The Daily COVID-19 Literature Surveillance Summary

December 07, 2020

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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

Understanding the Pathology

- Critical illness is associated with cerebral microbleeds for patients with severe COVID-19. A retrospective cohort study conducted at University Hospitals of Strasbourg, France compared 19 severe COVID-19 patients with MRI evidence of microhemorrhage to 18 COVID-19 patients with normal MRI and found more pronounced respiratory failure, higher D-dimer increases, and more frequent need for dialysis in the microhemorrhage group. The researchers hypothesize that blood-brain barrier dysfunction due to hypoxemia and levels of uremic toxins may be a key mechanism of COVID-19-related cerebral microhemorrhage, which clinicians should consider during severe COVID-19 patient management.

Transmission & Prevention

- A pooled surveillance testing program for asymptomatic SARS-CoV-2 infections was implemented on a college campus. This observational cohort study conducted by an interdisciplinary team at Duke University in North Carolina implemented mandatory masking, social distancing, and entry-and-surveillance SARS-CoV-2 testing with five-to-one pooled quantitative RT-PCR. Large-scale testing of 10,265 students (n=68,913 total tests) yielded 84 positive results (43 asymptomatic). Authors suggest pooled testing allows for high sensitivity and rapid results, while decreasing supply-chain disruptions by using fewer resources, which could be more successful in limiting transmission than testing only symptomatic individuals.

Adjusting Practice During COVID-19

- Decline in SARS-CoV-2 antibodies after mild infection was noted among frontline health care personnel. The CDC COVID-19 Response Team and IVY Network conducted an analysis of 3,284 frontline healthcare personnel, from 13 different hospitals across 12 states and found 194 had SARS-CoV-2 antibodies at initial baseline testing using ELISA assay (96% sensitivity and 99% specificity). About 60 days later, 156 returned for follow up testing, of which 93.6% had a decline in antibody response, and 108 reported COVID-19 symptoms. Additionally, among the cohort who initially tested positive, seroreversion was observed in 19.4% of those that reported symptoms, and 47.9% of those without symptoms. These results suggest antibodies to SARS-CoV-2 decline over time and negative serologic results do not exclude previous infection, highlighting there may be significant differences in interpretation on serological studies regarding COVID-19 epidemiology.

TABLE OF CONTENTS

ADULTS

PATTERN OF COGNITIVE DEFICITS IN SEVERE COVID-19

Beaud V, Crottaz-Herbette S, Dunet V, Vaucher J, Bernard-Valnet R, Du Pasquier R, Bart PA, Clarke S.. J Neurol Neurosurg Psychiatry. 2020 Nov 20:jnnp-2020-325173. doi: 10.1136/jnnp-2020-325173. Online ahead of print.
Level of Evidence: 4 - Case-series

BLUF

A case series conducted at Lausanne University Hospital in Switzerland by specialists in neuropsychology and neurorehabilitation including 13 COVID-19 patients with acute respiratory distress syndrome (ARDS) and no preexisting neurocognitive or neuropsychiatric conditions found 5 patients had moderate-severe cognitive dysfunction based on the Montreal Cognitive Assessment (MoCA), while Frontal Assessment Battery (FAB) showed cognitive issues in 8 patients (Table 1). Authors advocate for further research to explore the underlying pathophysiology of this potential correlation between critical illness seen in severe COVID-19 and subsequent cognitive deficits.

FIGURES

Table 1 Patient (P1–P13) characteristics and performance in cognitive tests

Patients	Age (years)	Sex	ICU stay (days)	Mechanical ventilation (days)	ICU discharge to cognitive assessment (days)	Brain atrophy	ICU delirium	MoCA scores (0–30)	FAB scores (0–18)	MoCA mean subtest scores (0–6)	FAB mean subtest scores (0–3)	Cognitive slowness (0–3)	Mental fatigue (0–3)	Mood (0–10) and anxiety* disturbances
P1	60s	m	46	38	4	rFgm; fv	N	*29*	*16.8*	Ex: 3.63	Fl:1.75	1	2	8*
P2	60s	f	12	11	6	–	N	*28*	*15.6*	Me: 5.10 VS: 5.63	Co: 2.50 Pr: 2.75	2	2	2
P3	70s	m	31	21	6	None	N	*26.9*	*15.6*	La: 5.70	Inh: 3.00	0	2	3
P4	60s	m	67	50	10	None	N	*26*	*14.4*	At: 5.75 Or: 6.00	Int: 3.00	1	2	1
P5	60s	m	16	10	9	None	Y	**23**	*16.8*	Ex: 2.25	Fl: 1.25	2	1	5
P6	50s	m	21	16	7	–	Y	**22**	**13.2**	Me: 3.00 At: 3.75	Pr: 2.00 Co: 2.50	2	2	0
P7	50s	m	21	17	5	None	Y	**21**	**14.4**	VS: 4.13	Inh: 2.75	2	2	3
P8	70s	f	14	13	4	None	N	**19**	**9.6**	Or: 5.25 La: 5.40	Int: 2.75	1	2	2*
P9	60s	m	21	17	4	None	N	**17**	**7.2**	Me: 0.48	Fl: 0.00	3	3	8*
P10	60s	m	27	19	2	rlFgm; lTgm; rlFwm; rlv; tv; fv	Y	**16.8**	**2.4**	VS: 1.13 Ex: 1.30 At: 2.00 Or: 3.40	Inh: 0.80 Pr: 0.80 Int: 1.00 Co: 1.60	3	3	3
P11	50s	m	40	23	2	rlFgm; rlCgm	Y	**13**	**9.6**	La: 4.08		2	2	2
P12	70s	m	25	25	7	rFgm; rlFwm; lPwm; rlOwm	Y	**10**	**4.8**			3	3	8
P13	70s	f	24	19	6	rlFgm; rPgm; rlTgm; rlv; tv	Y	**4**	**1.2**			3	3	6
MEAN:	64.8		28.1	21.5	5.5			19.7	10.9			1.9	2.2	3.9
SD:	7.6		15.2	11.2	2.4			7.5	5.5			1.0	0.6	2.8

CRITICAL ILLNESS-ASSOCIATED CEREBRAL MICROBLEEDS FOR PATIENTS WITH SEVERE COVID-19: ETIOLOGIC HYPOTHESES

Lersy F, Willaume T, Brisset JC, Collange O, Helms J, Schneider F, Chammas A, Willaume A, Meyer N, Anheim M, Cotton F, Kremer S.. J Neurol. 2020 Nov 21. doi: 10.1007/s00415-020-10313-8. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A retrospective cohort study conducted at University Hospitals of Strasbourg, France from March 17 to May 18, 2020 compared severe COVID-19 patients with MRI evidence of microhemorrhage (n=19) to COVID-19 patients with normal MRI (n=18) and found more pronounced respiratory failure, higher D-dimer increases, and more frequent need for dialysis in the microhemorrhage group (see summary). The researchers hypothesize that blood-brain barrier dysfunction due to hypoxemia and levels of uremic toxins may be a key mechanism of COVID-19-related cerebral microhemorrhage, which clinicians should consider during severe COVID-19 patient management.

