Coinfection with influenza viruses is associated with worse outcomes in severe Covid-19, an ISARIC4C / CO-CIN Report

7th February 2022

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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 have fewer such measures in place this winter,(2) we expect SARS-CoV-2 will circulate with other respiratory viruses, increasing the probability of co-infections.(1,3) The clinical impact of viral coinfections with SARS-CoV-2 is not known.

We addressed the impact of co-infection with influenza viruses, RSV and adenoviruses on clinical outcomes among 212,466 people with SARS-CoV-2 infection hospitalised in the United Kingdom between 6th February, 2020 and 8th December, 2021, using the ISARIC/WHO Clinical Characterisation Protocol UK (CCP-UK; isaric4c.net/).(4) Results of testing for respiratory viral co-infections were recorded for 6,995 patients, of whom 583 (8.4%) had confirmed viral co-infections (influenza: 227, RSV: 220, adenovirus: 136). Co-infection with influenza viruses was associated with higher odds of receiving invasive mechanical ventilation (IMV; OR 1.68; 95% CI 1.14-2.45). Both influenza virus and adenovirus co-infection were significantly associated with increased odds of death (OR 1.49; 95% CI 1.04-2.12 and OR 1.60; 95% CI 1.03-2.44, respectively). In order 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 1**). In this weighted multivariable regression analysis, influenza co-infection significantly increased the odds of receiving IMV (OR 4.14; 95% CI 2.00-8.49) and the odds of in-hospital mortality (OR 2.35; 95% CI 1.07-5.12). Details from this and other analyses can be found in the supplementary information.

As public health restrictions are lifted, respiratory virus co-infections are more likely to occur during this and future winters. The marked increase in risk among patients with coinfection has several implications for policy. It provides further support for vaccination against both SARS-CoV-2 and influenza viruses. Secondly, it suggests that testing for influenza is important in hospital in-patients with Covid-19 in order to identify patients at risk and to identify a cohort of patients who may have differential responses to immunomodulatory and antiviral therapy.

		Unweighted		Weighted	
		OR (95% CI)	**p value**	**OR (95% CI)**	**p value**
IMV	Adenovirus	1.22 (0.72-1.99)	0.435	0.64 (0.18-1.68)	0.415
	Influenza	1.68 (1.14-2.45)	**0.007**	4.14 (2.00-8.49)	**0.0001**
	RSV	1.05 (0.68-1.59	0.817	0.78 (0.15-2.70)	0.730
Mortality	Adenovirus	1.60 (1.03-2.44)	0.033	1.53 (0.67-3.33)	0.294
	Influenza	1.49 (1.04-2.12)	**0.027**	2.35 (1.07-5.12)	**0.031**
	RSV	1.20 (0.84-1.72)	0.311	0.60 (0.69-2.10)	0.473

Table 1: *Result of unweighted and weighted multivariable model adjusted for the following confounders: age, sex, number of comorbidities, treatment with corticosteroids, days since start pandemic and co-infection.*

IMV: invasive mechanical ventilation; RSV: respiratory syncytial virus

Funding

This work was supported by the National Institute for Health Research (NIHR) [CO-CIN-01], the Medical Research Council [MC_PC_19059] and by the NIHR Health Protection Research Unit (HPRU) in Emerging and Zoonotic Infections at University of Liverpool in partnership with Public Health England (PHE), in collaboration with Liverpool School of Tropical Medicine and the University of Oxford [200907], NIHR HPRU in Respiratory Infections at Imperial College London with PHE [200927], Wellcome Trust and Department for International Development [215091/Z/18/Z], and the Bill and Melinda Gates Foundation [OPP1209135], and Liverpool Experimental Cancer Medicine Centre (C18616/A25153), NIHR Biomedical Research Centre at Imperial College London [IS-BRC-1215-20013], EU Platform for European Preparedness Against (Re-) emerging Epidemics (PREPARE) [FP7 project 602525], Edinburgh-Leiden One Health solutions partnership and NIHR Clinical Research Network for providing infrastructure support for this research. JKB gratefully acknowledges funding support from a Wellcome Trust Senior Research Fellowship (223164/Z/21/Z), BBSRC Institute Strategic Programme Grant to the Roslin Institute (BB/P013732/1, BB/P013759/1), UKRI (MC_PC_20004, MC_PC_19025, MC_PC_1905, MRNO2995X/1), and the UK Intensive Care Society.

Acknowledgements

This work uses data provided by patients and collected by the NHS as part of their care and support. We are extremely grateful to the front-line NHS clinical and research staff and volunteer medical students who collected this data in challenging circumstances; and the generosity of the participants and their families for their individual contributions in these difficult times. We also acknowledge the support of Jeremy J Farrar (Wellcome Trust) and Nahoko Shindo (WHO). The authors would like to acknowledge the support of the eDRIS Team (Public Health Scotland) for their involvement in obtaining approvals, provisioning and linking data and the use of the secure analytical platform within the National Safe Haven

Conflicts of interest

All authors declare support from the NIHR, the Medical Research Council (MRC), the NIHR Health Protection Research Unit (HPRU) in Emerging and Zoonotic Infections at University of Liverpool, the NIHR HPRU in Respiratory Infections at Imperial College London, the NIHR Biomedical Research Centre (BRC) at Imperial College London, and the NIHR Clinical Research Network, for the submitted work. JKB and ABD report grants from the UK Department of Health and Social Care (DHSC), during the conduct of the study, and grants from Wellcome Trust,. PJMO reports personal fees from consultancies (GlaxoSmithKline, Janssen, Bavarian Nordic, Pfizer, and Cepheid) and from the European Respiratory Society, grants from MRC, MRC Global Challenge Research Fund, the EU, NIHR BRC, MRC–GlaxoSmithKline, Wellcome Trust, NIHR (HPRU in Respiratory Infection), and is an NIHR senior investigator outside the submitted work. PJMO's role as President of the British Society for Immunology was unpaid but travel and accommodation at some meetings was provided by the Society. JKB reports grants from MRC. MGS reports grants from DHSC, NIHR UK, MRC, HPRU in Emerging and Zoonotic Infections, and University of Liverpool, during the conduct of the study, and is chair of the scientific advisory board and a minority shareholder at Integrum Scientific, outside the submitted work.

