Respiratory viral infections, their interactions with SARS-CoV-2 and implications for a winter resurgence of COVID-19

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1. Introduction – definition of co-infections.

SARS-CoV-2 causes a range of clinical symptoms that can be mistaken for disease caused by other respiratory infections. Respiratory infections in humans (and animals) can act synergistically, an initial infection causing increased severity of subsequent infection; alternatively, an infection can transiently boost non-specific (innate) immune defenses thereby causing some protection against other infections.

When multiple pathogens are in circulation at the same time this can lead to cooperative or competitive forms of pathogen-pathogen interactions (1). This is illustrated in the 1918 Spanish influenza virus outbreak where secondary bacterial pneumonia was thought to be a leading cause of death (2). Several other infectious agents can be found in lungs of patients who have died of COVID-19 (Figure 1). Co-infections may play a pivotal role in reducing or enhancing disease severity and also, possibly, in onward transmission of pathogens.
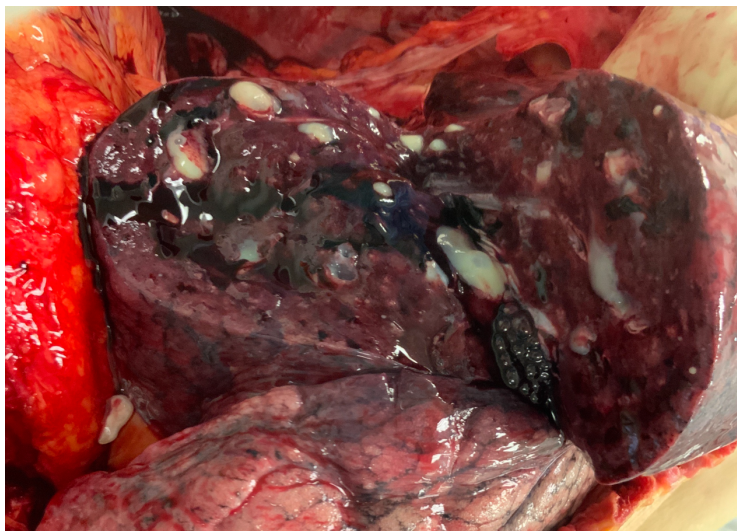
Figure 1. Image of a lung from a patient with COVID-19 illustrating severe bronchopneumonia and associated pus. Image courtesy of Dr David Dorward and Dr Chris Lucas and the ICECAP consortia.

The respiratory system has a complex underlying microbiome with an abundance similar to that of the skin. This is often co-detected in metagenomic and other screening strategies such as PCR and culture. However, co-infection describes a specific situation where two (or more) pathogens are present and both are involved in causing disease.

Co-infections can occur when two or more pathogens are in circulation at the same time and have the same seasonal pattern or overlap. This was not observed with the two other severe coronavirus infections, SARS-CoV and MERS-CoV, mainly because SARS-CoV caused a limited number of infections, was brought under control and then was eradicated while the transmission of MERS-CoV is sporadic in nature.

In the coming winter of 2020/2021, there will likely be a significant symptom overlap and challenges to clinical definition/case identification between SARS-CoV-2, influenza virus,

respiratory syncytial virus and other endemic respiratory viral infections. This will likely impact on segregation and cohorting policies, PPE usage and capacity challenges including ITU pressures. This paper focuses on the potential overlap between SARS-CoV-2 and other respiratory viral infections.

2. What viral co-infections and factors may contribute to a severe COVID-19 winter season?

As lock-down is eased in the summer months, the incidence of SARS-CoV-2 may stabilise or continue to decrease, in line with many circulating respiratory pathogens. However, the onset of winter is likely to lead to greater transmission of SARS-CoV-2 and a possible second wave of COVID-19 that co-incident with that of other respiratory pathogens. These may impact on the diagnosis of COVID-19 and the management of the disease, as well as putting pressures on the NHS. Particular pressures are expected from influenza, respiratory syncytial virus (RSV), and possibly from rhinoviruses and other endemic coronaviruses.

