Respiratory infections, their interactions with SARS-CoV-2 and implications for winter 2021/2022.

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SUMMARY

1. Social distancing measures over the last 18 months reduced the circulation of all respiratory viruses (ALMOST CERTAIN) and we are now seeing altered respiratory viral seasonality. Therefore, there is uncertainty about the epidemiology this winter and whether concurrent transmission of other respiratory virus with SARS-CoV-2 will occur.
2. The magnitude of any influenza outbreak this winter is dependent upon the dominant strain (and prior population exposure to similar strains), vaccination levels, vaccine-strain match, and social contact patterns (which in adults remain below normal levels). This makes it difficult to predict what will happen with influenza this season.
3. Due to waning population immunity, the next influenza season (whenever it occurs) is likely to be associated with a larger disease burden than would have occurred if influenza had circulated as normal in winter 2020/21 (HIGHLY LIKELY).
4. Note that this is <u>not</u> the probability that the next influenza season will be exceptionally large compared to historic outbreaks, rather it is the probability that the next influenza epidemic will be *larger* relative to what would have happened had we had a normal influenza season last winter.
5. A larger than normal RSV season is possible this winter since RSV epidemiology is governed by naturally acquired immunity (not vaccination) and contact patterns in children (which are now back to normal levels). (LIKELY).
6. Although 'competitive interference' between respiratory virus epidemics is a possibility, co-circulation of endemic respiratory viruses is likely this winter (LIKELY).
7. Co-infections with SARS-CoV-2 and other respiratory viruses are expected to occur this winter, with the potential to place pressures on the NHS and care services (LIKELY).
8. Based on (limited) animal and clinical data, there is a realistic possibility that co-infection with SARS-CoV-2 and influenza may cause increased disease severity than would be expected if influenza and SARS-CoV-2 acted independently (REALISTIC POSSIBILITY).
9. Observational data from wave 1 in the UK found that hospital patients with dual infection with SARS-CoV-2 and influenza virus had prolonged duration of admission. Patients with dual influenza and SARS-CoV-2 infection had more than twice the length of hospital stay than those who tested negative for influenza (16.4d vs 7.4d). This effect persisted when patients admitted with influenza and who then acquired COVID-19 in hospital were excluded. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/921524/S0774_Influenza_infection_in_patients_hospitalised_with_COVID-19.pdf.
10. Due to the possibility that co-infection may increase disease severity and poor outcomes (predominantly in vulnerable groups), there will be a need to distinguish viral aetiology

in order to offer appropriate infection prevention and control measures, enabling isolation and the prospect of cohorting patients by virus infection (this applies in hospitals but also care home settings).

11. Due to the therapeutic strategies available for COVID-19 (e.g., dexamethasone, tocilizumab and monoclonal antibodies), which are not indicated for other viral respiratory infections, there is a clinical need to distinguish the aetiology in patients presenting to hospital with viral pneumonia. A similar case can be made in primary care to guide prescribing of influenza antivirals and budesonide.
12. At risk patient groups and clinical symptoms overlap for respiratory virus infections and it is not possible to reliably distinguish the causal virus based on patient characteristics or clinical presentation alone, particularly in vaccinated individuals whose clinical presentation may be atypical. Multiplex Laboratory tests are therefore needed to establish viral diagnosis.
13. We strongly recommend supporting laboratories in delivering SARS-CoV-2 multiplexed with respiratory virus diagnostics (in line with proposals for a National Multiplex Syndrome Strategy) or point of care diagnostics (POCT).
14. In terms of IPC and patient flow within hospitals, there is established evidence for the benefit of point of care diagnostics (POCT) for respiratory viruses (published PHE guidance). We strongly recommend that influenza POCT are provided alongside SARS-CoV-2 POCT in emergency departments. This will help reduce nosocomial transmission and, therefore, pressure on healthcare (HIGHLY LIKELY).
15. Due to uncertainty about the impact of co-circulation and co-infection, we recommend implementing testing strategies or studies to assess the frequency of co-infections and to evaluate if co-infection is associated with increased disease severity and/or worse clinical outcomes.
16. Influenza antivirals may play a role in mitigating influenza burden. Current policies on influenza antiviral use should be revisited given the unique epidemiological situation that may arise this winter.
17. Co-infection might increase the probability of onward transmission of SARS-CoV-2 (LIKELY OR PROBABLE), although this requires animal models and epidemiological analysis to establish the risk.
18. We strongly recommend strengthened vaccination campaigns for both SARS-CoV-2 and influenza virus to mitigate the risk from co-infection for winter 2021/2022.
19. We recommend that individuals with symptomatic respiratory infections self-isolate, even if they receive a negative test result for SARS-CoV-2, as this will reduce respiratory virus transmission and potentially societal burden.

