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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

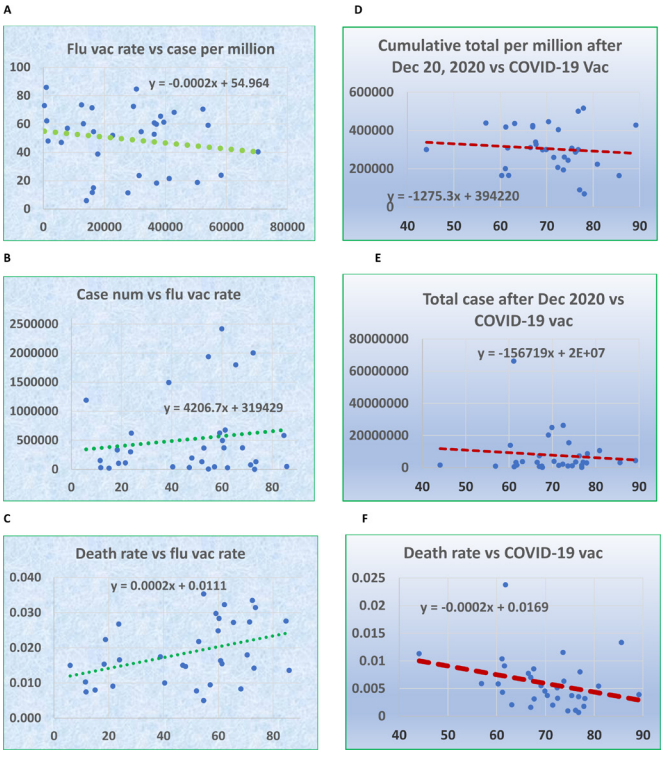

Figure 1 The difference and similarity in COVID-19 disease between the COVID-19 and influenza vaccines. Figure parts A, B and C are the case number per million, total case number and death rate, respectively, versus the influenza vaccination rate among 34 countries. Figure parts D, E and F are the effect of the COVID-19 vaccine on case number per million, total case number and death rate, respectively, among the same set of countries.

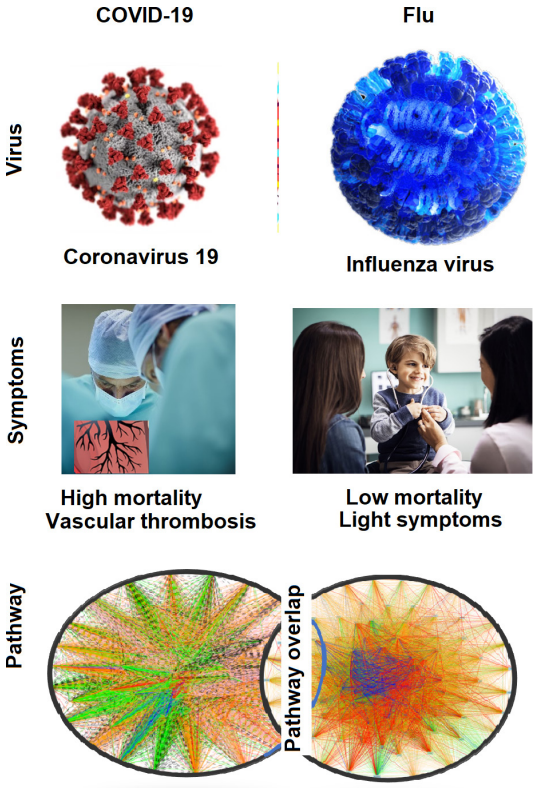

Figure 2 Differences in the virus, symptoms and the pathways between influence and COVID-19. Top panel: the difference in viral components between influenza and COVID-19; middle panel: difference in the disease symptoms; bottom panel: potential overlaps between the spectrum of molecular pathways caused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

Contributors LY, WG and JCG conceived and designed the project and prepared, revised and approved the manuscript. DS revised and approved the manuscript.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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Supplementary Table 1. Data of Flu vaccine and COVID-19 disease

