

The Weekly COVID-19 Literature Surveillance Summary

May 28, 2021



DISCLAIMER

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COVID-19 Daily Literature Surveillance

COVID19LST



Bringing you real time, distilled information for guiding best practices during the COVID-19 pandemic

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

Epidemiology

- [The incubation period during the pandemic of COVID-19: a systematic review and meta-analysis](#): Epidemiology experts from University of Sousse, Tunisia conducted a systematic review and meta-analysis of 42 studies to determine the incubation period of COVID-19. Mean and median incubation periods were 8 days and 12 days respectively, and pooled mean incubation period was determined to be 6.2 days (95% CI 5.4, 7.0) which may vary due to moderator variables such as population, severity, sex-ratio, study quality, and method of calculation. However, the 99th percentile of incubation time was 20.4 days, suggesting that a 14-day quarantine may not be sufficient to protect against the spread of COVID-19.
- [Prevalence and Mortality due to COVID-19 in HIV Co-Infected Population: A Systematic Review and Meta-Analysis](#): A systematic review and meta-analysis conducted by researchers affiliated with Maoming People's Hospital and Southern Medical University in China included 14 studies and found a prevalence of 0.774% and mortality rate of 8.814% of COVID-19 infection among people living with HIV/acquired immunodeficiency syndrome (PLWHA), however there was no association of increased mortality among PLWHA with COVID-19 compared to non-PLWHA (RR 0.96, 95% CI, 0.88-1.06). Increased mortality was found in PLWHA with the presence of comorbidities including DM (RR 5.2, 95% CI, 4.25-6.36), HTN and chronic cardiac disease (RR 4.2, 95% CI 1.09-16.10), and CKD (RR 8.43, 95% CI 5.49-12.93). These findings suggest the need for follow-up studies to investigate HIV viral load, CD4 count, and antiretroviral therapy in relation to COVID-19 outcomes.

Transmission & Prevention

- [Effectiveness of mRNA COVID-19 vaccines against SARS-CoV-2 infection in a cohort of healthcare personnel](#): A team of multidisciplinary researchers associated with Mayo Clinic and University of Minnesota conducted a retrospective study on 45,162 healthcare personnel (HCP) to analyze the effectiveness of Pfizer and Moderna mRNA SARS-CoV-2 vaccines. During the study period 1,125 HCP tested positive for SARS-CoV-2, and vaccine effectiveness was determined to be 78% for partial vaccination and 96% for complete vaccination after adjusting for age, gender, region, job, and week of vaccination. These results suggest the high effectiveness of the Pfizer and Moderna vaccines and the importance of bringing widespread immunity to SARS-CoV-2.
- [SARS-CoV-2 Infection after Vaccination in Health Care Workers in California](#): In a letter to the editor, researchers associated with UCSD and UCLA health systems discuss SARS-CoV-2 infection rates in vaccinated healthcare workers in California. 36,659 healthcare workers received the first vaccine dose, 28,184 received the second dose, and 379 vaccinated healthcare workers tested positive at least 1 day after vaccination. Vaccinated healthcare workers at UCSD had a 1.19% absolute risk of testing positive for SARS-CoV-2, while those at UCLA had a 0.97% risk. These results suggest the high efficacy of the Pfizer and Moderna vaccines.

Management

- [Pulmonary function and radiological features 4 months after COVID-19: first results from the national prospective observational Swiss COVID-19 lung study](#): A multicenter prospective observational cohort study conducted by researchers from multiple medical institutions in Switzerland enrolled 113 individuals diagnosed with COVID-19 between May 1 - September 15, 2020 and monitored respiratory outcomes 4 months later. Patients who had severe/critical COVID-19 had significantly lower TLC, FVC, FEV1, and DLCO compared to those with mild/moderate disease, and patients with severe/critical COVID-19 were more likely to have mosaic attenuation pattern with hypo-attenuated areas (66% versus 13%, p=0.007), reticulations (59% versus 13%, p=0.02), and architectural distortion (52% versus 13%, p=0.055). DLCO was the strongest independent factor associated with previous severe/critical disease, suggesting that systematic follow-up of pulmonary function is essential for patients who recover from severe and critical COVID-19 and DLCO is the single most important factor at 4-month follow-up.

R&D: Diagnosis & Treatments

- [Clinical Outcomes Associated With Methylprednisolone in Mechanically Ventilated Patients With COVID-19](#): A case-control study conducted by pharmacy, infectious disease, and pulmonary specialists from Columbia University Irving Medical Center on 117 mechanically ventilated COVID-19 patients, where the experimental group (n = 48) received methylprednisolone within 14 days of admission showed that the methylprednisolone group had significantly higher ventilator-free days ($p = 0.044$) and probability of extubation by day 28 ($p = 0.087$) compared to the control group. Overall, these results indicate the effectiveness of corticosteroid treatment in severe COVID-19 patients requiring mechanical ventilation.

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EPIDEMIOLOGY

SYMPTOMS AND CLINICAL PRESENTATION

THE INCUBATION PERIOD DURING THE PANDEMIC OF COVID-19: A SYSTEMATIC REVIEW AND META-ANALYSIS

Dhouib W, Maatoug J, Ayouni I, Zammit N, Ghammem R, Fredj SB, Ghannem H.. Syst Rev. 2021 Apr 8;10(1):101. doi: 10.1186/s13643-021-01648-y.

Level of Evidence: 2 - Systematic review of surveys that allow matching to local circumstances

BLUF

Epidemiology experts from University of Sousse, Tunisia conducted a systematic review and meta-analysis of 42 studies to determine the incubation period of COVID-19 (Figure 3). Mean and median incubation periods were 8 days and 12 days respectively, and pooled mean incubation period was determined to be 6.2 days (95% CI 5.4, 7.0) which may vary due to moderator variables such as population, severity, sex-ratio, study quality, and method of calculation (Table 4). However, the 99th percentile of incubation time was 20.4 days, suggesting that a 14-day quarantine may not be sufficient to protect against the spread of COVID-19.

SUMMARY

- Incubation period was significantly shorter in patients who had multiple COVID-19 exposures in the same province compared to those who had a travel history, suggesting that direct transmission was due to a higher infecting dose, leading to a shorter incubation period.

ABSTRACT

BACKGROUND: The aim of our study was to determine through a systematic review and meta-analysis the incubation period of COVID-19. It was conducted based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA). Criteria for eligibility were all published population-based primary literature in PubMed interface and the Science Direct, dealing with incubation period of COVID-19, written in English, since December 2019 to December 2020. We estimated the mean of the incubation period using meta-analysis, taking into account between-study heterogeneity, and the analysis with moderator variables. **RESULTS:** This review included 42 studies done predominantly in China. The mean and median incubation period were of maximum 8 days and 12 days respectively. In various parametric models, the 95th percentiles were in the range 10.3-16 days. The highest 99th percentile would be as long as 20.4 days. Out of the 10 included studies in the meta-analysis, 8 were conducted in China, 1 in Singapore, and 1 in Argentina. The pooled mean incubation period was 6.2 (95% CI 5.4, 7.0) days. The heterogeneity (I^2 77.1%; $p < 0.001$) was decreased when we included the study quality and the method of calculation used as moderator variables (I^2 0%). The mean incubation period ranged from 5.2 (95% CI 4.4 to 5.9) to 6.65 days (95% CI 6.0 to 7.2). **CONCLUSIONS:** This work provides additional evidence of incubation period for COVID-19 and showed that it is prudent not to dismiss the possibility of incubation periods up to 14 days at this stage of the epidemic.