SUMMARY

Further study findings as follows:
- hypoxemia due to increased length and severity of respiratory failure, higher FiO2, and increased use of extracorporeal membrane oxygenation in the microhemorrhage cohort (Table 3)
- microangiopathy due to higher D-Dimer levels and increased frequency of thrombotic events in the microhemorrhage cohort
- kidney failure due to increased creatinine levels (Table 4) and more frequent need for dialysis in the microhemorrhage cohort

ABSTRACT

BACKGROUND AND PURPOSE: During the COVID-19 outbreak, the presence of extensive white matter microhemorrhages was detected by brain MRIs. The goal of this study was to investigate the origin of this atypical hemorrhagic complication. METHODS: Between March 17 and May 18, 2020, 80 patients with severe COVID-19 infections were admitted for acute respiratory distress syndrome to intensive care units at the University Hospitals of Strasbourg for whom a brain MRI for neurologic manifestations was performed. 19 patients (24%) with diffuse microhemorrhages were compared to 18 control patients with COVID-19 and normal brain MRI. RESULTS: The first hypothesis was hypoxemia. The latter seemed very likely since respiratory failure was longer and more pronounced in patients with microhemorrhages (prolonged endotracheal intubation (p = 0.0002), higher FiO2 (p = 0.03), increased use of extracorporeal membrane oxygenation (p = 0.04)). A relevant hypothesis, the role of microangiopathy, was also considered, since patients with microhemorrhages presented a higher increase of the D-Dimers (p = 0.01) and a tendency to more frequent thrombotic events (p = 0.12). Another hypothesis tested was the role of kidney failure, which was more severe in the group with diffuse microhemorrhages (higher creatinine level [median of 293 micromol/L versus 112 micromol/L, p = 0.04] and more dialysis were introduced in this group during ICU stay [12 versus 5 patients, p = 0.04]). CONCLUSIONS: Blood-brain barrier dysfunction secondary to hypoxemia and high concentration of uremic toxins seems to be the main mechanism leading to critical illness-associated cerebral microbleeds, and this complication remains to be frequently described in severe COVID-19 patients.

FIGURES

	Population of COVID-19 patients with extensive white matter microhemorrhages ($n = 19$)	Population of COVID-19 patients without extensive white matter microhemorrhages ($n = 18$)	p value
Number of days intubated	24 (19–25)	8 (4–14)	***0.0002***
Higher FiO_2 (%)	100 (92–100)	75 (63–100)	***0.03***
Lower PaO_2/FiO_2	81 (59–104)	104 (80–124)	*0.07*
Extracorporeal membrane oxygenation	5 (26%)	0	***0.04***
Extension of pulmonary involvement with computed tomography (score from 0 (no injury) to 5 (≥ 75%)	4 (4–5)	4 (2.5–4)	***0.04***

Data are number and percentage or median associated with first and third quartile

All statistical test results are in italics. Statistically significant results are in bold italics

Table 3. Respiratory status during ICU stay

	Population of COVID-19 patients with extensive white matter microhemorrhages ($n=19$)	Population of COVID-19 patients without extensive white matter microhemorrhages ($n=18$)	p value
Laboratory findings at the time of ICU admission			
White blood cell count, $\times 10^9$/L	8.7 (4.9–12)	6.9 (5.8–9.7)	*0.36*
Lymphocyte count, $\times 10^9$/L	0.71 (0.47–1.24)	0.84 (0.68–1.12)	*0.6*
Haemoglobin, g/L	119 (96–134)	128 (118–137)	*0.18*
Platelet count, $\times 10^9$/L	200 (158–242)	168 (160–272)	*0.68*
C-reactive protein, mg/L	183 (112–281)	119 (91–189)	*0.15*
Alanine aminotransferase U/L	48 (30–63)	43 (26–81)	*0.98*
Aspartate aminotransferase, U/L	71 (59–91)	64 (34–89)	*0.45*
Urea, mmol/L	13 (8–17)	7 (5–10)	***0.003***
Creatinine, µmol/L	81 (69–248)	79 (67–102)	*0.35*
Prothrombin time, s	15.4 (14.3–16.1)	14.8 (13.4–17.4)	*0.5*
Activated partial thromboplastin time, s	39 (37–43)	38 (36–40)	*0.43*
International normalized ratio (INR)	1.17 (1.1–1.23)	1.1 (1–1.35)	*0.35*
Antithrombin III (%)	85 (72–96)	94 (78–101)	*0.23*
Fibrinogen, g/L	6.8 (6.3–7.8)	6.2 (5.5–7.4)	*0.27*
D-dimers, mg/L	3.1 (1.8–6.8)	1.7 (1.1–2)	***0.01***
Laboratory findings during ICU stay and before brain MRI			
Lower platelet count, $\times 10^9$/L	140 (108–204)	163 (152–195)	*0.36*
Lower fibrinogen, g/L	5.1 (4.5–5.8)	5.8 (4.9–7.2)	*0.44*
Higher prothrombin time, s	16.5 (15.9–17.5)	17.4 (15.8–19)	*0.46*
Higher D-dimers, mg/L	11.5 (7.5–20)	4.6 (3–12)	*0.08*
Disseminated intravascular coagulation According to the criteria endorsed by the ISTH	1 (5%)	2 (11%)	*0.6*
Higher fibrinogen, g/L	9 (7.6–10.4)	8.8 (6.8–9.4)	*0.26*
Higher C-reactive protein, mg/L	276 (185–382)	196 (117–294)	*0.09*
Higher Creatinine, µmol/L	293 (154–387)	112 (91–220)	***0.04***
Lupus anticoagulant, data are *n/N* (%)	15/19 (79%)	10/12 (83%)	*1*
Thrombotic events during ICU stay	7 (37%)	2 (11%)	*0.12*
Treatment initiated during hospitalization before brain MRI			
Dialysis	12 (63%)	5 (28%)	***0.04***
Anticoagulant therapy	19 (100%)	18 (100%)	*1*
Hydroxychloroquine	7 (37%)	8 (44%)	*0.74*
Lopinavir/ritonavir	7 (37%)	9 (50%)	*0.51*

Data are number and percentage or median associated with first and third quartile

All statistical test results are in italics. Statistically significant results are in bold italics

Table 4. Laboratory findings and significant events during ICU stay

CELLULAR EVENTS OF ACUTE, RESOLVING OR PROGRESSIVE COVID-19 IN SARS-COV-2 INFECTED NON-HUMAN PRIMATES

Fahlberg MD, Blair RV, Doyle-Meyers LA, Midkiff CC, Zenere G, Russell-Lodrigue KE, Monjure CJ, Haupt EH, Penney TP, Lehmicke G, Threeton BM, Golden N, Datta PK, Roy CJ, Bohm RP, Maness NJ, Fischer T, Rappaport J, Vaccari M.. Nat Commun. 2020 Nov 27;11(1):6078. doi: 10.1038/s41467-020-19967-4.
Level of Evidence: Other - Mechanism-based reasoning

BLUF

A group of scientists and physicians from Tulane University School of Medicine studied the immune aspects of COVID-19 in two types of non-human primates (NHP; African Green Monkeys (AGM) and Rhesus Monkeys (RM)), from the acute period of illness to about 4 weeks post-COVID-19 illness. Their findings (illustrated below) highlight different aspects of the immune response to COVID-19, including elucidation of the several different stages (an acute phase, switching to Th2-type responses, and resolution phase, Figure 6e) of this response. These findings further the understanding of immune function with relation to COVID-19 and suggest that NHPs have potential as models for evaluating immune treatments and vaccines.

