Review 1: "Nasally-delivered interferon- λ protects mice against upper and lower respiratory tract infection of SARS-CoV-2 variants including Omicron"

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RR:C19 Evidence Scale rating by reviewer:

- **Reliable.** The main study claims are generally justified by its methods and data. The results and conclusions are likely to be similar to the hypothetical ideal study. There are some minor caveats or limitations, but they would/do not change the major claims of the study. The study provides sufficient strength of evidence on its own that its main claims should be considered actionable, with some room for future revision.

Review:

The subject of this study is important and interesting. The authors have provided a beneficial dataset and information about the protective role of interferon-λ against SARS-CoV-2 infection using cutting-edge methodology. The manuscript is well-written and well-organized. In my opinion, a shortcoming of this manuscript is the lack of data about side effects of interferon therapy regarding liver injury and changes in liver enzymes i.e. aspartate transaminase (AST) and/or alanine aminotransferase (ALT).

According to the findings of the present study, interferon-λ can reduce viral load. Reducing viral load can decrease the disease severity. A study by Aiolfi et al.(<https://doi.org/10.1182/blood-2021-148713>) has demonstrated that clinical features characterizing severe COVID-19 cases, including inflammation and thrombosis, can be observed in K18 hACE2 transgenic mice. This mouse model has been used in the present study. I wonder if the authors have collected any data about reducing the virus load using interferon-λ and its relationship with clinical features of severe COVID-19 such as thrombosis.

The authors correctly referred to the limitations of their study. Although their findings are valuable, it is not clear to which extent their results may be related to COVID-19 patients. For instance, in the present study, the interval between virus inoculation and interferon injection is clear, while in COVID-19 patients, the time point of infection is not clear. While more investigations are needed to answer these questions, the present study has provided useful information about interferon-λ as a possible treatment for COVID-19 patients.