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SARS-CoV-2 co-infection with influenza viruses, respiratory syncytial virus, or adenoviruses

Measures to reduce transmission of SARS-CoV-2 have also been effective in reducing the transmission of other endemic respiratory viruses.^{1,2} As many countries decrease the use of such measures,² we expect that SARS-CoV-2 will circulate with other respiratory viruses, increasing the probability of co-infections.^{1,3} The clinical outcome of respiratory viral co-infections with SARS-CoV-2 is unknown.

We examined clinical outcomes of co-infection with influenza viruses, respiratory syncytial virus, or adenoviruses in 212 466 adults with SARS-CoV-2 infection who were admitted to hospital in the UK between Feb 6, 2020, and Dec 8, 2021, using the International Severe Acute Respiratory and Emerging Infection Consortium–WHO Clinical Characterisation Protocol.⁴ Details on patient recruitment, inclusion criteria, testing, and statistical analyses are included in the appendix (pp 2–3). Ethical approval was given by the South Central-Oxford C Research Ethics Committee in England (13/SC/0149), the Scotland A Research Ethics Committee (20/SS/0028), and the

WHO Ethics Review Committee (RPC571 and RPC572, April, 2013).

Tests for respiratory viral co-infections were recorded for 6965 patients with SARS-CoV-2. Viral co-infection was detected in 583 (8.4%) patients: 227 patients had influenza viruses, 220 patients had respiratory syncytial virus, and 136 patients had adenoviruses. Co-infection with influenza viruses was associated with increased odds of receiving invasive mechanical ventilation compared with SARS-CoV-2 mono-infection (table). SARS-CoV-2 co-infections with influenza viruses and adenoviruses were each significantly associated with increased odds of death.

To extrapolate these results from the tested population to a representative hospitalised population, we accounted for differences between tested and non-tested patients using inverse probability weighting (table). In this weighted multivariable regression analysis, influenza virus co-infection significantly increased the odds of receiving invasive mechanical ventilation and the odds of in-hospital mortality.

This study had several strengths. First, it is the largest study of people with COVID-19 undergoing additional testing for endemic respiratory viruses, reporting 583 confirmed co-infections and 6382 confirmed SARS-CoV-2

mono-infections. Second, we recruited patients over an 18-month duration. Finally, we report outcome data for most patients.

The study also has a few limitations. A risk of selection bias exists because tested patients differed from untested patients, particularly in severity of illness: being more unwell increased the probability of testing for co-infections (appendix p 4). After correction for these and other differences with inverse probability weighting analysis, influenza virus co-infection remained associated with receipt of invasive mechanical ventilation, with an odds ratio that was larger than in the unweighted analysis but with wider confidence intervals. As in the unweighted analysis, SARS-CoV-2 co-infection with respiratory syncytial virus or adenoviruses was not significantly associated with receipt of invasive mechanical ventilation. Furthermore, adenoviruses and respiratory syncytial virus co-infections did not have the same effect on the receipt of invasive mechanical ventilation as did influenza virus co-infection, making it unlikely that this association is limited to the tested population rather than the hospital population. A similar result was seen in the weighted multivariable regression analysis with in-hospital mortality as the outcome variable, with a larger odds ratio in the weighted analysis than in the unweighted analysis. The case report form used for data collection did not collect the date of testing for additional viruses, and testing would probably have been done after admission; therefore community versus nosocomial acquisition cannot be established. As hospital-acquired viral respiratory infection is rare,⁵ we assume that viral co-infection was present at the time of hospital admission in most study patients. Finally, because vaccination data for influenza viruses were not registered in the database, and since most patients were admitted before COVID-19 vaccinations were



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For the International Severe Acute Respiratory and Emerging Infection Consortium–WHO Clinical Characterisation Protocol see <https://isaric4c.net>

See Online for appendix

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	Unweighted		Weighted	
	OR (95% CI)	p value	OR (95% CI)	p value
Invasive mechanical ventilation				
Adenovirus	1.22 (0.72–1.99)	0.44	0.64 (0.18–1.68)	0.42
Influenza virus	1.68 (1.14–2.45)	0.0073	4.14 (2.00–8.49)	0.0001
Respiratory syncytial virus	1.05 (0.68–1.59)	0.82	0.78 (0.15–2.70)	0.73
In-hospital mortality				
Adenovirus	1.60 (1.03–2.44)	0.033	1.53 (0.67–3.33)	0.29
Influenza virus	1.49 (1.04–2.12)	0.027	2.35 (1.07–5.12)	0.031
Respiratory syncytial virus	1.20 (0.84–1.72)	0.31	0.60 (0.69–2.10)	0.47

Model is adjusted for the following confounders: age, sex, number of comorbidities, treatment with corticosteroids, days since the start of the pandemic, co-infection, and 4C Mortality Score. OR=odds ratio.