SUMMARY

Based on their findings, the authors summarized immune events in the lungs and blood of SARS-CoV-2-infected animals (Figure 6e):
"1. Recruitment of monocytes in the lung indicating an Initial inflammatory phase
2. Gradual switch from a type 1 to type 2 response
3. 'Make it or break it' phase with either:
   a. increase in anti-inflammatory cytokine IL-10 and regulatory cell subsets with suppressive activity
   b. IL-6, a pro-inflammatory cytokine associated with disease progression in humans"

Other related findings in this article:
1. In the 'acute' phase of the illness, there is an influx of CD16 monocytes and interstitial macrophages that migrate to the lung tissue. To break it down further, there are two groups of interstitial macrophages
   a. The transitional phase interstitial macrophages (CD11cCD16+) which increase IL-6 levels
   b. Long lasting interstitial macrophages (CD11bCD16+) that arise during the resolution of inflammation
2. The ratio of IL-10 to IL-6 found in plasma may correlate with a more advanced stage of disease
3. Dendritic cells and CD11b+ macrophages have been found to enhance the recruitment of T helper type 2 (Th2) lymphocyte in the lungs and also as an origin of TARC (CCL17). TARC was identified by the authors as being a "possible mediator of myeloid recruitment in the lung."
They then observed a rise in "Th2 lymphocytes into the airway" and "Th2-type cytokines [IL-5 and IL-13].

ABSTRACT

Understanding SARS-CoV-2 associated immune pathology is crucial to develop pan-effective vaccines and treatments. Here we investigate the immune events from the acute state up to four weeks post SARS-CoV-2 infection, in non-human primates (NHP) with heterogeneous pulmonary pathology. We show a robust migration of CD16 expressing monocytes to the lungs occurring during the acute phase, and we describe two subsets of interstitial macrophages (HLA-DR+CD206-): a transitional CD11c+CD16+ cell population directly associated with IL-6 levels in plasma, and a long-lasting CD11b+CD16+ cell population. Trafficking of monocytes is mediated by TARC (CCL17) and associates with viral load measured in bronchial brushes. We also describe associations between disease outcomes and high levels of cell infiltration in lungs including CD11b+CD16hi macrophages and CD11b+ neutrophils. Accumulation of macrophages is long-lasting and detectable even in animals with mild or no signs of disease. Interestingly, animals with anti-inflammatory responses including high IL-10:IL-6 and kynurenine to tryptophan ratios show less severe illness. Our results unravel cellular mechanisms of COVID-19 and suggest that NHP may be appropriate models to test immune therapies.

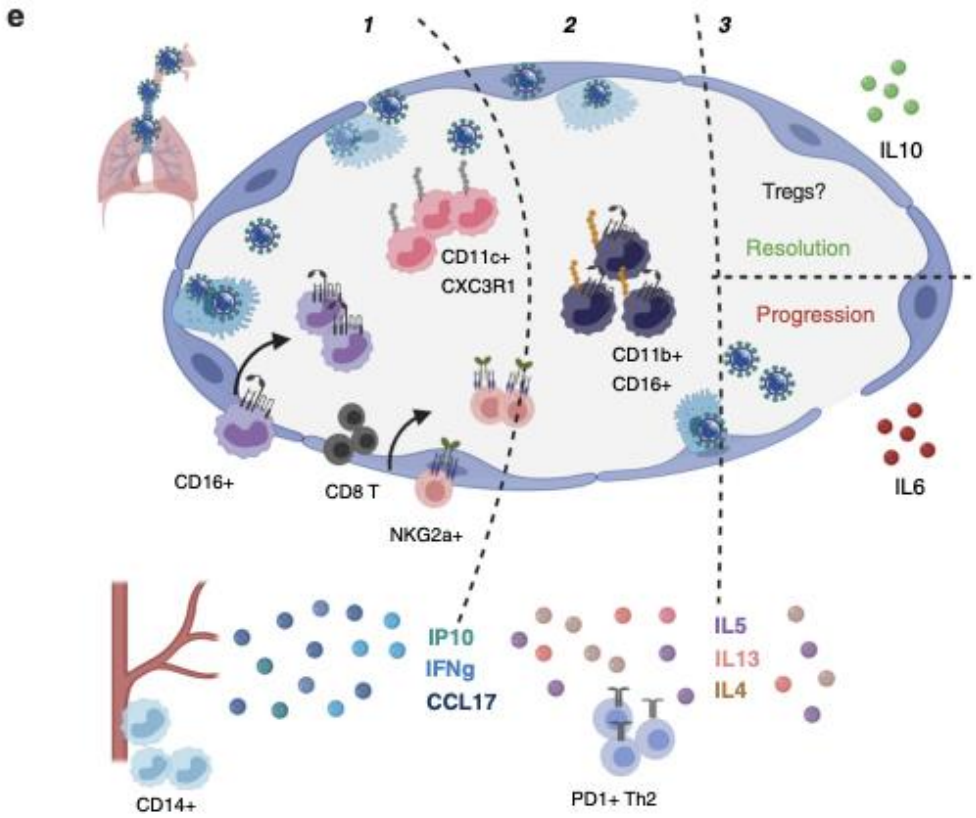


Figure 6e. Summary of immune events in the lungs and blood of SARS-CoV-2 infected animals, from the 1-acute phase 2-switch to Th2-type responses and 3-resolution phase.

STRUCTURAL ANALYSIS OF FULL-LENGTH SARS-COV-2 SPIKE PROTEIN FROM AN ADVANCED VACCINE CANDIDATE

Bangaru S, Ozorowski G, Turner HL, Antanasijevic A, Huang D, Wang X, Torres JL, Diedrich JK, Tian JH, Portnoff AD, Patel N, Massare MJ, Yates JR 3rd, Nemazee D, Paulson JC, Glenn G, Smith G, Ward AB.. Science. 2020 Nov 27;370(6520):1089-1094. doi: 10.1126/science.abe1502. Epub 2020 Oct 20.
Level of Evidence: Other - Mechanism-based reasoning

BLUF

Investigators primarily from The Scripps Research Institute (La Jolla, California) analyze, via cryo–electron microscopy and site-specific glycan analysis, the stability of a subunit COVID-19 vaccine candidate, NVAX-CoV2372 (Figure 1A), which was founded on a complete spike protein prepared in polysorbate 80 detergent. They found that the full length NVAX-CoV2372 glycoprotein of SARS-CoV-2 remains stable and "locked in the antigenically preferred perfusion confirmation," confirming its application and focus as a viable vaccine target.

