The Daily COVID-19 Literature Surveillance Summary

April 08, 2021

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COVID-19 Daily Literature Surveillance

COVID19LST

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LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".

Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

** OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson*

EXECUTIVE SUMMARY

Transmission & Prevention

- How effective have the vaccines been? A team from the United States Centers for Disease Control COVID-19 Response Team evaluated the effectiveness of messenger RNA (mRNA) COVID-19 vaccines against SARS-CoV-2 infection in a cohort of 3,950 health care personnel and other essential workers who underwent weekly SARS-CoV-2 testing for 13 consecutive weeks. They found vaccine effectiveness for prevention of infection was 90% for full immunization (0.04 infections per 1,000 person-days; ≥14 days after second dose) and 80% for partial immunization (0.19 infections per 1,000 person-days; ≥14 days after first dose and before second dose). The authors suggest mRNA vaccines effectively prevent SARS-CoV-2 infection and emphasize the importance of COVID-19 vaccination in all eligible individuals.

TABLE OF CONTENTS

QALYS FOR COVID-19: A COMPARISON OF US EQ-5D-5L VALUE SETS

Poteet S, Craig BM.. Patient. 2021 Mar 30. doi: 10.1007/s40271-021-00509-z. Online ahead of print.
Level of Evidence: 5 - Modeling

BLUF

Researchers from the Department of social science and economics at the University of Florida conducted a national questionnaire survey in November of 2020 with 1153 US adult participants to assess the quality-adjusted life-year (QALY) in COVID-19 patients using the EQ-5D-5L instrument and EQ-VAS decile to evaluate disease burden on the community. They used generalized linear analysis (GLM) with different models of analysis in both discounted/undiscounted future health outcomes and found that patients in the high-risk outcome group (Figure 1) with fever and at least one other symptom have a significant decrease of QALY ($p < 0.01$) (Table 2). The authors suggested that the evaluation of QALY in COVID-19 and the adverse effects of disease on the community need special considerations due to different characteristics (post-COVID syndrome) compared to other causes of pneumonia.

ABSTRACT

BACKGROUND: In economic evaluations, quality-adjusted life-years (QALYs) can serve as a unit of measurement for disease burden. Obtaining QALY values for COVID-19 presents a challenge owing to the availability of two US EQ-5D-5L value sets and the potentially asymptomatic presentation of the disease. The first value set was completed allowing for the discounting of future health outcomes while the second value set is undiscounted. OBJECTIVE: The objective of this study was to compare the distribution of QALY values using a national survey and the two published value sets; and to estimate the association between COVID-19 outcomes and QALY losses. METHODS: Between 9 and 11 November, 2020, 1153 US adults completed the EQ-5D-5L instrument (five items and a visual analog scale) as well as self-reported their demographics, COVID-19 symptoms, and memberships to populations that are at risk of COVID-19 infection. The two US value sets were applied to the EQ-5D-5L responses to produce QALY values. We estimated the mean QALYs by visual analog scale decile and a generalized linear model of COVID-19 outcomes. RESULTS: The discounted values are higher than the undiscounted values for each visual analog scale decile owing to methodological differences. Persons at increased risk, with a fever in the past day, and with one or more other symptoms have significantly greater QALY losses ($p < 0.01$). Overall, non-institutionalized individuals at risk of symptomatic clinical COVID-19 equal 0.68 for the 2016 value set (95% confidence interval 0.49-0.87) and 0.10 for the 2017 value set (95% confidence interval - 0.31 to 0.51) QALYs. CONCLUSIONS: Multiple studies have shown that decision makers discount future health outcomes, which increase QALY values. This study confronts the practical implications of these methodological advances for use in COVID-19 economic evaluations. Health economists will be able to use the QALY values in this study to better evaluate health interventions against COVID-19.

FIGURES

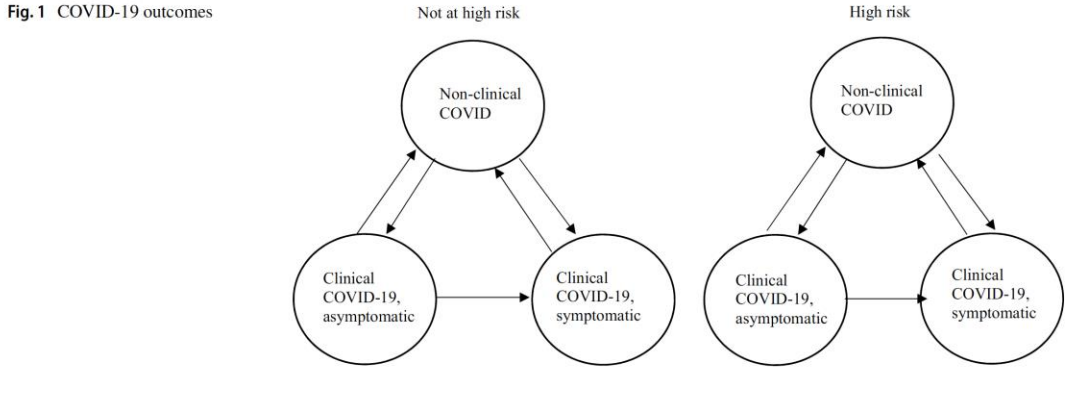


Figure 1. COVID-19 outcomes

Table 2 Generalized linear model analysis of ln QALY losses

	Discounted value set		Undiscounted value set	
	Craig and Rand [7]		Pickard et al. [8]	
	Model 1	Model 2	Model 3	Model 4
Demographic variables				
Female/other	− 0.11	0.12	− 0.06	0.09
Age adjusted	− 0.69***	− 0.38*	− 0.59***	− 0.31*
Age adjusted squared	− 0.28	− 0.17	− 0.12	− 0.03
Black	− 0.24	− 0.17	− 0.29**	− 0.21
Asian/other	− 0.29	0.14	− 0.29*	0.06
Hispanic	− 0.11	− 0.10	− 0.01	0.03
Health/risk variables				
At high risk		0.66***		0.55***
Clinical COVID-19		0.20		0.26
Fever		0.74***		0.61***
Cough		0.18		0.13
One or more symptoms		0.84***		0.79***
Constant term	− 2.81***	− 3.77***	− 1.65***	− 2.47***