FIGURES

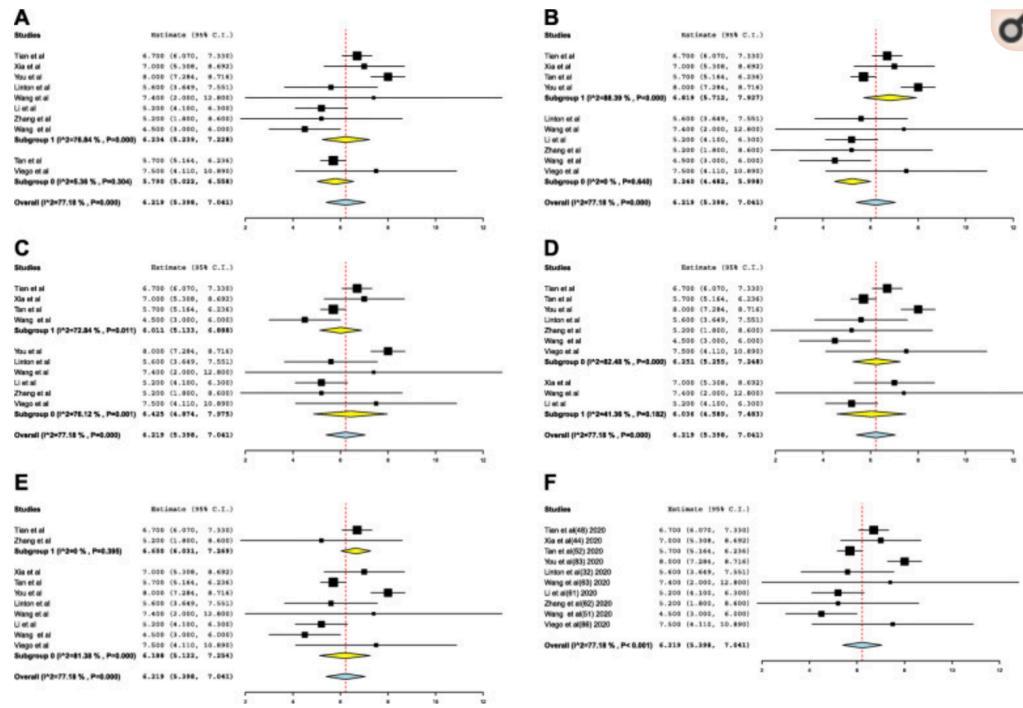


Figure 3. Forest-plot for mean incubation period in days

Table 4

Estimation of days of incubation with moderator variables

	Estimate	SE	95% CI	p-value
Intercept	6.219	0.419	(5.398; 7.041)	< 0.001
Population				
Chinese	6.234	0.507	(5.239; 7.228)	< 0.001
Not Chinese	5.790	0.392	(5.022; 6.558)	< 0.001
Severity				
Hospitalized	6.011	0.448	(5.133; 6.888)	< 0.001
Not hospitalized	6.425	0.791	(4.874; 7.975)	< 0.001
Sex ratio				
>1	6.036	0.738	(4.589; 7.483)	< 0.001
<1	5.805	0.435	(4.952; 6.659)	< 0.001
Quality of study				
Strong	6.650	0.316	(6.031; 7.269)	< 0.001
Moderate to weak	6.188	0.419	(5.122; 7.254)	< 0.001

CI confidence interval, SE standard error

Table 4. Estimation of days of incubation with moderator variables

THE RELATIONSHIP BETWEEN SMOKING AND COVID-19 PROGRESSION

Yue L, Zhang R, Duan G.. Nicotine Tob Res. 2021 May 4;23(5):880-881. doi: 10.1093/ntr/ntaa245.

Level of Evidence: 5 - Expert Opinion

BLUF

Epidemiologists affiliated with the College of Public Health at Zhengzhou University and Hainan Medical University in China present a letter to the editor responding to a published systematic review and meta analysis that concluded smoking was a risk factor for COVID-19 progression, alleging that some included studies failed to properly delineate never-smokers from current non-smokers. They also discuss how the inclusion of retrospective studies and case series reports could adversely increase the heterogeneity of the study. They conclude that caution should be taken in interpreting the results of this particular study.

ADULTS

PREVALENCE AND MORTALITY DUE TO COVID-19 IN HIV CO-INFECTED POPULATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

Liang M, Luo N, Chen M, Chen C, Singh S, Singh S, Tan S.. Infect Dis Ther. 2021 May 3. doi: 10.1007/s40121-021-00447-1. Online ahead of print.

Level of Evidence: 2 - Systematic review of surveys that allow matching to local circumstances

BLUF

A systematic review and meta-analysis conducted by researchers affiliated with Maoming People's Hospital and Southern Medical University in China included 14 studies (Figure 1) and found a prevalence of 0.774% and mortality rate of 8.814% of COVID-19 infection among people living with HIV/acquired immunodeficiency syndrome (PLWHA), however there was no association of increased mortality among PLWHA with COVID-19 compared to non-PLWHA (RR 0.96, 95% CI, 0.88-1.06) (Figure 4). Increased mortality was found in PLWHA with the presence of comorbidities including DM (RR 5.2, 95% CI, 4.25-6.36), HTN and chronic cardiac disease (RR 4.2, 95% CI 1.09-16.10), and CKD (RR 8.43, 95% CI 5.49-12.93) (Figure 5). These findings suggest the need for follow-up studies to investigate HIV viral load, CD4 count, and antiretroviral therapy in relation to COVID-19 outcomes.

ABSTRACT

INTRODUCTION: The coronavirus disease 2019 (COVID-19) was defined as a species of beta coronavirus causing atypical respiratory disease in humans. The COVID-19 pandemic has resulted in an unprecedented health and economic crisis worldwide. Little is known about the specifics of its influence on people living with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) (PLWHA). In this study, we aim to investigate the prevalence and mortality in PLWHA co-infected with COVID-19. **METHODS:** The databases PUBMED, EMBASE, BioRxiv, and medRxiv were searched up to 9 March 2021 to explore the prevalence and mortality rate of COVID-19 in PLWHA. Cohort studies and case series meeting the inclusion criteria were included in this review. **RESULTS:** We identified 14 eligible studies, 9 of which were cohort and 5 were case series. A total of 203,761 patients with COVID-19 were identified (7718 PLWHA vs. 196,043 non-PLWHA). Meta-analyses estimated the prevalence and mortality rate of COVID-19 in PLWHA was 0.774% [95% confidence interval (CI) 0.00393-0.01517] and 8.814% (95% CI 0.05766-0.13245) respectively. COVID-19 co-infected PLWHA do not seem to be associated with higher mortality, as compared to non-PLWHA [relative risk (RR) 0.96 (95% CI 0.88-1.06)]. The presence of comorbidities such as diabetes mellitus, RR 5.2 (95% CI 4.25-6.36), hypertension and chronic cardiac disease, RR 4.2 (95% CI 1.09-16.10), and chronic kidney disease, RR 8.43 (95% CI 5.49-12.93) were associated with an increased mortality in COVID-19 co-infected PLWHA. **CONCLUSION:** The estimated prevalence and mortality rate of COVID-19 in PLWHA were 0.774% and 8.814%, respectively. Since most of the included studies used unmatched populations, comparisons between PLWHA and non-PLWHA should be interpreted with caution. Further investigations are needed for a more comprehensive understanding of the relationship between cluster of differentiation 4 cell count, HIV viral load, antiretroviral therapy, and COVID-19 related prognosis in PLWHA.

FIGURES

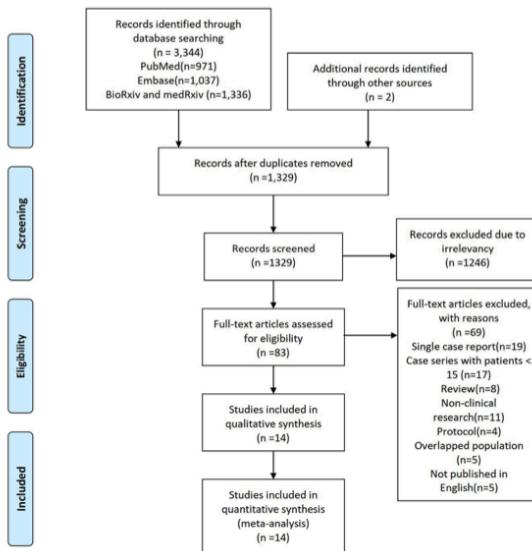


Figure 1. PRISMA flowchart of literature search and study selection

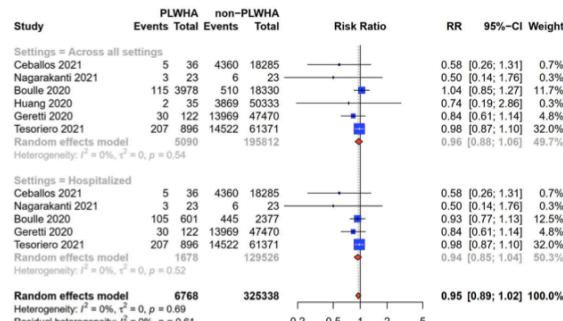


Figure 4. Comparison mortality between PLWHA and non-PLWHA due to COVID-19

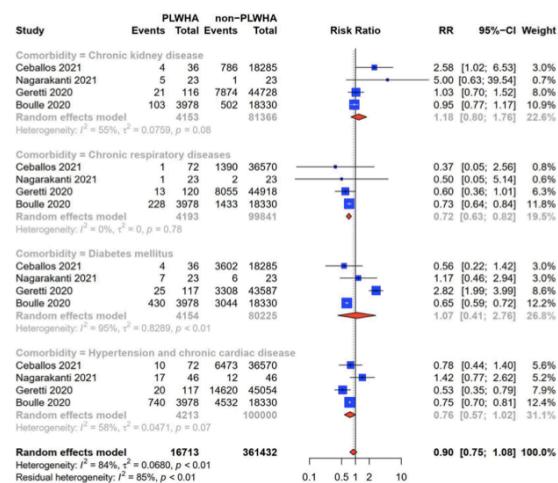


Figure 5. Comparison of comorbidity in the risk of COVID-19 co-infection between PLWHA and non-PLWHA

UNDERSTANDING THE PATHOLOGY

COILED-COIL HETERODIMERS WITH INCREASED STABILITY FOR CELLULAR REGULATION AND SENSING SARS-COV-2 SPIKE PROTEIN-MEDIATED CELL FUSION

Plaper T, Aupič J, Dekleva P, Lapenta F, Keber MM, Jerala R, Benčina M.. Sci Rep. 2021 Apr 28;11(1):9136. doi: 10.1038/s41598-021-88315-3.

Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Researchers affiliated with the National Institute of Chemistry, EN-FIST Centre of Excellence and the University of Ljubljana in Slovenia designed a model involving coiled-coil (CCs) dimer-forming peptides with increased stability and ability to regulate enzyme activity and transcriptional activation while also being able to fine-tune the affinity of the interaction (Figure 1). Orthogonal parallel heterodimeric coiled-coil (CCs) dimer-forming peptides were used to develop a fast assay to monitor the SARS-CoV-2 spike-protein-mediated cell-cell fusion (Figure 5) and were able to validate how the S-protein protease is essential for processing and binding to the ACE2 receptor for viral entry (Figure 6). This model allows for testing/determination of potential drugs that could inhibit the viral entry process to prevent viral infection and are valuable for investigation and regulation of many biological processes beyond SARS-CoV-2.

