

# Influenza infection in patients hospitalised with COVID-19: rapid report from CO-CIN data

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## Executive summary

The impact of Influenza virus infection in patients who have severe concurrent SARS-CoV-2 infection is unclear. The Coronavirus Clinical Information Network (CO-CIN) has collated clinical details and outcomes on approximately two thirds of all hospital admissions for covid-19 in England, Scotland and Wales. Data collated includes details of infectious pathogen test results.

In this analysis, we compare patients admitted with community acquired covid-19 and hospital acquired covid-19 who were recorded as being PCR negative for Influenza to those who tested positive for influenza viruses (A or B) during their stay.

There are inherent caveats to this analysis of hospitalised patients. First, patients included were admitted between February and June 2020, where Influenza virus activity in hospital and the community was low. Second, there is a testing bias. Most laboratories prioritised SARS-CoV-2 over multiplex PCR testing during the first wave for lack of capacity. Influenza ( $\pm$  other respiratory virus) PCR tests were more likely to be performed in sicker patients that were admitted to critical care to rule out other treatable diseases. Finally, reporting bias is likely, where only positive results have been entered into this dataset, meaning there may be underreporting of patients who had a negative Influenza test. Similarly, these data cannot account for the effects of prior influenza vaccination which may attenuate disease severity, nor possible different risks and effects of having community acquired influenza rather than community acquired SARS-CoV-2 on likelihood of admission to hospital.

Despite these limitations, 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 we excluded patients who acquired covid-19 in hospital.

We did not observe any difference in mortality associated with co-infection in univariate or multivariate analysis. Most positive influenza tests were in adults under 70 years old, who are at low risk of death, and in multivariate analysis there is a competition of risk as advanced age confers a magnitude higher risk of death from covid-19 alone. It must be emphasised that influenza activity was low in the community during the period of study,

and very low in the most vulnerable elderly age group, possibly because of prior vaccination.

In unadjusted analysis, dual infection was associated with moderately greater use of oxygen (83.9% vs 80.7%), critical care admission (43.5% vs 39.0%), receipt of mechanical ventilation (32.6% vs 28.5%) and greatly increased length of stay (16.4d vs 7.4d), all at p = or <0.001.

After adjustment for age, sex and selected comorbidities, dual infection remained strongly associated with a greatly increased length of stay .

## Interpretation and policy implication

In the context of the SARS-CoV-2 pandemic and winter flu season, co-infection is likely to place additional strain on hospital capacity and resources.

Great efforts should be made to encourage widespread influenza vaccination, ideally extending beyond traditional high-risk groups for severe influenza to the newly identified risk groups for severe covid-19 in the UK (Docherty AB et al. BMJ 2020).

Further research is required to understand

- 1: the effects of influenza plus covid-19 on outcomes and
- 2: plan for the likely consequences of the additional burden placed on healthcare facilities if significant numbers of patients have concurrent influenza and SARS-CoV-2 infection.

## Methods

We included patients of all ages admitted to any acute and general medical care hospital up to 8th June 2020, who were admitted 5 or more days following symptom onset. The later criterion applied so as to ensure a strict inclusion community acquired severe acute respiratory infection (SARI) for one of the pathogens of interest. Residential mental health units, units for long-term care of vulnerable adults and frail elderly people were excluded.

## Results

20 076 of the 78 769 people in CO-CIN met the strict definition of community acquired SARI and were enrolled as confirmed or highly probable covid-19.

779 patients had influenza test data available, of these 138 (17.72%) tested positive for influenza.

Most positive flu tests were in March and April 2020

Patients who received an influenza test were more likely to have already been admitted to a critical care unit during their stay. Similarly, patients who were tested for influenza were

younger. This suggests that there is a testing bias towards those in critical care units, reflecting the higher likelihood of patients getting tested in this clinical environment.