ABSTRACT

Vaccine efforts against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) responsible for the current COVID-19 pandemic are focused on SARS-CoV-2 spike glycoprotein, the primary target for neutralizing antibodies. We performed cryo-EM and site-specific glycan analysis of one of the leading subunit vaccine candidates from Novavax based on a full-length spike protein formulated in polysorbate 80 (PS 80) detergent. Our studies reveal a stable prefusion conformation of the spike immunogen with slight differences in the S1 subunit compared to published spike ectodomain structures. We also observed novel interactions between the spike trimers allowing formation of higher order spike complexes. This study confirms the structural integrity of the full-length spike protein immunogen and provides a basis for interpreting immune responses to this multivalent nanoparticle immunogen.

FIGURES

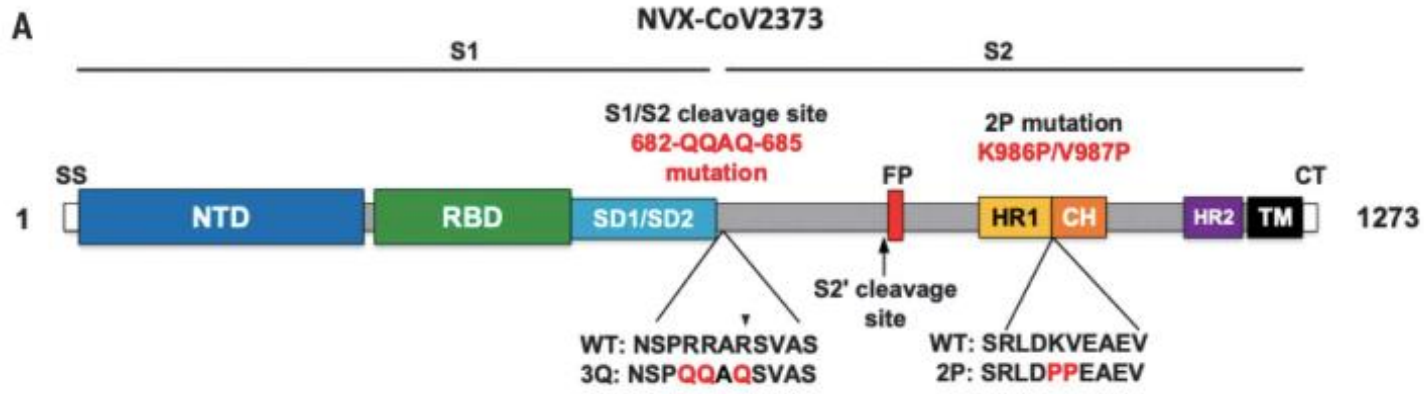


Figure 1A. Evaluation of SARS-CoV-2 3Q-2P-FL spike glycoprotein. Linear diagram of the sequence and structure elements of the FL SARS-CoV-2 spike protein showing the S1 and S2 ectodomain. Structural elements include a cleavable signal sequence (SS, white), NTD (blue), RBD (green), SD1 and SD2 (light blue), protease cleavage site 2′ (S2′, arrow), fusion peptide (FP, red), heptad repeat 1 (HR1,yellow), central helix (CH, brown), heptad repeat 2 (HR2, purple), TM domain (black), and CT (white). The native furin cleavage site was mutated (RRAR→QQAQ) to be protease resistant and stabilized by introducing two proline (2P) substitutions at positions K986P and V987P to produce SARS-CoV-2 3Q-2P-FL spike. A, Ala; D, Asp; E, Glu; K, Lys; L, Leu; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; V, Val.

IMPLEMENTATION OF A POOLED SURVEILLANCE TESTING PROGRAM FOR ASYMPTOMATIC SARS-COV-2 INFECTIONS ON A COLLEGE CAMPUS - DUKE UNIVERSITY, DURHAM, NORTH CAROLINA, AUGUST 2-OCTOBER 11, 2020

Denny TN, Andrews L, Bonsignori M, Cavanaugh K, Datto MB, Deckard A, DeMarco CT, DeNaeyer N, Epling CA, Gurley T, Haase SB, Hallberg C, Harer J, Kneifel CL, Lee MJ, Louzao R, Moody MA, Moore Z, Polage CR, Puglin J, Spotts PH, Vaughn JA, Wolfe CR.. MMWR Morb Mortal Wkly Rep. 2020 Nov 20;69(46):1743-1747. doi: 10.15585/mmwr.mm6946e1.
Level of Evidence: 3 - Non -randomized controlled cohort/follow-up study

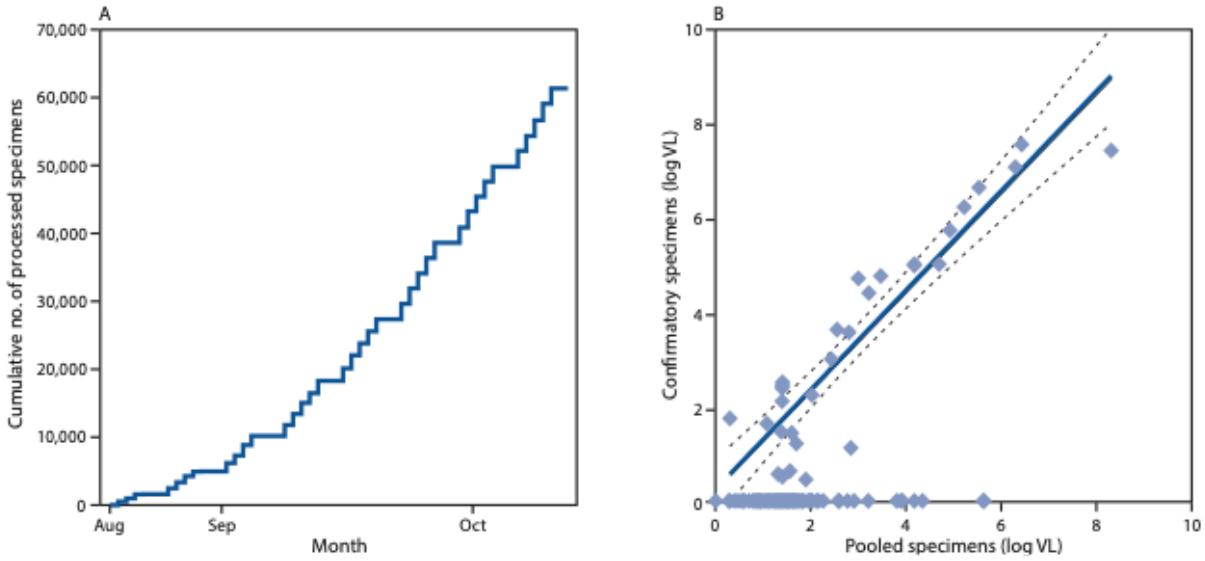
BLUF

This observational cohort study conducted by an interdisciplinary team at Duke University in North Carolina between August 2 and October 11, 2020 implemented mandatory masking, social distancing, and entry-and-surveillance SARS-CoV-2 testing with five-to-one pooled quantitative RT-PCR (Figure). Large-scale testing of 10,265 students (n=68,913 total tests) yielded 84 positive results (43 asymptomatic; Table 2). Authors suggest pooled testing allows for high sensitivity and rapid results, while decreasing supply-chain disruptions by using fewer resources, which could be more successful in limiting transmission than testing only symptomatic individuals.