ABSTRACT

Coiled-coil (CC) dimer-forming peptides are attractive designable modules for mediating protein association. Highly stable CCs are desired for biological activity regulation and assay. Here, we report the design and versatile applications of orthogonal CC dimer-forming peptides with a dissociation constant in the low nanomolar range. In vitro stability and specificity was confirmed in mammalian cells by enzyme reconstitution, transcriptional activation using a combination of DNA-binding and a transcriptional activation domain, and cellular-enzyme-activity regulation based on externally-added peptides. In addition to cellular regulation, coiled-coil-mediated reporter reconstitution was used for the detection of cell fusion mediated by the interaction between the spike protein of pandemic SARS-CoV2 and the ACE2 receptor. This assay can be used to investigate the mechanism of viral spike protein-mediated fusion or screening for viral inhibitors under biosafety level 1 conditions.

FIGURES

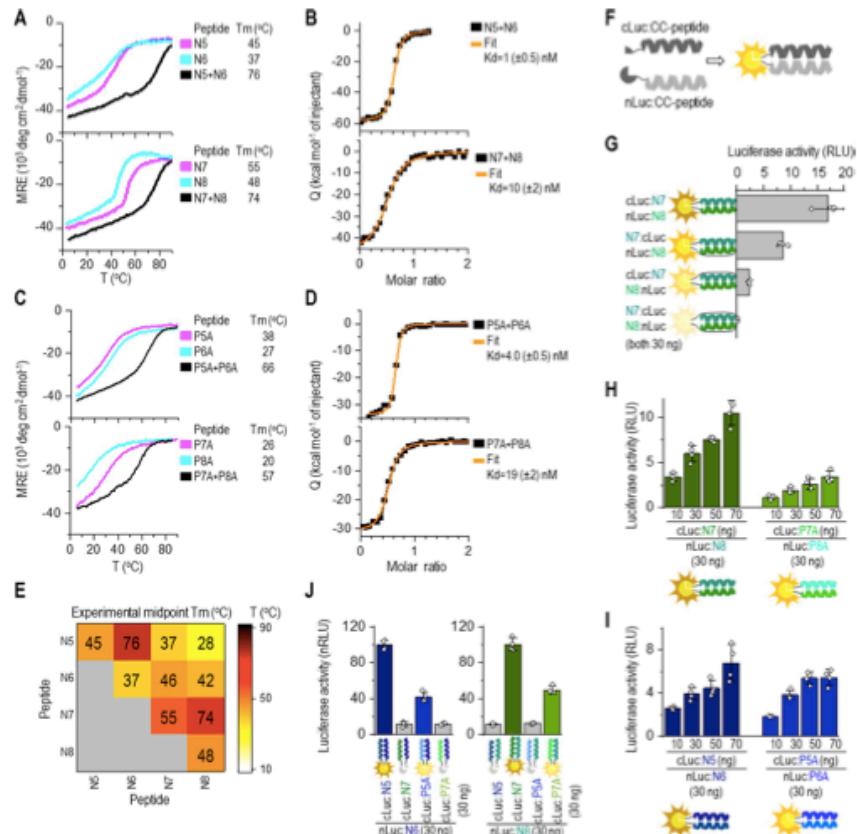


Figure 1. Orthogonal CC peptide pairs with Kd in the nanomolar range based on modifications at the b, c, and f sites. (A, C) Thermal denaturation profiles of peptides (40 μ M; magenta and cyan) and CCs (20 μ M each peptide; black) monitored by a CD signal at 222 nm. The midpoint Tm was calculated based on thermodynamic model fit35. (B, D) Isothermal titration calorimetry (ITC) analysis of the binding affinity of designated CC peptide pairs. The binding isotherms of heat release per injection are depicted as a function of the increasing peptide-to-peptide molar ratio. The dissociation constant, KdITC, was calculated using the two-state dimer association model. (E) Heat map of the matrix of the calculated midpoint Tm from thermal denaturation scans of all peptide combinations. (F) Scheme of reconstitution of CC-split luciferase managed by a CC-forming peptide pair. (G) Luciferase activity of reconstituted CC-split luciferase in HEK293T measured 48 h after transfection of HEK293T cells with a plasmid expressing a combination of nLuc tethered to N8 (30 ng) and cLuc tethered to N7 peptide (30 ng). (H, I) Luciferase activity determined 48 h after transformation of HEK293T cells with plasmids expressing nLuc:N8 or nLuc:N6 (30 ng); and cLuc tethered to N7 or P7A or cLuc tethered to N5 and P5A (10–70 ng). (J) Orthogonality of designed N peptide set in HEK293T cells by co-transfection of the nLuc:N8 or nLuc:N6 fusion encoding plasmid (30 ng), and cLuc:CC (CC stands for N5, P5A, N7, P7A) (30 ng). Reconstituted luciferase activity was measured 48 h after transfection. Amounts of plasmids are indicated in Table S2. The values (G–J) represent the means (\pm s.d.) from four independent cell cultures, individually transfected with the same mixture of plasmids, and are representative of two independent experiments.

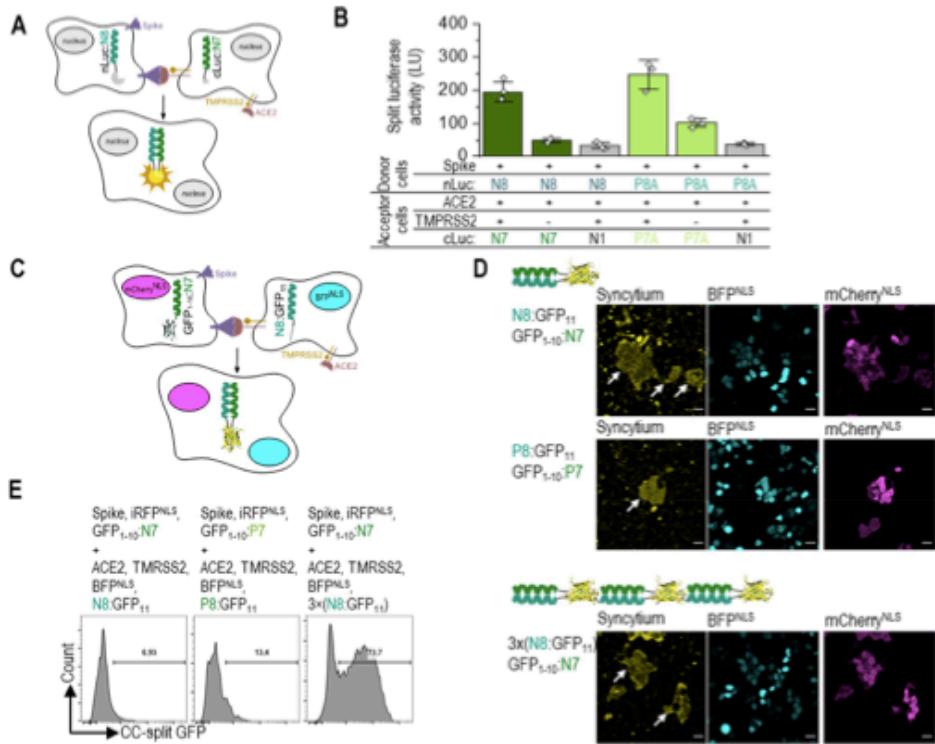


Figure 5. SARS-CoV-2 viral Spike protein-mediated syncytium formation assay based on designed CC split enzymes (A)

Schematic representation of S protein-mediated cell-cell fusion assay. The donor cell is identified as the cell co-expressing CoV-2 Spike protein and nLuc:N8, the acceptor cells with co-expression of ACE2 receptor, TMPRSS2, and cLuc:N7. Syncytium formation is detected with reconstituted CC-split luciferase activity. (B) Luciferase activity as an indicator of cell fusion. 24 h after transfection, donor HEK293T cells transfected with plasmids expressing nLuc:N8 or nLuc:P8A (1000 ng), CoV-2 Spike-protein (10 ng), and acceptor cells expressing cLuc:N7 or cLuc:P7A or cLuc:N1 as control (1000 ng), ACE2 (20 ng), with or without TMPRSS2 (30 ng) were mixed in 1:1 ratio. Luciferase activity was measured 3 h later. The values represent the means (\pm s.d.) from four independent cell cultures, individually transfected with the same mixture of plasmids, and are representative of two independent experiments. (C) Schematic representation of syncytium formation between the donor cells expressing CoV-2 Spike protein, CC-split GFP and mCherryNLS, and the acceptor cells expressing ACE2 receptor, TMPRSS2, CC-split GFP, and BFPNLS. The fused cells are identified with BFP and mCherry nuclei and reconstituted CC-split GFP. (D) Confocal microscopy images of a mixture of donor HEK293T cells expressing the CoV-2 Spike protein (25 ng), mCherryNLS (500 ng), and GFP1-10:N7 or GFP1-10:P7 (100 ng) and the acceptor cells expressing ACE2 receptor (40 ng), BFPNLS (120 ng), and N8:GFP11, P8:GFP11 or 3 × (N8:GFP11) (100 ng). After 3 h mixing of donor and acceptors cells, syncytia (indicated with an arrow) were observed by a reconstituted GFP (yellow) and co-localization of BFP (cyan) and mCherry (magenta). (E) Flow cytometry analysis of a mixture of donor cells expressing the CoV-2 Spike protein (50 ng), iRFPNLS (50 ng), and GFP1-10:N7 or GFP1-10:P7 (500 ng) and the acceptor cells expressing ACE2 receptor (250 ng), TMPRSS2 (50 ng), BFPNLS (50 ng), and N8:GFP11, P8:GFP11 or 3 × (N8:GFP11) (650 ng). Percent of reconstituted split GFP for double iRFP and BFP positive cells 3 h after mixing donor and acceptor cells. For gating strategy, see Fig S8B. Representative results of two independent experiments are shown. For amounts of plasmids, see Table S2. Statistical analyses and the corresponding p-values are listed in Table S3.