### Characteristics of patients who were tested for influenza

Patients who were younger, who had cancer, cardiac disease or who received critical care were more likely to be tested for influenza.

label	levels	Not tested for flu	Flu negative	Flu positive	p
Total N (%)		19297 (96.1)	641 (3.2)	138 (0.7)	
Age on admission	<50	3525 (18.3)	133 (20.7)	29 (21.0)	0.016
	50-69	7481 (38.8)	268 (41.8)	65 (47.1)	
	70-79	4026 (20.9)	123 (19.2)	21 (15.2)	
	80+	4244 (22.0)	117 (18.3)	22 (15.9)	
	(Missing)	21 (0.1)	0 (0.0)	1 (0.7)	
Sex at Birth	Female	7391 (38.3)	224 (34.9)	45 (32.6)	0.098
	Male	11876 (61.5)	416 (64.9)	92 (66.7)	
	(Missing)	30 (0.2)	1 (0.2)	1 (0.7)	
Chronic pulmonary disease	No	15596 (80.8)	531 (82.8)	110 (79.7)	0.946
	Yes	2656 (13.8)	87 (13.6)	19 (13.8)	
	(Missing)	1045 (5.4)	23 (3.6)	9 (6.5)	
Asthma	No	15283 (79.2)	521 (81.3)	102 (73.9)	0.451
	Yes	2954 (15.3)	102 (15.9)	26 (18.8)	
	(Missing)	1060 (5.5)	18 (2.8)	10 (7.2)	
Chronic cardiac disease	No	13827 (71.7)	502 (78.3)	105 (76.1)	0.008
	Yes	4466 (23.1)	126 (19.7)	22 (15.9)	
	(Missing)	1004 (5.2)	13 (2.0)	11 (8.0)	
Chronic kidney disease	No	15902 (82.4)	563 (87.8)	117 (84.8)	0.025
	Yes	2306 (12.0)	57 (8.9)	13 (9.4)	
	(Missing)	1089 (5.6)	21 (3.3)	8 (5.8)	
Malignant neoplasm	No	16768 (86.9)	565 (88.1)	115 (83.3)	0.484
	Yes	1335 (6.9)	46 (7.2)	13 (9.4)	
	(Missing)	1194 (6.2)	30 (4.7)	10 (7.2)	
Diabetes with complications	No	16655 (86.3)	581 (90.6)	119 (86.2)	0.741
	Yes	1108 (5.7)	36 (5.6)	6 (4.3)	
	(Missing)	1534 (7.9)	24 (3.7)	13 (9.4)	
Diabetes without complications	No	14590 (75.6)	500 (78.0)	101 (73.2)	0.676
	Yes	3219 (16.7)	119 (18.6)	25 (18.1)	
	(Missing)	1488 (7.7)	22 (3.4)	12 (8.7)	
Critical Care Admission	No	14639 (75.9)	391 (61.0)	78 (56.5)	<0.001
	Yes	4433 (23.0)	250 (39.0)	60 (43.5)	
	(Missing)	225 (1.2)	0 (0.0)	0 (0.0)	

### Timing of testing for influenza from time of admission

The majority of the positive flu tests were done 5 or more days after admission.

	Timing of flu test	Number tested with available data (%)
Total N (%)		632 (100.0)
Time from admission	Negative for flu in first 24 hours after admission	502 (79.4)
	Negative for flu in first 1 to 5 days after admission	58 (9.2)
	Negative for flu after first 5 days of admission	26 (4.1)
	Positive for flu in first 24 hours after admission	16 (2.5)
	Positive for flu in first 1 to 5 days after admission	6 (0.9)
	Positive for flu after first 5 days of admission	24 (3.8)

### Timing of testing for influenza in those who received critical care

Of the patients who had data available around date of flu testing and date of critical care admission, most patients were tested after admission to critical care units.

	Timing of flu test	Number tested with available data (%)
Total N (%)		561 (100.0)
Location of flu testing	Negative when tested for flu	529 (94.3)
	Positive for flu after critical care admission	27 (4.8)
	Positive for flu before critical care admission	5 (0.9)

