Review 1: "Recombinant SARS-CoV-2 genomes are currently circulating at low levels"

M Hossain¹, M. Nazmul Hoque²

¹University of Dhaka: Dhaka University Microbiology BANGLADESH,
²Bangabandhu Sheikh Mujibur Rahman Agricultural University, Gazipur-1706, Bangladesh

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**RR:C19 Evidence Scale** rating by reviewer:

- **Potentially informative.** The main claims made are not strongly justified by the methods and data, but may yield some insight. The results and conclusions of the study may resemble those from the hypothetical ideal study, but there is substantial room for doubt. Decision-makers should consider this evidence only with a thorough understanding of its weaknesses, alongside other evidence and theory. Decision-makers should not consider this actionable, unless the weaknesses are clearly understood and there is other theory and evidence to further support it.

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**Review:**

1. The authors reported that SARS-CoV-2 harbours only a small amount of genetic variation compared to RNA viruses that have been endemically circulating in humans. This statement is a bit contradictory, previously it has been reported that both SARS-CoV and SARS-CoV-2 show a high level of genetic divergence (DOI: 10.1126/sciadv.abb9153, DOI: 10.1038/s41586-020-2012-7).

2. The present study of around 537,000 SARS-CoV-2 genomes reported that the SARS-CoV-2 genomes have only 121 positions with nucleotide variants (covering only 1% of genomes sequenced to date), and only 15 positions have variants present in at least 10% of genomes. These results are too strange indeed since using around 2500 complete genomes of SARS-CoV-2 Islam et al. (2020) found 1,516 nucleotide variations and 744 amino-acid substitutions at different positions throughout the entire genome of SARS-CoV-2 (DOI: 10.1038/s41598-020-70812-6).

3. Analysing these voluminous data, the authors did not find any evidence for recombination hotspots in the SARS-CoV-2 genomes. This argument is inconsistent with many of the previous studies. For instance, structural and mutagenesis studies have identified two hotspots, K31 and K353, at the S/ACE2 interface in SARS-CoV. In SARS-CoV-2, these two hotspots were present but slightly weakened because of different residues on its S protein (DOI: 10.1126/sciadv.abb9153, DOI: 10.1038/s41586-020-2179-y). Shang et al. (2020) reported that several residue changes in the SARS-CoV-2 receptor-binding domain (RBD) stabilize two virus-binding hotspots at the RBD-ACE2 interface. Moreover, several naturally selected mutations in the SARS-CoV RBM surround these hotspots and regulate the infectivity, pathogenesis, cross-species and human-to-human transmissions of SARS-CoV (DOI: 10.1126/science.1116480, DOI: 10.1074/jbc.M111.325803). In another
study from China, Boni et al. (2020) reported that SARS-CoV and SARS-CoV-2—undergo frequent recombination and exhibit spatially structured genetic diversity on a regional scale in China (DOI: 10.1038/s41564-020-0771-4).