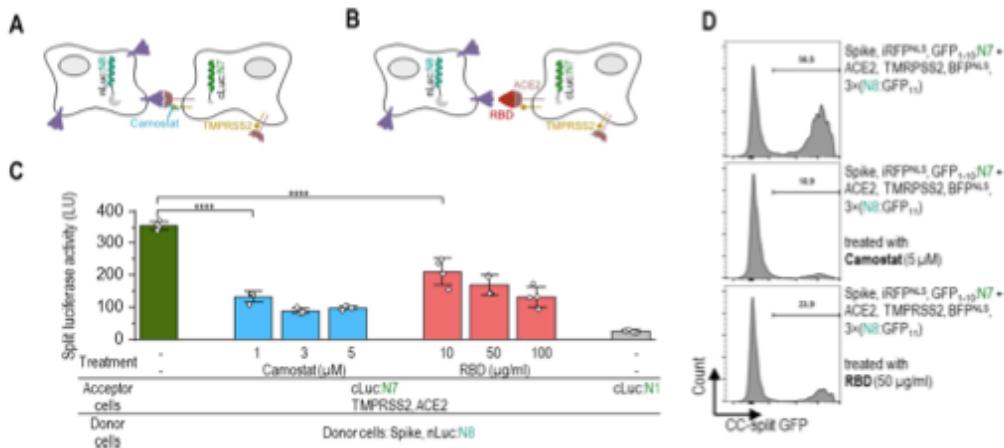


Figure 6. Detection of inhibition targeting different steps in Spike-protein-hACE2-mediated fusion determined by the CC-reporter assay. (A, B) Schematic representation of inhibition of SARS CoV-2 S protein-mediated cell-cell fusion by TMPRSS2 protease inhibitor Camostat (A) and soluble RBD protein domain binding to the ACE2 receptor (B). (C) Luciferase activity of a mixture of donor and receptor cells treated with Camostat or RBD. Donor cells were transfected with plasmids expressing nLuc:N8 (1000 ng), CoV-2 S protein (10 ng), and the acceptor cells expressed cLuc:N7 or cLuc:N1 as control (1000 ng), ACE2 (20 ng), TMPRSS2 (30 ng). The donor and acceptor cells were mixed and treated with RBD or Camostat. Luciferase activity was measured 3 h later. The values represent the means (\pm s.d.) from four independent cell cultures, individually transfected with the same mixture of plasmids, and are representative of two independent experiments. (D) Flow cytometry analysis of a mixture of donor cells expressing the SARS CoV-2 S protein (50 ng), iRFPNLS (50 ng), and GFP1-10:N7 or GFP1-10:P7 (500 ng) and the acceptor cells expressing ACE2 receptor (250 ng), TMPRSS2 (50 ng), BFPNLS (50 ng), and N8:GFP11, P8:GFP11 or 3 × (N8:GFP11) (650 ng). Percent of reconstituted split GFP for double iRFP and BFP positive population 3 h after mixing donor and acceptor cells treated with Camostat or RBD. For gating strategy, see Fig S8B. Representative results of two independent experiments are shown. For amounts of plasmids, see Table S2. Statistical analyses and the corresponding p-values are listed in Table S3.

TRANSMISSION & PREVENTION

PREVENTION IN THE COMMUNITY

THE STABILITY OF MODEL HUMAN CORONAVIRUSES ON TEXTILES IN THE ENVIRONMENT AND DURING HEALTH CARE LAUNDERING

Owen L, Shivkumar M, Laird K.. mSphere. 2021 Apr 28;6(2):e00316-21. doi: 10.1128/mSphere.00316-21.

Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Infectious disease researchers associated with De Montfort University, UK studied the environmental stability of human coronaviruses HCoV-OC43 and HCoV-229E on different textile types. The viral titer of HCoV-OC43 was detected on 100% cotton for up to 24 hours, on 99.3% polyester for up to 72 hours, and on 65%/35% polycotton for up to 6 hours (Figure 2). HCoV-OC43 was transferable from polyester to PVC and other fabrics up to 72 hours after inoculation ($p<0.05$). Dilution, agitation, temperature and use of detergents during laundering effectively removed infectious HCoV-OC43 from all textiles (Table 3). This data indicates the survivability of these viruses on different textiles, and how that might play a role in SARS-CoV-2 transmission.

ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) persists on stainless steel and plastic for up to 7 days, suggesting that coronavirus disease 2019 (COVID-19) could be spread by fomite transmission. There is limited research on the stability of SARS-CoV-2 on textiles, with the risk of textiles acting as fomites not being well understood. To date, there does not appear to be any published research on the stability of coronaviruses during laundering, which is required to determine the efficacy of current laundering policies in the decontamination of health care textiles. The aim of this study was to investigate the environmental stability of human coronaviruses HCoV-OC43 and HCoV-229E on different textile fiber types and the persistence of HCoV-OC43 on textiles during domestic and industrial laundering. This study demonstrated that human coronaviruses (5 log₁₀ 50% tissue culture infective doses [TCID₅₀]) remain infectious on polyester for ≥ 72 h, cotton for ≥ 24 h, and polycotton for ≥ 6 h; HCoV-OC43 was also able to transfer from polyester to PVC or polyester after 72 h. Under clean conditions, HCoV-OC43 was not detectable on cotton swatches laundered with industrial and domestic wash cycles without temperature and detergent ($\geq 4.57 - \log_{10} \text{TCID}_{50}$ reduction), suggesting that the dilution and agitation of wash cycles are sufficient to remove human coronaviruses from textiles. In the presence of interfering substances (artificial saliva), $\leq 1.78 \log_{10} \text{TCID}_{50}$ HCoV-OC43 was detected after washing domestically without temperature and detergent, unlike industrial laundering, where the virus was completely removed. However, no infectious HCoV-OC43 was detected when washed domestically with detergent. IMPORTANCE Synthetic textiles such as polyester could potentially act as fomites of human coronaviruses, indicating the importance of infection control procedures during handling of contaminated textiles prior to laundering. This study provides novel evidence that human coronaviruses can persist on textiles for up to 3 days and are readily transferred from polyester textile to other surfaces after 72 h of incubation. This is of particular importance for the domestic laundering of contaminated textiles such as health care uniforms in the United Kingdom and United States, where there may be a risk of cross-contaminating the domestic environment. It was demonstrated that human coronaviruses are removed from contaminated textiles by typical domestic and commercial wash cycles, even at low temperatures without detergent, indicating that current health care laundering policies are likely sufficient in the decontamination of SARS-CoV-2 from textiles.

FIGURES

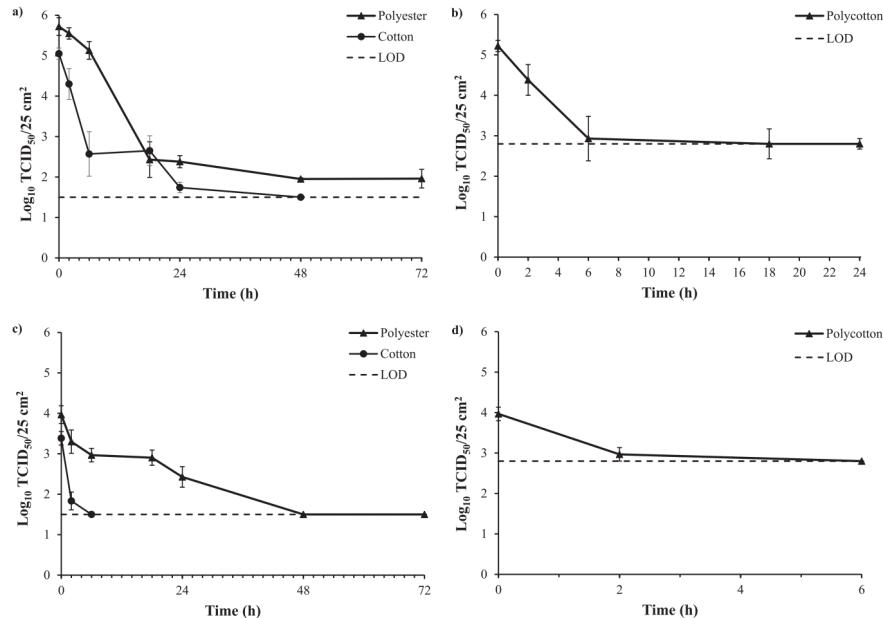


FIG 2 Stability (\log_{10} TCID₅₀/25 cm²) of HCoV-OC43 (a and b) and HCoV-229E (c and d) on textiles over time at ambient temperature (mean, $n = 3 \pm$ SEM). Inoculum, 5 \log_{10} TCID₅₀/25 cm².