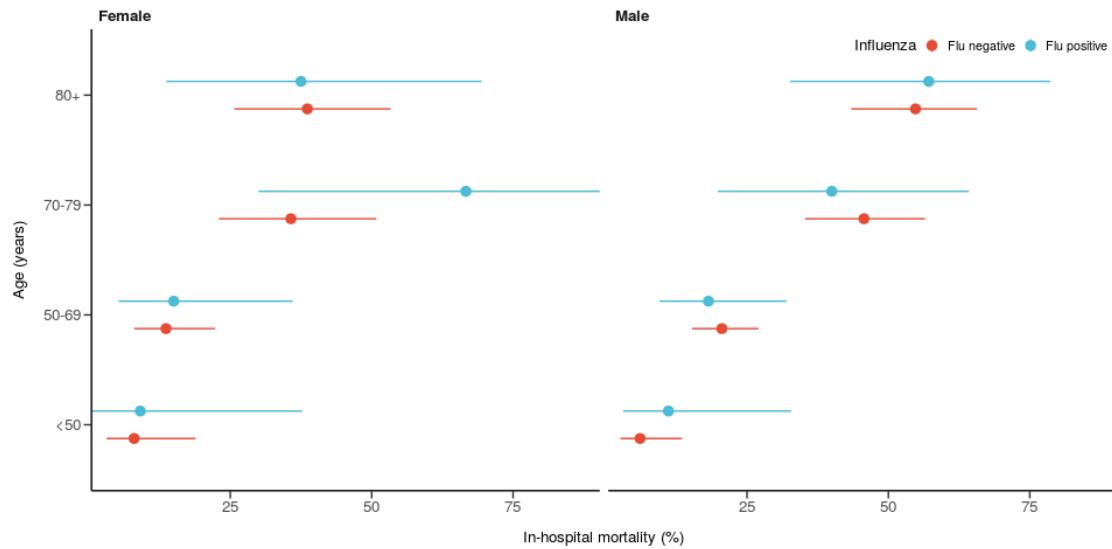
## Outcomes of patients who were tested for influenza

Patients who tested positive for influenza at any point in their hospital stay were more likely to be admitted to critical care, receive invasive ventilation and had nearly twice the length of stay. Death was similar across the testing groups. Patients who tested positive for flu had a significantly longer length of stay (over twice as long) than those who tested negative for flu.

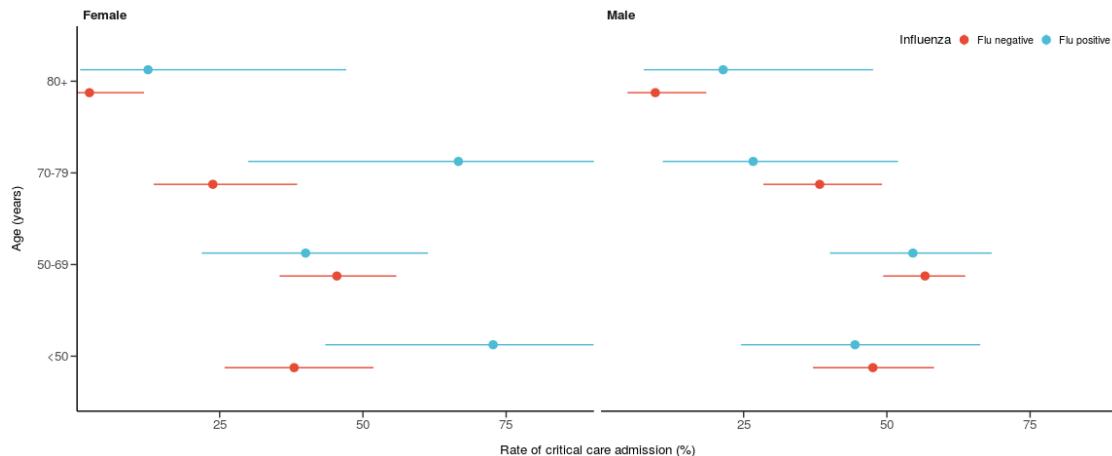
label	levels	Not tested for flu	Flu negative	Flu positive	p
Total N (%)		19297 (96.1)	641 (3.2)	138 (0.7)	
Death	No	13953 (72.3)	467 (72.9)	102 (73.9)	0.952
	Yes	5072 (26.3)	168 (26.2)	35 (25.4)	
	(Missing)	272 (1.4)	6 (0.9)	1 (0.7)	
Critical Care Admission	No	14639 (75.9)	391 (61.0)	78 (56.5)	<0.001
	Yes	4433 (23.0)	250 (39.0)	60 (43.5)	
	(Missing)	225 (1.2)	0 (0.0)	0 (0.0)	
Invasive Ventilation	No	16083 (83.3)	458 (71.5)	93 (67.4)	<0.001
	Yes	2936 (15.2)	183 (28.5)	45 (32.6)	
	(Missing)	278 (1.4)	0 (0.0)	0 (0.0)	
Received oxygen	No	4600 (24.4)	123 (19.3)	22 (16.1)	0.001
	Yes	14283 (75.6)	515 (80.7)	115 (83.9)	
Length of stay (for those alive)	Mean (SD)	9.6 (16.0)	7.4 (13.7)	16.4 (23.2)	<0.001

