Influence of Influenza on SARS-CoV-2 Transmission

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Paper

- "Influenza may facilitate the spread of SARS-CoV-2" by de Cellès *et al.* DOI:10.1101/2020.09.07.20189779
- Authors hypothesized (and show via statistical methods) influenza had an impact on first COVID-19 wave in Europe (in particular, Belgium, Italy, Norway and Spain).
- The idea of one virus influencing the transmission of another is not novel.
- Respiratory viruses like COVID-19, rhinovirus and influenza are often not epidemiologically independent!

Co-Existing Viruses

- One virus could "help" another (facilitatory) or "harm" another (antagonistic).
- (Antagonistic Ex.) - A ferret study shows influenza viruses can induce an antiviral state that limits secondary infection of RSV. https://doi.org/10.1093/infdis/jiy184

- (Facilitatory Example) - Recent study gives evidence that influenza can up-regulate the expression of ACE2 (a receptor of SARS-CoV-2 in human cells–in the respiratory epithelium). (https://doi.org/10.1016/j.devcel.2020.05.012)

Modelling Intro.

Authors developed a classical stochastic population model of COVID-19 transmission dynamics, including:

- A realistic distribution of generation time,
- A realistic distribution of the time from symptom onset to death,
- The assumption that 1% of all infections result in death.

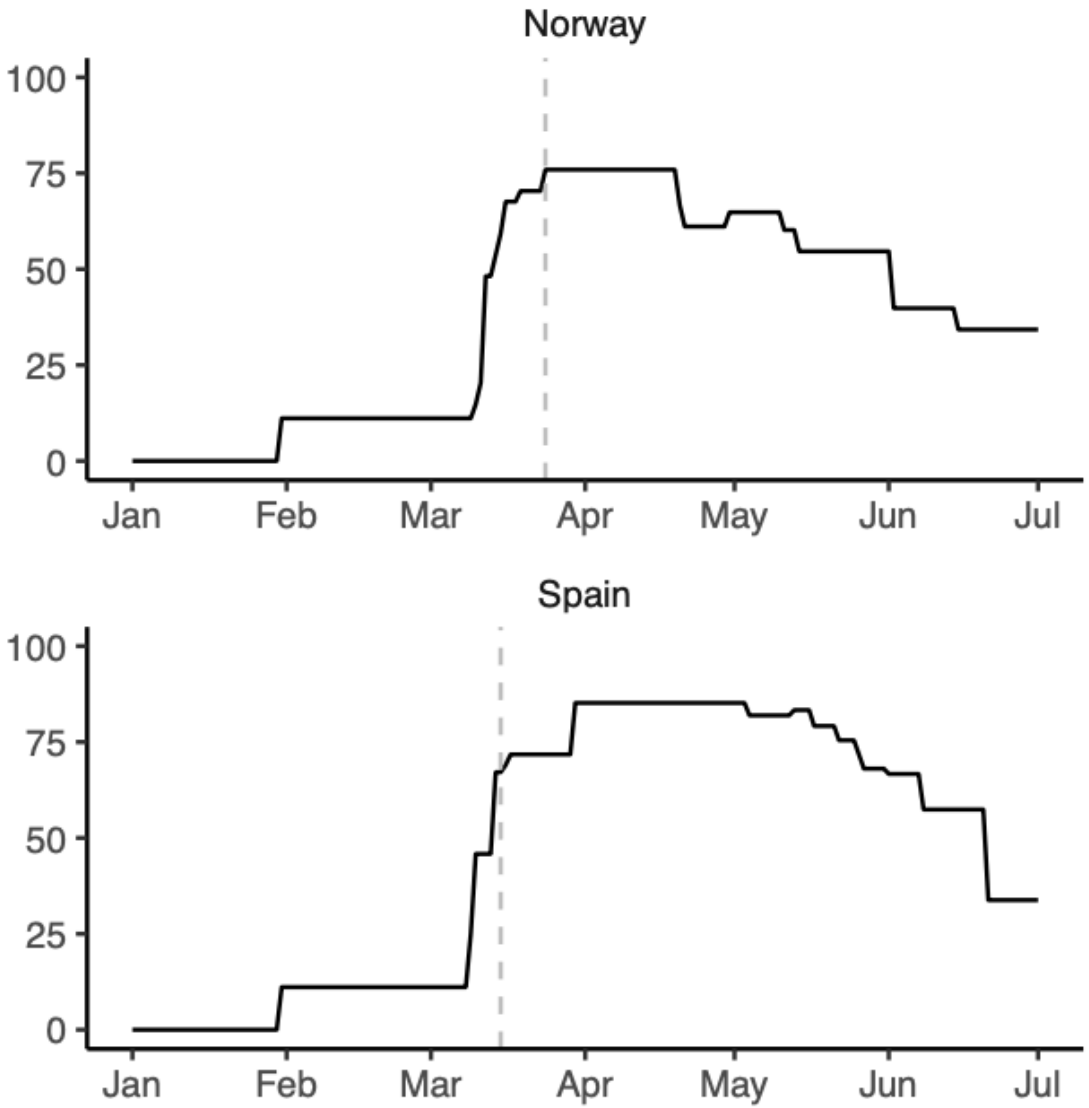
They also included some newer modifications:

- Renormalized time series of influenza incidence,
- A "stringency index".