Figure 2. Stability (\log_{10} TCID₅₀/25 cm²) of HCoV-OC43 (a and b) and HCoV-229E (c and d) on textiles over time at ambient temperature (mean, $n = 3 \pm$ SEM). Inoculum, 5 \log_{10} TCID₅₀/25 cm².

TABLE 3 \log_{10} TCID₅₀/25-cm² recovery of infectious HCoV-OC43 from 100% cotton following domestic 40°C, industrial 67°C, and OPL 75°C wash cycles with and without temperature and detergent^a

Condition	\log_{10} TCID ₅₀ /25 cm ² ^b (\log_{10} reduction ^c)		Domestic (swatch in pillowcase)		Industrial ^d		OPL ^d	
	Domestic		DMEM	Artificial saliva	DMEM	Artificial saliva	DMEM	Artificial saliva
	DMEM	Artificial saliva	DMEM	Artificial saliva	DMEM	Artificial saliva	DMEM	Artificial saliva
Ambient temp, no detergent	$\leq 1.5 \pm 0.00 (\geq 4.57)$	$\leq 1.78 \pm 0.19 (\geq 4.52)$	— ^e	— ^e	$\leq 1.54 \pm 0.04 (\geq 4.76)$	$\leq 1.5 \pm 0.00 (\geq 4.57)$	$\leq 1.5 \pm 0.00 (\geq 4.80)$	$\leq 1.5 \pm 0.00 (\geq 4.57)$
Ambient temp + detergent	$\leq 1.5 \pm 0.00 (\geq 4.57)$	$\leq 1.5 \pm 0.00 (\geq 4.80)$	—	—	$\leq 1.5 \pm 0.00 (\geq 4.80)$	—	—	—
Temp + detergent	$\leq 1.5 \pm 0.00 (\geq 4.57)$	$\leq 1.5 \pm 0.00 (\geq 4.80)$	—	—	$\leq 1.5 \pm 0.00 (\geq 4.80)$	—	$\leq 1.5 \pm 0.00 (\geq 4.80)$	$\leq 1.5 \pm 0.00 (\geq 4.80)$

^a $n = 6 \pm$ SEM. Inoculum, 8 \log_{10} TCID₅₀/25 cm².

^bThe detection limit was 1.5 \log_{10} TCID₅₀/25 cm². Where one or more samples reached the detection limit, the number of infectious virus is expressed as $\leq \log_{10}$ TCID₅₀/25 cm².

^c \log_{10} reduction calculated from initial viral load on swatch; DMEM, 6.07 \log_{10} TCID₅₀/25 cm²; artificial saliva, 6.30 \log_{10} TCID₅₀/25 cm².

^dFull industrial and OPL wash systems (temperature plus detergent) were tested against HCoV-OC43 in the presence of artificial saliva to confirm the removal of HCoV-OC43 by typical in-use conditions. However, the individual parameters of temperature and detergent were not tested, due to a lack of detectable virus on textiles when washed with water alone, preventing any effect of the detergent and temperature parameters above that of water alone from being detected.

^e—, not tested.

Table 3. Log₁₀ TCID₅₀/25-cm² recovery of infectious HCoV-OC43 from 100% cotton following domestic 40°C, industrial 67°C, and OPL 75°C wash cycles with and without temperature and detergent.

PREVENTION IN THE HOSPITAL

EFFECTIVENESS OF mRNA COVID-19 VACCINES AGAINST SARS-COV-2 INFECTION IN A COHORT OF HEALTHCARE PERSONNEL

Swift MD, Breeher LE, Tande AJ, Tommaso CP, Hainy CM, Chu H, Murad MH, Berbari EF, Virk A.. Clin Infect Dis. 2021 Apr 26:ciab361. doi: 10.1093/cid/ciab361. Online ahead of print.

Level of Evidence: 3 - Non-randomized controlled cohort/follow-up study

BLUF

A team of multidisciplinary researchers associated with Mayo Clinic and University of Minnesota conducted a retrospective study on 45,162 healthcare personnel (HCP) to analyze the effectiveness of Pfizer and Moderna mRNA SARS-CoV-2 vaccines. During the study period 1,125 HCP tested positive for SARS-CoV-2, and vaccine effectiveness was determined to be 78% for partial vaccination and 96% for complete vaccination after adjusting for age, gender, region, job, and week of vaccination (Table 1). These results suggest the high effectiveness of the Pfizer and Moderna vaccines and the importance of bringing widespread immunity to SARS-CoV-2.

ABSTRACT

In a large cohort of US healthcare personnel (HCP) without prior COVID-19 infection, 94,382 doses of mRNA COVID-19 vaccine were administered to 49,220 individuals. The adjusted vaccine effectiveness following two doses of each of the two available brands of mRNA vaccine exceeded 96%.

FIGURES

	Unvaccinate ^d	Partially Vaccinated ^b	Fully Vaccinated ^c	p-value
	N=23,931	N=3,210	N=44,011	
Demographics				
Age (SD)	40 (12)	46 (14)	44 (13)	<0.001
Male Gender	6,635 (27.7%)	841 (26.2%)	13,700 (31.1%)	<0.001
Direct Patient Contact Job ^e	9,511 (41.3%)	1,381 (44.1%)	29,781 (68.3%)	<0.001
Race/Ethnicity ^f				<0.001
American Indian or Alaska Native	75 (0.4%)	7 (0.2%)	137 (0.3%)	
Asian	1,183 (5.7%)	219 (7.1%)	3,281 (7.7%)	
Black	1,343 (6.5%)	196 (6.4%)	1,025 (2.4%)	
Hispanic	936 (4.5%)	144 (4.7%)	1,720 (4.0%)	
Native Hawaiian or Pacific Islander	27 (0.1%)	3 (0.1%)	36 (0.1%)	
White Non-Hispanic	16,892 (81.2%)	2,449 (79.9%)	35,864 (84.1%)	
Multiracial	323 (1.6%)	41 (1.3%)	481 (1.1%)	
Unknown	33 (0.2%)	7 (0.2%)	122 (0.3%)	
Vaccine Received^g				
Pfizer/BioNTech	1,573 (78.1%)	2,038 (63.6%)	40,887 (92.9%)	<0.001
Moderna	441 (21.9%)	1,166 (36.4%)	3,115 (7.1%)	
New Infection	997 (4.2%)	98 (3.1%)	30 (0.1%)	<0.001
Symptomatic Infection ^h	876 (89.2%)	66 (69.5%)	22 (73.3%)	<0.001
Incidence rate ratio and vaccine effectiveness				
Pfizer/BioNTech COVID Vaccine				
Crude IRR (95% CI)	-	0.237 (0.195, 0.289)	0.036 (0.025, 0.052)	<0.001
Adjusted ⁱ IRR (95% CI)	-	0.219 (0.180, 0.267)	0.032 (0.022, 0.047)	<0.001
VE (95% CI)	-	0.781 (0.711, 0.820)	0.968 (0.953, 0.978)	

Moderna COVID Vaccine				
Crude IRR (95% CI)	-	0.107 (0.048, 0.237)	0.017 (0.002, 0.123)	<0.001
Adjusted ⁱ IRR (95% CI)	-	0.088 (0.039, 0.194)	0.014 (0.002, 0.099)	<0.001
VE (95% CI)	-	0.912 (0.806, 0.961)	0.986 (0.901, 0.998)	

Footnotes:

^aReceived no vaccine, or received first dose within 14 days of end of observation period.

^bMore than 14 days from first dose and <=14 days from second dose

^cMore than 14 days from second dose

^dReported experiencing any COVID-19 symptom. Ascertained by interview following a positive test.

^eJob involves direct patient contact (e.g. physician, nurse practitioner, nurse, technician)

^fRace and ethnicity are stored as a single combined variable in the OHS record

^gIncludes initial doses received within 14 days of the end of the observation period classified as Unvaccinated

^hAdjusted for age, gender, job type, and geographic location

Table 1. SARS-CoV-2 Incidence Rate Ratios by Vaccination Status

SARS-COV-2 INFECTION AFTER VACCINATION IN HEALTH CARE WORKERS IN CALIFORNIA

Keehner J, Horton LE, Pfeffer MA, Longhurst CA, Schooley RT, Currier JS, Abeles SR, Torriani FJ.. N Engl J Med. 2021 May 6;384(18):1774-1775. doi: 10.1056/NEJMc2101927. Epub 2021 Mar 23.

Level of Evidence: 5 - Expert Opinion

BLUF

In a letter to the editor, researchers associated with UCSD and UCLA health systems discuss SARS-CoV-2 infection rates in vaccinated healthcare workers in California. 36,659 healthcare workers received the first vaccine dose, 28,184 received the second dose, and 379 vaccinated healthcare workers tested positive at least 1 day after vaccination (Table 1). Vaccinated healthcare workers at UCSD had a 1.19% absolute risk of testing positive for SARS-CoV-2, while those at UCLA had a 0.97% risk. These results suggest the high efficacy of the Pfizer and Moderna vaccines.

FIGURES

Table 1. New SARS-CoV-2 Infections among Vaccinated Health Care Workers from December 16, 2020, through February 9, 2021.