The Northern Hemisphere faces the prospect of a second wave of SARS-CoV-2 circulation and a simultaneous epidemic of seasonal influenza. In most temperate sites (Canada, UK, The Netherlands, New Zealand), the usual seasonal coronavirus peak occurs either slightly before or simultaneously with the influenza A and B peaks. Seasonality is not observed in tropical regions. A recent publication on seasonality suggested a large part of the reason the UK was hit hard for the first wave of SARS-CoV-2 was due to our climate - the most affected cities are all in the Green Climate Zone (3). Therefore, the prediction is that co-circulation is a real concern. However, the effect of the current non pharmaceutical interventions on influenza transmission dynamics are unknown. There are observations from Australia that prevention measures for COVID-19 (hand washing and social distancing) may significantly reduce influenza transmission (Figure 2).
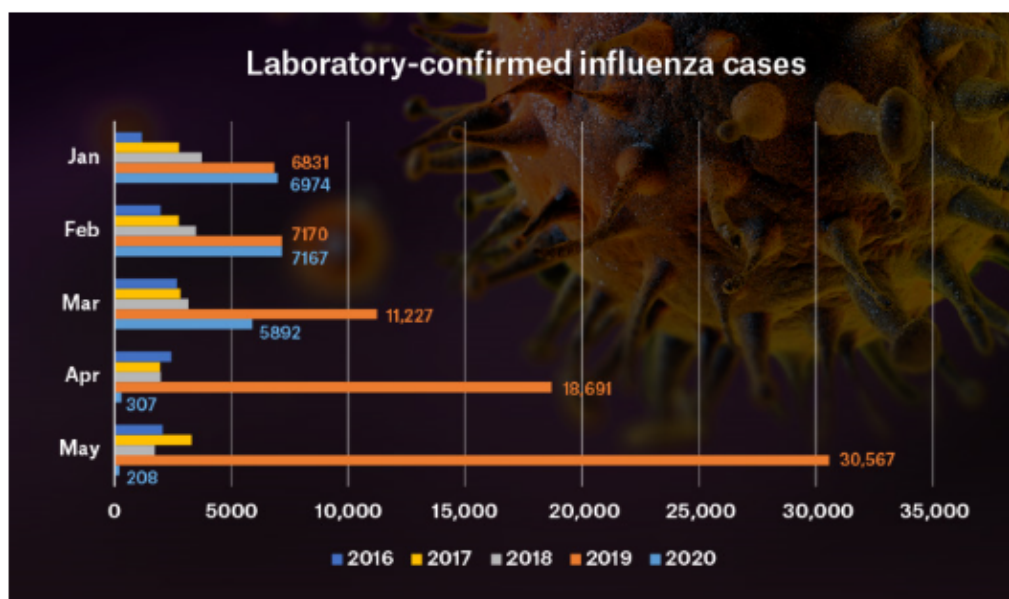

Figure 2. Statistics from the National Notifiable Diseases Surveillance System show Australia was experiencing above average influenza virus numbers before social distancing.

The R value for SARS-CoV-2 in an immune naïve population with usual societal mixing is approximately 3. However, with control measures the aim is to maintain this value below R<1 which aligns with seasonal influenza virus (R=1.5). For human coronavirus OC43 (HCoV-OC43) there is a strong incidence of co-infection with RSV, adenovirus and parainfluenza virus type 3. Whether these co-infections will contribute to disease severity associated with SARS-CoV-2 infection is unknown. Generally, coronaviruses display winter seasonality between the months of December and April and are not detected in summer months (4), which is a similar pattern seen with influenza viruses. Between 11 to 41% of patients with coronavirus infection test positive for other respiratory viruses (4). No differences in clinical outcome were observed for those coinfected with HRSV and endemic coronaviruses. Data from Northern California show that 20% of patients with COVID-19 had a co-infection and RSV one of the most common detections but there was on associated data on outcome (5).

A recent study has also examined the potential for within-host interactions between seasonal coronaviruses and other common respiratory viruses (6). This analyzed the non-random mixing of respiratory viruses among virus-positive patients using multivariable logistic regression. This identified a greater propensity for some types of coronaviruses to co-infect with other viruses over multiple seasons e.g. HCoV-OC43 to coinfect with RSV (OR 1.68, 95% CI 1.05-2.63, uncorrected p=0.027), adenovirus (OR 2.93, 95% CI 1.87-4.5, uncorrected p<0.001), and parainfluenza virus - PIV3 (OR 2.38, 95% CI 1.28-4.17, uncorrected p=0.004). The associations with AdV and PIV3 were supported following correction of p-values for multiple comparisons (p<0.001 and p=0.036 respectively).