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MCS, CDR, and LGV, PJMO, MGS, GHG, and JKB conceived the analysis. JKB and MGS conceived the study and led the study team. JKB, MGS and PJMO acquired the funding. EMH, ABD, and NL provided guidance on methodology and interpretation. MCS, CDR, EMH, and ABD curated the data.HEH and MG were project administrators. CDR, GHG, and JKB supervised the work. MCS did the formal analysis and wrote the original draft of the manuscript. CDR, EMH, ABD, NL, LGV, PJMO, MGS, GHG, and JKB reviewed and edited the manuscript.

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SUPPLEMENTARY MATERIAL

Coinfection with influenza viruses is associated with worse outcomes in severe Covid-19, an ISARIC4C / CO-CIN report

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Introduction

Co-infection with SARS-CoV-2 and additional endemic respiratory viruses has been reported in people with Coronavirus disease 2019 (COVID-19), potentially associated with increased disease severity (5,6). However, current knowledge on these co-infections is limited: most studies are small (median 116 patients investigated for co-infection, interquartile range 70-840; **Supplementary Table 1**), restricted to specific patient cohorts (ICU or high risk patients) (6–8), and do not report outcomes (3,5,8–12). The incidence of respiratory virus co-infection also differs widely between studies, from 0 to 63% of patients (3,5–9,11–14). Comparing results between studies is difficult given the use of different virologic diagnostic approaches. Furthermore, most studies were conducted over a short time (5,7–9,11,12,14) and/or out with the typical influenza season. (5)

Social distancing, self-isolation and the wearing of face coverings have reduced transmission of SARS-CoV-2. These non-pharmaceutical countermeasures have also reduced the transmission and associated disease burden of other endemic respiratory viruses, such as influenza and respiratory syncytial virus (RSV) (1,2,9,15). However, as these countermeasures are less stringently implemented and we enter the influenza season, (2) it is plausible we will see an increase in infections with SARS-CoV-2 and other respiratory viruses. (1,3) If co-infections lead to more severe disease, this could increase morbidity and mortality and use scarce hospital capacity, especially during traditional respiratory virus seasons.

Influenza has been the predominant cause of severe seasonal respiratory viral disease for decades. (15) Risk factors for severe viral pneumonia are similar in SARS-CoV-2 and influenza (6,16). Seasonal influenza virus can cause severe disease leading to ICU admission, the need for invasive mechanical ventilation (IMV) and death. (17) Both influenza virus and SARS-CoV-2 damage the epithelial cells and cause inflammation. (18,19) Whilst RSV mainly causes bronchiolitis in children, it can cause severe viral pneumonia in the elderly and immunocompromised. (2) Adenovirus can also cause severe viral pneumonia, especially in

immunocompromised people or those with many comorbidities. (20) Many that are discharged after severe infection suffer increased frailty. (21)

Overall, understanding the clinical consequences of co-infection with SARS-CoV-2 and endemic respiratory viruses is of importance for anticipating clinical demand during the respiratory virus season. We aimed to investigate clinical characteristics and outcomes of respiratory virus co-infections in hospitalised people with COVID-19 in the ISARIC/WHO CCP-UK multicentre prospective cohort study.

Methods

Study design

The International Severe Acute Respiratory and emerging Infections Consortium (ISARIC) WHO Clinical Characterisation Protocol UK (CCP-UK) study is an ongoing prospective observational cohort study recruiting inpatients in over 300 hospitals in England, Scotland, and Wales (National Institute for Health Research (NIHR) Clinical Research Network Central Portfolio Management System ID: 14152) performed by the ISARIC Coronavirus Clinical Characterisation Consortium (ISARIC4C). The study protocol is available online (isaric4c.net/protocols). Patients with confirmed or clinician-defined high-likelihood of SARS-CoV-2 infection were eligible for inclusion. A pre-specified case report form was used for data collection. 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).

For this analysis, we included only adults (≥18 years) with RT-PCR confirmed SARS-CoV-2 infection who were hospitalised between 6th February, 2020 and 8th December, 2021. Testing for additional respiratory viruses was done using RT-PCR for influenza virus (A or B), adenovirus and respiratory syncytial virus (RSV), at the discretion of the treating clinician. The type of influenza virus infection was not recorded. Subjects were included in the co-infected group if they had positive test results registered for influenza virus, adenovirus or RSV. Patients were included in the SARS-CoV-2 mono-infected group if they had a negative test result registered for influenza virus, adenovirus or RSV. Comorbidities were summarised as an overall comorbidity count, with each comorbidity having the same weight. Included comorbidities were chronic cardiac disease, chronic pulmonary disease (excluding asthma), asthma, liver disease, diabetes mellitus (type 1 or 2), chronic neurological disease, malignant neoplasm, rheumatological disease, dementia, HIV/ AIDS and chronic kidney disease. The main outcomes were the need for IMV and in-hospital mortality.

This project had several objectives. First, because of limited testing for respiratory viral co-infections during the pandemic we suspected the group that was tested was different from the group that was not tested. Therefore, our first objective was to describe and compare characteristics and outcome for patients who were tested for a second viral respiratory co-infection with influenza virus (A or B), adenovirus or RSV to those who were not tested. In the subgroup of tested patients, we then proceeded to analyse characteristics and outcome

between patients who tested positive to those who tested negative. In order to correct for possible differences between the tested and not tested population and to generalise our conclusion to the complete hospital population, we performed an inverse probability weighting (IPW) analysis.

