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Seasonal Influenza Vaccination and the Heightened Risk of Coronavirus and Other Pandemic Virus Infections: Fact or Fiction?

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During this ongoing severe acute respiratory illness coronavirus 2 (SARS-CoV-2) pandemic, few speculative reports on significant association of influenza vaccines with an increased risk of coronavirus infection appeared both in media and academic circles. The speculation of vaccines paradoxically increasing the risk of infections possibly originated first following 2009 influenza A (H1N1pdm09) pandemic when four Canadian studies suggested that receipt of seasonal influenza vaccine increased the risk of laboratory-confirmed 2009 pandemic influenza A (H1N1pdm09) virus infection [1]. This led to five additional studies, each of which substantiated these initial findings. One proposed mechanism behind this phenomenon is ‘original antigenic sin’ which was first used to describe how first exposure to influenza virus shapes the outcome of subsequent exposures to antigenically related strains. When an individual is infected by an ‘evolved’ strain with a new dominant antigen, slightly different from the ‘original’ strain against which the person has been vaccinated, the immune system produces antibodies against the ‘original’ strain through preformed high-affinity memory B cells that inhibit activation of naïve B cells resulting in a weak immune response against the new ‘dominant’ strain. Hence, the risk of infection paradoxically increased in vaccinated individuals as compared to naïve individuals [2].

Besides, viruses are known to interfere with the circulation of other viruses. For example, there is evidence that the circulation of rhinovirus in the community interferes and decreases the spread of seasonal and pandemic influenza viruses [3,4]. Viral interference is also well-known to interfere with “take” of oral polio vaccine. However, more recently a new phenomenon, ‘vaccine-associated virus interference’ has been suggested whereby a vaccine can paradoxically increase the circulation of other viruses. That is, vaccinated individuals may be at increased risk for other respiratory viruses because they do not receive the non-specific immunity associated with natural infection [5,6]. Rikin, et al. [5] found an increased incidence of acute respiratory infection in children by non-influenza respiratory viruses among 999 participants (out of which 68.8% were children) following influenza vaccination compared to unvaccinated children during the same period. In a study of 115 children [6], a significantly increased risk of virologically confirmed non-influenza respiratory
virus infections was found to be associated with receipt of inactivated influenza vaccine. Coronavirus was one of the non-influenza respiratory viruses [6]. Wolff, et al. [7] have recently performed a large study among defence personnel to investigate respiratory virus interference during the 2017–2018 influenza season by comparing respiratory virus status with their influenza vaccination status. They concluded that overall, receipt of influenza vaccination was not associated with virus interference among the study population. However, vaccine-derived virus interference by specific respiratory viruses was significantly associated with coronavirus and human metapneumovirus [7]. However, studies that have looked into the interference of influenza vaccine with specific non-influenza viral infections are scarce.

It is hypothesized that a respiratory virus infection confers immunity against the same and other respiratory viruses for a short time, perhaps a few weeks. This immune protection is associated with activation of the innate immune response to viral infection mediated by the release of type I interferons and other cytokines that have broad protective effects against a range of viruses [8]. This immunologic mechanism, known as heterosubtypic ‘temporary non-specific immunity’, has been proposed as the biological mechanism behind the paradoxical findings. Natural influenza infection that could have provided the host with some temporary immunity against other respiratory viruses is prevented by influenza vaccination. Hence, the risk of infection by non-influenza viruses (including the coronaviruses) is paradoxically increased [6].

The contentious issue of higher risk of non-influenza respiratory viruses to influenza vaccinated individuals has gained traction during the ongoing SARS-CoV-2 pandemic, which is also a coronavirus infection. Currently, we do not have sufficient data to establish or refute the association between influenza vaccination and higher susceptibility to coronavirus infection. We need to perform systematic studies urgently to find an answer to this question with regard to SARS-CoV-2. This is of vital importance since it is going to have far-ranging implications.

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