by Kadnur and Ray regarding our article through their correspondence. We offer a reply to the points raised by them.

They have appropriately mentioned that there has been a paradigm shift in the discharge policy in India from test-based to symptom plus duration based now. This has also been mentioned by us in the article. They have also referenced CDC, USA guidelines to state that infection prevention precautions be discontinued after 10 days for most COVID-19 patients. However, it is important to note that in India, the Ministry of Health and Family Welfare (MoHFW) guidelines are being followed. It recommends home isolation for 17 days after symptom onset or remaining in home isolation for 7 days after being discharged from a 10 days-hospital stay. We have taken this home-isolation duration of 17 days as the base and have recommended its extension to 21 days (3 weeks), as applicable to the Indian situation. This is since 95% SARS-CoV-2 infected individuals (including both symptomatics and asymptomatics) were found to have virus persistence of up to 20.92 days.

Further, they go on to state that ‘as per test-based strategy for asymptomatic patients, two respiratory specimens (≥ 24 hours apart) are required to be negative, irrespective of initial date of COVID-19 detection’. However, as stated earlier, test-based discharge policy has been completely discontinued in India starting 8 May 2020, in favour of a symptom plus duration-based approach. This is saving considerable testing resources. Test-based discharge is not practicable with an overwhelming number of SARS-CoV-2 infected individuals and a large proportion of them undergoing home isolation. That said, some tertiary care centres might still be
following a test-based approach, but this is not as per the national policy. Therefore, duration-based recommendations based on evidence remain pertinent to guide the home isolation and discharge policy.

Wölfel et al (reference 3 in correspondence and also referenced by CDC) had indeed found a decline in sub-genomic m-RNA in sputum (which is taken as a proxy for viable virions) and decline in possibility of obtaining a positive viral culture after 10 days. However, Wölfel et al themselves cautiously conclude that - “Early discharge with ensuing home isolation could be chosen for patients who are beyond day 10 of symptoms and have less than 100,000 viral RNA copies per ml of sputum”. They have only suggested discharge and not ceasing subsequent home isolation, which is in agreement with MoHFW India COVID-19 guidelines and has also been replicated by All India Institute of Medical Sciences (AIIMS), New Delhi, India.

Further, Chen et al (reference no. 4 in correspondence) find that median shedding duration was 12 days and 95 percent stopped shedding only after 28 days, which in fact agrees with our findings. Kampen et al (reference 5 in correspondence) have included only 23 patients out of whom only one patient had a 20 days viral shedding. The estimates of prolonged shedding are likely to be more accurate when a larger number of patients are enrolled.

We only referenced Bullard et al in stating that higher viral load indicated by cyclic threshold values < 24 correlates with cell culture infectivity which is a laboratory finding. Since we didn’t have cyclic threshold values which could be compared between asymptomatics and symptomatics, we had opined that there could be infection spreaders even among asymptomatics when individuals with varying viral loads were considered in a large population.
Variation in findings of SARS-CoV-2 persistence might be found due to viral and host characteristics and difference in study procedures. Replication competence in cell culture is dependent on laboratory expertise, cell lines and protocols used\textsuperscript{9,10} due to which they could be limited in their ability to predict the infectious process in real-world situation. Therefore, we feel that all available evidence should be appraised for development of COVID-19 guidelines and a selective approach is best avoided. Implementing reduced duration of infection prevention precautions without cautiously assessing evidence could weaken the objective of interrupting SARS-CoV-2 transmission.

We maintain that there is nothing contradictory in the recommendations of our study which are based on our own findings. Emerging evidence can of course lead to better understanding of disease process and transmission dynamics which could prompt amendment in guidelines.

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