SARS-CoV-2 and seasonal flu – transmission reduction a double win

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Summary

While attention has, of course, been on SARS-CoV-2, seasonal influenza is a material killer. Evidence from the below-average spread of seasonal flu in the Southern Hemisphere in their last winter makes us think that the winter just starting in the Northern Hemisphere may be mild as far as flu is concerned.

But the risk of a 'double hit' remains. There is some evidence that flu vaccination has some effect against COVID-19, and so the flu vaccine could also provide a form of protective 'counter double hit' – as would the social distancing that has already become routine for many.

Introduction

As mid-Winter arrives in the northern hemisphere ('NH'), with only a few hours of weak sunlight -, temperatures dropping to freezing and people retreating indoors, conditions become ideal for the spread of seasonal flu. What should we expect? So far levels of flu have been low, but is there a chance it will emerge, adding to the current coronavirus burden, and further straining resources? Or will see little to no influenza activity, flattened by the measures aimed at COVID-19?

Seasonal flu, like SARS-CoV-2, spreads through human-to-human contact. Certain respiratory symptoms that help to facilitate spread are a feature of almost all flu infections and many COVID-19 cases. But COVID-19 has a far wider range of manifestations, and in a substantial proportion of cases leads to a variety of non-respiratory effects. But there are just as many differences as similarities.

If seasonal flu leads to serious illness, it does so mainly in the elderly and the very young – a U-shaped age severity curve. For COVID-19, the likelihood of serious illness is at its lowest amongst the young, and its highest in the elderly.

Children are big spreaders of flu, but don't play as large a role in spreading CoV-2. Measures designed to reduce the impact of CoV-2 are not a perfect match with measures that affect flu, despite both viruses having respiratory effects. Understanding each, and how they interact, will give us some insights into how flu may develop.

Lessons from the Southern Hemisphere ('SH')

SARS-CoV-2 has been present through a winter season though, and perhaps we can learn from this. The new coronavirus emerged in China in the latter half of the SH summer, and by the time winter arrived it had reached most countries. Looking at what happened in the SH over the last six months is probably a good place to start when trying to figure out what may happen in the NH this winter.

In practically all the SH countries where influenza is a seasonal phenomenon (close to the equator it spreads year-round, but more rapidly in the wettest periods), the number of cases decreased substantially. Argentina saw a 64% drop in flu cases in the period January to June 2020, compared

with 2019. In Australia, in the period May to mid-August, there were 627 cases and one death recorded, while in recent years this averaged 22,047 cases resulting in 130 deaths.

South Africa's surveillance system has recorded one case since March, compared with 700 in prior years over the same time period. Why is this the case, and how likely is a similar scenario in the NH?

Strict lockdowns and relatively strong measures were very much a feature of the most recent SH winter. Our early understanding of the transmission dynamics of SARS-CoV-2 was based, to a large extent, on its manifestation as a respiratory illness. The measures implemented focused on reducing the transmission opportunities facilitated by symptoms such as coughing and sneezing, and by normal activities like speaking. Putting distance between people in public spaces was key. These measures reduced the spread of both viruses, but had a bigger effect on flu than on the coronavirus.

SARS-CoV-2 is more infectious than flu: seasonal flu typically has an R0 of between 1.1 and 1.4, while SARS-CoV-2 has an R0 more than twice that. If measures taken to limit the spread of coronavirus have enough of an impact on flu, its ability to infect increasing numbers of people will be strongly curtailed. A range of measures had the effect of reducing both, but flu transmission was affected to a far larger extent given its lower rate of reproduction.

What are the prospects then for the NH, considering measures and factors that are likely to have an impact? The following table evaluates the relative effect of these.

