



RESEARCH HIGHLIGHT

Double insult: flu bug enhances SARS-CoV-2 infectivity

Shan Su¹, Zezhong Liu¹ and Shibo Jiang¹ *Cell Research* (2021) 31:491–492; <https://doi.org/10.1038/s41422-021-00498-6>

The continuing COVID-19 pandemic and emergence of SARS-CoV-2 variants may cause this disease to transit into endemicity like seasonal flu. In a recent study, Bai et al. reported that preinfection of influenza A virus enhanced SARS-CoV-2 infectivity, calling for the development of a pan-flu-COVID-19 vaccine to combat infection of IAV, SARS-CoV-2, or their coinfection.

The COVID-19 pandemic, caused by SARS-CoV-2, may become even more serious by the emergence of variants with altered transmissibility, pathogenesis, and virulence, or a combination, under evolutionary pressure. In addition, antibodies in COVID-19 convalescents or vaccinees may drive SARS-CoV-2 to further adapt and mutate into escape variants. It is anticipated that COVID-19 may transit into endemicity like seasonal flu and the common cold caused by other human coronaviruses (HCoVs).¹ This is a matter of concern on the combined effect of coinfection between SARS-CoV-2 and other common viruses, especially the influenza A virus (IAV), which causes respiratory symptoms similar to some coronaviruses.

In a recent report in *Cell Research*, Bai et al.² found that cells, whether susceptible or not to SARS-CoV-2, became significantly more sensitive to SARS-CoV-2 after infection with IAV (A/WSN/1933(H1N1)). In addition, coinfection of IAV and SARS-CoV-2 in mice resulted in increased viral load of SARS-CoV-2 and more severe lung damage. These findings are consistent with results from other groups. For instance, Yuen and colleagues also found that simultaneous or sequential coinfection by SARS-CoV-2 and IAV (A/H1N1/pdm09) caused more weight loss, more severe lung inflammatory damage, and increased tissue cytokine/chemokine expression when compared to infection by either virus alone in hamsters.³ In addition, sequential infection with IAV (A/HKx31(X31, H3N2)), followed by SARS-CoV-2, leads to more severe lung damage and encephalitis, while exacerbating extrapulmonary manifestations in K18-hACE2 transgenic mice.⁴ The similarity of findings in these different animal models portends that coinfection of IAV and SARS-CoV may also cause more severe disease in human. Therefore, potential coinfection of IAV and SARS-CoV-2 should be a driver of increased clinical awareness.

Bai et al.² also found that other respiratory viruses, such as human respiratory syncytial virus (HRSV), human parainfluenza-virus (HPIV), and human rhinovirus 3 (HRV3), did not appear to promote SARS-CoV-2 infection, thus providing a tentative diagnostic basis for pathogen co-monitoring, alongside SARS-CoV-2, in the clinic. This study also reported that the auxo-action of IAV to SARS-CoV-2 infection may come from the elevated ACE2 expression induced by IAV (Fig. 1). Interestingly, the enhanced

SARS-CoV-2 infectivity induced by IAV infection is independent of interferon (IFN) signaling although ACE2 has been reported to be an IFN-stimulated gene (ISG) in human airway epithelial cells.⁵ The addition of IFN α even significantly inhibited pseudo-SARS-CoV-2 infectivity in cells susceptible to SARS-CoV-2, indicating that IFN may have contradictory functions of inhibiting SARS-CoV-2 infection and increasing its infection by promoting the expression of ACE2, among which the inhibitory effect may be more dominant in these cell lines. If confirmed, such pathway could serve as a therapeutic target to block the synergistic effect of IAV/SARS-CoV-2 coinfection.

Oddly, however, the 2020 flu season did not bring an increased mortality of COVID-19. According to the data from UK, the number of flu sufferers in England plunged by > 95% to levels not seen for 130 years because of lockdowns and new health habits due to the COVID-19 epidemic.⁶ This could explain why further surges of COVID-19 were not seen as a result of IAV coinfection. Nonetheless, as vaccination increases and restrictions relax, we may experience COVID-19 transition to endemicity, making it essential to develop a pan-flu-COVID-19 vaccine to prevent IAV infection, SARS-CoV-2 infection, or IAV/SARS-CoV-2 coinfection.