QALY quality-adjusted life-year

Coefficients are reported in changes in ln QALY losses; the negative values on the coefficients (female, Hispanic) would correspond to higher QALYs; age adjusted = (age − 45)/45

*$p < 0.10$; **$p < 0.05$; ***$p < 0.01$

Table 2. Generalized linear model analysis of ln QALY losses

THE SPATIAL LANDSCAPE OF LUNG PATHOLOGY DURING COVID-19 PROGRESSION

Rendeiro AF, Ravichandran H, Bram Y, Chandar V, Kim J, Meydan C, Park J, Foox J, Hether T, Warren S, Kim Y, Reeves J, Salvatore S, Mason CE, Swanson EC, Borczuk AC, Elemento O, Schwartz RE.. Nature. 2021 Mar 29. doi: 10.1038/s41586-021-03475-6. Online ahead of print.
Level of Evidence: 3 - Cohort study or control arm of randomized trial

BLUF

A retrospective cohort study conducted at Weill Cornell Medicine by a group of pathologists and medical professionals to elucidate the spatial context, cellular composition, and interplay between immune and structural cell types during SARS-CoV-2 infection in the lung. Utilizing imaging mass cytometry, the authors examine postmortem lung tissue from a cohort of 23 individuals (Figure 1) who had COVID-19, other ARDS-causing lung infections, or were otherwise healthy. The study demonstrate that SARS-CoV-2 predominantly infects alveolar epithelial cells and induces a localized hyper-inflammatory cell state associated with lung damage ($p<0.05$) (Extended Data Figure 1), suggesting a potential therapeutic benefit of early immunological interventions that suppress excessive complement activation (Summary).

SUMMARY

- Spike alveolar epithelial cells cells do not differentially interact with cells of the immune system despite extensive immune filtration in the lung.

- Despite it's shared viral pathogenic origin with influenza, the expansion of mesenchymal cells and fibroblasts particularly seen in late COVID-19 likely reflects a response to the extensive tissue damage from complement activation.

- The high mortality rate of COVID-19 is at odds with productive recovery from tissue damage and healing, highlighting the need for further investigation into complement activation induced damage to the lung, and additional immunological factors such as microthrombi formation and neutrophil extracellular traps.

ABSTRACT

Recent studies have provided insights into the pathology and immune response to coronavirus disease 2019 (COVID-19)1-8. However, thorough interrogation of the interplay between infected cells and the immune system at sites of infection is lacking. We use high parameter imaging mass cytometry9 targeting the expression of 36 proteins, to investigate at single cell resolution, the cellular composition and spatial architecture of human acute lung injury including SARS-CoV-2. This spatially resolved, single-cell data unravels the disordered structure of the infected and injured lung alongside the distribution of extensive immune infiltration. Neutrophil and macrophage infiltration are hallmarks of bacterial pneumonia and COVID-19, respectively. We provide evidence that SARS-CoV-2 infects predominantly alveolar epithelial cells and induces a localized hyper-inflammatory cell state associated with lung damage. By leveraging the temporal range of COVID-19 severe fatal disease in relation to the time of symptom onset, we observe increased macrophage extravasation, mesenchymal cells, and fibroblasts abundance concomitant with increased proximity between these cell types as the disease progresses, possibly as an attempt to repair the damaged lung tissue. This spatially resolved single-cell data allowed us to develop a biologically interpretable landscape of lung pathology from a structural, immunological and clinical standpoint. This spatial single-cell landscape enabled the pathophysiological characterization of the human lung from its macroscopic presentation to the single-cell, providing an important basis for the understanding of COVID-19, and lung pathology in general.