Statistical analysis

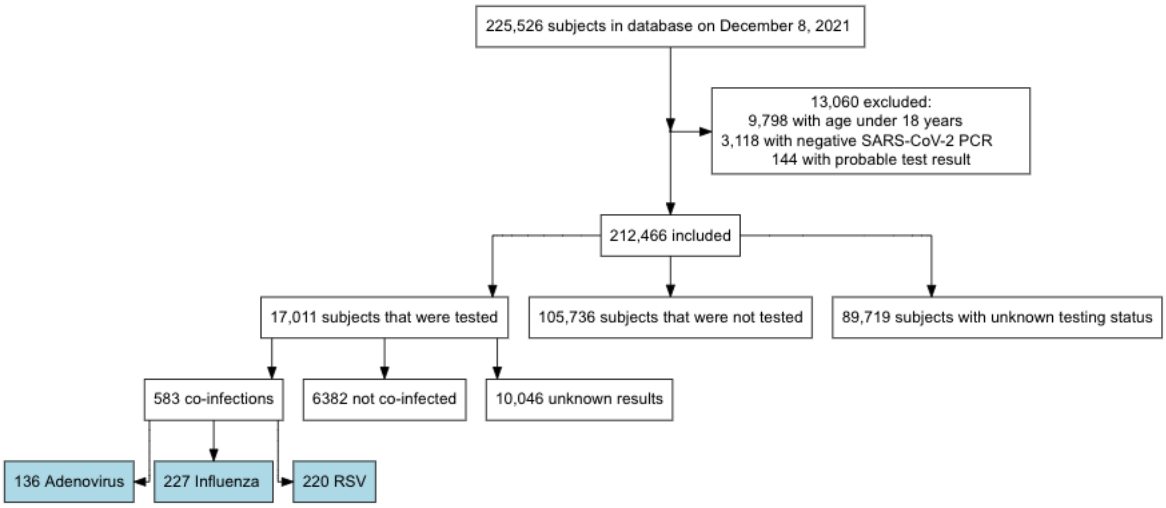
Mean and standard deviations (SD) were used to describe continuous normally distributed variables. Significance testing was done using the Welch two sample t-test for 2 groups (testing yes/no) and a one-way anova for viral co-infections.

Median and interquartile range (IQR) were used to describe continuous non-normally distributed values. Significance testing was done using the Mann Whitney-U test for 2 groups and the Kruskal Wallis test for comparing the viral co-infections.

Categorical variables were described as a frequency and percentage, and comparisons were done using a chi-squared test. A regression analysis was performed to analyse the effect of viral co-infection independent of other variables. Given the change in hospital mortality between the first and second wave of the COVID19 pandemic, (22) we created a time trend variable that captures when in the pandemic a patient was admitted to the hospital, using the day of hospital admission. For both mortality and need of IMV, a separate univariable regression analysis was performed. The confounders used were age, sex, number of comorbidities, immunocompromised status, 4C Mortality score, presence of a viral respiratory co-infection, treatment with corticosteroids during admission and the time trend variable. All clinically relevant variables and variables significantly associated with the outcome variable (IMV or mortality) were included in a multivariable regression analysis, to predict the odds of receiving IMV and mortality. IPW involved determining the probability of co-infection testing for each patient using a logistic regression model built using known confounders. The inverse of these probabilities was used in weighted analyses. Balance of patient characteristics after weighting was checked graphically using the standardised mean difference. A p value of 0.05 or less was considered to indicate statistical significance. Statistical analysis was performed using R Statistical Software (version 4.0.5).

Results

212,466 participants met our inclusion criteria and were included in the analysis, with an outcome recorded on or before 8th December, 2021 (**Supplementary figure 1**). 17,011 (8%) underwent testing for additional respiratory viruses (influenza virus, adenovirus or RSV) in addition to SARS-CoV-2. Of these patients undergoing additional testing, 6965 had a documented result, including 583 who had a confirmed respiratory virus co-infection. Influenza virus was the co-infecting pathogen in 227/583 cases (39%), RSV in 220/583 (38%) and adenovirus in 136/583 (23%).



Supplementary figure 1: Study flowchart

Clinical features associated with respiratory virus co-infection

We first sought to understand the characteristics of the sub-group of patients undergoing testing for respiratory viruses in addition to SARS-CoV-2 (**Supplementary table 2**). Overall, additional testing was associated with more severe disease. The proportion of patients admitted to critical care was higher among those undergoing additional testing (27.6% vs. 16.4%) as was the proportion of people who received IMV (10.4% vs 4.7%).

Within the sub-group of tested patients with a documented positive or negative result (n=6965) we then analysed patient characteristics and outcomes associated with co-infection (**Supplementary table 3**). In an unadjusted analysis, patients with respiratory virus co-infections were older. The highest proportion of people needing IMV was observed in people with influenza co-infection (23.5%), followed by 16.8% of RSV co-infected patients, 16.2% of SARS-CoV-2 mono-infected patients and 15.4% of adenovirus co-infections. In-hospital mortality was higher in all co-infection groups compared to SARS-CoV-2 mono-infection.

