Rapid Reviews COVID-19

Review 1: "The effect of influenza vaccination on trained immunity: impact on COVID-19"

Ming-Jim Yang¹

¹University of Florida, Hospital Medicine, USA

Published on: Nov 29, 2020

DOI: 10.1162/2e3983f5.5c1a7096

License: [Creative Commons Attribution 4.0 International License \(CC-BY 4.0\)](https://creativecommons.org/licenses/by/4.0/)

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.

Review:

I read this manuscript with significant interest. The group poses the hypothesis that the flu vaccination may train the innate immune system and thus prevent future SARS-CoV-2 infection and subsequent COVID-19 disease. As we are all aware, this is a very relevant topic at this time given the new increase in cases around the world and the upcoming influenza season. Their findings consist mostly of cellular work with some extrapolation into clinical findings. While their benchwork has merit and puts forward new ideas that may help in the fight to control this current pandemic, their clinical findings are weak at best. They, unfortunately, do not present any direct evidence that supports their hypothesis that trained immunity, either with the influenza vaccination or the BCG vaccination, can prevent SARS-CoV-2 infection. Their manuscript, as it stands, seems like 2 separate papers—a basic science paper and a clinical paper. The basic science paper seems to revolve more around how trained immunity with BCG can potentially protect against SARS-CoV-2 infection. Their clinical work is related to the influence of the influenza vaccination on SARS-CoV-2 infection. Issues that I believe will need to be addressed:

- 1) In order to appropriately conclude that healthcare workers who were vaccinated were protected against COVID-19, the difference in the two groups must be controlled for patient-contact and other risk factors for contracting COVID-19. As the authors state in their manuscript that they are unable to gather some of this data, what data can they get? At the very least, the analysis to control for direct patient contact should be done though.

2) Do we know the vaccination status of the healthy blood donors? Given that we are concerned with previous exposures to viral antigens affecting PBMC's, I think knowing the healthy subjects' prior vaccination status will play a role. It may also explain the lack of any sort of significant release when initially exposed to the flu vaccine in Fig 2.

3) The negative control or "0" dilution in Fig 2 and Fig 3 are unclear. I think it is better just to designate the negative control as it can be confusing for readers when they see a '0" dilution.

4) At this point, their argument that trained immunity can prevent a SARS-COV-2 infection is weak. Do they know of any data that shows that trained immunity can prevent other viral infections that we can draw parallels with? Have the authors measured the trained response to other viruses such as influenza and how do the responses compare? If the cytokine release after training by the influenza vaccine is similar to SARS-CoV-2, then I think that would help support their argument that this particular response to SARS-CoV-2 actually has a clinical significance.