FIGURES

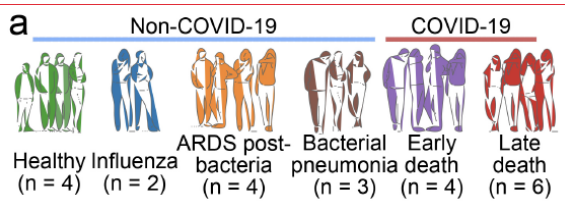
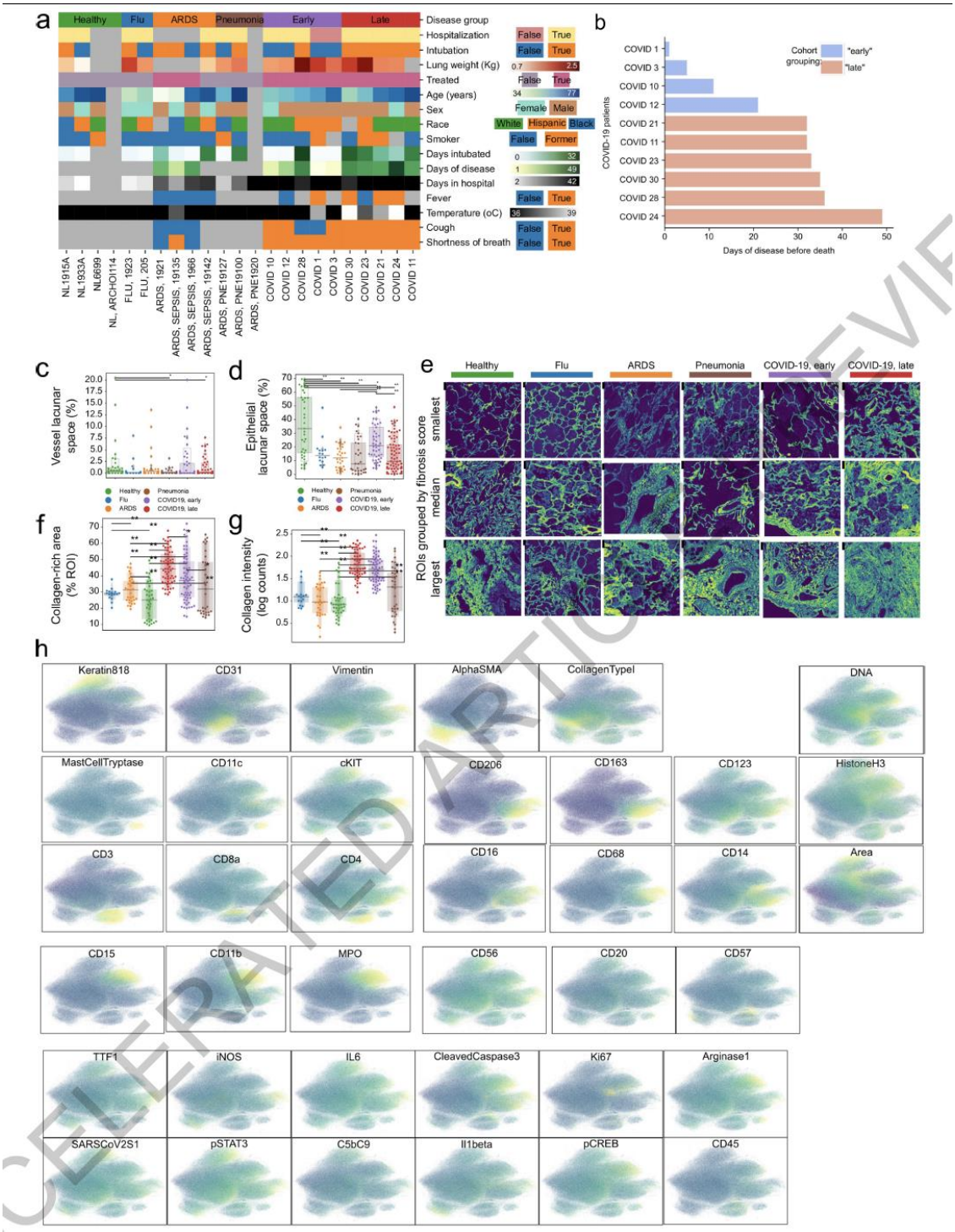


Figure 1a. Composition of lung infection cohort and schematic procedure to acquire highly multiplexed spatially resolved data with IMC from post-mortem lung samples.



Extended data Figure 1. a) Heatmap depicting the values of each individual for all acquired clinical and demographic variables. Grey color indicates missing or non-applicable values. b) Time of death relative to start of symptoms in COVID-19 patients. c-d) Percentage of lacunar space attributed to a) vessel or b) epithelial space per image grouped by disease. e) Collagen type I in images from lungs of healthy individuals, or lung pathology patients and the associated fibrosis score. Images with lowest, median and highest fibrosis scores are depicted. f) Percentage of image covered in Collagen type I for each image grouped by disease group. g) Mean intensity of Collagen type I in lung IMC images grouped by disease group. h) UMAP projection of all single-cells where cells are colored by the intensity of each channel. For panels c), d), f), and g): ** $p < 0.01$; * $p < 0.05$, two-sided Mann-Whitney U-test, pairwise between groups, Benjamini-Hochberg FDR adjustment.

INTERIM ESTIMATES OF VACCINE EFFECTIVENESS OF BNT162B2 AND MRNA-1273 COVID-19 VACCINES IN PREVENTING SARS-COV-2 INFECTION AMONG HEALTH CARE PERSONNEL, FIRST RESPONDERS, AND OTHER ESSENTIAL AND FRONTLINE WORKERS - EIGHT U.S. LOCATIONS, DECEMBER 2020-MARCH 2021

Thompson MG, Burgess JL, Naleway AL, Tyner HL, Yoon SK, Meece J, Olsho LEW, Caban-Martinez AJ, Fowlkes A, Lutrick K, Kuntz JL, Dunnigan K, Odean MJ, Hegmann KT, Stefanski E, Edwards LJ, Schaefer-Solle N, Grant L, Ellingson K, Groom HC, Zunie T, Thiese MS, Ivacic L, Wesley MG, Lamberte JM, Sun X, Smith ME, Phillips AL, Groover KD, Yoo YM, Gerald J, Brown RT, Herring MK, Joseph G, Beitel S, Morrill TC, Mak J, Rivers P, Harris KM, Hunt DR, Arvay ML, Kutty P, Fry AM, Gaglani M.. MMWR Morb Mortal Wkly Rep. 2021 Apr 2;70(13):495-500. doi: 10.15585/mmwr.mm7013e3.
Level of Evidence: 3 - Non-randomized controlled cohort/follow-up study

BLUF

A team from the United States Centers for Disease Control COVID-19 Response Team evaluated the effectiveness of messenger RNA (mRNA) COVID-19 vaccines against SARS-CoV-2 infection in a cohort of 3,950 health care personnel and other essential workers (see summary) who underwent weekly SARS-CoV-2 testing for 13 consecutive weeks (Table 1). They found vaccine effectiveness for prevention of infection was 90% for full immunization (0.04 infections per 1,000 person-days; ≥14 days after second dose) and 80% for partial immunization (0.19 infections per 1,000 person-days; ≥14 days after first dose and before second dose) (Table 2). The authors suggest mRNA vaccines effectively prevent SARS-CoV-2 infection and emphasize the importance of COVID-19 vaccination in all eligible individuals.

SUMMARY

All participants had no documented history of prior SARS-CoV-2 infection, with the following portion vaccinated:
- 2,479 (62.8%) received both mRNA doses (full immunization)
- 477 (12.1%) received one mRNA dose (partial immunization)
- 994 (25.2%) unvaccinated

Reverse transcription-polymerase chain reaction (RT-PCR) was used to confirm infection.