	Adenovirus co-infection (n=136)	Influenza co-infection (n=227)	RSV co-infection (n=220)	No co-infection (n=6382)	p value
Sex, male (%)	72 (52.9)	146 (64.9)	125 (57.1)	3657 (57.4)	0.101
Median age, years (IQR)	71.0 (53.8 to 83.0)	68.0 (56.0 to 80.5)	71.0 (57.0 to 82.0)	64.0 (51.0 to 77.0)	<0.001
Median number of comorbidities (IQR)	1.0 (0.0 to 2.0)	1.0 (0.0 to 2.0)	1.0 (0.0 to 2.0)	1.0 (0.0 to 2.0)	0.002
Immunocompromised (%)	20 (15.2)	37 (17.0)	32 (15.1)	882 (14.5)	0.784
Median 4C Mortality score (23) (IQR)	9.0 (6.0 to 11.0)	9.0 (6.0 to 11.5)	10.0 (6.8 to 12.0)	8.0 (5.0 to 11.0	<0.001
Median clinical frailty (IQR)	4 (2 to 6)	4 (2 to 5.3)	4 (3 to 6)	3 (2 to 5)	<0.001
Median respiratory rate, per minute (IQR)	22.0 (18.0 to 26.3)	21.0 (18.0 to 28.0)	22.0 (20.0 to 28.0)	22.0 (18.0 to 27.0)	0.300
Temperature, degrees Celsius (mean (SD))	37.5 (0.9)	37.6 (1.1)	37.6 (0.9)	37.5 (1.0)	0.400
Median systolic blood pressure, mmHg (IQR)	107 (99 to 135)	124 (102 to 145)	117 (104 to 133)	109 (102 to 118)	0.020

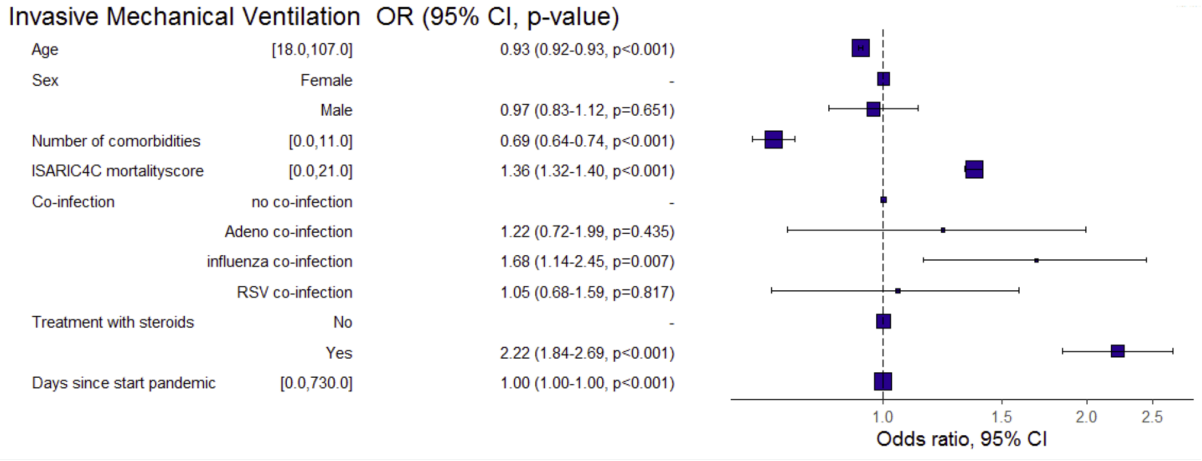
Median diastolic blood pressure, mmHg (IQR)	66 (54 to 70)	69 (57 to 79)	67 (58 to 82)	61 (54 to 70)	0.025
Median SaO2 (IQR)	94 (92 to 96)	94 (91 to 96)	93 (90 to 95)	94 (91 to 96)	0.017
Median FiO2 (IQR)	0.35 (0.28 to 0.60)	0.40 (0.29 to 0.60)	0.37 (0.29 to 0.61)	0.40 (0.29 to 0.75)	<0.001
Median hospital length of stay, days (IQR)	11 (5 to 23)	13 (6 to 29)	11 (6 to 21)	11 (6 to 23)	0.087
Critical care admission (%)	30 (22.6)	72 (33.0)	51 (23.4)	2239 (36.1)	<0.001
Treated with steroids *	41 (67.2)	40 (85.1)	36 (72.0)	4006 (85.3)	<0.001
Invasive mechanical ventilation (%)	21 (15.4)	52 (23.5)	37 (16.8)	1016 (16.2)	0.037
In-hospital mortality (%)	40 (29.4)	70 (30.8)	67 (30.5)	1357 (21.3)	<0.001

Supplementary table 3: Characteristics and outcomes associated with respiratory virus co-infections *Patients were defined as being immunocompromised if they had received a solid organ transplant, bone marrow or stem cell transplantation in the last 6 months, active chemotherapy, lung cancer with radical radiotherapy, cancer of the blood or bone marrow, immunotherapy for cancer or other targeted cancer treatment that affect the immune system, inborn errors of metabolism (such as severe combined immunodeficiency (SCID) or homozygous sickle cell), HIV positive or used pre-admission immunosuppressive therapy. *Treatment with systemic corticosteroids included treatment with dexamethasone, hydrocortisone, prednisolone, prednisone or methylprednisolone. Only includes patients hospitalised after the release of the RECOVERY trial who also needed supplemental oxygen.*

