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Dear Sonja Schmid,

We are writing to submit the manuscript “Quantifying the effects of single mutations on viral escape from broad and narrow antibodies to an H1 influenza hemagglutinin” for consideration at *Nature Communications*.

This manuscript was originally submitted to *Nature Microbiology*, where it received four reviews. All reviewers agreed that the manuscript was technically sound, but they split on the impact of the work. Some thought it was a good fit for *Nature Microbiology*, but others thought that it did not have sufficient impact. After consulting with the *Nature Microbiology* editor Nonia Pariente, we have decided to transfer the manuscript to *Nature Communications*.

In this transfer, I have included a detailed point-by-point response to the *Nature Microbiology* reviews as well as a tracked-changes version showing all revisions made to the manuscript. These files are uploaded as Related Manuscript Files. I have also included the revised manuscript. As you will see, we have been able to respond to all of the small number of scientific concerns / questions from the original reviewers.

Please let me know if you anticipate being able to consider the manuscript with the current reviews / reviewers. If you plan to instead send it to completely new reviewers for a fresh evaluation, please update me first because in that case I may instead submit to another journal rather than *Nature Communications*.

Briefly, here is the importance of our manuscript: The discovery of broadly neutralizing antibodies against influenza virus has inspired hopes that it might be possible to design vaccines or therapeutics that are more resistant to viral escape. However, the fundamental conceptual basis for these approaches – the idea that the virus has an inherently more difficult time escaping from some antibodies – has never been formally tested. The primary reason is that existing approaches to characterize viral antibody escape do not provide comprehensive quantitative data that can be compared across antibodies in a meaningful way.

We completely experimentally map how *all* single amino-acid mutations to influenza virus hemagglutinin affect neutralization by both broadly neutralizing and narrow strain-specific

antibodies. We use a novel computational framework to quantify the antigenic effects of all mutations in a way that can be directly compared across antibodies.

We show that there are mutations that enhance influenza virus's resistance to even the broadest antibodies. However, the magnitudes of these antigenic effects vary dramatically across antibodies. The virus can escape some broad antibodies very easily, but it can only modestly shift its sensitivity to others. Our work therefore provides the first rigorous comparison of the ease of viral escape from different antibodies, and so will be of value in guiding efforts to better control influenza. Our work also is the first characterization of mutations that mediate escape (albeit weakly) from some of the broadest anti-influenza antibodies.

We expect that our manuscript will be of interest to virologists, evolutionary biologists studying viruses, and immunologists interested in antibodies. Therefore, we think that the manuscript is appropriate for a broad journal such as *Nature Communications*.

Finally, I note that I have only uploaded some of the supplementary files. Three of these supplementary files are ZIP files that contain data and code, and I cannot upload those through the online system. Perhaps I can provide them separately when they are needed.

Thanks for your time and consideration.

Sincerely,



Jesse D. Bloom, Ph.D.