ABSTRACT

Messenger RNA (mRNA) BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) COVID-19 vaccines have been shown to be effective in preventing symptomatic COVID-19 in randomized placebo-controlled Phase III trials (1,2); however, the benefits of these vaccines for preventing asymptomatic and symptomatic SARS-CoV-2 (the virus that causes COVID-19) infection, particularly when administered in real-world conditions, is less well understood. Using prospective cohorts of health care personnel, first responders, and other essential and frontline workers* in eight U.S. locations during December 14, 2020-March 13, 2021, CDC routinely tested for SARS-CoV-2 infections every week regardless of symptom status and at the onset of symptoms consistent with COVID-19-associated illness. Among 3,950 participants with no previous laboratory documentation of SARS-CoV-2 infection, 2,479 (62.8%) received both recommended mRNA doses and 477 (12.1%) received only one dose of mRNA vaccine. Among unvaccinated participants, 1.38 SARS-CoV-2 infections were confirmed by reverse transcription-polymerase chain reaction (RT-PCR) per 1,000 person-days. In contrast, among fully immunized (>=14 days after second dose) persons, 0.04 infections per 1,000 person-days were reported, and among partially immunized (>=14 days after first dose and before second dose) persons, 0.19 infections per 1,000 person-days were reported. Estimated mRNA vaccine effectiveness for prevention of infection, adjusted for study site, was 90% for full immunization and 80% for partial immunization. These findings indicate that authorized mRNA COVID-19 vaccines are effective for preventing SARS-CoV-2 infection, regardless of symptom status, among working-age adults in real-world conditions. COVID-19 vaccination is recommended for all eligible persons.

FIGURES

TABLE 1. Characteristics of health care personnel, first responders, and other essential and frontline workers with reverse transcription–polymerase chain reaction (RT-PCR)–confirmed SARS-CoV-2 infections and percentage receiving one or more doses of a messenger RNA (mRNA) COVID-19 vaccine — eight U.S. locations, December 14, 2020–March 13, 2021

Characteristic	No. (column %) of participants	SARS-CoV-2 infection		Unvaccinated	Vaccinated with ≥1 dose*	
		No. (row %)	p-value†	No. (row %)	No. (row %)	p-value†
Total	**3,950 (100)**	**205 (5.2)**	—	**989 (25.0)**	**2,961 (75.0)**	—
Cohort location						
Phoenix, Arizona	555 (14.1)	39 (7.0§)	<0.001	147 (26.5)	408 (73.5)	<0.001
Tucson, Arizona	1,199 (30.4)	79 (6.6§)		325 (27.1)	874 (72.9)	
Other, Arizona	320 (8.1)	16 (5.0§)		88 (27.5)	232 (72.5)	
Miami, Florida	221 (5.6)	19 (8.6§)		118 (53.4)	103 (46.6¶)	
Duluth, Minnesota	448 (11.3)	12 (2.7)		47 (10.5)	401 (89.5¶)	
Portland, Oregon	468 (11.8)	4 (0.9)		61 (13.0)	407 (87.0¶)	
Temple, Texas	289 (7.3)	18 (6.2§)		71 (24.6)	218 (75.4)	
Salt Lake City, Utah	450 (11.4)	18 (4.0)		132 (29.3)	318 (70.7)	
Sex						
Female**	2,453 (62.1)	109 (4.4)	0.007	529 (21.6)	1,924 (78.4)	<0.001
Male	1,497 (37.9)	96 (6.4)		460 (30.7)	1,037 (69.3)	
Age group, yrs						
18–49	2,839 (71.9)	146 (5.1)	0.83	735 (25.9)	2,104 (74.1)	0.48
≥50	1,111 (28.1)	59 (5.3)		254 (22.9)	857 (77.1)	
Race						
White	3,408 (86.3)	178 (5.2)	0.92	814 (23.9)	2,594 (76.1)	<0.001
Other	542 (13.7)	27 (5.0)		175 (32.3)	367 (67.7)	
Ethnicity						
Hispanic/Latino	674 (17.1)	57 (8.5)	<0.001	236 (35.0)	438 (65.0)	<0.001
Other	3,276 (82.9)	148 (4.5)		753 (23.0)	2,523 (77.0)	
Occupation††						
Primary health care personnel	835 (21.1)	16 (1.9)	<0.001	65 (7.8)	770 (92.2)	<0.001
Other allied health care personnel	1,335 (33.8)	67 (5.0)		242 (18.1)	1,093 (81.9)	
First responder	852 (21.6)	75 (8.8)		308 (36.2)	544 (63.8)	
Other essential and frontline worker	928 (23.5)	47 (5.1)		374 (40.3)	554 (59.7)	
Chronic condition						
None§§	2,723 (68.9)	141 (5.2)	0.92	711 (26.1)	2,012 (73.9)	0.11
≥1	1,227 (31.1)	64 (5.2)		278 (22.7)	949 (77.3)	

* Total vaccinated includes 477 participants who received one mRNA vaccine dose, 2,479 who received two mRNA vaccine doses, and five who received a single dose of the Janssen COVID-19 vaccine (Johnson & Johnson); these five participants contribute unvaccinated person-days until their vaccination date and then no longer contribute to the analysis.

† P-values (comparing the percentage of SARS-CoV-2 infections by sociodemographic and health categories and comparing the percentage vaccinated by these categories) calculated using Pearson's chi-square test (cells with ≥5 observations) or Fisher's exact test (cells with <5 observations).

§ Sites identified had statistically higher percentages of participants with RT-PCR-confirmed SARS-CoV-2 infections than the other sites (chi-square = 31.0, p-value <0.001).

¶ The Minnesota and Oregon sites had the statistically highest percentage vaccinated with at least one vaccine dose. Florida had the lowest (chi-square = 62.1, p-value <0.001).

** 10 participants were missing biologic sex and were imputed as the more common category (female).

†† Occupational categories: primary health care personnel (physicians, physician assistants, nurse practitioners, and dentists), other allied health care personnel (nurses, therapists, technicians, medical assistants, orderlies, and all other persons providing clinical support in inpatient or outpatient settings), first responders (firefighters, law enforcement, corrections, and emergency medical technicians), other essential and frontline workers (workers in hospitality, delivery, and retail; teachers; and all other occupations that require contact within 3 feet of the public, customers, or coworkers as a routine part of their job).