ABSTRACT

On university campuses and in similar congregate environments, surveillance testing of asymptomatic persons is a critical strategy (1,2) for preventing transmission of SARS-CoV-2, the virus that causes coronavirus disease 2019 (COVID-19). All students at Duke University, a private research university in Durham, North Carolina, signed the Duke Compact (3), agreeing to observe mandatory masking, social distancing, and participation in entry and surveillance testing. The university implemented a five-to-one pooled testing program for SARS-CoV-2 using a quantitative, in-house, laboratory-developed, real-time reverse transcription-polymerase chain reaction (RT-PCR) test (4,5). Pooling of specimens to enable large-scale testing while minimizing use of reagents was pioneered during the human immunodeficiency virus pandemic (6). A similar methodology was adapted for Duke University's asymptomatic testing program. The baseline SARS-CoV-2 testing plan was to distribute tests geospatially and temporally across on- and off-campus student populations. By September 20, 2020, asymptomatic testing was scaled up to testing targets, which include testing for residential undergraduates twice weekly, off-campus undergraduates one to two times per week, and graduate students approximately once weekly. In addition, in response to newly identified positive test results, testing was focused in locations or within cohorts where data suggested an increased risk for transmission. Scale-up over 4 weeks entailed redeploying staff members to prepare 15 campus testing sites for specimen collection, developing information management tools, and repurposing laboratory automation to establish an asymptomatic surveillance system. During August 2-October 11, 68,913 specimens from 10,265 graduate and undergraduate students were tested. Eighty-four specimens were positive for SARS-CoV-2, and 51% were among persons with no symptoms. Testing as a result of contact tracing identified 27.4% of infections. A combination of risk-reduction strategies and frequent surveillance testing likely contributed to a prolonged period of low transmission on campus. These findings highlight the importance of combined testing and contact tracing strategies beyond symptomatic testing, in association with other preventive measures. Pooled testing balances resource availability with supply-chain disruptions, high throughput with high sensitivity, and rapid turnaround with an acceptable workload.

FIGURE. Cumulative number of nasal swab specimens processed for pooled SARS-CoV-2 real-time reverse transcription–polymerase chain reaction testing, August 18–October 11, 2020 (A) and viral load estimates for pooled (n = 158) and confirmatory specimens (n = 30), August–October 2020 (B)* — Duke University, Durham, North Carolina



Abbreviation: VL = viral load.
* In addition to data for students, plot includes data for one faculty member with a positive test result.

TABLE 2

Number of tests[±] positive for SARS-CoV-2 among students, by test category — Duke University, Durham, North Carolina, August 2–October 11, 2020

Test category	No. of tests performed	No. of positive tests	No. (%) of persons† asymptomatic at testing
Entry testing	8,873	17	9 (53)
Pooled testing§	59,476	29	29 (100)
Contact tracing¶	379	23	5 (22)
Symptom monitoring¶	185	15	0 (0)
Total	**68,913**	**84**	**43 (51)**

* Testing was performed on specimens from a total population of 10,265 undergraduate and graduate students residing on Duke University campus or in the surrounding Durham community.

† Who received positive test results.

§ Total number of positive pools = 158, which upon deconvolution yielded 29 individual positive specimens among students.

¶ Because numbers for total tests in contact tracing and symptom monitoring were encoded together, classifications of tests as resulting from contact tracing or symptom monitoring in this table represent an estimate.

TABLE 2. Number of tests* positive for SARS-CoV-2 among students, by test category — Duke University, Durham, North Carolina, August 2– October 11, 2020

SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 OUTBREAK RELATED TO A NIGHTCLUB, GERMANY, 2020

Muller N, Kunze M, Steitz F, Saad NJ, Mühlemann B, Beheim-Schwarzbach JI, Schneider J, Drosten C, Murajda L, Kochs S, Ruscher C, Walter J, Zeitlmann N, Corman VM.. Emerg Infect Dis. 2020 Dec 2;27(2). doi: 10.3201/eid2702.204443. Online ahead of print.
Level of Evidence: 5 - Case report

BLUF

Authors from several institutions in Berlin, in conjunction with the European Center for Disease Prevention and Control, report a large COVID-19 outbreak traced back to three crowded events at a nightclub in Germany in February and March. The three events resulted in a total of 74 primary cases of COVID-19 (Figure 1) with potentially substantial additional spread throughout the community. This outbreak provides an example of the dangers of superspreading events in indoor settings and helps validate continued closures of nightclubs.

ABSTRACT

We report an outbreak of coronavirus disease with 74 cases related to a nightclub in Germany in March 2020. Staff members were particularly affected (attack rate 56%) and likely caused sustained viral transmission after an event at the club. This outbreak illustrates the potential for superspreader events and corroborates current club closures.

FIGURES

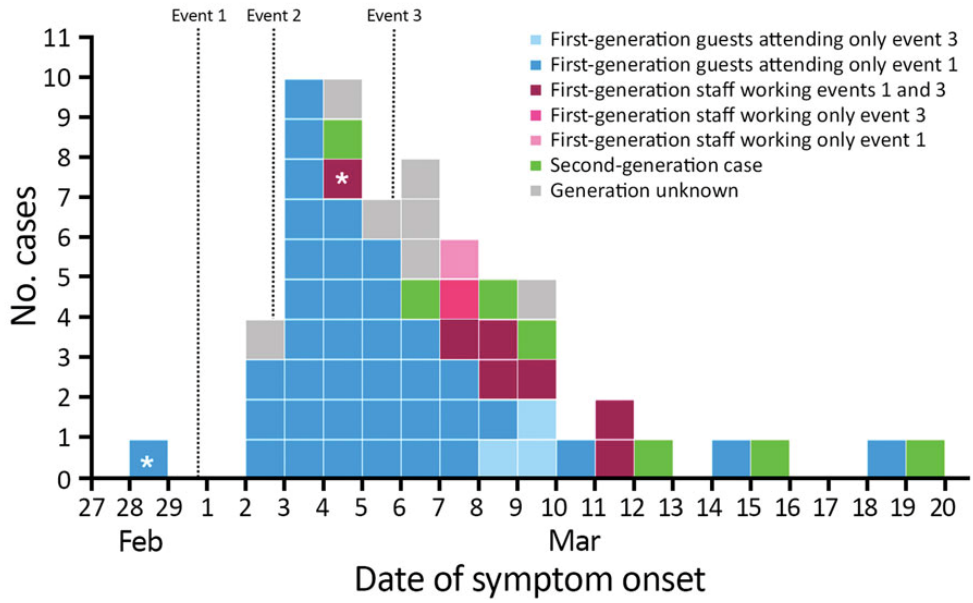


Figure 1. Date of symptom onset among 64 coronavirus disease cases linked to an outbreak in a nightclub Berlin, Germany, March 2020. The asterisks indicate cases with symptom onset prior attending event 1 (symptom onset on February 28, 2020) and event 3 (symptom onset on March 4, 2020). No guests among cases reported attending event 2, but all attended either event 1 or event 3. No staff among cases attended only event 2; all attended event 1, event 3, or both events.