SUPPORTING INFORMATION.

General considerations on co-circulation

1. When multiple pathogens are in circulation at the same time this can lead to cooperative or competitive forms of pathogen-pathogen interactions (1).
2. One infection can transiently boost non-specific (innate) immune defenses thereby providing some short-lived protection against other viral infections (2). This can affect population level epidemic dynamics. This 'competitive interference' (one epidemic excluding or delaying the other) has been reported between influenza and other respiratory viruses such as RSV and rhinoviruses.
3. The effect of outbreaks of COVID-19 and influenza on one another is not known, but competitive interference is a possibility.
4. Conversely, co-circulation may lead to co-infection and the potential for increased disease burden (see below)
5. 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.
6. As with several other severe viral pneumonias, COVID-19 can be associated with secondary bacterial pneumonia in between one-third and a half of fatal cases. (3)
7. Respiratory infections in humans (and animals) can act synergistically either in series or concomitantly (co-infection).
8. An initial infection may cause increased risk or severity of subsequent infection with a different pathogen e.g. prior influenza results in enhanced pneumococcal disease (4).
9. Co-infections may enhance disease severity (5). This is clearly true with bacterial superinfection of viral pneumonias, as was seen in the 1918 influenza pandemic (6).
10. Evidence of increased disease severity with respiratory virus coinfections is mixed (2).
11. Co-infection may alter the transmission of pathogens (7) as occurs between Plasmodium and HIV-1 (8).

Specific considerations on COVID-19 co-circulation

12. Winter 2020/2021 saw low levels of respiratory viral activity, including influenza, due to the ongoing behavioral and environmental interventions in place to reduce SARS-CoV-2 transmission, which was the dominant circulating respiratory virus.
13. Due to waning natural immunity (and possibly vaccine mismatch), the next influenza season is almost certain to be associated with a greater number of cases, hospitalizations and deaths than would have occurred if influenza had circulated as normal in winter 2020/21.[*] Unpublished modeling of influenza activity has been undertaken by the University of Warwick and indicated the 2021 to 2022 influenza season in the UK could be up to 50% larger than typically seen (https://www.gov.uk/government/publications/jcvi-interim-advice-on-a-potential-coronavirus-covid-19-booster-vaccine-programme-for-winter-2021-to-2022/jcvi-

[*] Impact of a diminished influenza season on epidemiological outcomes in the subsequent influenza season. Edward Hill, Matt Keeling. O3 August 2021.

interim-advice-potential-covid-19-booster-vaccine-programme-winter-2021-to-2022#fn:5). PHE have also raised concerns that it is possible the influenza season will begin earlier than usual.

14. Experience from Australia and South Africa in 2020 demonstrated an increase in RSV in the summer, following an RSV-free winter in lockdown (9). This was then modelled for the UK in May which estimated between 20 and 50 per cent increase in cases requiring hospitalisation than normal, which was likely to fall over the summer, or early Autumn.
15. The easing of social restrictions over summer 2021 led to a rise in respiratory viral infections with altered seasonality (parainfluenza and rhinovirus), of note RSV has been a major cause of bronchiolitis and hospitalisation of young children (10).
16. School summer holidays have had a moderate impact on RSV transmission, checking epidemic growth or causing modest declines in different regions. Any decline has occurred from below peak levels typically expected in winter, suggesting a high pool of susceptible individuals remains following the missed season. This, in combination with the high prevalence at the start of the usual transmission window may give rise to a higher force of RSV infection across all age groups, and rapid rise in incidence.
17. This coming winter of 2021/2022, there will likely be a significant change in respiratory viral transmission dynamics due to the removal of social restrictions, however, the trajectory of SARS-CoV-2 incidence is uncertain. Case numbers might continue to plateau or decrease, or the impact of the return to schools and work may result in a resurgence of cases.
18. In a UK test-negative design study, influenza infection was associated with a lower risk of SARS-CoV-2 infection, suggesting that there may be pathogenic competition between these two viruses (i.e. infection with one pathogen reduces the risk of being infected concomitantly with the other). (17)
19. In the last few weeks of August 2021, emergence of influenza has been seen in India and Nepal, predominantly H3N2, with increased pressure on clinical services.
20. SARS-CoV-2 causes a range of clinical symptoms that can be mistaken for other respiratory infections. Co-circulation of SARS-CoV-2 with other respiratory viral pathogens will lead to symptom overlap and challenges to clinical definition/case identification between SARS-CoV-2, influenza virus, respiratory syncytial virus (RSV) and other endemic respiratory viral infections. This will likely impact on segregation and cohorting policies, PPE usage and capacity challenges, including ITU pressures.