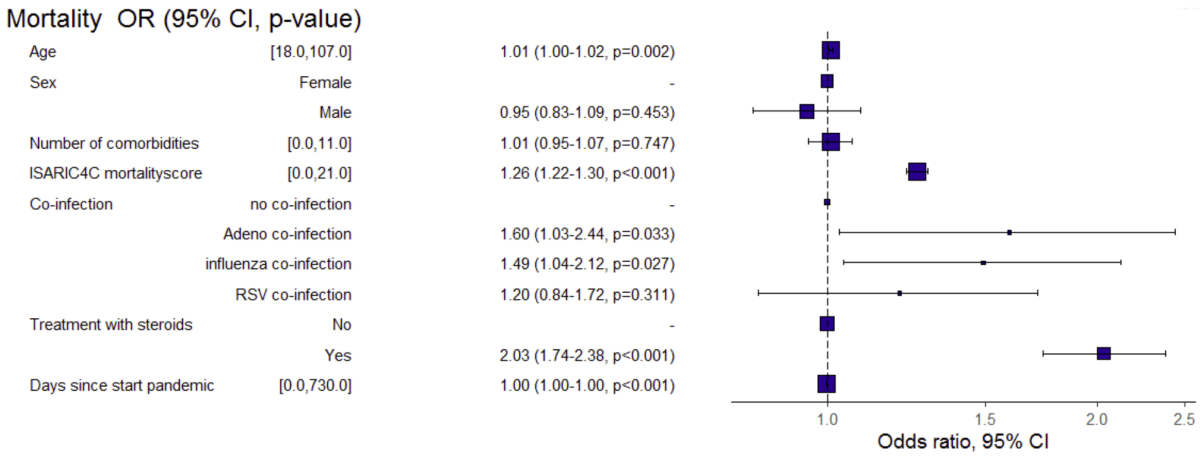
We then performed a logistic regression analysis to investigate the odds of receiving IMV (**Supplementary figure 2A**) and in-hospital mortality (**Supplementary figure 2B**) for different variables. The odds of receiving IMV are higher for patients with an influenza co-infection compared to those without co-infection whereas this was not observed for people with RSV or

adenovirus co-infection. Co-infection with either adenovirus or influenza was associated with increased odds of in-hospital mortality.

Supplementary figure 2: Multivariable logistic regression model *Treatment with systemic corticosteroids included treatment with dexamethasone, hydrocortisone, prednisolone, prednisone or methylprednisolone*



A) Multivariable logistic regression model with IMV as the outcome variable



B) Multivariable logistic regression model with in-hospital mortality as the outcome variable.

Inverse probability weighting

To correct for the observed differences between the tested and the untested populations (**supplementary table 2**), an inverse probability weighting analysis was performed. This weight was based on the probability to have undergone additional testing. Standardised mean differences before and after weighting for the tested and not tested group can be found in **supplementary figure 3**. The multivariable regression analysis with IMV as the outcome variable was repeated with the same predictor variables as in the unweighted analysis (**Supplementary table 4**). The OR for IMV in influenza co-infection was 4.14 (95% CI 2.00-8.49, p=0.0001). Similarly, the multivariable regression analysis with in-hospital mortality as the outcome variable was repeated. The OR for in-hospital mortality in influenza co-infected patients was 2.35 (95% CI 1.07-5.12, p value 0.031) (**Supplementary table 5**)

	OR for receiving IMV (95% CI)	p value
SARS-CoV-2 mono-infection	1	
Adenovirus co-infection	0.64 (0.18-1.68)	0.415
Influenza virus co-infection	4.14 (2.00-8.49)	0.0001
RSV co-infection	0.78 (0.15-2.70)	0.730

Supplementary table 4*: Weighted multivariable logistic regression analysis with IMV as the outcome variable*

	OR for in-hospital mortality (95% CI)	p value
SARS-CoV-2 mono-infection	1	
Adenovirus co-infection	1.53 (0.67-3.33)	0.294
Influenza virus co-infection	2.35 (1.07-5.12)	0.031
RSV co-infection	0.60 (0.69-2.10)	0.473

Supplementary table 5*: Weighted multivariable logistic regression analysis with in-hospital as the outcome variable*

Discussion

In this study of hospitalised people with COVID-19, we demonstrated that influenza co-infection was associated with increased odds of receiving IMV, and both adenovirus and influenza co-infection were associated with increased in-hospital mortality.

The number of viral co-infections in COVID-19 differs widely between studies, and absolute numbers are small making comparison difficult. (3,6,9–11,13,25) In our population 1.3% of SARS-CoV-2 positive patients also tested positive for influenza virus, a bit higher than some pooled estimates from meta-analysis (0.3-0.8). (25–27) In our study, 1.2% had an RSV co-infection, lower than some previously reported numbers (5,11,28) Finally, 0.8% of our population had an adenovirus co-infection. Previous studies reported both similar (28) and lower (5,11) numbers of adenovirus co-infections. Of course, the prevalence of co-infections is mostly determined by the prevalence of these infections in the community.

Most earlier research (**supplementary table 1**) consisted of small studies and only a few reported outcome data or compared outcomes between people with/without co-infection. Ding and colleagues (29) identified 5 patients co-infected with influenza and SARS-CoV-2, out of 115 SARS-CoV-2 positive hospitalised patients. These 5 patients did not need ICU admission or IMV and all were discharged alive. Chekuri and colleagues (30) did compare SARS-CoV-2 mono-infected patients to co-infected patients. In this co-infected group, other human coronaviruses were most common, followed by rhinovirus/enterovirus. No influenza co-

infections were found. Compared to the SARS-CoV-2 only group, the co-infected group was less likely to require oxygen treatment and was not associated with worse outcomes in an adjusted analysis. Drake and colleagues (31) found 138 influenza co-infected patients, including children, in which a prolonged duration of hospital admission was found, although this was not corrected for likelihood of being tested. Finally, Alosaimi and colleagues (6) identified 30 co-infected patients out of 48 hospitalised (14 ICU) SARS-CoV-2 positive patients and found that influenza co-infection was associated with mortality.