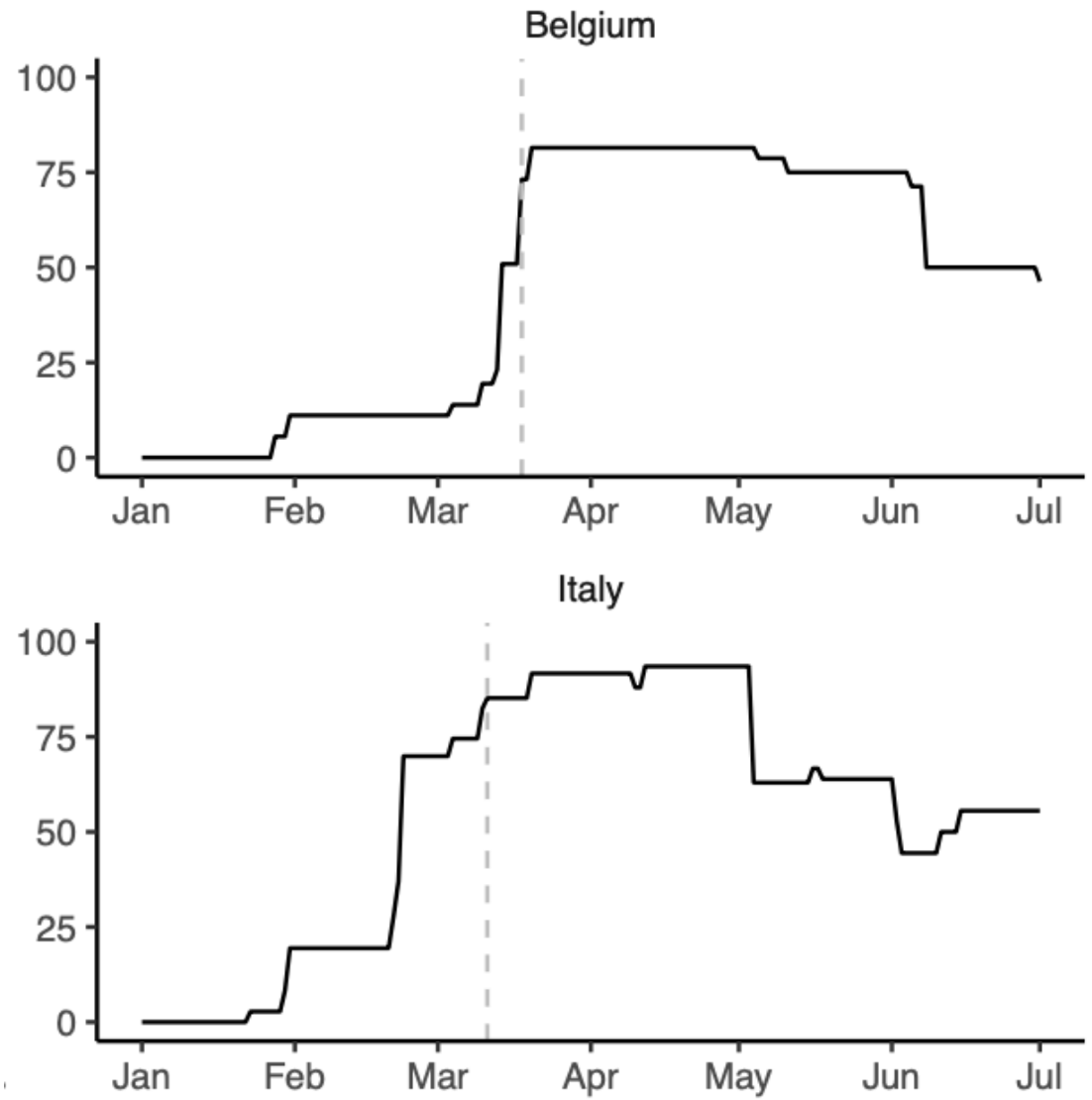
The Stringency Index $s(t)$

- An aggregate measure of the number and of the strictness of non-pharmaceutical control measures implemented by governments.
- Lockdowns, travel bans, school closures, ...
- $0 \leq s(t) \leq 100$
- $0 \implies$ no intervention
- $100 \implies$ maximum number and maximal intensity of control measures.