These observations are limited in that they do not provide evidence on the potential impact of co-infection on the clinical severity or outcome with COVID-19. For this we have limited data from UK observations over the end of the 2019/20 influenza season.

There have been some studies on the interference between flu/other respiratory viruses and SARS-CoV-2. There is a suggestion that inactivated influenza vaccination is associated with an increased risk of seasonal coronavirus (7, 8). Nevertheless, any interference is likely to be short lived, and given the morbidity and mortality associated with influenza as well as the possible increased risk of mortality with coinfection, this evidence would not support avoiding influenza vaccination. If there is displacement of coronavirus by influenza this effect may also be seen with live attenuated influenza vaccination (LAIV).

Many of the co-infections, such as RSV, are classically associated with paediatric disease, but recent reviews highlight the insidious but major impact that such viruses may have in adults (9-11). Several studies have focused on COVID-19 in children (12-15) and have identified that co-infections are present including influenza A virus and metapneumovirus (16). However, a lack of case controls precludes any interpretation that co-infection with SARS-CoV-2 results in greater disease severity.

There are three major concerns with co-infections. First, is co-circulation of SARS-CoV-2 and common endemic respiratory viruses will place exceptional pressures on the NHS and care services. Second, there is potential for one or infection in a person with COVID-19 increasing the severity of the disease, requiring additional clinical management and prolonged admission to hospital. Third, misclassification may occur because of overlapping clinical syndromes and the currently imperfect detection of viral pathogen in respiratory samples.

3. What co-infections have been described for other severe coronavirus infections?

There has been one previous severe outbreak of coronavirus infection in humans (caused severe acute respiratory syndrome coronavirus - SARS-CoV) and one ongoing (caused by Middle East respiratory syndrome coronavirus – MERS-CoV). For SARS-CoV co-circulation of human metapneumovirus was reported in an outbreak in Hong Kong, however, data suggested that outcomes were not different between co-infected patients and those with SARS-CoV alone (17). Studies in an experimental mouse model of SARS have shown that co-infection of a respiratory bacterium can exacerbate pneumonia (18). Co-detection of other respiratory viruses such as parainfluenza virus, rhinovirus, influenza A or B virus, respiratory syncytial virus, enteroviruses, and human metapneumovirus and nosocomial bacterial (Klebsiella pneumoniae, Staphylococcus aureus, Acinetobacter sp., Candida sp.) infections has been reported in MERS patients receiving intensive care (19, 20). This includes a case of a patient with TB and MERS (21). Four cases of co-infection with influenza A virus and MERS-CoV in patients have been described although there was no real data presented on either increased or decreased severity of symptoms associated with MERS-CoV (22). In general, influenza virus infection was managed with oseltamivir and antibiotics were also given. Similar to anecdotal evidence around diagnosis of SARS-CoV-2 infection, some of the patients were originally negative for influenza virus: suggesting that positivity of nasal swabs for influenza is specimen type and technique dependent. We note from unpublished data that co-infection with influenza virus has also been found in fatal cases of MERS.

Key summary/finding
Co-infections with other severe coronavirus infections have been described and patients are managed appropriately.

4. What is the evidence that co-infections play a role in severe cases of COVID-19?

The cases of COVID-19 have far eclipsed those of SARS and MERS. Several studies have investigated whether co-infections contribute to severe cases of COVID-19, these include post-mortem studies and analysis of patients on ITU. Two post-mortem studies illustrate current knowledge. One study from Italy found no evidence of viral co-infections and their potential contribution to mortality. In contrast, post-mortem studies from patients with COVID-19 in Beijing (n=85) identified influenza A virus in 10% of patients, influenza B virus in 5% of patients and 3% of patients had RSV (23). However, data about influenza prevalence in the population would have been useful as a comparator. This study neither confirms nor excluded the possibility of viral co-infection being associated with mortality. This has generally been reflected in a meta-analysis of co-infections in people, where common infections/co-detection were influenza virus, entero/rhinoviruses, other coronaviruses and RSV (24). Representative data is shown in Figure 3.