DECLINE IN SARS-COV-2 ANTIBODIES AFTER MILD INFECTION AMONG FRONTLINE HEALTH CARE PERSONNEL IN A MULTISTATE HOSPITAL NETWORK - 12 STATES, APRIL-AUGUST 2020

Self WH, Tenforde MW, Stubblefield WB, Feldstein LR, Steingrub JS, Shapiro NI, Ginde AA, Prekker ME, Brown SM, Peltan ID, Gong MN, Aboodi MS, Khan A, Exline MC, Files DC, Gibbs KW, Lindsell CJ, Rice TW, Jones ID, Halasa N, Talbot HK, Grijalva CG, Casey JD, Hager DN, Qadir N, Henning DJ, Coughlin MM, Schiffer J, Semenova V, Li H, Thornburg NJ, Patel MM; CDC COVID-19 Response Team; IVY Network.. MMWR Morb Mortal Wkly Rep. 2020 Nov 27;69(47):1762-1766. doi: 10.15585/mmwr.mm6947a2.

Level of Evidence: 3 - Local non-random sample

BLUF

The CDC COVID-19 Response Team and IVY Network conducted an analysis of 3,284 frontline healthcare personnel, from 13 different hospitals across 12 states from April 3 through June 19, 2020 and found 194 had SARS-CoV-2 antibodies at initial baseline testing using ELISA assay (96% sensitivity and 99% specificity). About 60 days later, 156 returned for follow up testing, of which 93.6% had a decline in antibody response, and 108 reported COVID-19 symptoms. Additionally, among the cohort who initially tested positive, seroreversion was observed in 19.4% of those that reported symptoms, and 47.9% of those without symptoms (Figure 1). These results suggest antibodies to SARS-CoV-2 decline over time and negative serologic results do not exclude previous infection, highlighting there may be significant differences in interpretation on serological studies regarding COVID-19 epidemiology.

ABSTRACT

Most persons infected with SARS-CoV-2, the virus that causes coronavirus disease 2019 (COVID-19), develop virus-specific antibodies within several weeks, but antibody titers might decline over time. Understanding the timeline of antibody decline is important for interpreting SARS-CoV-2 serology results. Serum specimens were collected from a convenience sample of frontline health care personnel at 13 hospitals and tested for antibodies to SARS-CoV-2 during April 3-June 19, 2020, and again approximately 60 days later to assess this timeline. The percentage of participants who experienced seroreversion, defined as an antibody signal-to-threshold ratio >1.0 at baseline and <1.0 at the follow-up visit, was assessed. Overall, 194 (6.0%) of 3,248 participants had detectable antibodies to SARS-CoV-2 at baseline (1). Upon repeat testing approximately 60 days later (range = 50-91 days), 146 (93.6%) of 156 participants experienced a decline in antibody response indicated by a lower signal-to-threshold ratio at the follow-up visit, compared with the baseline visit, and 44 (28.2%) experienced seroreversion. Participants with higher initial antibody responses were more likely to have antibodies detected at the follow-up test than were those who had a lower initial antibody response. Whether decay in these antibodies increases risk for reinfection and disease remains unanswered. However, these results suggest that serology testing at a single time point is likely to underestimate the number of persons with previous SARS-CoV-2 infection, and a negative serologic test result might not reliably exclude prior infection.

FIGURES

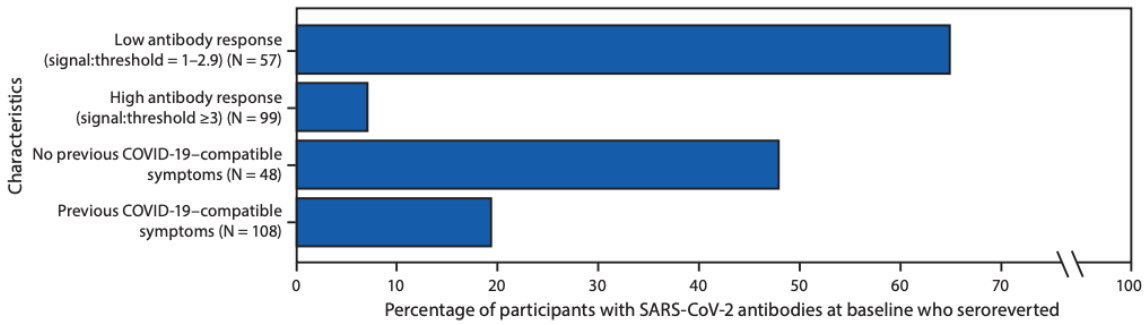


Figure 1. Percentage of 156 participants with SARS-COV-2 antibodies at baseline who seroreverted approximately 60 days later, by baseline antibody response* and history of COVID-19–compatible symptoms before baseline testing† — 13 academic medical centers, United States, 2020.

CRITICAL CARE

SARS-COV-2 ANALYSIS ON ENVIRONMENTAL SURFACES COLLECTED IN AN INTENSIVE CARE UNIT: KEEPING ERNEST SHACKLETON'S SPIRIT

Escudero D, Boga JA, Fernández J, Forcelledo L, Balboa S, Albillos R, Astola I, García-Prieto E, Álvarez-Argüelles ME, Martín G, Jiménez J, Vázquez F.. Intensive Care Med Exp. 2020 Nov 23;8(1):68. doi: 10.1186/s40635-020-00349-5.
Level of Evidence: Other - Guidelines and Recommendations

BLUF

This prospective study by intensivists and microbiologists at Hospital Universitario Central de Asturias in Spain analyzed SARS-CoV-2 contamination in the intensive care unit (ICU) after implementation of a cleaning protocol using detergent and 0.05% sodium hypochlorite twice per shift, negative pressure of -10 Pa, and an air change rate of 20 cycles per hour (Figure 2). Samples from various locations (i.e. ventilators, bed rails, keyboards) tested via RT-PCR were negative for SARS-CoV-2 (n=102), and there were no infections among ICU workers (n=237). In light of these results, authors suggest these safety protocols could prevent environmental contamination to ensure protection of health care workers and patients.

ABSTRACT

BACKGROUND: Intensive care unit workers are at high risk of acquiring COVID-19 infection, especially when performing invasive techniques and certain procedures that generate aerosols (< 5 mum). Therefore, one of the objectives of the health systems should implement safety practices to minimize the risk of contagion among these health professionals. Monitoring environmental contamination of SARS-CoV-2 may help to determine the potential of the environment as a transmission medium in an area highly exposed to SARS-CoV-2, such as an intensive care unit. The objective of the study was to analyze the environmental contamination by SARS-CoV-2 on surfaces collected in an intensive care unit, which is dedicated exclusively to the care of patients with COVID-19 and equipped with negative pressure of - 10 Pa and an air change rate of 20 cycles per hour. Furthermore, all ICU workers were tested for COVID-19 by quantitative RT-PCR and ELISA methods. RESULTS: A total of 102 samples (72 collected with pre-moistened swabs used for collection of nasopharyngeal exudates and 30 with moistened wipes used in the environmental microbiological control of the food industry) were obtained from ventilators, monitors, perfusion pumps, bed rails, lab benches, containers of personal protective equipment, computer keyboards and mice, telephones, workers' shoes, floor, and other areas of close contact with COVID-19 patients and healthcare professionals who cared for them. The analysis by quantitative RT-PCR showed no detection of SARS-CoV-2 genome in environmental samples collected by any of the two methods described. Furthermore, none of the 237 ICU workers was infected by the virus. CONCLUSIONS: Presence of SARS-CoV-2 on the ICU surfaces could not be determined supporting that a strict cleaning protocol with sodium hypochlorite, a high air change rate, and a negative pressure in the ICU are effective in preventing environmental contamination. These facts together with the protection measures used could also explain the absence of contagion among staff inside ICUs.