Successful combined vaccines have been developed, e.g., Tdap vaccine (for adult tetanus, diphtheria, pertussis) and MMR vaccine (for measles, mumps and rubella). Nevertheless, IAV contains many subtypes, and new HxNy IAVs may emerge in the future.⁷ It has been recently reported that the first human case of H5N8 avian influenza occurred in Russia.⁸ Therefore, a pan-flu-COVID-19 vaccine needs to contain a pan-IAV vaccine. For example, we and collaborators have found that a 2',3'-cyclic guanosine monophosphate-adenosine monophosphate (cGAMP)-based adjuvant can boost the ability of the IAV H1N1 vaccine to elicit strong cross-protection against distant IAV H1N1, H3N2, H5N1, and H7N9 strains.⁹ Therefore, we hypothesized the possibility of developing a pan-flu-COVID-19 vaccine by combining a seasonal flu vaccine, a licensed SARS-CoV-2 vaccine, and a cGAMP analog as an adjuvant. Our most recent study has also shown that the neutralizing antibodies induced by SARS-CoV-2 RBD linked with a human IgG Fc fragment (RBD-Fc) could cross-neutralize infection by SARS-CoV-2 and its variants.¹⁰ These findings suggest the possibility of designing a pan-flu-COVID-19 vaccine by combining a seasonal flu vaccine, an RBD-Fc-based SARS-CoV-2 vaccine, and a cGAMP analog as an adjuvant, which could be further developed for prevention of infection by divergent IAVs, SARS-CoV-2 and its variants, or IAV/SARS-CoV-2 coinfection (Fig. 1).

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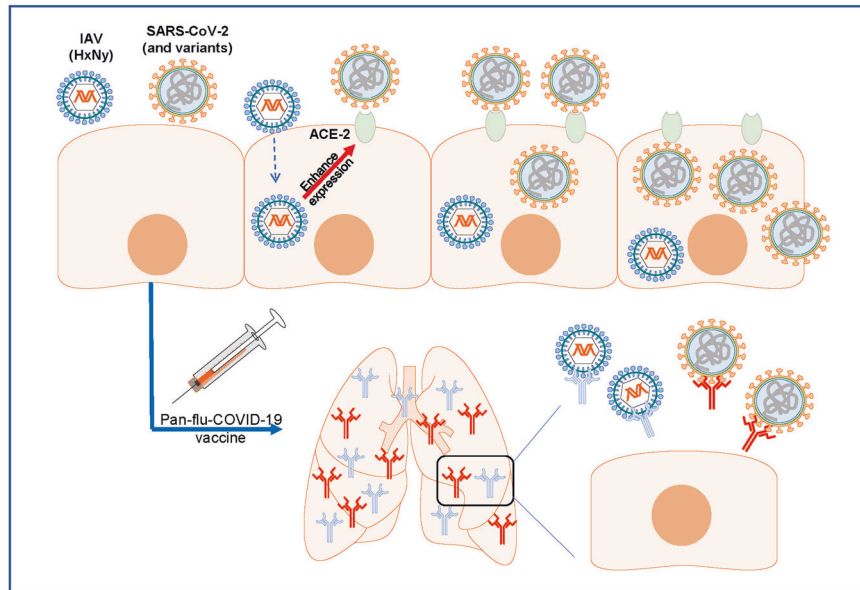


Fig. 1 Schematic diagram of auxo-action of IAV to SARS-CoV-2 infection and the mechanism of action of a pan-flu-COVID-19 vaccine. The infection of IAV can enhance the expression of ACE2, the receptor for SARS-CoV-2, on host cells, resulting in more SARS-CoV-2 entry into the cells for coinfection. Inoculation of a pan-flu-COVID-19 vaccine can induce neutralizing antibodies against both IAV and SARS-CoV-2, which can protect host from the infection by divergent IAVs, SARS-CoV-2 and its variants, or IAV/SARS-CoV-2 coinfection.

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