Specific considerations on COVID-19 co-infections

Viral co-infections:

21. Few co-infections were 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 eradicated, while the incidence of MERS-CoV is generally low and sporadic in nature.
22. On review of the historical data and viral dynamics for human coronavirus OC43 (HCoV-OC43), 11 to 44 % of patients tested positive for a co-infection such as RSV, adenovirus and parainfluenza virus type 3 (11).

23. Data from animal models shows a clear sustained higher inflammatory response when influenza A virus and SARS-CoV-2 are present in a co-infection, compared to the individual viruses alone (12), with increased neurological pathology (13).

24. The animal model work showed that prior infection with FluMist (live nasal spray flu vaccine) provided a short window of protection against SARS-CoV-2 (unpublished). However, this did not occur with more pathogenic variants of influenza virus.

25. Viral co-infections were not a major factor in severe COVID-19 infection during the 2020 spring wave of the pandemic in the UK. However, the first wave occurred outside of the respiratory viral season and with extensive social distancing interventions in place.

26. Few data are available on the impact of coinfections on disease severity, other than a few small case series (14-16). The best data currently available are from a UK test-negative design study. In this study, a multivariable analysis adjusting for age, sex, ethnicity, co-morbidity and coinfection status found that patients with a SARS-CoV-2 and influenza coinfection were around twice as likely to die (OR 2.27, 95% CI: 1.23–4.19) compared with those with SARS-CoV-2 alone. In addition, patients with a SARS-CoV-2 and influenza coinfection were around twice as likely to be ventilated during admission (OR 2.15, 95% CI: 1.20–3.84) or to be admitted to an ICU (OR 2.08, 95% CI: 1.17–3.70) compared with those with SARS-CoV-2 alone. The affect appears to be beyond the additive effect of the two viruses acting independently, suggesting a possible synergistic effect between SARS-CoV-2 and influenza once an individual is coinfected (17).

27. There is, therefore, a realistic possibility that co-infection with SARS-CoV-2 and influenza may cause increased disease severity than would be expected if influenza and SARS-CoV-2 acted independently.

28. Several studies have focused on COVID-19 in children and have identified that co-infections are present including influenza A virus and metapneumovirus (18). However, a lack of case controls precluded any interpretation of the impact of co-infection with SARS-CoV-2 on disease severity. Importantly RSV predominantly infects children under 2 years of age, in whom incidence of SARS-CoV-2 infection is low.

29. Co-infection may facilitate the transmission of infection. Asymptomatic individuals with SARS-CoV-2 may contract another respiratory infection that exacerbates the transmission SARS-CoV-2. Prevention of other infections will reduce this risk.

Other co-infections:

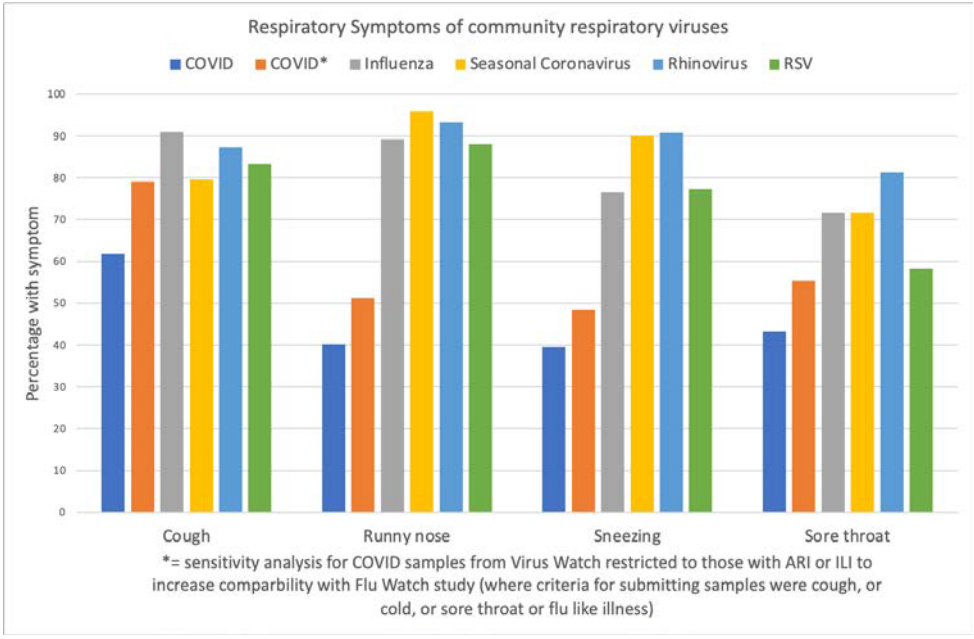
30. Bacterial co-infection. The ISARIC WHO CCP-UK Study looked at 48,902 patients admitted to hospital in the first wave and assessed the presence of bacterial co-infections and found Staphylococcus aureus and Haemophilus influenzae were the most common pathogens causing respiratory co-infections (diagnosed ≤2 days after admission) but overall bacterial co-infection remained rare. In summary, bacterial coinfection is very uncommon at presentation to hospital with COVID-19. Most bacterial co-infection is hospital-acquired and increases in frequency during hospital stay. Increased alertness among clinical teams (the NHS) regarding the possibility of bacterial co-infections (both early in illness, and during hospital stay) is important this winter, and should be supported by appropriate clinical microbiological testing, and surveillance/research. (19)(20).

