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Editorial article

Influenza vaccination in the time of SARS-CoV-2☆

La vacunación de la gripe en el tiempo del SARS-CoV-2

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Influenza is a disease of viral aetiology which annually, during the winter months, causes epidemics and occasionally pandemics. In general it is a mild and self-limited disease, but when it affects the elderly population or people with underlying chronic diseases, it can present high morbidity and even mortality.[1] Despite the shorter duration of the season from 2019 to 2020 in Spain, the National Epidemiology Centre estimated that there were 619,000 confirmed cases of influenza in primary care, 27,700 hospitalisations with confirmed influenza and about 3900 deaths attributable to influenza.[2] Therefore, and in the face of this epidemiological situation, the best public health strategy is prevention through the application of the appropriate influenza vaccine.

The current situation of an enduring and ongoing epidemic caused by the SARS-CoV-2 virus, raises the probability that this will actively coincide with the anticipated annual influenza epidemic. Therefore, a logistical strategy for the clinical and virological diagnosis of SARS-CoV-2 virus is key, and this identifies the importance of knowing the role the influenza vaccine may play in the COVID-19 disease caused by the virus.

Several studies seem to indicate a significant decrease in the incidence of influenza in the countries of the southern hemisphere during the time it coincided with the SARS-CoV-2 epidemic. Sakamoto et al.[1] were among the first to report a significant decrease in the influenza activity for the 2019–20 season, with it being much lower than previous seasons, especially during the start of the COVID-19 epidemic. The data provided by the World Health Organization (FluNet), regarding the incidence of influenza in the southern hemisphere (June–August 2020) confirm this significant decrease in influenza activity[3]; and these data are similar to those reported by Olsen et al.[4] in USA, with a 61% decrease in the number of suspected influenza respiratory samples studied, and significantly a 98% decrease in their positivity. Very similar data have been reported in our country, with a decrease and an interruption to the influenza circulating in mid-to-late February 2020.[5]

All these studies seem to indicate that the social mitigation measures implemented in these countries, such as schools closing, social distancing, lockdown, the use of masks, hand hygiene, and probably influenza vaccination, have affected and reduced the interhuman transmission, not only of the flu, but of the rest of respiratory viruses, drastically reducing their detection among patients with respiratory symptoms.[1,3,4]

Like SARS-CoV-2, influenza is also transmitted primarily by air (drops and aerosols), however, the low transmissibility of seasonal influenza (Ro = 1.28) compared to that of the new coronavirus (Ro = 2–3.5) seems to have contributed to a significant interruption of influenza transmission, with the SARS-CoV-2 epidemiologically constraining it.[6] These data suggest that the mitigation measures may only have been supplementary to the necessary vaccination against influenza, especially in populations at risk or complications.[4]

Several studies seem to indicate that co-infections between influenza viruses and SARS-CoV-2 are rare; thus, Richardson et al.[7] detected in New York a single case of co-infection with influenza virus A (0.01%) out of 5700 patients diagnosed with COVID-19. Likewise, in Spain, Reina et al.[8] also detected a single case of co-infection with influenza virus B (0.5%) and Kim et al.[9] reported 0.9% of co-infections with any influenza virus, compared to 20.7% with the other respiratory viruses. Some studies have observed a lower number of co-infections than expected among adults, although this has not been the case among children.[10] It has also not been possible to definitively demonstrate whether these co-infections determine a greater severity of COVID-19; although the initial study by Ding et al.[11] on mixed SARS-CoV-2/influenza infections did not show a worsening or worse prognosis than infection alone. In addition, a large study by Public Health England shows that, despite the fact that co-infections are rare, patients co-infected with both viruses are 2.4 times more likely to die than those who are infected by only one of these viruses. This data is especially relevant in individuals >65 years of age, reporting deaths of more than 50% of co-infected persons.[12] These data support the need to protect the general population, and especially the risk groups, to avoid these possible co-infections (ẗhe perfect storm¨), which seem to significantly increase the morbidity and mortality.[13]

In accordance with this hypothesis, Marín-Hernández et al.[14] studied the possible existence of a relationship between influenza vaccination in >65 years and the evolution of COVID-19 in different regions of Italy. It found a strong correlation between a higher percentage of those vaccinated and a lower number of deaths from

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COVID-19. A large study also carried out in Italy showed a significant inverse association between vaccination coverage against influenza, the population-based seroprevalence rate against SARS-CoV-2 (spread of infection), the prevalence of hospitalised patients, ICU hospital admissions and the number of deaths attributable to this virus. This study estimated that an increase of 1% in vaccination coverage of those >65 years of age would avoid more than 350 hospital admissions and almost 2000 deaths throughout the country.[15] In another study carried out in Brazil on 90,000 patients diagnosed with COVID-19, of which 31.1% had been vaccinated against influenza with the seasonal trivalent inactivated vaccine, it was confirmed that those vaccinated before or during the SARS-CoV-2 epidemic had lower mortality and less admissions to intensive care.[16]

