Influenza vaccination may have only minimum or no effect on COVID-19 in the aged population

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SUMMARY BOX
⇒ Influenza vaccination is a common practice across the world.
⇒ The effect of influenza vaccination on COVID-19 reported in Nature is questionable.
⇒ Data from no other countries reflect the effect of influenza vaccination on a large scale.
⇒ Extensive data suggest that the COVID-19 vaccine is effective against severe COVID-19.
⇒ Influenza vaccination has either minimal or no effect on severe COVID-19.

REPORTED EFFECT OF INFLUENZA VACCINATION ON SEVERE COVID-19 IS UNEXPECTED

As the COVID-19 pandemic enters its third year, many people wonder what researchers and healthcare workers have been doing during the last 3 years and why the effectiveness of influenza vaccination was not discovered. Many drugs, chemicals, and therapies have been tested since the outbreak of the COVID-19 pandemic, including injecting patients with disinfectants or bombarding them with UV light. Therefore, the high effect of influenza vaccination as stated in one report is somewhat unexpected.

While we should welcome the good news even though it comes late, we also checked the basis of such a claim and suggest that the findings should be interpreted with great caution.

First of all, influenza vaccination is a common practice across the world, especially in developed countries. If the vaccination is highly effective in the prevention of COVID-19 infection and in reducing severe illness, data from these countries should have reflected such a situation. As such data have not been reported, the isolated report from Qatar may have been influenced by other factors. Second, because many factors influence data collection and reporting of COVID-19,4 the quality and accuracy of data from different countries may vary greatly. One may argue that the data from Qatar are well planned and controlled, therefore would be believable. However, the question is why data from other countries do not reflect the effect of influenza vaccination on a large scale. It would be hard to believe that data from all of these countries are incorrect.

LARGE-SCALE DATA DID NOT SHOW THE EFFECT OF INFLUENZA VACCINATION ON SEVERE COVID-19

We strongly believe that if the data are correctly reflecting the effect of influenza vaccination on the development of severe COVID-19, countries with high influenza vaccination coverage should show lower death rates than countries with low influenza vaccination coverage. To examine data with reliable sources, we collected the accumulated COVID-19 data on 20 December 2020 from the WHO COVID-19 Weekly Surveillance Update. We collected the data on influenza vaccination rates in 33 countries from the Organisation for Economic Co-operation and Development (OECD) website (DOI:10.1787/27e0fc9d-en) (online supplemental table 1). It made sense to compare the OECD countries because of their similar population demographics, economies, healthcare systems and social structures.
The influenza vaccination coverage ranged from as little as 5.9% to 85.8%. We then analysed the correlation between influenza vaccination rates and COVID-19 data (Figure 1). Our analysis indicates that the r-value between the influenza vaccination coverage and the cases per million population is 0.194. The r-value between the influenza vaccinations and total cases of COVID-19 is −0.166. Surprisingly, there is a potentially positive correlation between influenza vaccination coverage and the COVID-19 death rate, with r=0.397.

Considering the fact that many factors may influence the COVID-19 death rate and the reported data could contain errors, the positive association between influenza vaccination and COVID-19 death rate might not be accurate. However, it suggests that the influenza vaccination did not significantly reduce the death rate, if not increased it.

ON THE CONTRARY, EXTENSIVE DATA SUGGEST THAT COVID-19 VACCINATION IS EFFECTIVE AGAINST SEVERE COVID-19

In the same argument, if COVID-19 vaccines work, countries with different vaccination coverage should show the difference in the infection rates as well as the death rates. To test such a possibility, we collected COVID-19 data between December 2020 and the end of May 2022. We obtained data on vaccination at the end of December 2021 (online supplemental table 2). We then analysed the correlation between COVID-19 vaccination coverage and COVID-19 disease data (Figure 1). We obtained an r-value of −0.098 between the COVID-19 vaccination rate and the cases per million population. The r-value between the total cases and the COVID-19 vaccination rate is −0.109. However, unlike the influenza vaccination rate, the COVID-19 vaccination rate showed a potential negative correlation with the death rate, with an r-value of −0.301, suggesting a potential reduction of the death rate due to COVID-19 vaccination.

These data reflect differences in the effects of influenza vaccines and COVID-19 vaccines. The data for the effect of influenza vaccines and COVID-19 vaccines were collected from the same set of countries, with similar economic levels and social systems. If there were any variation among these countries, the influences on these two datasets should be the same, or at least similar.

POTENTIAL OVERLAP IN MOLECULAR PATHWAYS BETWEEN INFLUENZA AND COVID-19 VACCINES

Both influenza and COVID-19 are caused by viruses with significant differences (Figure 2). It is common knowledge that, although influenza and COVID-19 are both contagious respiratory diseases, they are caused by different viruses. COVID-19 is caused by a coronavirus...
first identified in 2019,\(^8\) while influenza is caused by influenza viruses.\(^7\)

These two diseases cause significantly different clinical symptoms. COVID-19 leads to more severe adverse outcomes than influenza. It is well known that patients with COVID-19 have a high possibility of vascular thrombosis, including deep venous thrombosis and pulmonary embolism.\(^8\,^9\) One possibility is that the dosage of influenza vaccination in young people and adults somehow triggered the immune system, but given the same dosage, this does not occur in the population aged 65 and over. A low level of stimulation may trigger the immune system of young people but not ageing populations.

Studies have indicated the molecular targets and pathways of COVID-19 are different from those of influenza,\(^10\,^11\) while there is a little overlap in the pathways of the two diseases.\(^11\)

Since the quadrivalent influenza vaccine is designed to protect against four different influenza viruses, and the pathogen of the two disease viruses are both enveloped, single-stranded RNA viruses, and both are encapsulated by nucleoproteins,\(^12\) it cannot be ruled out that overlaps in the molecular pathways and immune stimuli systems of the vaccines to both diseases could exist. However, such overlaps are unlikely to be in the core or key steps of the molecular pathways. Thus, when a strong immune system is triggered by either the COVID-19 or influenza vaccination, an overlap could exist between the wide ranging molecular spectrum of the immune systems between these two viral pathways. However, the effectiveness of such overlapping pathways is minimal.

**OUR CONCLUSION: NO EFFECT OF INFLUENZA VACCINE ON SEVERE COVID-19**

If errors on reports or other factors have influenced the data about the effect of influenza vaccination on the COVID-19 death rate, then there is no reason to assume that the data from the same set of countries show the efficiency of the COVID-19 vaccination. Thus, it is unlikely that the two datasets have been caused by accident on the same subject from the same set of data. Based on our current data, we believe that, as the author stated, ‘these findings may not generalise to the elderly population or the wider general population’; therefore, the effectiveness of the influenza vaccine on COVID-19 is either minimal or non-existing, especially for the aged population.

However, given the complexity in assessing factors that affect both the severity of infection and mortality from COVID-19, prospective studies will be needed in the future to better assess the impact of influenza vaccination on COVID-19 in order to control the analysis from potential confounders. Data from large populations with multiple subpopulations and diversity of environmental factors could be analysed with multiple regression models to explore situations where the potential influence of influenza vaccination on COVID-19 may be maximised.

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