Our study had several strengths. Firstly, this 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. Secondly, we recruited patients over an 18-month period. Finally, we report outcome data for the majority of patients (>98% available for IMV and >99% for mortality)

There are some weaknesses in our study. Firstly, there is a risk of selection bias because the subjects that were tested differed from untested patients (**Supplementary table 2**), particularly in severity of illness: being more unwell increased the probability of testing for co-infections. Patients were tested or not tested for a variety of reasons, like illness severity, but also laboratory capacity. In order to correct for these differences and extrapolate our results from the tested to the complete hospital population, an inverse probability weighting analysis was performed, which confirmed the results from the unweighted multivariable logistic regression analysis. Influenza co-infection remained associated with receipt of IMV in the re-weighted population, with an OR that was larger than in the unweighted analysis (3.93 vs 1.68, respectively) but with wider confidence intervals. As in the unweighted analysis, neither RSV nor adenovirus co-infection had a significant association with IMV. Furthermore, adenovirus and RSV co-infection do not show the same effect on IMV as influenza co-infection shows, 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 using in-hospital mortality as the outcome variable, with a larger OR in the weighted analysis compared to the unweighted analysis (2.46 vs 1.49, respectively). The case report form used for data collection did not collect the date of testing for additional viruses and it is likely testing would have been done after admission and therefore community versus nosocomial acquisition cannot be determined. As hospital acquired viral respiratory infection is rare (24), we assume that viral co-infection was present at hospital admission in the majority of our study patients. Lastly, most patients were admitted before COVID-19 vaccinations were available.

Influenza virus and SARS-CoV-2 can both cause severe damage in the lungs and lead to ARDS. (6,19) In a comparison of plasma samples from fatal H1N1 influenza A virus infection and SARS-CoV-2, we have previously demonstrated that in comparison to COVID-19, influenza is associated with a comparatively greater elevation in concentrations of some pro-inflammatory cytokines (IL-18, IL-1β) and pro-thrombotic mediators (vWF-A2, tissue factor, thrombomodulin), and equivalent concentrations of IL-6. (32) In contrast, elevated GM-CSF is a distinct feature of COVID-19. It is plausible that co-infection with influenza viruses and SARS-CoV-2 could 'synergise' activation of innate immunity and exacerbate immunopathology, increasing pulmonary damage and progression to ARDS. (6) Testing this hypothesis in samples from co-infected patients is an important research goal.

Although respiratory viral co-infections were uncommon during the first two years of the pandemic, as public health guidance changes and social mixing increases, co-circulation of additional respiratory viruses will also increase leading to more co-infections. Concerningly, we report an association between influenza co-infection and receipt of IMV and in-hospital mortality, in addition to adenovirus and in-hospital mortality. This emphasises the importance of preventive measures to reduce the disease burden associated with these viruses, in particular influenza vaccination. The adoption of more widespread testing would facilitate identification of hospital inpatients at high risk of deterioration and death, and may identify patients in whom different therapeutic strategies may be more effective.

Funding

This work was supported by the National Institute for Health Research (NIHR) [CO-CIN-01], the Medical Research Council [MC_PC_19059] and by the NIHR Health Protection Research Unit (HPRU) in Emerging and Zoonotic Infections at University of Liverpool in partnership with Public Health England (PHE), in collaboration with Liverpool School of Tropical Medicine and the University of Oxford [200907], NIHR HPRU in Respiratory Infections at Imperial College London with PHE [200927], Wellcome Trust and Department for International Development [215091/Z/18/Z], and the Bill and Melinda Gates Foundation [OPP1209135], and Liverpool Experimental Cancer Medicine Centre (C18616/A25153), NIHR Biomedical Research Centre at Imperial College London [IS-BRC-1215-20013], EU Platform for European Preparedness Against (Re-) emerging Epidemics (PREPARE) [FP7 project 602525], Edinburgh-Leiden One Health solutions partnership and NIHR Clinical Research Network for providing infrastructure support for this research. JKB gratefully acknowledges funding support from a Wellcome Trust Senior Research Fellowship (223164/Z/21/Z), BBSRC Institute Strategic Programme Grant to the Roslin Institute (BB/P013732/1, BB/P013759/1), UKRI (MC_PC_20004, MC_PC_19025, MC_PC_1905, MRNO2995X/1), and the UK Intensive Care Society.

Acknowledgements

This work uses data provided by patients and collected by the NHS as part of their care and support. We are extremely grateful to the front-line NHS clinical and research staff and volunteer medical students who collected this data in challenging circumstances; and the generosity of the participants and their families for their individual contributions in these difficult times. We also acknowledge the support of Jeremy J Farrar (Wellcome Trust) and Nahoko Shindo (WHO). The authors would like to acknowledge the support of the eDRIS Team (Public Health Scotland) for their involvement in obtaining approvals, provisioning and linking data and the use of the secure analytical platform within the National Safe Haven

Conflicts of interest

All authors declare support from the NIHR, the Medical Research Council (MRC), the NIHR Health Protection Research Unit (HPRU) in Emerging and Zoonotic Infections at University of Liverpool, the NIHR HPRU in Respiratory Infections at Imperial College London, the NIHR Biomedical Research Centre (BRC) at Imperial College London, and the NIHR Clinical Research Network, for the submitted work. JKB and ABD report grants from the UK Department of Health and Social Care (DHSC), during the conduct of the study, and grants from Wellcome Trust,. PJMO reports personal fees from consultancies (GlaxoSmithKline, Janssen, Bavarian Nordic, Pfizer, and Cepheid) and from the European Respiratory Society, grants from MRC, MRC Global Challenge Research Fund, the EU, NIHR BRC, MRC–

GlaxoSmithKline, Wellcome Trust, NIHR (HPRU in Respiratory Infection), and is an NIHR senior investigator outside the submitted work. PJMO's role as President of the British Society for Immunology was unpaid but travel and accommodation at some meetings was provided by the Society. JKB reports grants from MRC. MGS reports grants from DHSC, NIHR UK, MRC, HPRU in Emerging and Zoonotic Infections, and University of Liverpool, during the conduct of the study, and is chair of the scientific advisory board and a minority shareholder at Integrum Scientific, outside the submitted work.