§§ 133 participants who did not respond to the self-report question were imputed as "none."

TABLE 2. Person-days, SARS-CoV-2 infections, and vaccine effectiveness among health care personnel, first responders, and other essential and frontline workers, by messenger RNA immunization status — eight U.S. locations, December 14, 2020–March 13, 2021

COVID-19 immunization status	Person-days	SARS-CoV-2 infections		Unadjusted vaccine effectiveness*	Adjusted vaccine effectiveness*,†
		No.	Incidence rate per 1,000 person-days	% (95% CI)	% (95% CI)
Unvaccinated	116,657	161	1.38	N/A	N/A
Partially immunized	41,856	8	0.19	82 (62–91)	80 (59–90)
≥14 days after receiving first dose only§	15,868	5	0.32		
≥14 days after first dose through receipt of second dose	25,988	3	0.12		
Fully immunized					
≥14 days after second dose	78,902	3	0.04	91 (73–97)	90 (68–97)

Abbreviations: CI = confidence interval; N/A = not applicable.

* Vaccine effectiveness was estimated using a Cox proportional hazards model accounting for time-varying immunization status.

† Hazard ratio is adjusted for study site.

§ Participants received first dose but had not received second dose by the end of the study period.

VACCINATION AGAINST SARS-COV-2 AND PSORIASIS: THE THREE THINGS EVERY DERMATOLOGIST SHOULD KNOW

Diotallevi F, Campanati A, Radi G, Martina E, Rizzetto G, Barbadoro P, D'Errico MM, Offidani A.. J Eur Acad Dermatol Venereol. 2021 Mar 29. doi: 10.1111/jdv.17256. Online ahead of print.
Level of Evidence: 5 - Opinion

BLUF

Dermatologists from the Polytechnic University of the Marche Region in Italy review COVID-19 vaccination in the context of psoriasis. Since the pathophysiologies of both COVID-19 and psoriatic disease involve angiotensin-converting enzyme, authors suggest patients with psoriasis may be at higher risk for poor outcomes in COVID-19. Though vaccine efficacy in this population is unknown, authors strongly recommend use of the SARS-CoV-2 vaccine in patients with psoriatic disease due to the positive risk-benefit ratio.

ABSTRACT

Currently there are two vaccines already authorized from FDA and EMA for Emergency Use (1). They are the BNT162b2 and the mRNA-1273, respectively produced by Pfizer/BioNTech and Moderna (Tab.1). Both vaccines consist of nucleic acid, mRNA able to induce our human cells to use protein factories to make the antigen (viral spike protein) that will trigger an immune response.

CRITICAL CARE

EFFECT OF TIMING OF INTUBATION ON CLINICAL OUTCOMES OF CRITICALLY ILL PATIENTS WITH COVID-19: A SYSTEMATIC REVIEW AND META-ANALYSIS OF NON-RANDOMIZED COHORT STUDIES

Papoutsi E, Giannakoulis VG, Xourgia E, Routsi C, Kotanidou A, Siempos II.. Crit Care. 2021 Mar 25;25(1):121. doi: 10.1186/s13054-021-03540-6.
Level of Evidence: 1 - Systematic review of randomized trials or n-of-1 trials

BLUF

A meta-analysis of 12 cohort studies (PRISMA, Fig. 1) published through December 2020 (n=8944 COVID-19 critically ill patients) conducted by intensivists and pulmonologists of National and Kapodistrian University of Athens Medical School, investigated the relationship between early versus late intubation of COVID-19 patients (less or more than 24 hours of ICU admission respectively) on primary (all-cause mortality and duration of mechanical ventilation) and secondary (ICU length of stay and a need for renal replacement therapy) outcomes. No relationship between early intubation and decrease in overall morbidity or mortality was found, suggesting that the watch and see approach could be more appreciable for the management of COVID-19 patients.

SUMMARY

Primary outcomes:
1-No relationship between all-cause mortality rate and early versus late intubation (3981 deaths; 95% CI 0.99–1.15, p = 0.08), (Fig. 2).
2-Duration of mechanical ventilation is not related to early or late intubation, in 6 studies that provided data (1892 patients; 95% CI − 3.06 to 1.89 days, p = 0.65) (Fig. 3).

Secondary outcomes:
1-No difference in ICU length of stay in two groups in 5 studies evaluated
(433 patients; 95% CI − 6.05 to 2.38 days, p = 0.39).
2-No difference between two groups in renal replacement therapy (p = 0.75).

ABSTRACT

BACKGROUND: Although several international guidelines recommend early over late intubation of patients with severe coronavirus disease 2019 (COVID-19), this issue is still controversial. We aimed to investigate the effect (if any) of timing of intubation on clinical outcomes of critically ill patients with COVID-19 by carrying out a systematic review and meta-analysis. METHODS: PubMed and Scopus were systematically searched, while references and preprint servers were explored, for relevant articles up to December 26, 2020, to identify studies which reported on mortality and/or morbidity of patients with COVID-19 undergoing early versus late intubation. "Early" was defined as intubation within 24 h from intensive care unit (ICU) admission, while "late" as intubation at any time after 24 h of ICU admission. All-cause mortality and duration of mechanical ventilation (MV) were the primary outcomes of the meta-analysis. Pooled risk ratio (RR), pooled mean difference (MD) and 95% confidence intervals (CI) were calculated using a random effects model. The meta-analysis was registered with PROSPERO (CRD42020222147). RESULTS: A total of 12 studies, involving 8944 critically ill patients with COVID-19, were included. There was no statistically detectable difference on all-cause mortality between patients undergoing early versus late intubation (3981 deaths; 45.4% versus 39.1%; RR 1.07, 95% CI 0.99-1.15, p = 0.08). This was also the case for duration of MV (1892 patients; MD - 0.58 days, 95% CI - 3.06 to 1.89 days, p = 0.65). In a sensitivity analysis using an alternate definition of early/late intubation, intubation without versus with a prior trial of high-flow nasal cannula or noninvasive mechanical ventilation was still not associated with a statistically detectable difference on all-cause mortality (1128 deaths; 48.9% versus 42.5%; RR 1.11, 95% CI 0.99-1.25, p = 0.08). CONCLUSIONS: The synthesized evidence suggests that timing of intubation may have no effect on mortality and morbidity of critically ill patients with COVID-19. These results might justify a wait-and-see approach, which may lead to fewer intubations. Relevant guidelines may therefore need to be updated.