Days after Vaccination	Vaccinated Persons		
	With New Infection (N=379)	Tested (N=14,604)* number	Eligible for Testing (N=36,659)† number (percent)
Dose 1			
Days 1–7	145	5794	35,673 (97.3)
Days 8–14	125	7844	34,404 (93.8)
Days 15–21	57	7958	32,667 (89.1)
Day 22 or later, before dose 2	15	4286	32,327 (88.2)
Dose 2			
Days 1–7	22	5546	23,100 (63.0)
Days 8–14	8	4909	16,082 (43.9)
Day 15 or later	7	4167	14,990 (40.9)

* Shown are the numbers of unique health care workers who underwent testing (not the number of individual tests).

† Shown are the numbers and percentages of persons among 36,659 vaccinated health care workers who were eligible to undergo testing each week as of February 9, 2021.

Table 1. New SARS-CoV-2 Infections among Vaccinated Health Care Workers from December 16, 2020 through February 9, 2021.

MANAGEMENT

MEDICAL SUBSPECIALTIES

PULMONARY FUNCTION AND RADIOLOGICAL FEATURES 4 MONTHS AFTER COVID-19: FIRST RESULTS FROM THE NATIONAL PROSPECTIVE OBSERVATIONAL SWISS COVID-19 LUNG STUDY

Guler SA, Ebner L, Aubry-Beigelman C, Bridevaux PO, Brutsche M, Clarenbach C, Garzoni C, Geiser TK, Lenoir A, Mancinetti M, Naccini B, Ott SR, Piquilloud L, Prella M, Que YA, Soccal PM, von Garnier C, Funke-Chambour M.. Eur Respir J. 2021 Apr 29;57(4):2003690. doi: 10.1183/13993003.03690-2020. Print 2021 Apr.

Level of Evidence: 3 - Cohort study or control arm of randomized trial

BLUF

A multicenter prospective observational cohort study conducted by researchers from multiple medical institutions in Switzerland enrolled 113 individuals diagnosed with COVID-19 between May 1 - September 15, 2020 and monitored respiratory outcomes 4 months later (Figure 1). Patients who had severe/critical COVID-19 had significantly lower TLC, FVC, FEV1, and DLCO compared to those with mild/moderate disease (Figure 2), and patients with severe/critical COVID-19 were more likely to have mosaic attenuation pattern with hypo-attenuated areas (66% versus 13%, p=0.007), reticulations (59% versus 13%, p=0.02), and architectural distortion (52% versus 13%, p=0.055) (Figure 3). DLCO was the strongest independent factor associated with previous severe/critical disease, suggesting that systematic follow-up of pulmonary function is essential for patients who recover from severe and critical COVID-19 and DLCO is the single most important factor at 4-month follow-up.

ABSTRACT

BACKGROUND: The coronavirus infectious disease (COVID-19) pandemic is an ongoing global health care challenge. Up to one third of hospitalised patients develop severe pulmonary complications and ARDS. Pulmonary outcomes following COVID-19 are unknown. **METHODS:** The Swiss COVID-19 lung study is a multicentre prospective cohort investigating pulmonary sequela of COVID-19. We report on initial follow-up 4 months after mild/moderate or severe/critical COVID-19 according to the WHO severity classification. **RESULTS:** 113 COVID-19 survivors were included (mild/moderate 47, severe/critical 66). We confirmed several comorbidities as risk factors for severe/critical disease. Severe/critical disease was associated with impaired pulmonary function, i.e. diffusing capacity (DLCO) %-predicted, reduced 6-MWD, and exercise-induced oxygen desaturation. After adjustment for potential confounding by age, sex, and BMI, patients after severe/critical COVID-19 had a 20.9 (95% CI 12.4-29.4, p=0.01) lower DLCO %-predicted at follow up. DLCO %-predicted was the strongest independent factor associated with previous severe/critical disease when age, sex, BMI, 6MWD, and minimal SpO₂ at exercise, were included in the multivariable model (adjusted odds ratio [OR] per 10%-predicted 0.59 [95% CI 0.37-0.87], p=0.01). Mosaic hypoattenuation on chest computed tomography at follow-up was significantly associated with previous severe/critical COVID-19 including adjustment for age and sex (adjusted OR 11.7 [95%CI 1.7-239], p=0.03). **CONCLUSIONS:** Four months after SARS CoV-2 infection, severe/critical COVID-19 was associated with significant functional and radiological abnormalities, potentially due to small airway and lung parenchymal disease. A systematic follow-up for survivors needs to be evaluated to optimise care for patients recovering from COVID-19.

FIGURES

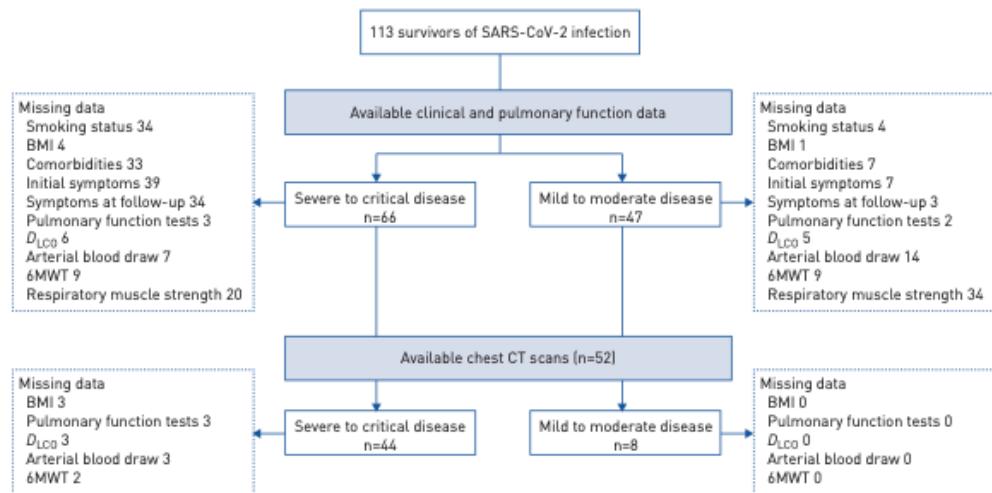


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the study. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; BMI: body mass index; DLCO: diffusing capacity of the lung for carbon monoxide; 6MWT: 6-min walk test; CT: computed tomography.

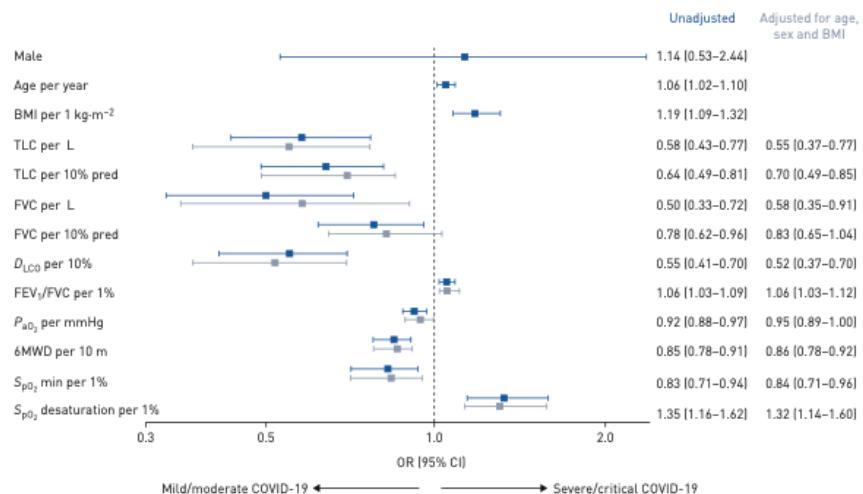


Figure 2. Variables associated with past coronavirus disease 2019 (COVID-19) severity. Association of demographic and functional parameters with mild/moderate and severe/critical COVID-19. Odds ratios and corresponding 95% confidence intervals from unadjusted analysis and individual multivariable models for each parameter adjusting for confounding by age and sex. BMI: body mass index; TLC: total lung capacity; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; FEV₁: forced expiratory volume in 1 s; PaO₂: arterial oxygen tension; 6MWD: 6-min walk distance; SpO₂: peripheral oxygen saturation.

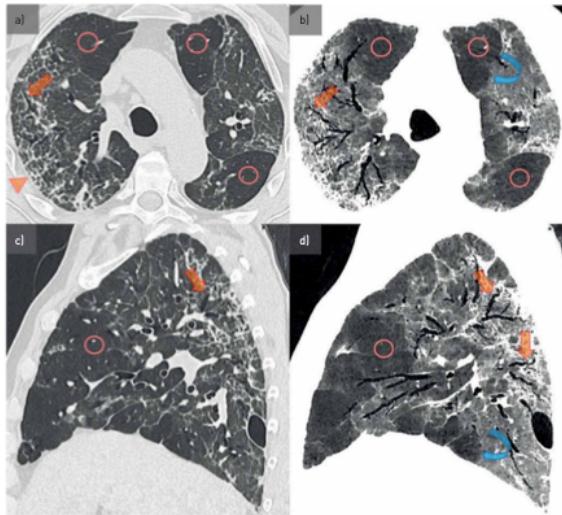


Figure 3. Characteristic radiological changes of a patient with severe sequelae 3 months after coronavirus disease 2019 (COVID-19) pneumonia. Extensive involvement of both lungs is present in a patient 3 months after severe COVID-19 pneumonia. Diffuse mosaic attenuation pattern in all lung lobes seen on a) axial 1-mm-thick computed tomography (CT) scan and b) 10-mm-thick minimum intensity projection (mIP) slices, c) 1-mm-thick CT and d) 10-mm-thick mIP sagittal reformats in lung windowing. This combines classical features of lung fibrosis with architectural distortion, reticulations, honeycombing (arrowhead in a) and traction bronchiectasis (straight arrows in a-d), as well as sharply demarcated areas of low attenuation in both lungs (circles in a-d). Clusters of contiguous hypoattenuating lobules and traction bronchiectasis are better visualised on mIP images with narrow window settings (b and d). Note the bulging of the interlobular septae (b and d, curved arrows) as well as the subpleural pneumatocele in c and d.