Countries	influ rate	case 20 December 2020	death 20 December 2020	Death rate	case per million	Flu Vac Rate	Death Rate
Australia	62.2	28128	908	0.032281	1103	62.2	0.032
Austria	18.3	334629	5127	0.015321	37155	18.3	0.015
Belgium	59.1	625928	18616	0.029741	54008	59.1	0.030
Canada	60.2	495346	14040	0.028344	13124	60.2	0.028
Chile	84.7	583354	16101	0.027601	30516	84.7	0.028
Czech Republic	23.9	624140	10331	0.016552	58282	23.9	0.017
Denmark	52	131606	1019	0.007743	22721	52	0.008
Estonia	15	21794	174	0.007984	16429	15	0.008
Finland	47	32582	489	0.015008	5880	47	0.015
France	59.9	2418439	60043	0.024827	37051	59.9	0.025
Germany	38.8	1494009	26049	0.017436	17832	38.8	0.017
Greece	73.5	130485	4102	0.031437	12519	73.5	0.031
Hungary	23.6	302989	8099	0.02673	31364	23.6	0.027
Iceland	54.6	5621	28	0.004981	16472	54.6	0.005
Ireland	71.4	78776	2154	0.027343	15954	71.4	0.027
Israel	68.2	371373	3075	0.00828	42906	68.2	0.008
Italy	54.6	1938083	68447	0.035317	32055	54.6	0.035
Japan	48	195880	2873	0.014667	1549	48	0.015
Korea	85.8	49665	674	0.013571	969	85.8	0.014
Latvia	11.7	30297	226	0.007459	16062	11.7	0.007
Lithuania	21.5	112359	1019	0.009069	41274	21.5	0.009
Luxembourg	40.4	44067	440	0.009985	70397	40.4	0.010
Netherlands	61.3	676589	10454	0.015451	39486	61.3	0.015
New Zealand	73	1760	25	0.014205	365	73	0.014
Norway	57	42775	404	0.009445	7890	57	0.009
Portugal	60.8	370787	6063	0.016352	36363	60.8	0.016
Slovak Republic	11.5	151336	1555	0.010275	27719	11.5	0.010
Slovenia	18.8	105013	2347	0.02235	50513	18.8	0.022
Spain	65.5	1797236	48926	0.027223	38440	65.5	0.027
Sweden	52.8	367120	7993	0.021772	36351	52.8	0.022
Turkey	5.9	1189947	17851	0.015002	14109	5.9	0.015
United Kingdom	72.4	2004223	67075	0.033467	29523	72.4	0.033
United States	70.5	17314834	311150	0.01797	52310	70.5	0.018
R	0.193873	0.233872	0.397432	-0.16614			

Supplementary Table 2. Data of COVID-19 vaccine and disease

Countries	Vaccine rate Dec 2021	Cases - cumulative total permillion	cumulative total permillion after dec 20, 2020	Deaths - cumulative total	Total case after dec 2020	Total death after dec 2020	death rate	Vaccine rate Dec 2021	death rate
Australia	76.2	287922	286819	8612	7313850	7704	0.0011	76.2	0.0011
Austria	70.4	482618.5	445463.5	19938	3961189	14811	0.0037	70.4	0.0037
Belgium	75.4	360926.5	306918.5	31768	3532826	13152	0.0037	75.4	0.0037
Canada	77.1	102618.9	89494.94	41105	3377714	27065	0.0080	77.1	0.0080
Chile	85.6	194616.8	164100.8	57920	3136980	41819	0.0133	85.6	0.0133
Czech Republic	61.6	366630.7	308348.7	40290	3296586	29959	0.0091	61.6	0.0091
Denmark	77.9	538942.3	516221.3	6372	3006527	5353	0.0018	77.9	0.0018
Estonia	61.2	434071	417642	2574	555076	2400	0.0043	61.2	0.0043
Finland	73.6	200027.6	194147.6	4627	1072629	4138	0.0039	73.6	0.0115
France	72.5	441080.2	404029.2	145123	26269134	85080	0.0032	72.5	0.0032
Germany	69.9	318061.7	300229.7	139313	24958139	113264	0.0045	69.9	0.0045
Greece	66.5	322900	310381	29869	3330540	25767	0.0077	66.5	0.0077
Hungary	61.8	196513.1	165149.1	46547	1616851	38448	0.0238	61.8	0.0238
Iceland	76.8	517092.6	500620.6	153	182670	125	0.0007	76.8	0.0007
Ireland	76.8	315437.4	299483.4	7381	1487194	5227	0.0035	76.8	0.0035
Israel	63.1	479020.8	436114.8	10860	3774811	7785	0.0021	63.1	0.0021
Italy	73.8	292714.9	260659.9	166835	15519867	98388	0.0063	73.8	0.0063
Japan	78.1	70317.23	68768.23	30677	8697595	27804	0.0032	78.1	0.0032
Korea									
Latvia	67	434559.4	418497.4	5828	798701	5602	0.0070	67	0.0070
Lithuania	67.6	380428	339154	9147	950591	8128	0.0086	67.6	0.0086
Luxembourg	67.7	397650.3	327253.3	1079	204905	639	0.0031	67.7	0.0031
Netherlands	67	464669.7	425183.7	22325	7412188	11871	0.0016	67	0.0016
New Zealand	74.6	244624	244259	1163	1177874	1138	0.0010	74.6	0.0010
Norway	71.5	267156.5	259266.5	3172	1391209	2768	0.0020	71.5	0.0020
Portugal	89.2	463827.8	427464.8	23243	4404742	17180	0.0039	89.2	0.0039
Slovak Republic	44.1	327969.7	300250.7	20103	1638681	18548	0.0113	44.1	0.0113
Slovenia	56.9	489372.2	438859.2	7783	920643	5436	0.0059	56.9	0.0059
Spain	80.9	261818.2	223378.2	106511	10595302	57585	0.0054	80.9	0.0054
Sweden	72.4	242976.9	206625.9	19014	2142246	11021	0.0051	72.4	0.0051
Turkey	60.3	178727.6	164618.6	98969	13883775	81118	0.0058	60.3	0.0058
United Kingdom	69.1	328578.7	299055.7	178749	20301674	111674	0.0055	69.1	0.0055
United States	61.1	252419.1	200109.1	998070	66236552	686920	0.0104	61.1	0.0104
R			-0.0982		-0.109				-0.3007