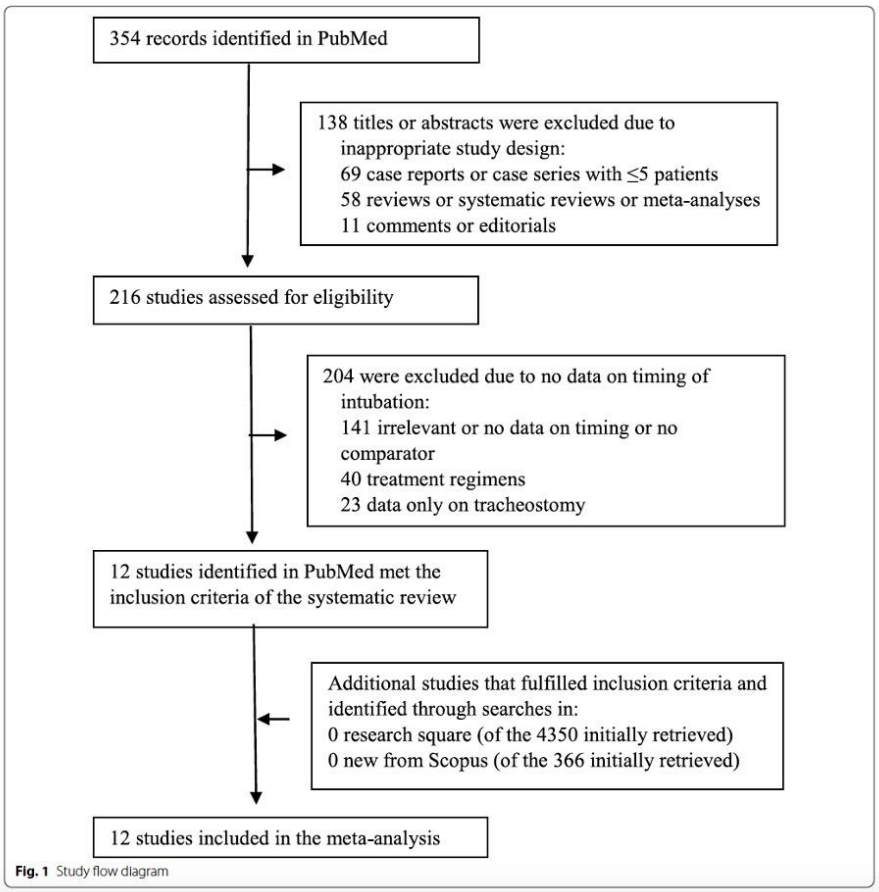


Fig. 1 Study flow diagram

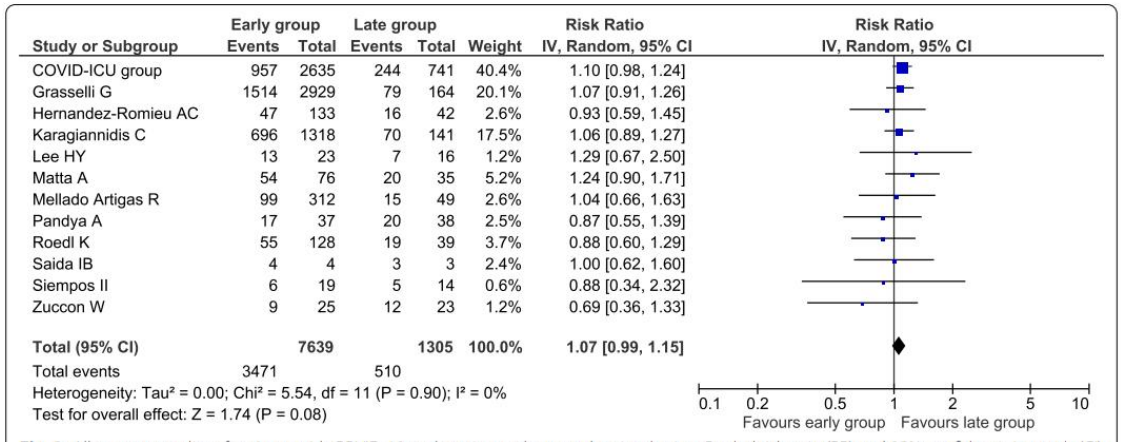


Fig. 2 All-cause mortality of patients with COVID-19 undergoing early versus late intubation. Pooled risk ratio (RR) and 95% confidence intervals (CI) were calculated using a random effects model

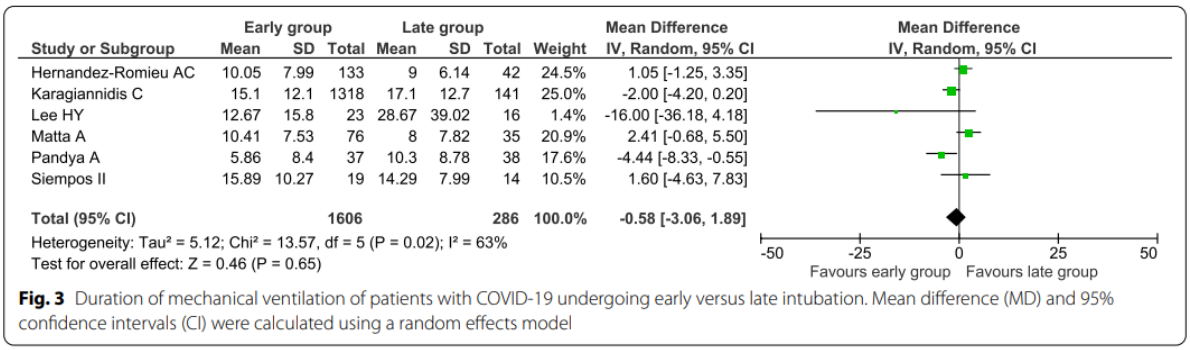


Fig. 3 Duration of mechanical ventilation of patients with COVID-19 undergoing early versus late intubation. Mean difference (MD) and 95% confidence intervals (CI) were calculated using a random effects model

