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Editor  
Nature

Dear Editor

Please find enclosed the manuscript entitled “**Emergenet: Fast Scalable Pandemic Risk Assessment of Influenza A Strains Circulating In Non-human Hosts**” for your consideration for publication in Nature as an original research article. In this study we develop a computational approach to learn the emergent rules guiding evolutionary change in Influenza viruses to quantitatively assess the pandemic potential of animal strains that are **not yet known to circulate in humans**. This capability might be crucially important to enable preemptive pandemic mitigation strategies, the relevance of which cannot be overstated in the light of the recent pandemic.

While zoonotic emergence is suspected to have caused multiple devastating pandemics in the past, and despite vast amounts of money and effort being spent globally on bio-surveillance to collect thousands of strains annually, our ability to risk-rank these collected strains remains limited.

The state-of-the-art Influenza Risk Assessment Tool (IRAT) from the CDC to assess such risk includes time-consuming experimental assays, taking possibly weeks to evaluate each strain (only 22 have been analyzed in past 6-8 years, while 6,000 strains have been collected post-2020). Our calculations take about 6 sec/strain, while strongly correlating with the published scores, and thus may provide the foundation on which a proactive intervention strategy can be built in future. As an added advantage, our approach is shown to be able to predict dominant strains of the seasonal epidemic, sufficiently ahead of time, better than what has been reported before, and thus may be used to improve vaccine cocktail recommendations.

Furthermore, with growing vaccine hesitancy in the US, it might be easier as a public health measure to preemptively inoculate animals against targeted strains, than it is to field such policies in the human population.

We are led by a multi-disciplinary team of experts in machine learning (Chattopadhyay), and vaccine design (Esser-Kahn), and is a collaboration between the Department of Medicine and the Pritzker School of Molecular Engineering, at the University of Chicago. We believe that the potential importance of our results in predicting emergence, ranking risky pathogens and potentially improving the design of the annual flu-shot, merits consideration for publication in Nature. We look forward to, and hope for your positive response.

Sincerely,

Ishanu Chattopadhyay  
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Thursday 1<sup>st</sup> December, 2022