ADJUSTING PRACTICE DURING COVID-19

ALLERGY AND IMMUNOLOGY

ANAPHYLAXIS IN THE EMERGENCY DEPARTMENT UNIT: BEFORE AND DURING COVID-19

Pur Ozigit L, Khalil G, Choudhry T, Williams M, Khan N. Allergy. 2021 Apr 27. doi: 10.1111/all.14873. Online ahead of print.
Level of Evidence: 4 - Case-series, case-control, or historically controlled studies

BLUF

In a letter to the editor, allergy specialists from Leicester, UK discuss their observational retrospective study of adult patients coming into the Emergency Department Unit (EDU) of University Hospitals of Leicester with a systemic allergic reaction and mast cell tryptase elevation in January - June 2019 compared to 2020. In 2019, 62 patients came into the EDU with a systemic allergic reaction compared to 10 in 2020 (Table 1) ($p<0.0001$). While 52% of these patients in 2019 presented with only mild symptoms, the majority (80%) of patients in 2020 had more moderate reactions ($p=0.007$). These findings suggest a significant reduction in anaphylactic episodes due to closure of restaurants and an increased reluctance for those with mild symptoms to go to the EDU.

FIGURES

	Pre-COVID (2019)	During COVID (2020)	<i>p</i> value
Number of adult patients attended A&E (n)	87545	64230	<.0001
Number of adult patients attended A&E with symptoms of systemic allergic reaction and elevated tryptase value (n)	62	10	
Age (mean, SD, in years)	51 ± 17	45 ± 18	.7
% female	45	40	.7
Mast cell tryptase value (mean, SD, in µg/L)	19.1 ± 8	20.8 ± 12	.1
Brown classification (%)			
• Mild	52	10	.007
• Moderate	40	80	
• Severe	8	10	
Possible culprit trigger (%)			
• Food	9	20	.2
• Drug	40	60	
• Venom	5	0	
• Not indicated	46	20	
Adrenaline usage in EDU (%)	50	80	.09
Referral to Allergy Service (%)	60	100	.03

Note: Data are summarized as number, percentage or mean ± standard deviation (SD).

Continuous variables were analysed using Student's *t* test and "N-1" chi-squared test. Comparisons of the qualitative data were performed with chi-square test.

Bold values indicate $p < .05$.

Table 1. Comparison of two groups

NEPHROLOGY

PREVALENCE OF ANTIBODIES AGAINST SARS-COV-2 IN HEMODIALYSIS PATIENTS

Arteaga-Müller GY, Olivo-Gutierrez M, Favela-Aragon KL, Hernández-Castillo PA, Esquivel-Gomez V, Camacho-Ortiz A.. Int Urol Nephrol. 2021 Apr 23. doi: 10.1007/s11255-021-02852-4. Online ahead of print.

Level of Evidence: 4 - Local non-random sample

BLUF

In a letter to the editor, epidemiology specialists from Universidad Autónoma de Nuevo León, Mexico discuss their study on the prevalence of SARS-CoV-2 antibodies in hemodialysis (HD) patients. All 154 HD patients were tested after 1 positive COVID-19 PCR test in the facility: 18 were positive for SARS-CoV-2, 11 tested positive for IgG, 3 for IgG and IgM, and 4 for IgM only. These data suggest that due to decreased immunity in HD patients, monitoring of antibodies can help avoid rapid transmission.

SUMMARY

- Of the antibody-positive patients, 33% displayed at least one symptom and 67% were pauci-symptomatic
- Of the antibody-negative patients, 19% presented with at least 1 symptom, and 81% were pauci-symptomatic

R&D: DIAGNOSIS & TREATMENTS

DEVELOPMENTS IN TREATMENTS

CLINICAL OUTCOMES ASSOCIATED WITH METHYLPREDNISOLONE IN MECHANICALLY VENTILATED PATIENTS WITH COVID-19

Nelson BC, Laracy J, Shoucri S, Dietz D, Zucker J, Patel N, Sobieszczyk ME, Kubin CJ, Gomez-Simmonds A.. Clin Infect Dis. 2021 May 4;72(9):e367-e372. doi: 10.1093/cid/ciaa1163.

Level of Evidence: 4 - Case-series, case-control studies, or historically controlled studies

BLUF

A case-control study conducted by pharmacy, infectious disease, and pulmonary specialists from Columbia University Irving Medical Center on 117 mechanically ventilated COVID-19 patients, where the experimental group (n = 48) received methylprednisolone within 14 days of admission showed that the methylprednisolone group had significantly higher ventilator-free days ($p = 0.044$) and probability of extubation by day 28 ($p = 0.087$) compared to the control group (Table 2). Overall, these results indicate the effectiveness of corticosteroid treatment in severe COVID-19 patients requiring mechanical ventilation.

SUMMARY

- The protocol dosage for methylprednisolone was one mg/kg/day with a max dose of 80 mg per day, with recommended duration of five days, although the course could be extended at the discretion of the treating physician. The protocol recommended that steroids only be started in patients at least five to seven days after symptom onset and only in those with evidence of systemic inflammation
- After controlling for age, SOFA score, white blood cell count, LDG, and D-dimer, multivariable linear regression analysis showed methylprednisolone to be associated with improved outcome ($p = 0.015$) overall compared to hydroxychloroquine, azithromycin, or tocilizumab

ABSTRACT

BACKGROUND: The efficacy and safety of methylprednisolone in mechanically ventilated patients with acute respiratory distress syndrome due to coronavirus disease 2019 (COVID-19) are unclear. In this study, we evaluated the association between use of methylprednisolone and key clinical outcomes. **METHODS:** Clinical outcomes associated with the use of methylprednisolone were assessed in an unmatched, case-control study; a subset of patients also underwent propensity-score matching. Patients were admitted between March 1 and April 12, 2020. The primary outcome was ventilator-free days by 28 days after admission. Secondary outcomes included extubation, mortality, discharge, positive cultures, and hyperglycemia. **RESULTS:** A total of 117 patients met inclusion criteria. Propensity matching yielded a cohort of 42 well-matched pairs. Groups were similar except for hydroxychloroquine and azithromycin use, which were more common in patients who did not receive methylprednisolone. Mean ventilator free-days were significantly higher in patients treated with methylprednisolone (6.21+7.45 versus 3.14+6.22; $P = 0.044$). The probability of extubation was also increased in patients receiving methylprednisolone (45% versus 21%; $P = 0.021$), and there were no significant differences in mortality (19% versus 36%; $P = 0.087$). In a multivariable linear regression analysis, only methylprednisolone use was associated with higher number of ventilator-free days ($P = 0.045$). The incidence of positive cultures and hyperglycemia were similar between groups. **CONCLUSIONS:** Methylprednisolone was associated with increased ventilator-free days and higher probability of extubation in a propensity-score matched cohort. Randomized, controlled studies are needed to further define methylprednisolone use in patients with COVID-19.

FIGURES

Table 2. Effectiveness and Safety Outcomes

	Overall Cohort (117) ^a			Propensity-matched Cohort (84) ^a		
	Control (69)	MP (48)	P	Control (42)	MP (42)	P
Primary outcome						
28-d ventilator-free days	2.46 (± 6.55)	5.77 (± 7.21)	.058	3.14 (± 6.22)	6.21 (± 7.45)	.044
Secondary outcomes						
28-d extubation	16 (23)	21 (44)	.019	9 (21)	19 (45)	.021
28-d death	20 (33)	10 (21)	.139	15 (36)	8 (19)	.087
28-d discharge	14 (20)	8 (17)	.622	8 (19)	7 (17)	.776
60-d extubation	36 (54)	31 (46)	.182	23 (55)	27 (64)	.374
60-d death	29 (42)	15 (31)	.236	17 (41)	13 (31)	.362
60-d discharge	26 (38)	23 (48)	.270	15 (36)	19 (45)	.374
Safety outcomes^b						
Positive cultures	32 (46)	26 (54)	.407	19 (45)	22 (52)	.513
Culture site			.834			.721
- Pulmonary	25 (36)	21 (44)		15 (36)	17 (41)	
- Urinary tract	5 (7)	4 (8)		2 (5)	4 (10)	
- Intravascular	2 (2)	1 (1)		2 (5)	1 (1)	
Days with blood glucose ≥ 180 mmol/L	8 (3–14)	9 (3–16)	.454	8 (2–14)	9 (3–17)	.415

Abbreviation: MP, methylprednisolone.

^aCategorical variables are presented as number (percent), ventilator free days are presented as mean (standard deviation), and days with blood glucose ≥ 180 mmol/L are presented as median (interquartile range).

^bCulture data were evaluated through hospital day 28. Blood glucose values were evaluated through hospital day 21.

