

Epidemiological evidence for association between higher influenza vaccine uptake in the elderly and lower COVID-19 deaths in Italy

To the Editor,

The Italian COVID-19 epidemic may finally be slowing, although the virus has spread from the North in Lombardy throughout the rest of the country. Although there have been more than 233,000 confirmed cases and a mortality rate estimated around 14%, Italy will now navigate an exit from lockdown with continued testing, monitoring, and contact tracing of any new infections. The higher mortality rate in Italy compared with China has been attributed to a higher prevalence of elderly people living in Italy and a different strain of SARS-CoV-2.¹ However, as the virus has now spread throughout the country, regional differences in mortality rate from COVID-19 have been observed.

We investigated whether there was any relationship between influenza vaccination and COVID-19 outcome in Italy. For the 2019 to 2020 influenza season, a quadrivalent cell-based influenza vaccine (QIV) was available for the first time in Italy and the rest of Europe, in addition to the trivalent inactivated vaccine (TIV) and the adjuvanted TIV.^{2,3} The QIV vaccine uses the Madin-Darby Canine Kidney (MDCK) cell line, instead of fertilized chicken eggs, for growing the influenza virus.⁴ The MDCK cell line is made available to vaccine manufacturers from cell banks that have produced the cell line in accordance with good manufacturing practice guidelines, and has been tested for purity, identity, and for the absence of contaminating viruses as required by Food and Drug Administration, EMMA, and World Health Organization guidelines.⁵ All three forms of the influenza vaccine were available for potential prescription and use.

We used publicly available data to compute a Pearson product-moment correlation for assessment of the relationship between the percentage of vaccinated adults greater than 65 years old⁶ and the percentage of COVID-19 deaths from each region in Italy up to 2 May 2020.⁷ We calculated a simple linear regression to predict the percentage of COVID-19 deaths based on the percentage of adults greater than 65 years old vaccinated against influenza.

We found a moderate to strong negative correlation ($r = -.5874$, $n = 21$, $P = .0051$), meaning that where there were higher influenza vaccination rates, less deaths from COVID-19 occurred. Then, we calculated a simple linear regression to predict the percentage of COVID-19 deaths based on the percentage of adults greater than 65 years old vaccinated against influenza. A significant regression equation was found ($F(1,19) = 10.01$, $P = .01$), with a R^2 of 0.3450. Each region's percentage of COVID-19 deaths decreased by 0.3450

for each unit of percentage of adults greater than 65 years old vaccinated against influenza, as shown in the scatterplot (Figure 1).

There could be several independent or linked explanations for this significant association, including a possible protective effect of influenza vaccination against COVID-19 acquisition or disease. This might occur if the vaccine could stimulate sufficient trained innate immune memory that when another respiratory pathogen like SARS-CoV-2 occurred, the local lung immune system would be primed for a rapid response, and that could impact acquisition of SARS-CoV-2 or the COVID-19 disease course. However, this scenario would be more likely to occur with the live attenuated influenza vaccine, which would be more likely to lead to local trained immunity than the inactivated vaccine. Another explanation for the negative association could be that the uptake of the influenza vaccine might occur in higher economic groups, who had overall better health. It is also possible that the observed association could have occurred by chance, is related to seasonal respiratory virus infections,⁸ or is mechanistically unrelated. However, as vaccination against influenza is encouraged to help reduce hospitalization and to help in the differential diagnosis of viral-mediated adult respiratory distress, there are already known benefits of influenza vaccination in regions experiencing SARS-CoV-2 infection. Further epidemiological,

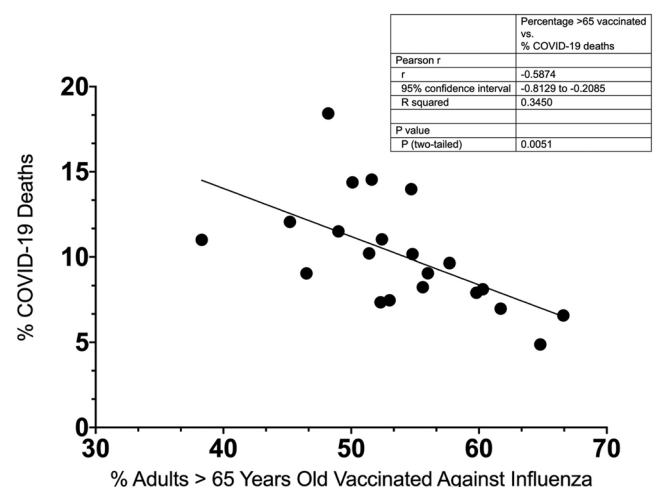




FIGURE 1 Relationship between the percentage of vaccinated adults greater than 65 years old and the percentage of COVID-19 deaths from each region in Italy up to 2 May 2020

observational, and vaccination studies are needed to determine whether any link between the higher uptake of influenza vaccination and lower deaths from COVID-19 in Italy is causally associated or not.

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