Authorship contributions

MCS, CDR, and LGV, PJMO, MGS, GHG, and JKB conceived the analysis. JKB and MGS conceived the study and led the study team. JKB, MGS and PJMO acquired the funding. EMH, ABD, and NL provided guidance on methodology and interpretation. MCS, CDR, EMH, and ABD curated the data.HEH and MG were project administrators. CDR, GHG, and JKB supervised the work. MCS did the formal analysis and wrote the original draft of the manuscript. CDR, EMH, ABD, NL, LGV, PJMO, MGS, GHG, and JKB reviewed and edited the manuscript.

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Supplementary information

Author	Year	Location	No-infections tested	Number of sars-cov-2 positive patients tested for co-infection	Number of co-infections founds	Influenza co-infection	RSV co-infection	Adeno co-infection	Duration of study	Study group	Outcome reported
Alosaimi (6)	2021	Saudi Arabia	Adenovirus, HCoV (NL63, HKU1, 229E, OC43), MPV, Rhinovirus, Influenza, Bocavirus, PIV, RSV	48	30 (62.5%)	7 (14.6%)	0 (0%)	10 (20.8%)	NA	Hospital patients, 14 ICU	Icu admission and mortality
Bhatraju (7)	2020	USA	Influenza, RSV	23	0	0	0	NA	2 weeks in February/ March 2020	ICU patients	-
Castillo (8)	2020	USA	Adenovirus, HCoV, MPV, Rhinovirus, Influenza, PIV, RSV	23	1 (4%)	1 (4%)	0 (0%)	0 (0%)	2 weeks in March 2020	Patients with high risk at COVID-19	No
Chekuri (30)	2021	USA	Adenovirus, HCoV (NL63, HKU1, 229E, OC43), MPV, Rhinovirus,	306	14 (4.6%)	0 (0%)	1 (6.7%)	1 (6.7%)	1 month	SARS-CoV-2 positive patients presenting at the emergency	Hospital admission, IMV, mortality

			Influenza, PIV, RSV							department	
Chen (14)	2020	China	Adenovirus, SARS-CoV-1, MERS, Influenza, PIV, RSV	99	0	0	0	0	3 weeks in January 2020	SARS-CoV-2 positive patients	-
Ding (29)	2020	China	Influenza	115	5 (4.4%)	5 (4.4%)	NA	NA	NA	Hospitalised patients	ARDS, ICU admission, mortality
Drake* (31)	2020	UK	Influenza	779	138 (17.7%)	138 (17.7%)	NA	NA	February-June 2020	Hospitalised confirmed or highly probable SARS-CoV-2	Critical care admission, IMV, hospital length of stay
Kawai (3)	2021	Japan	Influenza	193	0 (0%)	0 (0%)	NA	NA	February-April 2020	Hospitalised COVID-19 patients	-
Kim (11)	2020	USA	Adenovirus, HCoV (NL63, HKU1, 229E, OC43), MPV, Rhinovirus, Influenza, PIV, RSV	116	25 (21.6%)	1 (0.9%)	6 (5.2%)	0 (0%)	March 2020	Patients tested for SARS-CoV-2	No
Kim (9)	2021	Australia	Rhinovirus, influenza	92	7 (8%)	2 (2%)	0 (0%)	0 (0%)	March-May 2020	SARS-CoV-2 positive hospitalised patients	No

Nowak (13)	2020	USA	Adenovirus, HCoV (NL63, HKU1, 229E, OC43), MPV, Rhinovirus, Influenza, PIV, RSV	1204	37 (3.07%)	1 (0.08%)	4 (0.31%)	2 (0.18%)	March-April 2020	Patients tested for SARS-CoV-2	No
Singh (5)	2021	USA	Adenovirus, HCoV (NL63, HKU1, 229E, OC43), MPV, Rhinovirus, Influenza, Bocavirus, PIV, RSV, EBV, HHV6, VZV	4259	146 (3.4%)	1 (0.02%)	5 (0.11%)	13 (0.3%)	March-August 2020	Patients tested for SARS-CoV-2	No
Takahashi (12)	2020	USA	Influenza	902	3 (0.33%)	3 (0.33%)	NA	NA	March-May 2020	Patients tested for SARS-CoV-2	No

Supplementary table 1*. PIV=parainfluenza virus, MPV= human metapneumovirus, HHV= human herpes virus 6, EBV = epstein barr virus, VZV= varicella zoster virus. *This was a report prepared by the ISARIC4C investigators as part of the COVID-19 Clinical Information Network (CO-CIN) for the UK Scientific Advisory Group for Emergencies (SAGE); it includes some overlapping patients and also includes children. The original SAGE report is available here: https://www.gov.uk/government/publications/co-cin-influenza-infection-in-patients-hospitalised-with-covid-19-rapid-report-from-co-cin-data-23-september-2020*