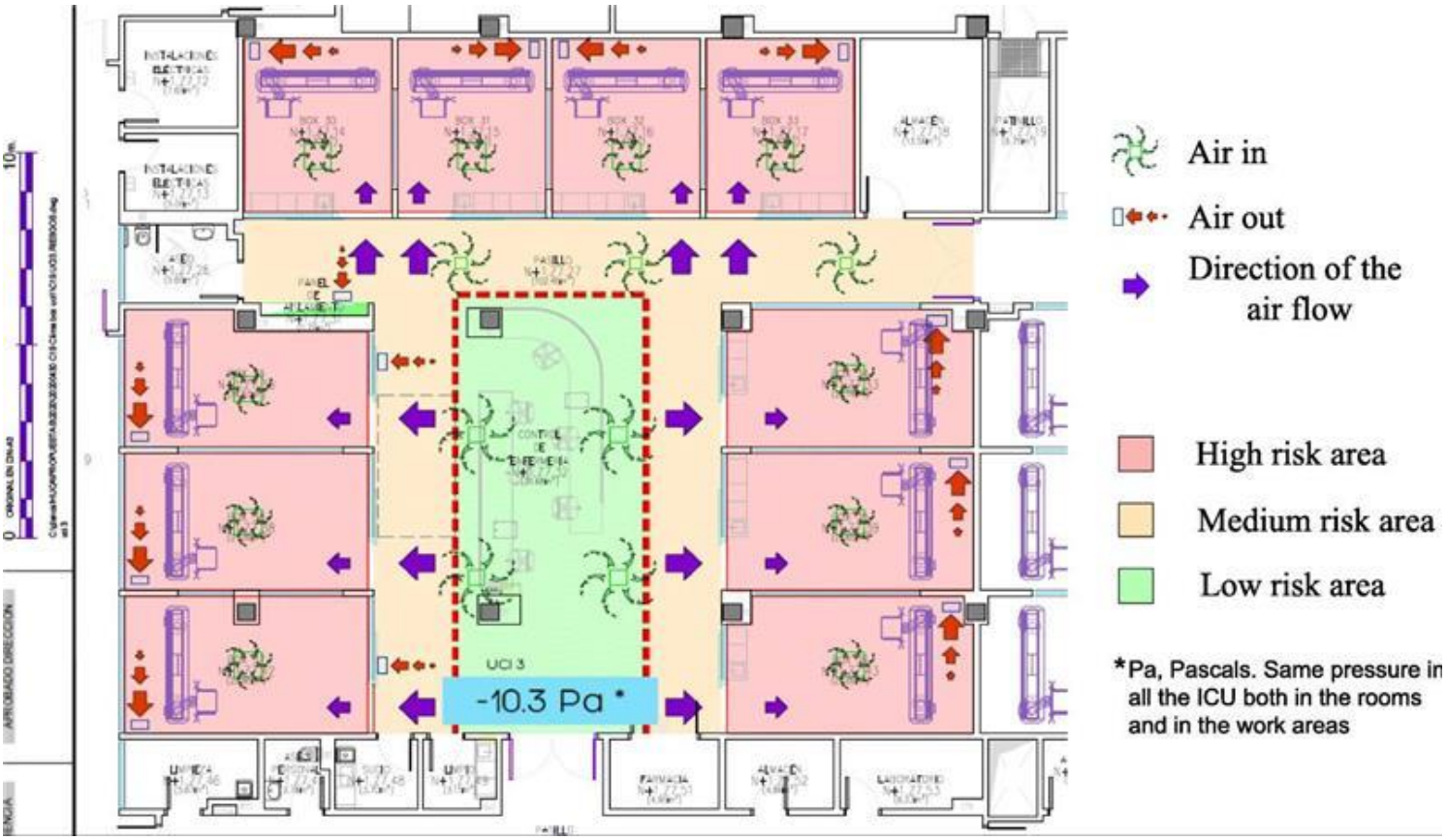


Figure 2. Map showing the high, medium, and low risk areas, as well as directions of the air flows of the intensive care unit. The value of the negative pressure is indicated

ANTIRETROVIRALS FOR PROPHYLAXIS AGAINST COVID-19; A COMPREHENSIVE LITERATURE REVIEW

Alavian G, Kolahdouzan K, Mortezazadeh M, Torabi ZS.. J Clin Pharmacol. 2020 Nov 20. doi: 10.1002/jcph.1788. Online ahead of print.

Level of Evidence: Other - Review / Literature Review

BLUF

A literature review by specialists in pharmacy and oncology at Tehran University of Medical Sciences, Iran from June to October 2020 found limited evidence regarding efficacy of protease inhibitors and nucleotide reverse transcriptase inhibitors (NRTIs) on SARS-CoV-2 disease progression. While some studies found protease inhibitors and NRTIs bind RdRp on SARS-CoV-2 in vitro (Figure 1), others found no significant difference in clinical outcomes between treatment with these drugs and controls. Authors suggest protease inhibitors and NRTIs may have inhibitory activity against SARS-CoV-2 but there is limited clinical evidence for using antiretroviral therapy as prophylaxis against COVID-19.

ABSTRACT

Although people living with human immunodeficiency virus(PLWH) and other comorbidities are expected to experience griever consequences with COVID-19, recent cohort studies do not indicate this. Antiretrovirals(ARVs) might have a prophylactic role in these patients. The purpose of this study is to review the most recently published articles on the possible role of ARVs for pre or post-exposure prophylaxis against COVID-19. From June to October 2020, we searched scientific databases using specific keywords to identify ongoing trials or articles published before October 2020 investigating any subgroups of ARVs for prophylaxis against COVID-19. Apart from molecular docking studies, in vitro, animal, and human studies are very limited for evaluating the prophylactic role of ARVs against SARS-CoV-2 infection. According to our findings, there is no definite evidence to support use of protease inhibitors for this purpose, despite the promising results of molecular studies and limited clinical evidence for ritonavir boosted lopinavir, darunavir, and nelfinavir when used early in the course of the disease. Nucleotide/nucleoside reverse transcriptase inhibitors(NRTI) also have shown binding affinity to SARS-CoV-2 main enzymes in molecular, in vitro and animal studies. NRTIs like tenofovir and emtricitabine might exhibit prophylactic role against SARS-CoV-2 infection. In conclusion, currently there is no evidence to justify the use of ARVs for prophylaxis against COVID-19. This article is protected by copyright. All rights reserved.