## Mortality by influenza positivity, stratified by age and sex

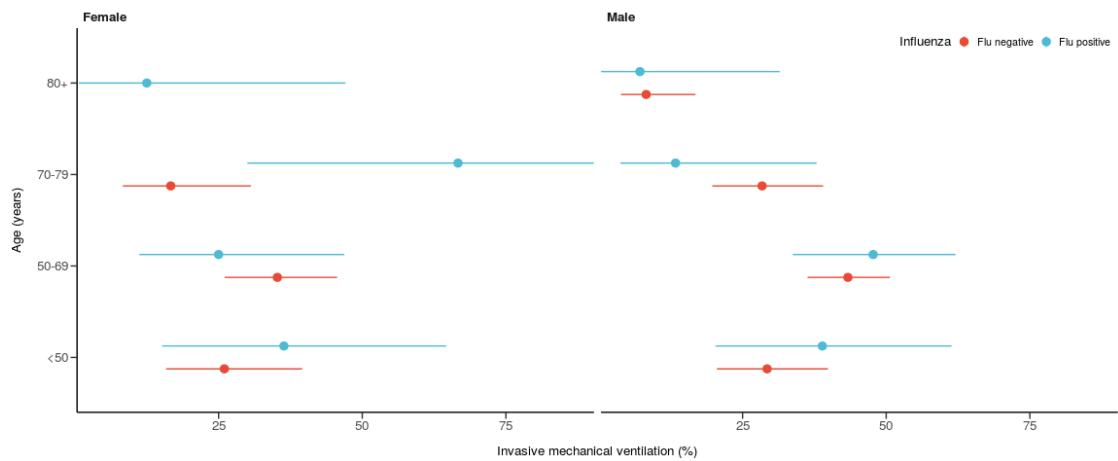
There are no significant differences in our data, which is likely due to the study having low numbers of patients with influenza (given recruitment did not coincide with flu season).



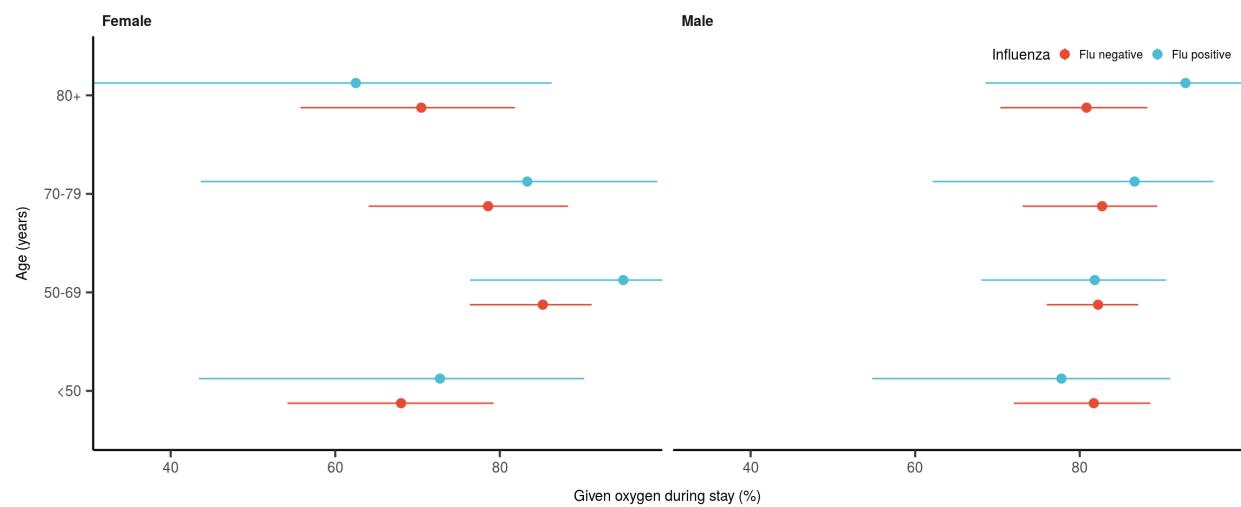
## Critical care admission by influenza positivity, stratified by age and sex