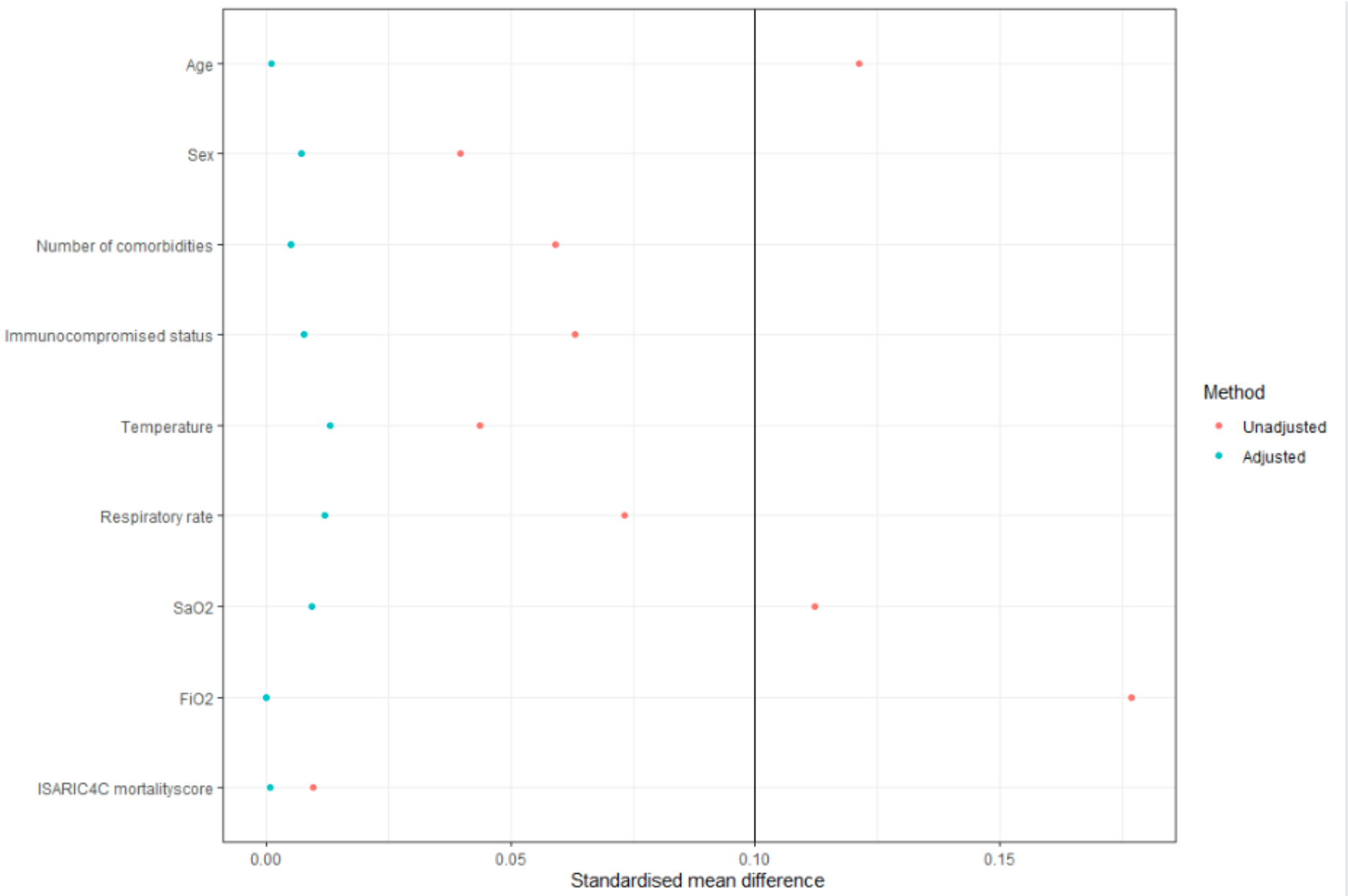
	Not tested (n=105736)	Tested (n=17011)	p value

Sex, male (%)	56527 (53.5)	9587 (56.4)	<0.001
Median age, years (IQR)	69.0 (53.0 to 81.0)	66.0 (52.0 to 79.0)	<0.001
Median number of comorbidities (IQR)	1.0 (0.0 to 2.0)	1.0 (0.0 to 2.0)	0.678
Immunocompromised (%)	11694 (12.2)	2297 (14.4)	<0.001
Median 4C Mortality score (23) (IQR)	8.0 (5.0 to 11.0)	9.0 (5.0 to 11.0)	<0.001
Median clinical frailty (IQR)	4 (2-6)	3 (2-5)	<0.001
Median respiratory rate, per minute (IQR)	20.0 (18.0 to 24.0)	21.0 (18.0 to 26.0)	<0.001
Temperature, degrees Celsius (mean (SD))	37.4 (0.91)	37.5 (0.94)	<0.001

Median systolic blood pressure, mmHg (IQR)	107 (102 to 116)	108 (102 to 117)	0.101
Median diastolic blood pressure, mmHg (IQR)	63 (56 to 71)	62 (55 to 70)	0.102
Median SaO2 (IQR)	94 (92 to 96)	94 (91 to 96)	<0.001
Median FiO2 (IQR)	0.37 (0.29 to 0.60)	0.37 (0.29 to 0.61)	<0.001
Critical care admission (%)	16758 (16.4)	4567 (27.6)	<0.001
Invasive mechanical ventilation (%)	4882 (4.7)	1747 (10.4)	<0.001
In-hospital mortality (%)	19877 (18.8)	3344 (19.7)	0.008

Supplementary table 2: Characteristics of hospitalised people with COVID-19 undergoing testing for additional respiratory viruses. *Patients were defined as being immunocompromised if they had received a solid organ transplant, bone marrow or stem cell transplantation in the last 6 months, active chemotherapy, lung cancer with radical radiotherapy, cancer of the blood or bone marrow, immunotherapy for cancer*

or other targeted cancer treatment that affect the immune system, inborn errors of metabolism (such as severe combined immunodeficiency (SCID) or homozygous sickle cell), HIV positive or used pre-admission immunosuppressive therapy.


Age
Sex
Number of comorbidities
Immunocompromised status
Temperature
Respiratory rate
SaO2
FiO2
ISARIC4C mortalityscore
0.00
0.05
0.10
0.15
Standardised mean difference
Method
Unadjusted
Adjusted

Supplementary figure 3: standardised mean differences for variables included in the inverse probability weighting analysis, before (unadjusted) and after weighting (adjusted)