Seasonal factors may come into play. A retrospective cohort study of 7 UK hospitals, with 254 patients managed on ICU with COVID-19 found that on the day of admission, co-infection was present in 4 patients (1.6%), rising to 14 patients (5.5%) within 48 hours of hospital admission. Fifteen pathogens were identified from 14 patients within 48 hours; 14 bacterial pathogens and one viral pathogen (metapneumovirus**Error! Reference source not found.**). During the course of ICU stay, a high proportion of bacterial co-pathogens was identified (124 co-pathogens in 77 patients), which is generally reflective of post-mortem studies by other groups. However, this phenomenon is also recognised in general for people receiving invasive mechanical ventilation as the innate immune defence of the respiratory tract is breached by the continual presence of the endotracheal tube. It is notable that no viral co-pathogens were identified. One of the implications of this work is that viral co-infections were not a major factor in severe COVID-19 infection during the 2020 spring wave of the pandemic. However, it must be recognised that this first wave occurred outside of the respiratory viral season.
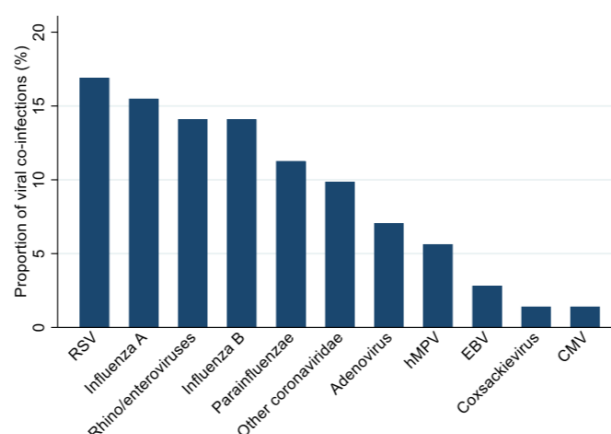
Figure 3: Viral pathogens as a proportion of all viral detections in patients with COVID-19.

A case report in the Lancet (25) described four patients with co-infections between SARS-CoV-2 and influenza virus. All four patients had a medical history of hypertension. Patients 1 and 4 had a history of end-stage kidney disease on haemodialysis, and patients 2 and 4 had type

2 diabetes. The patients were given oseltamivir. In this very limited set of patients, the clinical and analytical courses in these patients did not differ from those reported for COVID-19 alone.

The UK was moving out of the influenza and respiratory syncytial virus seasons when the peak of SARS-CoV-2 occurred. 65 influenza-SARS-CoV-2 coinfections were detected in England and Scotland of (Table 1). Mortality rates for those that had both infection with SARS-CoV-2 and influenza virus, compared to COVID-19 cases who tested negative for influenza are shown in Table 2. After adjustment for age and sex those with coinfection had a higher odds of death using data (OR 1.95; 95% CI 1.05-3.62; p=0.035; unpublished PHE data).

Table 1: Influenza - SARS-CoV-2coinfections by influenza type and week (England and Scotland)

Week	FluA H1N1	FluA H3N2	FluA unsubtyped	FluB	FluA+FluB	Flu type unknown	Total
202010	2		4	1		1	8
202011	3		9	6		1	19
202012	1		11	6	1		19
202013	1		5	1			7
202014	1		4	4			9
202015			2	1			3
Total	8	0	35	19	1	2	65

Table 2: Mortality among influenza-SARS-CoV-2 coinfections by age group (England and Scotland)

	Coinfections (flu pos & SARS-CoV-2 pos)			Flu neg & SARS-CoV-2 pos (England only)		
	Total	Died	Mortality rate	Total	Died	Mortality rate
<5y				39		0.0
5-9y	2		0.0	8		0.0
10-19y	4		0.0	36	1	2.8
20-29y	1		0.0	168	5	3.0
30-39y	7	1	14.3	301	7	2.3
40-49y	2		0.0	439	31	7.1
50-59y	6	1	16.7	673	100	14.9
60-69y	7	3	42.9	684	184	26.9
70-79y	16	10	62.5	837	372	44.4
80+	20	13	65.0	1354	745	55.0
Total	65	28	43.1	4539	1445	31.8

Key summary/finding

There is no strong evidence from the first pandemic wave to suggest that viral co-infections are associated with more severe symptoms associated with COVID-19. There is some indication of higher mortality rates among COVID-19 cases who have also had influenza detected. However, data from influenza virus co-infections is limited due to the lack of confluence of the influenza virus season with the peak of the outbreak, this is also true for RSV.