## Invasive ventilation by influenza positivity, stratified by age and sex



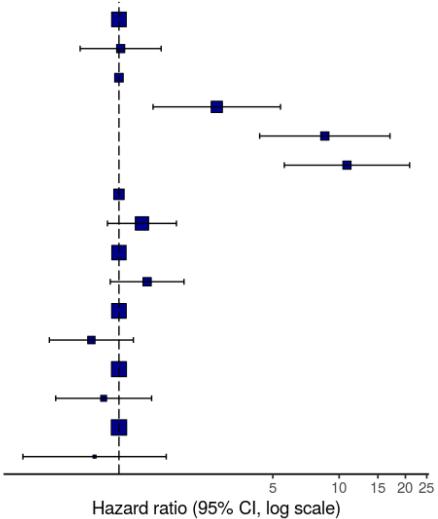
## Oxygen use by influenza positivity, stratified by age and sex



## Adjusted survival by flu status

Survival (mortality): HR (95% CI, p-value)

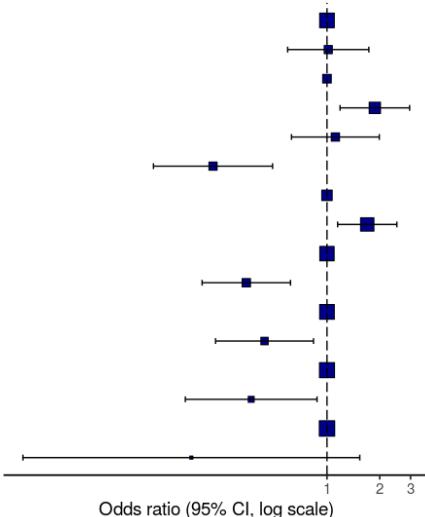
Influenza coinfection	Flu negative	-
	Flu positive	1.02 (0.67-1.55, p=0.934)
Age on admission	<50	-
	50-69	2.78 (1.43-5.42, p=0.003)
	70-79	8.61 (4.36-17.02, p<0.001)
	80+	10.85 (5.64-20.90, p<0.001)
Sex at Birth	Female	-
	Male	1.27 (0.89-1.82, p=0.191)
Chronic cardiac disease	No	-
	Yes	1.34 (0.91-1.97, p=0.134)
Chronic pulmonary disease	No	-
	Yes	0.75 (0.48-1.16, p=0.198)
Malignant neoplasm	No	-
	Yes	0.85 (0.52-1.41, p=0.532)
Dementia	No	-
	Yes	0.77 (0.37-1.64, p=0.505)



## Adjusted odds of Critical Care by flu status

Critical Care Admission: OR (95% CI, p-value)

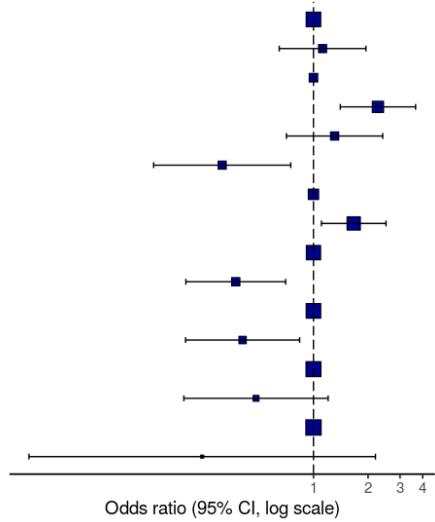
Influenza coinfection	Flu negative	-
	Flu positive	1.02 (0.60-1.73, p=0.951)
Age on admission	<50	-
	50-69	1.88 (1.19-2.96, p=0.007)
	70-79	1.12 (0.63-1.99, p=0.707)
	80+	0.22 (0.10-0.49, p<0.001)
Sex at Birth	Female	-
	Male	1.70 (1.15-2.51, p=0.008)
Chronic cardiac disease	No	-
	Yes	0.35 (0.19-0.62, p<0.001)
Chronic pulmonary disease	No	-
	Yes	0.44 (0.23-0.84, p=0.012)
Malignant neoplasm	No	-
	Yes	0.37 (0.16-0.88, p=0.024)
Dementia	No	-
	Yes	0.17 (0.02-1.54, p=0.114)



