Doctopic: Analysis and Interpretation
22tl0824corr
PII

SARS-CoV-2 co-infection with influenza virus, respiratory syncytial virus, or adenoviruses [A: New title OK?]

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 [A: edit OK?],[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 viral co-infections with SARS-CoV-2 is unknown.

We examined clinical outcomes of co-infection with influenza viruses [A: please could you clarify whether we should use influenza, influenza virus, or influenza viruses throughout? It would be great to keep this consistent], respiratory syncytial virus, or adenoviruses in 212 466 people with SARS-CoV-2 infection hospitalised [A: do you mean admitted to hospital?] in the UK between Feb 6, 2020, and Dec 8, 2021, using the International Severe Acute Respiratory and Emerging Infection Consortium Coronavirus Clinical Characterisation Consortium [A: correct name? Please clarify if not] and WHO Clinical Characterisation Protocol UK.[4] [A: Please briefly list the important methodological details that are listed in the appendix, including the page numbers (eg, "Details of patient recruitment, testing, and data collection [etc, with relevant detail] are included in the appendix pp XX–XX"). Please include in the main text here the details of ethical approval if any]

Respiratory viral co-infections were recorded for 6965 patients with SARS-CoV-2. Viral co-infection was detected in 583 (8·4%) patients: 227 had influenza virus, 220 patients had respiratory syncytial virus, and 136 had adenovirus. Co-infection with influenza viruses was associated with increased odds of receiving invasive mechanical ventilation compared with SARS-CoV-2 mono-infection (table [A: please note that I have removed some data here and cited the table instead to avoid repetition]). SARS-CoV-2 co-infections with influenza virus and adenovirus 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 weightin (table). In this weighted multivariable regression analysis, influenza co-infection significantly increased the odds of receiving invasive mechanical ventilation and the odds of in-hospital mortality. Details from this and other analyses [A: please could you specify the types of analyses?] are available in the appendix (pp XX–XX [A: please provide page numbers]).

[A: Note, we have drawn the following text in from the supplementary material as it an important aspect of a balanced discussion] 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 monoinfections. 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 [A: please provide page number]). Patients were tested or not tested for a variety of reasons, such as illness severity and laboratory capacity. After correction for these differences with inverse probability weighting analysis, influenza 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

	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	1·68 (1·14–2·45)	0·007	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	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, and co-infection. [A: Please check that the confounders listed here are correct] OR=odds ratio. [A: Please provide p values in red to two significant figures, unless p<0·0001 (eg, 0·0013, but capped at four decimal places)?]

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

For the **International Sever Acute Respiratory and Emerging Infection Consortium Coronavirus Clinical Characterisation Consortium** see https://isaric4c.net

See Online for appendix

Submissions should be made via our electronic submission system at http://ees.elsevier.com/thelancet/

Correspondence

analysis, SARS-CoV-2 co-infection with respiratory syncytial virus or adenovirus were not significantly associated with receipt of invasive mechanical ventilation. Furthermore, adenovirus and respiratory syncytial virus co-infection did not have the same effect on the need for invasive mechanical ventilation as did influenza 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 influenza vaccination data were not registered in the database, and since most patients were admitted before COVID-19 vaccinations were available, we were unable to establish the effect of influenza or SARS-CoV-2 vaccination on outcome in monoinfected and co-infected patients.

As public health restrictions are lifted, respiratory virus co-infections are more likely to occur during this and future winters **[A: I suggest updating this statement to account for the current time of year—instead, could we say "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 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.

All authors declare support from the National Institute for Health Research (NIHR), the Medical Research Council (MRC), the NIHR Health Protection Unit (HPRU) in Emerging and Zoonotic Infections at the University of Liverpool, the NIHR HPRU in Respiratory Infections at Imperial College London, the NIHR Biomedical Research Centre at Imperial College London, and the NIHR Clinical Research Network. JKB and ABD report grants from the UK Department of Health and Social Care (DHSC), during the conduct of the study, and grants from the Wellcome Trust. PJMO reports personal fees from consultancies (ie, GlaxoSmithKline, Janssen, Bavarian Nordic, Pfizer, and Cepheid) and for the European Respiratory Society; grants from the MRC, MRC Global Challenge Research Fund, EU, NIHR Biomedical Research Centre, MRC–GlaxoSmithKline, Wellcome Trust, and NIHR (HPRU in Respiratory Infection); and is an NIHR senior investigator, unrelated to this Correspondence. PJMO's role as president of the British Society for Immunology was unpaid, but travel and accommodation at some meetings were paid for by the society. JKB reports grants from MRC. MGS reports grants from DHSC, NIHR UK, MRC, HPRU in Emerging and Zoonotic Infections, and the University of Liverpool, during the conduct of the study, and is chair of the scientific advisory board and a minority shareholder at Integrum Scientific, unrelated to this Correspondence. GHG, MGS, and JKB contributed equally. ISARUC4C Investigators are listed in the appendix **[A: Please note that the list of investigators, funding, and acknowledgments should be included in the appendix so I have removed them here—please check that the desired information is included in the appendix and revise the appendix as you see fit. Please submit the final version of your appendix to me as a PDF. If you wish for the investigators to be indexed as collaborators on PubMed, then please provide a two-column table in a word document, listing the authors' first names in the left column and family names in the right column]**.

Maaike C Swets, Clark D Russell, Ewen M Harrison, Annemarie B Docherty, Nazir Lone, Michelle Girvan, Hayley E Hardwick, ISARIC4C Investigators, Leonardus G Visser, Peter J M Openshaw, Geert H Groeneveld, Malcolm G Semple, J Kenneth Baillie
[A: Please note that we allow only one corresponding author—please choose one author. I have added a note to the declaration of interests section stating that GHG, MGS, and JKB are joint last authors and contributed equally]

g.h.groeneveld@lumc.nl OR m.g.semple@liverpool.ac.uk OR j.k.baillie@ed.ac.uk [A: Please indicate the corresponding author and we will update the email address here accordingly]

Department **[A: Department of X?]**(MCS), Centre for Inflammation Research (CDR), Centre for Medical Informatics, Usher Institute (EMH, ABD, NL), and Roslin Institute (JKB), University of Edinburgh, Edinburgh, UK; Liverpool Clinical Trials Centre (MG) and Institute of Infection, Veterinary and Ecological Sciences, Faculty of Health and Life Sciences (HEH, MGS), University of Liverpool, Liverpool, UK; Leiden University Medical Centre, Leiden University, Leiden, Netherlands (LGV, GHG); National Heart and Lung Institute, Imperial College London, London, UK (PJMO); Department of Respiratory Medicine, Alder Hey Children's Hospital, Liverpool, UK (MGS) **[A: Please check affiliations carefully and let me know if any are missing or incorrect. Please provide the postcode for the corresponding author]**

1 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.
2 Gomez GB, Mahé C, Chaves SS. Uncertain effects of the pandemic on respiratory viruses. *Science* 2021; **372:** 1043–44.
3 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.
4 Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ* 2020; **369:** m1985.
5 Aitken C, Jeffries DJ. Nosocomial spread of viral disease. *Clin Microbiol Rev* 2001; **14:** 528–46.