FIGURES

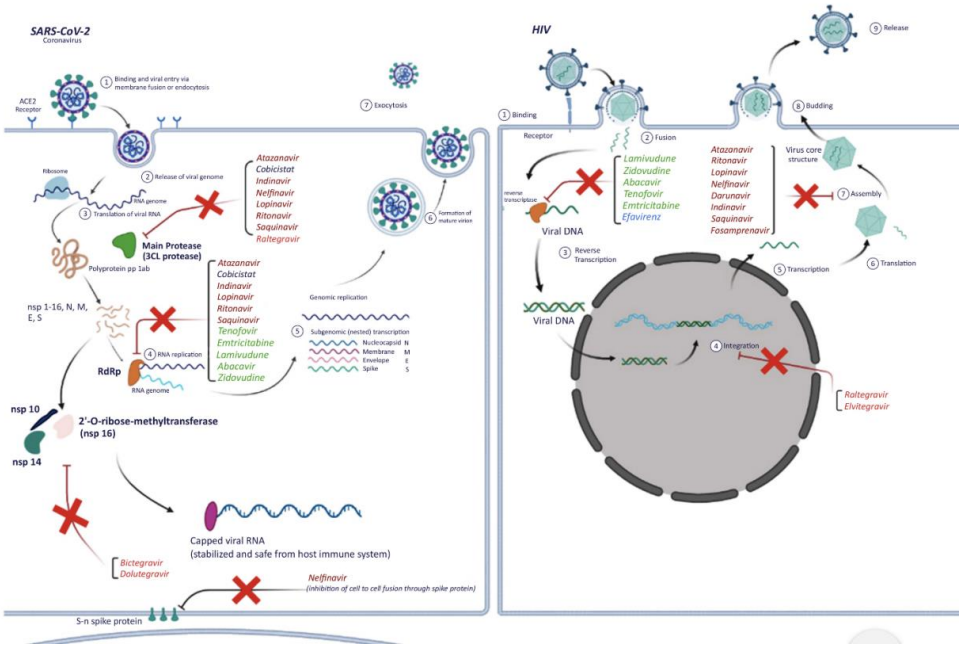


Figure 1. Mechanism of action of antiretroviral drugs through the life cycle of HIV and SARS-CoV-2 viruses. Figure was created using BioRender.com.

HOW TO INVESTIGATE A SERIOUS ADVERSE EVENT REPORTED DURING A CLINICAL TRIAL FOR A COVID-19 VACCINE

Shakir S, Lane S, Davies M.. Drug Saf. 2020 Nov 21. doi: 10.1007/s40264-020-01018-y. Online ahead of print.
Level of Evidence: Other - Guidelines and Recommendations

BLUF

This editorial by pharmacological experts from the United Kingdom outlines a method to evaluate adverse events in COVID-19 vaccine trials. Using a modified World Health Organization Algorithm (Figure 1), they propose a checklist to identify and qualify the relevance of adverse events to safely and appropriately proceed with vaccine trials (see summary).

SUMMARY

The Brighton Collaboration has created a checklist to determine significance of adverse events for the Data and Safety Monitoring Board in the United Kingdom. The checklist is summarized below:
1. "Is there evidence for any other cause?"
2. "Is there a known causal association with the vaccine or vaccination?"
3. "Is there strong evidence against a causal association?"
4. "What are the other qualifying factors?"

Further proposed objectives:
1. Protect the health of all involved.
2. Ensure that actions made by the Data and Safety Monitoring Board are rooted in scientific evidence.
3. Ensure integrity in the process by blinding sponsors.
4. Maintain high ethical standards throughout.

FIGURES

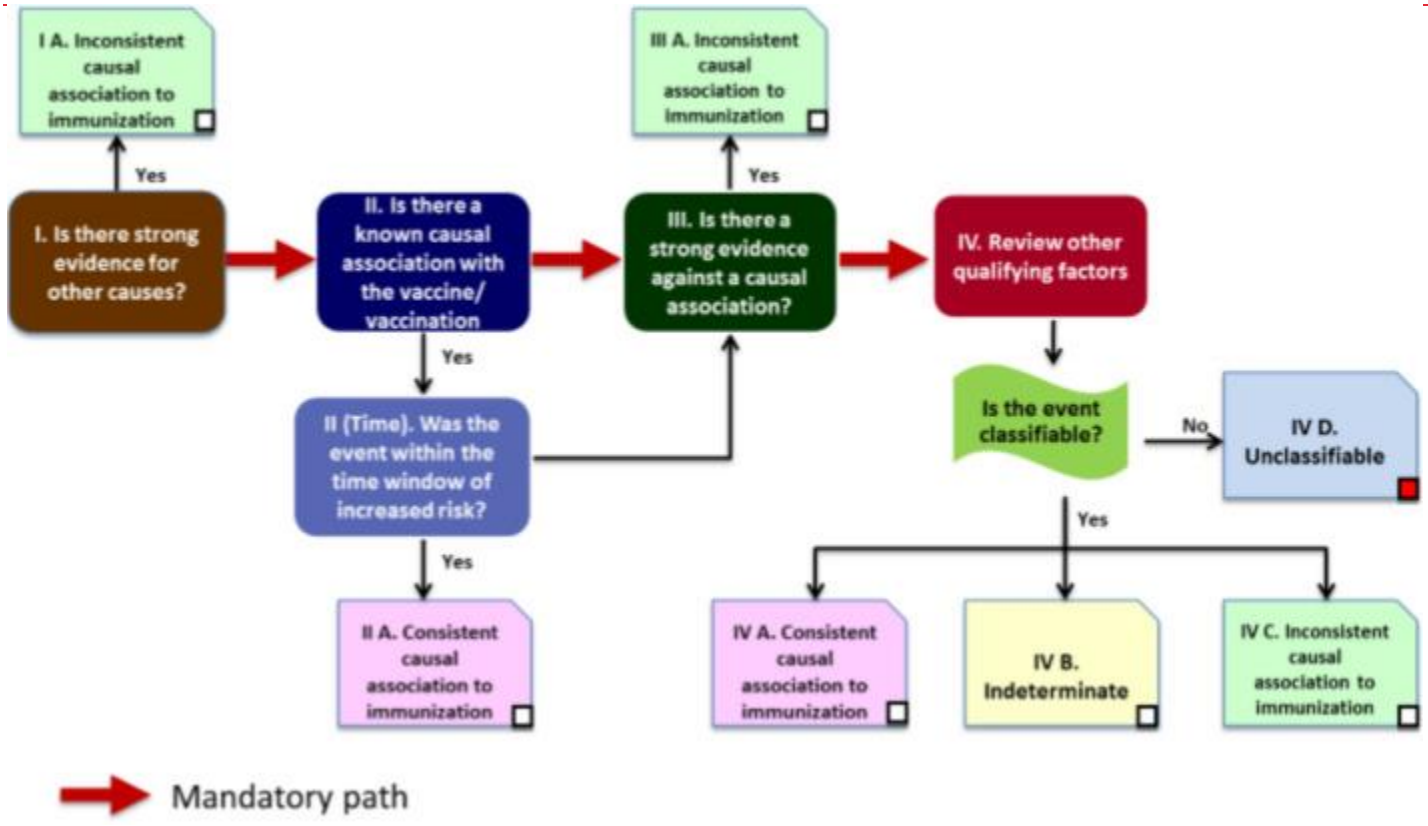


Figure 1. Causality assessment algorithm

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