BISPECIFIC IGG NEUTRALIZES SARS-COV-2 VARIANTS AND PREVENTS ESCAPE IN MICE

De Gasparo R, Pedotti M, Simonelli L, Nickl P, Muecksch F, Cassaniti I, Percivalle E, Lorenzi JCC, Mazzola F, Magrì D, Michalcikova T, Haviernik J, Honig V, Mrazkova B, Polakova N, Fortova A, Tureckova J, Iatsiuk V, Di Girolamo S, Palus M, Zudova D, Bednar P, Bukova I, Bianchini F, Mehn D, Nencka R, Strakova P, Pavlis O, Rozman J, Gioria S, Sammartino JC, Giardina F, Gaiarsa S, Pan-Hammarström Q, Barnes CO, Bjorkman PJ, Calzolai L, Piralla A, Baldanti F, Nussenzweig MC, Bieniasz PD, Hatziioannou T, Prochazka J, Sedlacek R, Robbiani DF, Ruzek D, Varani L.. Nature. 2021 Mar 25. doi: 10.1038/s41586-021-03461-y. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Biology researchers from Italy, the Czech Republic, United States, and Switzerland developed a new monoclonal antibody (mAb: CoV-X2) by combining two important convalescent COVID-19 patients' antibodies (C121 and C135 IgG against RBD) to increase the efficacy against SARS-CoV-2 infection and limit the viral potency of mutation during treatment with mAb. They tested CoV-X2 with the computational model against different viral variants, showing more effectiveness in neutralizing and inhibition of virus escape compared with its parent antibodies alone (Figure 1). Researchers then conducted an animal study that reported infected mice that received CoV-X2 had lower viral RNA burden and weight loss during the follow up ($P<0.0001$), (Figure 2). This study suggests that treatment with a bispecific mAb (COV-X2) may be more effective and decrease the severity of COVID-19 infection.

ABSTRACT

Neutralizing antibodies targeting the receptor binding domain (RBD) of the SARS-CoV-2 Spike (S) are among the most promising approaches against coronavirus disease 2019 (COVID-19)1,2. We developed a bispecific, IgG1-like molecule (CoV-X2) based on two antibodies derived from COVID-19 convalescent donors, C121 and C1353. CoV-X2 simultaneously binds two independent sites on the RBD and, unlike its parental antibodies, prevents detectable S binding to Angiotensin-Converting Enzyme 2 (ACE2), the virus cellular receptor. Furthermore, CoV-X2 neutralizes SARS-CoV-2 and its variants of concern, as well as the escape mutants generated by the parental monoclonals. In a novel animal model of SARS-CoV-2 infection with lung inflammation, CoV-X2 protects mice from disease and suppresses viral escape. Thus, simultaneous targeting of non-overlapping RBD epitopes by IgG-like bispecific antibodies is feasible and effective, combining into a single molecule the advantages of antibody cocktails.

