Co-infection, SARS-CoV-2 and influenza: an evolving puzzle

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The co-circulation of influenza virus and the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) this autumn and winter has the potential for taxing in-patient and intensive care capacity [1] and has led to calls for increasing influenza vaccination [2]. This is far and away the most important threat that co-circulation of these viruses poses, but co-infection, while rare, is another possible consequence. Co-infection refers to the simultaneous infection of a host by multiple pathogens; co-infecting organisms can be of the same general type (e.g., viruses) or different types (e.g., a virus and a bacterium or a bacterium and a fungus). It is a complex phenomenon and hinges on the biology of the individual infecting agents, their commensal or parasitic interrelationships, and which one infected the host first. There are multiple examples of this ranging from the classical necrotizing *Streptococcus pneumoniae* superinfection in patients whose lungs have been damaged by influenza A [3] to the interaction of tuberculosis in patients with HIV-associated immunodeficiency [4] to the competition for CD4+ receptor sites between HIV and GB virus-C (formerly hepatitis G virus) [5].

In a systematic review of the literature, Lansbury and colleagues found that 30 series of hospitalized patients with SARS-CoV-2 infection reported bacterial co-infection in 7% and viral co-infection in 3% [6] Reviewing the literature, we found 16 reports of 35 patients with co-infection with SARS-CoV-2 and influenza from Iran, China, Turkey, Taiwan, Brazil, Japan, Germany, Spain, Italy, and the United States [7-22]. Eighteen of the influenza isolates were influenza A, 10 were influenza B, 1 was both A and B, and 6 were not specified. All but three patients were hospitalized and 31% received mechanical ventilation--not surprising in series of largely hospitalized patients who were sick enough to merit further investigation. Four other case series from Iran and China provided only aggregate numbers of coinfected patients without individual patient-level detail [23-26]. Hashemi and colleagues reported that influenza was the "most prevalent co-infection" [23]. Ma and colleagues, Yu and colleagues, and Yue and colleagues together reported 530 Chinese COVID-19 patients, of whom 286 (54%) were co-infected with influenza A or B [24-26].

To these clinical series, Zhang and colleagues have brought rigorous basic science to help us understand the interaction between influenza virus and SARS-CoV-2 [27]. They performed a series of *in vitro* experiments in which they intranasally inoculated Syrian hamsters with SARS-CoV-2 alone, an influenza A (H1Ni)pdm09 strain alone, both simultaneously, and both again sequentially (influenza followed 24 hours later by SARS CoV-2 and SARS-CoV-2 followed by influenza). They found that hamsters inoculated simultaneously with both viruses had more weight loss, more severe pulmonary damage, higher tissue cytokine and chemokine expression, a longer clinical course, and lower antibody titers on recovery than those inoculated with a single virus alone. However, when hamsters were initially infected with influenza A and 24 later with SARS-CoV-2, they had lower SARS-CoV-2 viral loads in their lungs than with SARS-CoV-2 infection alone and higher influenza A viral loads than with influenza A alone. Thus, influenza A appears to not only make SARS-CoV-2 infection worse but, if established before SARS-CoV-2 infection, it appears to attenuate the infection. This is

consistent with the clinical observation that, in children, rhinovirus and respiratory syncytial virus co-infection appears to attenuate the severity of influenza [28].

Zhang and colleagues' elegant work coupled with the clinical series indicate that co-infection with influenza viruses and SARS-CoV-2 occurs, but that the pathophysiology may be more complex than simply two viral infection operating in parallel and causing more damage than a single one alone. What is clear, however, is that co-infection does lead to greater pulmonary damage and should be avoided. With the approach of the Northern Hemisphere's winter, vaccination against influenza becomes even more important if there is a major outbreak of influenza. However, based on data from Australia, the influenza season may not be as severe this year as it has been in past years, possibly owing to widespread masking and social distancing [29]. This has also been seen with respiratory syncytial virus infection in children in Western Australia, Brazil, and Alaska [30]. Nonetheless, we encourage universal influenza vaccination in everyone over 6 months of age who does not have a contraindication [31]. We also encourage the rapid evaluation of patients presenting in respiratory distress to emergency departments for both SARS-CoV-2 and influenza and, if co-infected, treatment with antiviral agents both for influenza A and B and, as they become available, for SARS-CoV-2.

Conflict of interest: The authors declare that they have no conflict of interest.

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