5. Other effects of co-infection – increasing risk of transmission.

Simultaneous infection with different pathogens can lead to disease enhancement but also increase the risk of transmission. For example, the Americas recently experienced concurrent infections of two or more viruses from chikungunya, dengue, and Zika virus. Co-infection can facilitate the transmission and spread of disease, and perhaps is best illustrated with the synergy between HIV and malaria (26). The spread of influenza virus and other respiratory infections may be influenced by co-infection with each other (27). Although unknown for SARS-CoV-2, we postulate that co-infection with other respiratory or gastro-intestinal infections may lead to an increased risk of transmission. For example, asymptomatic individuals with COVID-19 may contract another respiratory infection that results in increased shedding of SARS-CoV-2. Likewise, children, who are reportedly asymptomatic for SARS-CoV-2, are in environments where they contract winter vomiting disease, if these occur in parallel then one may exacerbate the transmission of the other. Thus, prevention of other infections will reduce this risk. Primarily, we feel this should be focused on control of influenza virus, and in paediatric hospital settings scrupulous attention to infection prevention and control procedures for all respiratory and enteric infective cases. The maintenance of social distancing and extensive hand washing measures should reduce the incidence and co-incidence of both respiratory and gastrointestinal infections in the general population and healthcare settings.

Key summary/finding
Other infections may increase transmission of SARS-CoV-2 although this requires animal models to establish the risk.

6. Recommendations.

1. We should expect co-infections (HIGH CONFIDENCE) and therefore prepare accordingly.

2. There is limited evidence to suggest that co-infections in general are associated with severe infection, although given the timing of SARS-CoV-2, we have limited experience of this and small datasets. Therefore, we have LOW CONFIDENCE there is sufficient data to dismiss co-infections as a problem. We recommend monitoring the situation in the Southern Hemisphere.

3. Co-infection with influenza virus has been identified in other severe coronavirus infections including patients with MERS. Influenza virus infection in those patients was treated with neuraminidase inhibitors. We anticipate this anti-viral efficacy against influenza, in the setting of COVID-19 co-infection, will translate with MEDIUM CONFIDENCE due to the limited data available.

4. We recommend the potential synergistic effects of influenza virus (or other pathogens such as respiratory syncytial virus or GI tract infections) be evaluated immediately in appropriate animal models to assess whether co-infection exacerbates disease and/or results in increase viral shedding/transmission of SARS-CoV-2. We consider this HIGH PRIORITY research.

5. Clinical symptoms will be similar for all respiratory viruses, especially with influenza co-infection, therefore laboratory tests are crucial to establish viral diagnosis. There is established evidence for the clinical benefit of point of care diagnostics (POCT) for respiratory viruses (published PHE guidance) in terms of infection control measures and patient flow within hospitals. Our recommendation, as a HIGH PRIORITY, is that a SARS-CoV-2 POCT is developed/made available aligned to the PHE recommendations, and that wherever possible, SARS-CoV2 POCT is provided alongside FLU POCT.

6. We recommend supporting laboratories in delivering SARS-CoV-2 multiplexed with respiratory virus diagnostics (in line with proposals for a National Multiplex Syndrome Strategy). HIGH PRIORITY.

7. In the advent of co-circulation of influenza virus and SARS-CoV-2 we anticipate logistic problems: including significant ITU pressure and PPE usage (HIGH CONFIDENCE).

8. Influenza virus vaccine. We recommend ensuring that at risk groups are made aware of the potential impact of SARS-CoV-2 infection. We note that take up of the influenza vaccine in the 65+ year old risk group is good (71.6%), but not in the younger clinical risk groups (43.1% in under 65 years and 42.8% in pregnant women). We recommend with HIGH PRIORITY a campaign to target these groups to mitigate the risk of co-infection this winter. We also note that the use of the live attenuated influenza vaccine (LAIV) in children reduces the incidence of community transmission of influenza virus. If there are widespread school closures in a second wave then this will affect uptake of this vaccine. Therefore, we recommend with HIGH PRIORITY alternative options for delivery of this program are considered and how uptake rates of LAIV can be sustained/maximized.

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