31. Fungal co-infection. COVID-19-associated pulmonary aspergillosis (CAPA) and Influenza-associated pulmonary aspergillosis (IAPA) are recognised complications in

the clinical course of critically ill patients. The aetiology is thought to be due to direct damage to the airway epithelium, impaired ciliary clearance and immune dysregulation, enabling aspergillus to invade tissue and causing secondary Aspergillus infection (21). In addition, reports from India have described patients with COVID-19 also developing Mucormycosis or 'black fungus' infection (22). This can result in infection of the sinuses and brain (23), skin, lungs and stomach/intestines. Contamination in hospital may be through equipment, the processes of mechanical ventilation and unsterilised oxygen cylinder tubes. Mucormycosis may be associated with high-dose steroid therapy. Mucormycosis, however, is not an issue within the UK.

Differentiation of COVID-19 from other viral respiratory illnesses

32. Differentiation of COVID-19 from other viral respiratory illnesses will be required for two main reasons:
    a. In hospital and closed/care home settings, accurate diagnosis is needed to inform subsequent decision making around infection control practice, appropriate isolation/cohorting of COVID and influenza patients and prevention of nosocomial transmission. Nosocomial transmission risks of COVID-19 and influenza are well established in hospital and closed/care home settings, with associated increased morbidity and mortality of patients. Therefore, in addition to implementation of mitigating measures around the hierarchy of controls, rapid differentiation of COVID-19 and influenza is an imperative IPC measure.
    b. Due to the therapeutic strategies available for COVID-19 (e.g. dexamethasone, tocilizumab and monoclonal antibodies), which are not indicated for other viral respiratory infections, there is a clinical need to distinguish the viral aetiology in patients presenting to hospital with viral pneumonia. A similar case can be made in primary care to guide prescribing of influenza antivirals and budesonide.
33. Differentiation of COVID-19 from other respiratory viral infections based on patients' characteristics or symptoms is not possible.
34. In adults SARS-CoV-2 infection was associated with more severe outcomes compared with other respiratory viruses and was independently associated with younger age (e.g. 58 years for SARS-CoV-2 compared to 68 years for influenza virus), male sex, obesity, diabetes, hypertension and tachypnoea, ICU admission, 30 day mortality and pulmonary embolism (24). In children SARS-CoV-2 patients were older and had lower prevalence of chronic cardiac and respiratory diseases.
35. However, despite these associations there was substantial overlap in patient characteristics, which they concluded precluded discrimination of COVID-19 from other respiratory viral infection based on these characteristics (24).
36. The Flu Watch and Virus Watch studies show that symptoms overlap between the viruses and cannot be used to distinguish one respiratory virus infection from another (below Figure).



Recommendations

37. We strongly recommend supporting laboratories in delivering SARS-CoV-2 multiplexed with respiratory virus diagnostics (in line with proposals for a National Multiplex Syndrome Strategy) or point of care diagnostics (POCT).
38. POCT utility in respiratory viral management has demonstrated a reduction in length of patient stay, improved influenza detection and antiviral prescribing and reduced antimicrobial prescribing. This will reduce pressure on hospitals. Very rapid turnaround times are also associated with higher rates of early discharge and early discontinuation of antibiotics compared to longer turnaround times (cut off 2 hrs) in adults with acute respiratory illness (25).
39. We recommend implementing surveillance or research studies to assess the frequency of co-infections and to evaluate if co-infection is associated with increased disease severity and/or worse clinical outcomes.
40. Influenza virus vaccine. We strongly recommend strengthened vaccination campaigns to target vulnerable groups to mitigate the risk from co-infection for winter 2021/2022.
41. Influenza antivirals may play a role in mitigating influenza burden and current policies on influenza antiviral use should be revisited given the unique epidemiological situation that may arise this winter.
42. Social distancing, face coverings, ventilation, and hand washing should reduce the incidence and co-incidence of both respiratory and gastrointestinal infections in the general population and in health and social care settings. It may be necessary to maintain or re-introduce some of these strategies to help prevent or mitigate resurgence of respiratory viral transmission, particularly in high risk settings.
43. We recommend that individuals with symptomatic respiratory infections self-isolate, even if they receive a negative test result for SARS-CoV-2, as this will reduce respiratory virus transmission and potentially societal burden.

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