## Adjusted odds of Invasive Mechanical Ventilation by flu status

Invasive Mechanical Ventilation: OR (95% CI, p-value)

Influenza coinfection	Flu negative	-
	Flu positive	1.12 (0.65-1.95, p=0.681)
Age on admission	<50	-
	50-69	2.27 (1.41-3.66, p=0.001)
	70-79	1.31 (0.71-2.41, p=0.390)
	80+	0.31 (0.13-0.75, p=0.009)
Sex at Birth	Female	-
	Male	1.67 (1.11-2.51, p=0.015)
Chronic cardiac disease	No	-
	Yes	0.37 (0.20-0.70, p=0.002)
Chronic pulmonary disease	No	-
	Yes	0.41 (0.20-0.84, p=0.015)
Malignant neoplasm	No	-
	Yes	0.48 (0.19-1.20, p=0.119)
Dementia	No	-
	Yes	0.24 (0.03-2.20, p=0.208)



### Linear regression model for length of stay by flu status

When adjusted for age, sex and selected comorbidities, testing positive for influenza was associated with a significantly longer length of stay.

Dependent: Length of stay (for those alive)		unit	value	Coefficient (univariable)	Coefficient (multilevel)
Influenza coinfection	Flu negative	Mean (sd)	7.4 (13.7)	-	-
	Flu positive	Mean (sd)	16.4 (23.2)	9.01 (5.55 to 12.46, p<0.001)	4.85 (1.45 to 8.25, p=0.003)
Age on admission (years)	<50	Mean (sd)	8.9 (15.8)	-	-
	50-69	Mean (sd)	8.4 (15.2)	-0.48 (-3.73 to 2.78, p=0.774)	0.71 (-1.96 to 3.38, p=0.301)
	70-79	Mean (sd)	11.9 (19.2)	2.97 (-1.43 to 7.37, p=0.186)	2.79 (-1.00 to 6.57, p=0.075)
	80+	Mean (sd)	7.5 (14.9)	-1.44 (-6.17 to 3.29, p=0.550)	0.41 (-3.81 to 4.62, p=0.425)
Sex at Birth	Female	Mean (sd)	8.4 (15.7)	-	-
	Male	Mean (sd)	9.5 (16.6)	1.09 (-1.75 to 3.93, p=0.452)	0.18 (-2.14 to 2.49, p=0.440)
Chronic cardiac disease, including congenit...t hypertension)	No	Mean (sd)	8.3 (15.3)	-	-
	Yes	Mean (sd)	11.9 (20.0)	3.61 (-0.22 to 7.44, p=0.065)	5.67 (2.37 to 8.98, p<0.001)
Chronic pulmonary disease (not asthma)	No	Mean (sd)	8.8 (15.7)	-	-
	Yes	Mean (sd)	9.2 (18.0)	0.42 (-3.70 to 4.54, p=0.841)	-1.15 (-4.73 to 2.43, p=0.264)
Malignant neoplasm	No	Mean (sd)	9.1 (16.3)	-	-
	Yes	Mean (sd)	5.2 (10.9)	-3.91 (-9.15 to 1.32, p=0.143)	-2.42 (-6.98 to 2.14, p=0.149)
Dementia	No	Mean (sd)	8.8 (15.9)	-	-
	Yes	Mean (sd)	14.6 (21.1)	5.88 (-3.71 to 15.47, p=0.229)	9.41 (1.34 to 17.47, p=0.011)