SARS-CoV-2 related factors affecting flu development this winter – most significant to least

Factor	**Relative scale of factor (NH vs SH)**	**Impact on seasonal flu**
Reduced air travel	Much lower than normal, but slightly higher than in SH	Substantial effect – leading to delayed development
Seeding source	Very low seeding of NH by SH	Substantial effect – also delaying
Lockdowns	Less stringent, of shorter duration, & if needed national but regional preferred	Moderate effect - less than in SH
School closures & other measures (masks, contact bubbles, etc)	Local, regional or individual school closures as needed to reduce transmission, or if national then for a shorter, defined duration	Other measures will have some effect, as will limited closures - mild effect overall. Young people are key to flu spread - re-opening will enable this.
Mask wearing	Higher than in SH, mostly in periods of high transmission	Moderate effect but more than in SH
Social distancing, avoiding crowds, isolating if sick, hand hygiene, test & trace	Less stringent & lower compliance	Minimal impact

Note that this table is speculative, but based on current understanding of the broader impact of measures

Summarising the factors identified and their effects in the NH compared with SH, the biggest effect is likely to come from reduced air travel and the resulting reduction in opportunities for seeding flu spread. The reduced reservoir of flu in the SH will further affect this, given that it's a significant source of NH seeding. These two factors alone are probably largely responsible for the very low level of flu so far in the NH winter. Lockdowns, even though milder, will continue to present further barriers to flu

transmission, and the fact that schools will largely be open will likely have a only a small effect in the other direction.

The situation in the NH until recently is reported in a recent surveillance report issued by Public Health England (here we used the 3 December report, based on data to 8 November). Seasonal flu levels were described as very low, with only sporadic infections in some regions. This part of winter is when the reproduction value of flu reaches its highest levels. If the R-value is able to rise much above 1 at all during this winter it'll be in the next few weeks when temperatures are at their lowest, or if behaviour to constrain the spread of Cov-2 is relaxed. It's worth remaining vigilant.

Aside from the factors already mentioned a few more are worth considering, but are highly uncertain, so should perhaps be treated as open questions rather than known factors:

- The downward pressure on flu transmission may be applying evolutionary pressure on competing strains. Would this allow more infectious strains to ultimately become more prevalent ?
- Winter to summer temperature differences in the populated parts of the SH are on average smaller than for those in the NH, with less clustering indoors leading to lower reproduction rates than in the NH. Does this make suppression of flu easier in the SH than in the NH?
- Seasonal flu in each hemisphere is seeded mostly by mutated versions of previously seen flu viruses from the opposite hemisphere. The scarcity of flu in the SH means less seeding from regions that are further south, and possibly a higher share of seeding from mid-latitudes (countries or areas close to the equator). What effect will this have on strains that emerge, if any, and if any do emerge?

Concurrent spread

Having examined the risk of spread of flu, the question then is: should some seasonal flu emerge while there are still a substantial number of COVID-19 cases, what effect would concurrent spread have and what issues would arise?

First, there's the need for correct diagnosis. If a person started to experience certain respiratory symptoms, the question at an early stage will be – is it COVID-19, or is it flu? Finding out is not especially important if the person is known to be at low risk of serious disease for both. If they are elderly, however, or have certain health conditions that are known risk factors, it would be prudent to test for both. The need to quickly identify the nature of the illness will place further strain on already stressed testing systems.

Secondly, the supply of resources: in addition to the testing system being under additional pressure, there's the problem that testing for each disease relies on supplies and resources common to both, possibly leading to shortages (of swabs for example). Lab capacity will need to be ready to ramp up to deal with a surge of either flu or COVID-19, and it would be prudent to procure additional stocks of certain items which could otherwise run short.

Thirdly, the pressures on bed availability in ICU. After diagnosis, depending on severity, some patients may need only a low level of care, while others will require critical care. The burden on ICU during the early waves of COVID-19 was lower than originally predicted, and most hospitals did not run out of ICU capacity. Spare capacity remained largely because of the success of measures to reduce spread.

