Review 1: "Phase transitions may explain why SARS-CoV-2 spreads so fast and why new variants are spreading faster"

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RR:C19 Evidence Scale rating by reviewer:

- **Misleading.** Serious flaws and errors in the methods and data render the study conclusions misinformative. The results and conclusions of the ideal study are at least as likely to conclude the opposite of its results and conclusions than agree. Decision-makers should not consider this evidence in any decision.

Review:

The preprint by JC Phillips and colleagues attempts to demonstrate that 'phase transitions may explain why SARS-CoV-2 spreads so fast and why new variants are spreading faster.' The statement is based on a thermodynamic model of protein conformation that fails to pass a rigorous inspection and is never adequately explained in the paper. The manuscript is a series of unsubstantiated claims that are poorly written with logical inconsistencies. It generates no dependable conclusions. The 'phase transitions' that occupy the bulk of the discussion of the paper are never defined and their relationship to the hydropathy scale that represents the only quantitative content is not well developed. The paper depends heavily on an earlier paper (reference 2) by the first author that asserts essentially the same theories with the same specious claims. Whereas the earlier paper focused on the comparison of CoV-1 with CoV-2, this paper focuses on the comparison of CoV-2 with the variants B.1.1.7 and B.1.351.

The authors state that the CoV-2 spike protein can be 'better understood as a thermodynamic object immersed in water.' Better than what is unclear. The claim that this hypothesis has been validated by the prediction that vaccines based on the spike protein would be effective has no value. There may well be good reasons for depicting a protein as a thermodynamic system for the demonstration of some properties. However, the impact of a phase transition on protein structure or dynamics, or the expected behavior of a protein at a critical point of said transition is never clearly communicated.

The theory appears to rest on a novel measure of hydropathy as a function of position along with the amino acid of the spike protein. These plots have well-defined maxima and minima that are examined in detail in the paper. The authors refer to these peaks in hydropathy as 'edges' and suggest that there is significance in their similar

magnitudes, and the symmetry of their shapes, indicating that the symmetry is a sign of a critical point and lends the hydrophilic domains more conformational mobility particularly for action 'in synchrony'. There is no biochemical basis for these claims. That surface residues will, on average, be more hydrophobic than interior residues is not in doubt. But there is no basis for the claim that two sequence regions having very similar hydrophobicity is significant - or for the apparent interest of the authors in the 'symmetry' of the 'edges' in the hydropathy plots.

Even the suggestion of a potentially intriguing relationship between the hydrophobicity of the spike protein and the stability of the virus in aerosols is tempered by the authors apparently failing to include E484K in their list of amino acid changes in B.1.351.