Table 2. Effectiveness and Safety Outcomes

STERILIZING IMMUNITY AGAINST SARS-COV-2 INFECTION IN MICE BY A SINGLE-SHOT AND LIPID AMPHIPHILE IMIDAZOQUINOLINE TLR7/8 AGONIST-ADJUVANTED RECOMBINANT SPIKE PROTEIN VACCINE*

Jangra S, De Vrieze J, Choi A, Rathnasinghe R, Laghlali G, Uvyn A, Van Herck S, Nuhn L, Deswarde K, Zhong Z, Sanders NN, Lienenklaus S, David SA, Strohmeier S, Amanat F, Krammer F, Hammad H, Lambrecht BN, Coughlan L, García-Sastre A, De Geest BG, Schotsaert M.. Angew Chem Int Ed Engl. 2021 Apr 19;60(17):9467-9473. doi: 10.1002/anie.202015362. Epub 2021 Mar 11.

Level of Evidence: 5 - Mechanism-based reasoning

BLUF

An international group of multidisciplinary researchers studied the amphiphilic imidazoquinoline (IMDQ-PEG-CHOL) TLR7/8 adjuvant in mice as a potential vaccine candidate for SARS-CoV-2 and influenza (Figure 1). Results indicated that the adjuvant induces robust Th1 skewed antibody responses and translocation to the draining lymph node, as seen in microscopic and flow cytometry (Figure 3). Virus-specific neutralizing antibodies were seen in H1N1 and SARS-CoV-2-infected mice vaccinated with QIV + IMDQ-PEG-CHOL and S protein + IMDQ-PEG-CHOL, respectively (Figure 5). Overall, these results indicate that a S protein-based SARS-CoV-2 vaccine with adjuvant IMDQ-PEG-CHOL therapy can provide protective immunity in mice, and could be further researched in humans as well.

SUMMARY

- Mice vaccinated with the quadrivalent influenza vaccine (QIV) + IMDQ-PEG-CHOL had higher total IgG antibody titers compared to the control group given QIV + PEG-CHOL.
- 4 out of 6 mice that received QIV and IMDQ-PEG-CHOL could inhibit hemagglutination of chicken red blood cells in vitro by the H1V1 component in QIV.

ABSTRACT

The search for vaccines that protect from severe morbidity and mortality as a result of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19) is a race against the clock and the virus. Here we describe the use of a novel amphiphilic imidazoquinoline (IMDQ-PEG-CHOL) TLR7/8 adjuvant, consisting of an imidazoquinoline conjugated to the chain end of a cholesterol-poly(ethylene glycol) macromolecular amphiphile. This amphiphile is water soluble and exhibits massive translocation to lymph nodes upon local administration, likely through binding to albumin, affording localized innate immune activation and a dramatic reduction in systemic inflammation. The adjuvanticity of IMDQ-PEG-CHOL was validated in the context of a licensed vaccine setting (i.e. the quadrivalent influenza vaccine) and an experimental trimeric recombinant SARS-CoV-2 spike protein vaccine, showing robust IgG2a and IgG1 antibody titers in mice that could neutralize viral infection in vitro and in vivo in a mouse model.

FIGURES

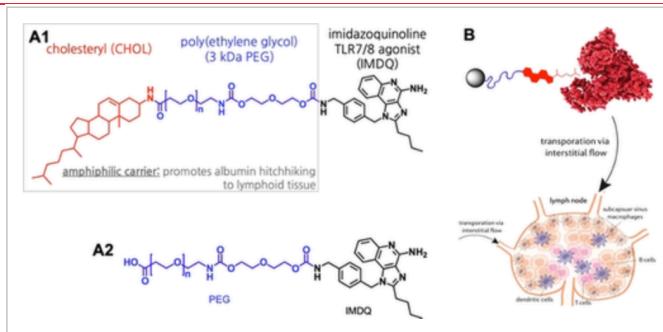


Figure 1. A) Molecular structure of (A1) IMDQ-PEG-CHOL and (A2) IMDQ-PEG. Conjugation was performed by amide bond formation between, respectively cholesterylamine and PEG and PEG and IMDQ. B) Representation of albumin hitchhiking-mediated lymphatic transportation.

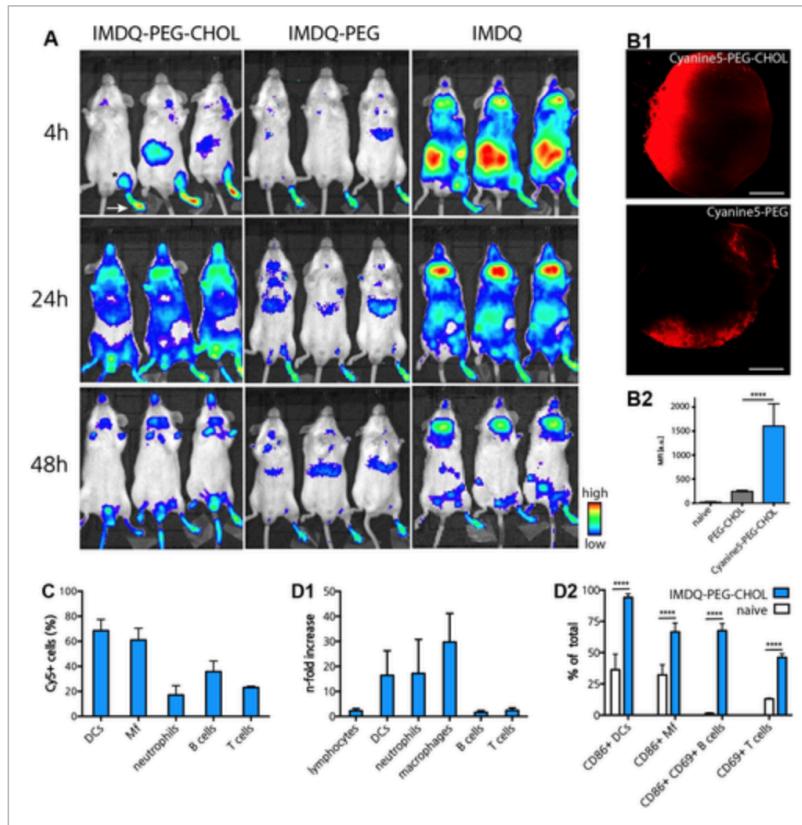


Figure 3. A) Bioluminescence images of luciferase reporter mice ($\text{IFN}\beta^+/\Delta\beta\text{-luc}$); images taken 4, 24 and 48 h post footpad injection of IMDQ-PEG-CHOL, IMDQ-PEG and native IMDQ. B1) Confocal microscopy images of lymph node tissue sections 48 h post subcutaneous injection of Cyanine5-PEG-CHOL, respectively Cyanine5-PEG, into the footpad of mice. Scale bar: 100 μm . B2) Flow cytometry analysis of the draining popliteal lymph node 48 h post subcutaneous injection of Cyanine5-PEG-CHOL, respectively Cyanine5-PEG into the footpad of mice. (n=3, mean + SD; Student's t-test: ****: p<0.0001) C) Translocation of Cyanine5-PEG-CHOL to the draining popliteal lymph node analyzed 24 h post injection into the footpad, measured by flow cytometry. (n=6, mean + SD) D) Flow cytometry analysis of the innate immune response in the draining popliteal lymph node 24 h post injection of IMDQ-PEG-CHOL into the footpad (D1) Relative increase in innate immune cell subsets, B and T cell numbers relative to a naïve control and (D2) maturation/activation of innate immune cell subsets, B and T cells (n=6, mean + SD; Student's t-test: ****: p<0.0001).

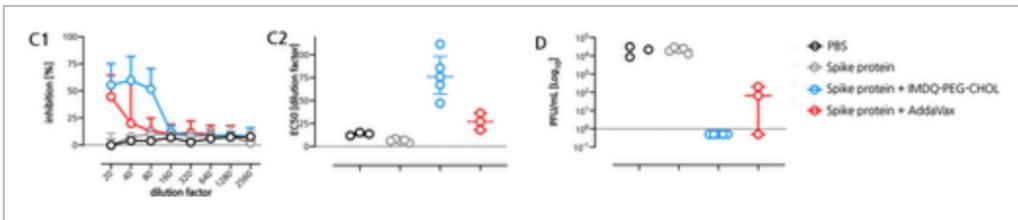


Figure 5. IMDQ-PEG-CHOL induces a balanced neutralizing antibody response to SARS-CoV-2 infection. A) Outline of the Spike protein vaccination and SARS-CoV-2 challenge. B) ELISA titers (titers are expressed on the X axis as the reciprocal of the dilution factor) for total IgG, IgG1, and IgG2a and IgG2a/IgG1 ratio (based on the AUC (OD at 450 nm) curve of the individual serum samples) in mice sera collected 3 weeks post-vaccination. C) Control versus vaccinated sera examined for presence of virus-neutralizing antibodies by microneutralization assay, using 100 tissue culture infectious dose 50 (TCID50) of SARS-CoV-2 virus. The outcome is represented as a percentage inhibition of viral growth in (C1) and as the half maximal inhibitory concentration IC50 calculated by a non-linear regression analysis of percentage inhibition curve in (C2). D) Viral lung titers represented as Plaque-forming-unit (PFU) mL⁻¹ (geometric mean with geometric SD). The Ad5-hACE2 transduced mice were challenged with 5×10⁴ PFU of SARS-CoV-2 and the lungs were harvested on day-4 post infection.

ACKNOWLEDGEMENTS

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