Stringency Index (Norway & Spain)



Stringency Index (Belgium & Italy)



Modelling

The model is formulated as:

$$\begin{aligned}
\dot{S} &= -\lambda(t)S \\
\dot{E}_1 &= \lambda(t)S - \sigma E_1 \\
\dot{E}_2 &= 2\sigma(E_1 - E_2) \\
\dot{I}_1 &= 2\sigma E_2 - 2\gamma I_1 \\
\dot{I}_2 &= 2\gamma(I_1 - I_2) \\
\dot{R} &= 2\gamma I_2
\end{aligned}$$

- I_1 contains pre-sympatomatic infected people,
- I_2 is infectives with symptoms,
- $\lambda(t) = \beta(t)\frac{I_1+I_2}{N}$, N is constant, $R_e(t) = \frac{\beta(t)}{\gamma}$.

Stringency Index and Transmission $\beta(t)$

- The authors account for public health and governmental interventions with the stringency index. But we want to understand disease transmission.
- How would you map the "degree" (number and intensity) of public health interventions into a reduction in transmission of COVID-19?

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- How would you map the "degree" (number and intensity) of public health interventions into a reduction in transmission of COVID-19?
- The authors use $\beta(t) = \mathcal{R}_0\gamma[1 - r_\beta(t)]e^{\beta_F F(t)}$
- $r_\beta(t) = \min(1, b \times \frac{s(t)}{100})$
- $F(t)$ is the renormalized time series of influenza incidence,
- β_F is the impact of influenza on COVID-19 transmission. $\beta_F > 0 \implies$ that influenza increases transmission, and the opposite is true if $\beta_F < 0$.

Two Exposed Classes

- Normally (in the SEIR model), we move out of E and into I at the rate of 1/latent period.
- Now we move out of E_1 and E_2 at twice the normal rate $(2 \times \sigma)$ and E_2 and I_1 by 2 times the 1/latent period $(2 \times \sigma)$
- So why have two exposed classes?

Two Exposed Classes: Why?

- Per the work of Wearing et al. (cite: 10.1371/journal.pmed.0020174), the traditional SEIR model assumes that the rate of leaving the exposed or infectious class is constant over time.
- "While mathematically very convenient, this assumption gives rise to exponentially distributed latent and infectious periods, which is epidemiologically unrealistic for most infections" (0622)
- "A more sensible formulation would be to specify the probability of leaving a class as a function of the time spent within the class, such that initially the chance of leaving the class is small, but the probability increases as the mean infectious/latent period is reached " (0622).
- "This would give rise to a more realistic distribution of latent and infectious periods, with a stronger central tendency" (0622).

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Why include two infectious classes I_1, I_2? Why not just I?

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- As has been established in previous research, individuals who are infected with COVID-19 can infect others before symptoms occur. So we need a model that allows for the possibility of transmission before symptoms occur.
- By splitting infectives into pre-symptomatic (I_1) and symptomatic (I_2), we can separate and understand the two different modes of transmission.

What did they find? Results

The Model fit well!

- During the period of co-circulation, influenza was associated with a mean 2-2.5 fold population-level increase in COVID-19 transmission in the four European countries of interest.
- Model with influenza predicts $\mathcal{R}_0$ between 2 (Italy and Spain) and 3.3 (Belgium). A model without influenza leads to a range of 2.5-5.
(`https://doi.org/10.1038/s41586-020-2405-7`)

Model Robustness

To verify the robustness of results, the authors conducted three additional analyses:

1. Allowed influenza to modulate the mortality of COVID-19 in addition to transmission. This model only weakly fit in Spain, and nowhere else.
2. Reduction of COVID-19 transmission is allowed to scale non-linearly with the stringency index, as opposed to the linear mapping originally assumed. This model did not outperform the linear scaling function in Belgium, Norway, and Spain, but it did fit well in Italy.
3. Relax the assumption of homogeneous mixing, and found that the force of infection scaled sub-linearly with COVID-19 prevalence.

Predictions

The authors use the model to make a few testable predictions:

1. "a recent influenza infection should be an independent risk factor for subsequent SARS-CoV-2 infection" (5).
2. We're likely to underestimate co-infection with influenza and COVID-19, because the incubation period of COVID-19 (5.7 days in the article) exceeds that of influenza (A: 1.4 days or B: 0.6). In other words, by if you have both COVID-19 and influenza, by the time you can test positive for COVID-19, your influenza infection is likely no longer detectable.
3. To quantify this result, authors find that a large, 30–50% of co-infections may not be detectable at all using direct calculation of probabilities.
4. Propose that influenza vaccination should associate to a lower risk of COVID-19 infection, because the flu vaccine makes it less likely you will get the flu, which affects dynamics of COVID-19.

Methodological considerations

A few drawbacks to the methodology of the article.

1. No age structure, even though influenza severity and lethality vary strongly with age (6).
2. the mapping between control measures and transmission is probably non linear. The authors account for a nonlinear mapping in a different model and claim it doesn't improve model fit except for in Italy, where the better fit may be indicative of unique circumstances in Lombardy at the start of the pandemic, and not of the disease dynamics as a whole.
3. Did not model asympomtomatic cases fully, probably affects the relability of any $\mathcal{R}_0$ estimates produced.