One of the possible explanations could be the possibility that the influenza vaccine protected, albeit partially, against infection by SARS-CoV-2. This fact could occur if the vaccine were able to sufficiently stimulate innate immunity against other respiratory viruses, including SARS-CoV-2. In this way, the local respiratory immune system would provoke an intense and rapid response that would hamper other respiratory viral infections. From an immunological point of view, the influenza vaccine is designed to induce a long-lasting adaptive response through the production of neutralising antibodies and T-cell responses.[17] Despite the poor genetic similarity between influenza viruses and SARS-CoV-2, it is possible that some CD8+ T lymphocytes recognise minor epitopes present in SARS-CoV-2. However, due to the extraordinary antigenic diversity of influenza viruses, the production of neutralising antibodies and T-cells against other RNA viruses, including SARS-CoV-2, seems unlikely.[17] Therefore, according to Fink et al.[16] the most likely mechanism for the possible benefits of vaccination would be the induction of innate immunity. There is abundant evidence that the immunological memory is not a characteristic exclusive to the adaptive immune response, but it can also be detected in innate immunity cells (dendritic cells) and stem cells present in lymphoid tissues. This innate immunity is induced both by natural infections and by vaccines, determining an off-target protective effect, which would affect viruses not initially contained in the vaccine. Furthermore, it has been seen that some vaccines, probably including the influenza vaccine, induce non-specific immunotherapeutic mechanisms that increase the host's response to other pathogens through a complex process called ẗrained immunity.̈[18]

Immunological studies carried out on the influenza viruses suggest that the immunity induced by the complete inactivated vaccine depends on the fixation of a single viral RNA chain to the Toll-like receptor 7 (TLR7). This receptor is responsible for recognising the so-called pathogen-associated molecular patterns (PAMPs), with the single-stranded RNAs being their main targets. This recognition determines not only an increase in the neutralising antibody titre and an activation of the T-cells, but also an increase in the activation of the memory of the natural killer cells (NK) and the respiratory tissue response in IL-12p40 and IFN-1.[17,18] These memory NK cells, induced by the influenza vaccine, could later be stimulated by other single-stranded RNA viruses such as SARS-CoV-2. This mechanism postulated by Fink et al.[16] would be consistent with the various protective effects of the influenza vaccine seen in older people. In this population group, post-vaccination adaptive immunity would be lower due to immunosenescence processes and immune dysfunctions associated with age, requiring a robust innate immunity.[17]

Also, in this study, it has been observed how influenza vaccination administered at the onset of symptoms, or shortly after the onset of COVID-19 also determined a decrease in the severity of this disease. It could be that the innate immunity induced by the vaccine determines a rapid and efficient elimination of SARS-CoV-2 from the upper respiratory tract, preventing or decreasing its dissemination to the lung parenchyma, or that it interferes in the cytokine inflammatory processes observed in COVID- 19.[16] This process, in theory, would be more intense if an attenuated influenza vaccine were used,[17] since this induces a greater innate response because it is the complete virus rather than the inactivated one (one that only contains hemagglutinin as antigen). Thus, in the United Kingdom it is recommended that influenza vaccination in children (over two years) be carried out with an attenuated nasal vaccine as far as possible to increase the spectrum of the immune response.[19]

Another non-virological explanation for the protective effect of the influenza vaccine could be that the highest percentage of vaccinations are given in a social-economically higher strata, to individuals who already present a better baseline state of health. It is also possible that this correlation is due to chance or due to the epidemiological behaviour of the other respiratory viruses. Therefore, more studies are needed to establish the relationship between the flu vaccine and the SARS-CoV-2 infection and the COVID-19 disease.[14]

The influenza vaccination reduces the prevalence of influenza, as well as its symptoms that can be confused with those of COVID-19. In this way, the prevention and reduction of the severity of influenza and the reduction of the disease in the community, hospitalizations and ICU admissions through the application of the flu vaccination will reduce and relieve the pressure on healthcare throughout the global health field, thereby allowing greater attention to be given to patients with COVID-19 or other pathologies.

For all these reasons, it is evident that the influenza vaccination should continue to be implemented and intensified as much as possible to continue preventing this disease with a non-negligible mortality, regardless of its impact on the evolution of SARS-CoV-2. In addition, it should be remembered that in the 2020/21 season the vaccine composition has been updated. Three of its antigenic components (H1, H3 and B/Victoria lineage) are different, leading us to understand that people who were vaccinated in previous seasons will have a low immunity against these viruses.[5] Additionally, and due to the common symptoms between these two infections, the vaccination will allow diagnostic and clinical decisions to be adopted that reduce the possible saturation of the health system.

Due to the limited clinical experience in influenza vaccination of COVID-19 patients, it is recommended that in those who present compatible symptoms or lab confirmation of SARS-CoV-2, a delay in the influenza vaccination until the patient has fully recovered should be considered. In these circumstances the patient should be reminded of the need to join the vaccination programme as soon as it is possible.[4,20]

In short, the annual flu vaccination remains the best and perhaps the only cost-effective public health tool, with a demonstrated impact on the epidemiology and prevention of seasonal influenza.

Conflict of interest

The author declares having no conflict of interest.

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