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

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Nature news and Nature daily brief recently reported the possibility that influenza vaccination may prevent the COVID-19.[1 2] These editorials were based on the preprint by Tayar *et al*,[3] which reported the data on 'a population of 30 774 healthcare workers in Qatar during the 2020 annual influenza vaccination campaign'. The most astonishing statement in these articles was that 'those who got a influenza shot were 90% less likely to develop severe COVID-19 over the next few months'.

SUMMARY BOX

⇒ Influenza vaccination is a common practice over the world.
⇒ Nature reported effect of influenza vaccination on COVID-19 is questionable.
⇒ Data from none of other countries reflect the effect of influenza vaccination in a large scale.
⇒ Large data suggest that COVID-19 vaccine is effective on the severe COVID-19.
⇒ Influenza vaccine has either minimum or non-effect on the severe COVID-19.

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

As the pandemics of COVID-19 enters its third year, many people wonder what the 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 COVID-19 pandemic, including injecting patients with disinfectants or bombarding them with UV light. Therefore, the high effect of influenza vaccination as stated in the report[3] 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 over the world, especially in the developed countries. If the vaccination is highly effective in prevention of COVID-19 infection and in the lessening the severe illness, data from these countries should have reflected such a situation. As such data have not been reported, the isolated report from Qatar[3] may have been influenced by other factors. Second, due to the fact that many factors influence the data collection and reporting in COVID-19,[4] the quality and

accuracy of data reported from different countries may vary greatly. One may argue that the data from Qatar is well planned and controlled, therefore is believable. However, the question is why the data from none of other countries reflect the effect of influenza vaccination in a large scale. It would be hard to believe that data from all of these countries are wrong.

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

We strongly believe that, if the data are correctly reflecting the effect of the influenza vaccination on the development of severe COVID-19, the death rate in the countries with high influenza vaccination coverage should show a lower death rate than the countries with low influenza vaccination coverage. To examine the data with reliable sources, we collected the accumulated COVID-19 data on 20 December 2020 from WHO COVID-19 Weekly Surveillance Update. We collected the data on influenza vaccination rates in 33 countries from the web page of the Organisation for Economic Co-operation and Development (DOI: 10.1787/27e0fc9d-en) (online supplemental table 1). It made sense to compare the OECD countries because of their similar population demographics, economy, healthcare system and social structure. The
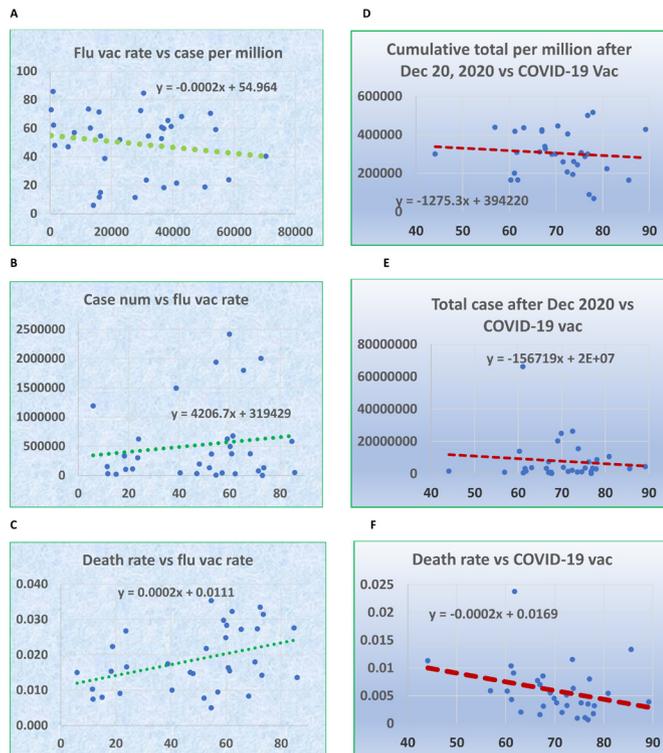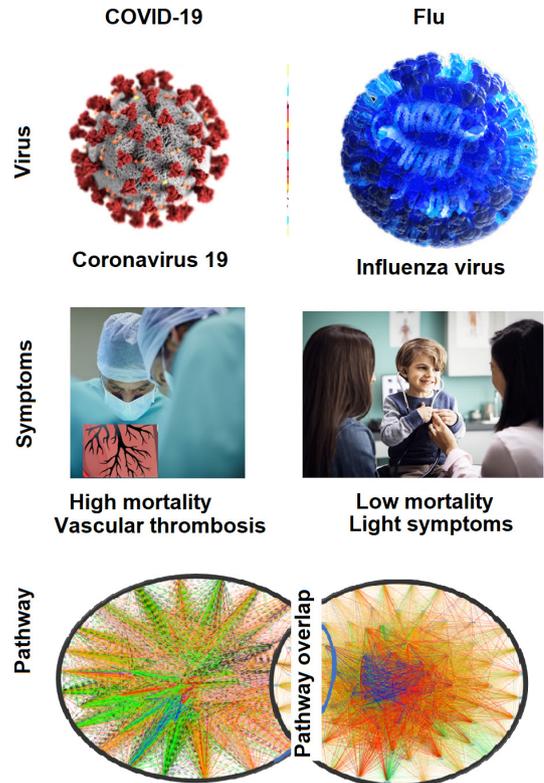
Figure 1 The difference and similarity in COVID-19 disease between the COVID-19 and influenza vaccines. Figure parts A, B and C are the case number per million, total case number and death rate, respectively, versus the influenza vaccination rate among 34 countries. Figure parts D, E and F are the effect of the COVID-19 vaccine on case number per million, total case number and death rate, respectively, among the same set of countries.