Table: Multivariable model of the effect of co-infection compared with SARS-CoV-2 mono-infection

available, we were unable to establish the effect of influenza viruses or SARS-CoV-2 vaccination on outcome in mono-infected and co-infected patients.

As public health restrictions are lifted, respiratory virus co-infections are more likely to occur during future winters. The marked increase in risk among patients with co-infection has several implications for policy. First, our results provide further support for vaccination against both SARS-CoV-2 and influenza viruses. Second, they suggest that testing for influenza viruses is important in hospital inpatients with COVID-19 to identify patients at risk and a cohort of patients who might have different responses to immunomodulatory and antiviral therapy.

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For more on the **University of Liverpool drug interaction checker** see <https://www.hiv-druginteractions.org>

For more on the **COVID-19 interaction checker** see <https://www.covid19-druginteractions.org>

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- Olsen SJ, Azziz-Baumgartner E, Budd AP, et al. Decreased influenza activity during the COVID-19 pandemic—United States, Australia, Chile, and South Africa, 2020. *Am J Transplant* 2020; **20**: 3681–85.
- Gomez GB, Mahé C, Chaves SS. Uncertain effects of the pandemic on respiratory viruses. *Science* 2021; **372**: 1043–44.
- Kawai S, Fukushima K, Yomota M, et al. Number of patients with influenza and COVID-19 coinfection in a single Japanese hospital during the first wave. *Jpn J Infect Dis* 2021; **74**: 570–72.
- Dunning JW, Merson L, Rohde GGU, et al. Open source clinical science for emerging infections. *Lancet Infect Dis* 2014; **14**: 8–9.
- Aitken C, Jeffries DJ. Nosocomial spread of viral disease. *Clin Microbiol Rev* 2001; **14**: 528–46.

Ritonavir and COVID-19: pragmatic guidance is important

We thank Joseph Heskin and colleagues¹ for highlighting the crucial issue of drug–drug interactions (DDIs) with ritonavir, the pharmacoenhancer or booster co-formulated with the novel SARS-CoV-2 protease inhibitor, PF-07321332 (Paxlovid, Pfizer [New York, NY, USA]).² Since Paxlovid will be primarily administered to non-hospitalised individuals and prescribed by clinicians who might not routinely manage complex interactions or have access to their full medication list, an awareness of the DDI potential and clear pathways to support safe decision making are essential, ideally led by pharmacists who have speciality

knowledge in this area. If managed appropriately, DDI should, in most cases, not necessitate a change in antiviral management.

The onset of ritonavir's inhibitory effect on the CYP3A4 isoenzyme, and to a lesser degree CYP2D6, is rapid, but the inhibition is also lost rapidly after drug cessation, mostly within 2 days.³ This information is important to guide dose adjustment or pause of concomitant medication where advised. As Heskin and colleagues clearly highlight, ritonavir also induces several cytochrome P450 isoenzymes, but this induction effect is slow to develop and is unlikely to be of clinical importance when used in a short course. However, an important consideration in people established on strong CYP3A inducers, such as carbamazepine, phenytoin, and rifampicin, is that these inducers are likely to reduce nirmatrelvir exposure and, as induction persists for about 2 weeks after cessation, are a contraindication to its use.

The clinical impact of DDIs depends on a number of factors including: the therapeutic window of the co-administered drug; the degree to which co-administered drugs are metabolised via CYP3A4 (ie, higher DDIs magnitudes are anticipated for those extensively metabolised by CYP3A4, for instance simvastatin); and the clinical indication and relative benefit treatment for the individual. We, of course, advise prescribers to consult the relevant summaries of product characteristics, and appropriate prescribing tools. Heskin and colleagues¹ refer to the University of Liverpool HIV drug interaction checker, and, although this is an invaluable tool, we encourage clinicians to refer to their specific COVID-19 interaction checker, as the advice might differ for short-term ritonavir use. However, the real-life effect of known or predicted DDIs, and recommended practice, might differ from prescribing advice, and sources of advice might be inconsistent. Antiretrovirals are