FIGURES

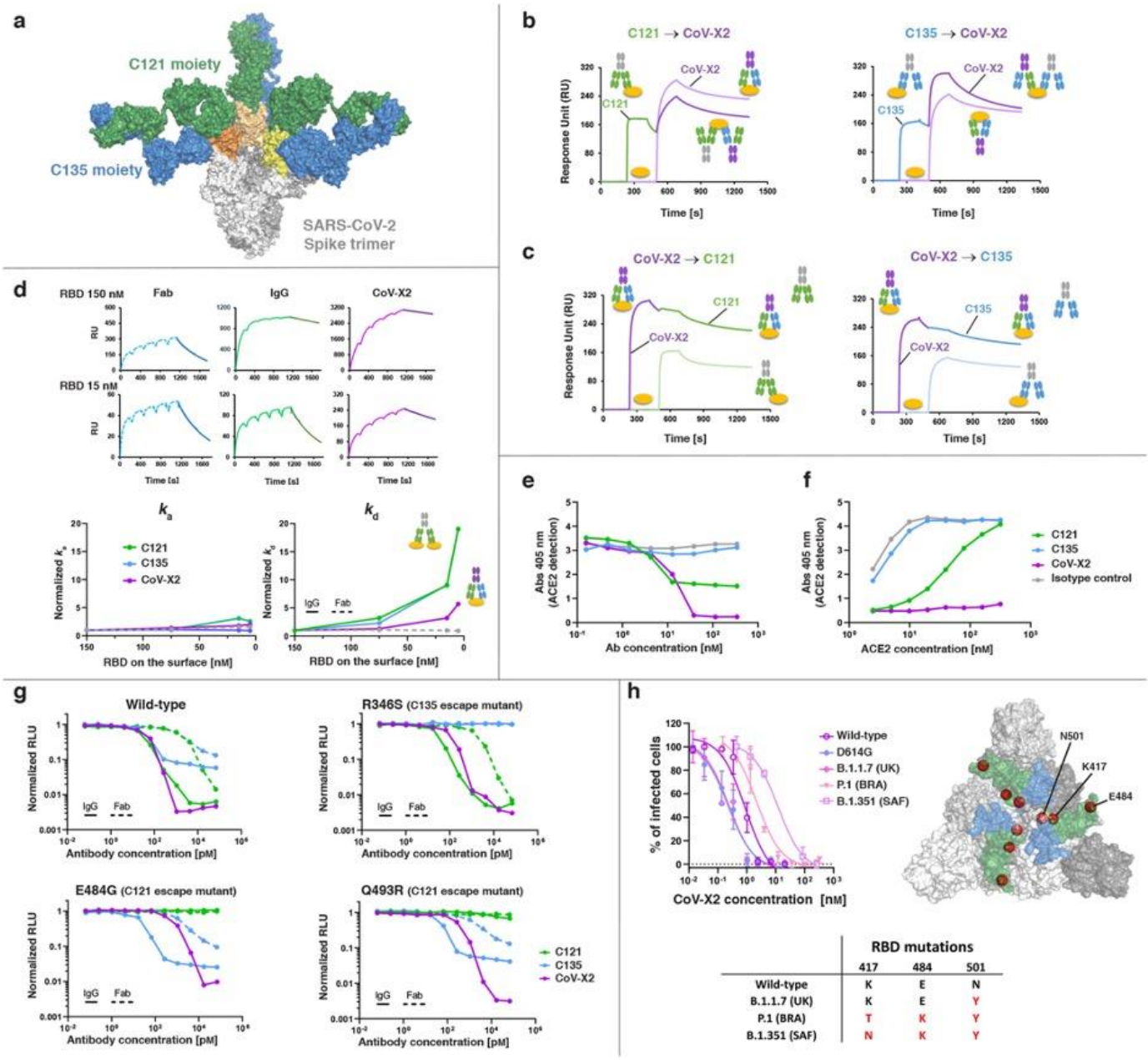


Figure 1 | Biochemical and in vitro neutralizing properties of CoV-X2 are superior to its parental mAbs.

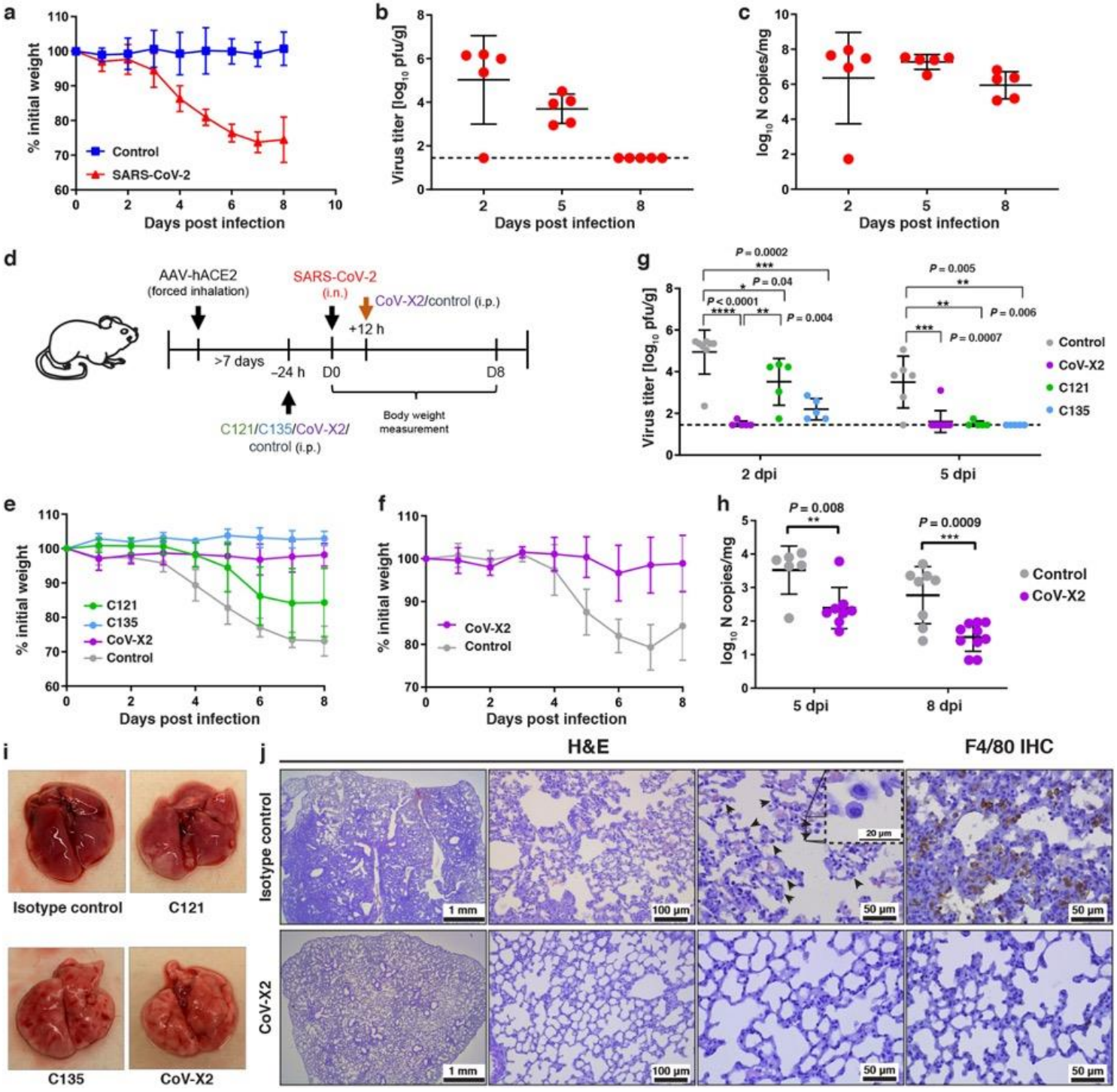


Figure 2 | CoV-X2 protects AAV-hACE2-transduced mice against SARS-CoV-2 disease.

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CONTRIBUTORS

Michael Wang
Nicolas Longobardi
Reza Aghaei
Zainab Awan

EDITORS

Julia Ghering
Maresa Woodfield

SENIOR EDITORS

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