Figure 2 Differences in the virus, symptoms and the pathways between influence and COVID-19. Top panel: the difference in viral components between influenza and COVID-19; middle panel: difference in the disease symptoms; bottom panel: potential overlaps between the spectrum of molecular pathways caused by viruses of influenza and COVID-19.

influenza vaccination coverage ranged from as less as 5.9% to as much as 85.8%. We then analysed the correlation between the influenza vaccination rates and the 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 the influenza vaccination coverage and the death rate of COVID-19, with an r value of 0.397.

Considering the fact that many factors may influence the death rate of the COVID-19 and the reported data may contain errors,[4] the positive association between the influenza vaccination and death rate of the COVID-19 may not necessary be true. However, it suggests that at least the influenza vaccination did not significantly reduce the death rate, if not increased it.

ON THE CONTRARY, LARGE DATA SUGGEST THAT COVID-19 VACCINE IS EFFECTIVE ON THE 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 rate. To test such a possibility, we collected the COVID-19 data between December 2020 and end of May 2022. We obtained

the data on vaccination at the end of December 2021[5] (online supplemental table 2). We then analysed the correlation between the COVID-19 vaccination coverage and the 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 to the death rate, with an r value of −0.301, suggestion of potential reduction of death rate by COVID-19 vaccination.

These data reflect the difference between the effect of influenza vaccines and the CIVID-19 vaccines. It is because of the similarities in economic level and social systems among these countries and the data for influenza vaccines and COVID-19 are collected from the same set of the countries. If there is any variation among these countries, their influences on these two sets of data should be the same, or at least the similar.

THE POTENTIAL OVERLAP IN THE MOLECULAR PATHWAYS BETWEEN THE 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,[6] while influenza is caused by influenza viruses.[7]

These two diseases cause significantly different clinical symptoms. COVID-19 leads to much 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 the influenza vaccination in youth and adult somehow trigged the immune system, but given the same dosage, it does not work on the population aged 65 years or above. A low level of stimulation may trigger the immune system of young people but not ageing populations.

Considerable studies have indicated the molecular targets, and pathway of COVID-19 is different from that of the influenza,[10 11] while there is a little overlap in the pathways of two diseases.[11]

Since the quadrivalent influenza vaccine is designed to protect against four different influenza viruses and that the pathogen of these two disease viruses, both enveloped, single-stranded RNA viruses, and both are encapsulated by nucleoprotein,[12] one could not rule out that possibilities of overlaps in the molecular pathways and immune stimuli systems of these vaccines to both diseases. However, such an overlap is most likely not in the core or key steps of the molecular pathways. Thus, when a strong immune system is triggered by either COVID-19 or influenza vaccine, there will be an overlap between the wide range of molecular spectrum of the immune systems between these two viral pathways. However, the effectiveness of such overlapped pathway is at the minimum level.

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

If the data about the effect of influenza vaccine on the death rate of COVID-19 is caused by errors on reports or other factor, then no reason that the data from the same set of the countries shows the efficiency of the COVID-19. Thus, it is not likely the two sets of the data are caused by accident on the same subject from the same set of data. Therefore, based on our current data, we believe that, as the author stated 'these findings may not generalize to the elderly population or the wider general population',[3] the effeteness of the influenza vaccine on the COVID-19 is either minimum or none, especially for aged population.

However, given the complexity in assessing the factors that affect both severity of the 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 so as to control the analysis from potential confounders. Data from large population with multiple subpopulations and diversity of environmental factors may be analysed with multiple regression model to explore situations where potential influence of influenza vaccine on COVID-19 may be maximised.

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