Flu cases, if they emerge in any numbers, will likely peak in February. Some of the vaccines for CoV-2 are being rolled out, or will soon be. Some health workers and some of those at greatest risk of severe illness will soon have had their first dose of vaccine, and will have immunity by the end of January. It therefore seems unlikely that ICU will be overburdened, much less so by flu cases on top of Covid-19

cases. If behaviour relaxes too early though, because of the mistaken impression that the vaccine has already given enough protection, this could of course all be up-ended. Continued efforts to reduce transmission must be maintained.

Does flu vaccine help against COVID-19?

Flu of course has its own vaccine. Widespread use of this vaccine, particularly by groups at high risk of serious illness or those with especially high numbers of daily contacts with other people may be one of the most effective measures to reduce the burden on health systems. Interestingly, while targeted at giving protection against the flu, this vaccine may well have some effect on the risk posed by SARS-CoV-2.

A study in the US at the end of the last flu season looked at the effect of SARS-CoV-2 in those over 65, examining different areas with different vaccination rates[1]. After controlling for a range of confounding factors, they found that a 10% increase in vaccination rates in over 65's was accompanied by a 28% decrease in the COVID-19 death rate in that population. Various explanations are given for this, all involving the effects of the vaccine and possible absence of flu infection on the functioning of various components of the immune system.

A study in Brazil, this time studying individuals of all ages who had been diagnosed with COVID-19, compared those who had been vaccinated against flu with those who hadn't[2]. As in the US study, a wide variety of possible confounders were identified. The result, after all known potential confounders had been considered, showed a 17% lower risk of death from COVID-19 amongst those vaccinated against flu as compared to those not vaccinated. This was the case only if vaccinated for the flu in the 2019/2020 flu season. Vaccination with prior vaccines offered no benefit. Even if some of this difference is down to confounders that proved impossible to eliminate, it's very unlikely that all of it is. It seems likely that the flu vaccine offers some protection against the worst effects of COVID-19, with explanations given in this paper being broadly similar to those in the US paper.

Similarly, a letter to the *Journal of Medical Virology* by Douglas F Nixon and others describes a protective effect against COVID-19 in Italy, in over 65's vaccinated against seasonal flu during the last flu season[3].

Conclusion

Given the targeted protection against flu offered by flu vaccination, the possibility of a secondary cross-benefit against the most serious effects of COVID-19, and the limited availability of the Covid-19 vaccines over the next few months, it looks as if flu vaccination may materially help if co-circulation emerges later this winter. Higher production (the number of vaccine doses available is over 15% higher this year than last) and higher demand (which initially led to some shortages) have already reduced the risk.

While the flu vaccine is beneficial it has its limits. It seems flu transmission will be muted while COVID-19, in its present form, is still in play. With COVID-19 vaccines beginning to be administered, and an end in sight (even if still some way away), we should remain cautious. For the moment the most effective and widely available 'vaccine' against both flu and COVID-19 is our behaviour. By keeping ourselves informed and engaging in protective practices we can keep ourselves safe over these next few months until Covid-19 vaccines are rolled out and protection is achieved.

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[1] Zanettini, C., Omar, M., Dinalankara, W., Imada, E. L., Colantuoni, E., Parmigiani, G., Marchionni, L. (2020, June 26). Influenza Vaccination and COVID19 Mortality in the USA ; *medRxiv.*; https:// doi: 10.1101/2020.06.24.20129817

[2] Fink, G., Orlova-Fink, N., Schindler, T., Grisi, S., Ferrer, A., Daubenberger, C., & Brentani, A. (2020, July 1). Inactivated trivalent influenza vaccine is associated with lower mortality among Covid-19 patients in Brazil ; *medRxiv.*; https://doi.org/10.1101/2020.06.29.20142505

[3] Marín-Hernández, D., Schwartz, R. E., & Nixon, D. F. (2020). Letter to the editor - Epidemiological evidence for association between higher influenza vaccine uptake in the elderly and lower COVID-19 deaths in Italy. *Journal of Medical Virology*, https://doi.org/10.1002/jmv.26120