The Daily COVID-19 Literature Surveillance Summary

April 07, 2021

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COVID-19 Daily Literature Surveillance

COVID19LST

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LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

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

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

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

How to cite the Levels of Evidence Table

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

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

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

EXECUTIVE SUMMARY

Transmission & Prevention

- Transmission of SARS-CoV-2 infection appears to be promising among children in summer schools that are applying stringent control measures in Barcelona, Spain. Epidemiologists from Barcelona University evaluated SARS-CoV-2 transmission rates in 1,905 children attending summer schools with strict preventive measures for 5 weeks between June and July of 2020 compared to general population transmission rates in the same period. They found reproduction number was lower in children attending summer school (normalized reproduction rate [Re]=1.3) compared to the general population (Re=1.9). Authors conclude risk for SARS-CoV-2 transmission in schools is low and schools can be opened safely with strict preventive measures in place.

- Transmissibility may be an important consideration in immunocompromised patients. Internists, infectious disease physicians, and a pulmonologist from the University of Toledo summarized the findings of 21 studies reporting data on the infectiousness and shedding of SARS-CoV-2 in a total of 69 immunocompromised patients. They found that all patients had positive RT-PCR for > 3 weeks (median 50.5 days, IQR 35-74 days). Though RT-PCR cannot differentiate between viable and dead virus, authors suggest immunocompromised patients may transmit SARS-CoV-2 for prolonged periods and emphasize the importance of isolation precautions and follow-up in this population.

R&D: Diagnosis & Treatments

- Escape of SARS-CoV-2 501Y.V2 from neutralization by convalescent plasma: Investigators from various academic and medical institutions in South Africa, Israel, London, United States, and Germany collected and analyzed plasma from patients positive for SARS-CoV-2 501Y.V2 variant with K417N, E484K, and N501Y mutations in the spike receptor binding domain (RBD), then compared viral growth response verses non-variant strains using a live neutralizing assay (LVNA). The results revealed the strongest neutralization of both the variant and non-variant strains of SARS-CoV-2 when treated with plasma elicited by E484K mutation, suggesting the possibility of novel treatments and targets with adequate protection from variant strains, a concern with the current vaccines.

TABLE OF CONTENTS

EPIDEMIOLOGY

DECREASED INCIDENCE, VIRUS TRANSMISSION CAPACITY, AND SEVERITY OF COVID-19 AT ALTITUDE ON THE AMERICAN CONTINENT

Arias-Reyes C, Carvajal-Rodriguez F, Poma-Machicao L, Aliaga-Raduán F, Marques DA, Zubieta-DeUrioste N, Accinelli RA, Schneider-Gasser EM, Zubieta-Calleja G, Dutschmann M, Soliz J.. PLoS One. 2021 Mar 29;16(3):e0237294. doi: 10.1371/journal.pone.0237294. eCollection 2021.
Level of Evidence: 1 - Local and current random sample surveys (or censuses)

BLUF

An epidemiological study conducted by researchers from multiple medical institutions in Canada, Peru, Switzerland, and Australia investigated COVID-19 infection rates in 23 countries in North, Central, and South America as of May 23, 2020. After controlling for population densities, they found significantly decreased incidence of infection (Figure 1), lesser transmission (Table 2), and decreased severity of COVID-19 infection (Table 3) in highland areas > 1000 m above sea level. These findings suggest possible beneficial effects of low barometric pressure, barometrical hypoxia, and physiologic characteristics of altitude at above 1000 m above sea level are related to decreased infectivity of COVID-19 infection and could facilitate discovery of new treatment strategies based on these mechanisms.

ABSTRACT

The coronavirus disease 2019 (COVID-19) outbreak in North, Central, and South America has become the epicenter of the current pandemic. We have suggested previously that the infection rate of this virus might be lower in people living at high altitude (over 2,500 m) compared to that in the lowlands. Based on data from official sources, we performed a new epidemiological analysis of the development of the pandemic in 23 countries on the American continent as of May 23, 2020. Our results confirm our previous finding, further showing that the incidence of COVID-19 on the American continent decreases significantly starting at 1,000 m above sea level (masl). Moreover, epidemiological modeling indicates that the virus transmission rate is lower in the highlands (>1,000 masl) than in the lowlands (<1,000 masl). Finally, evaluating the differences in the recovery percentage of patients, the death-to-case ratio, and the theoretical fraction of undiagnosed cases, we found that the severity of COVID-19 is also decreased above 1,000 m. We conclude that the impact of the COVID-19 decreases significantly with altitude.

FIGURES

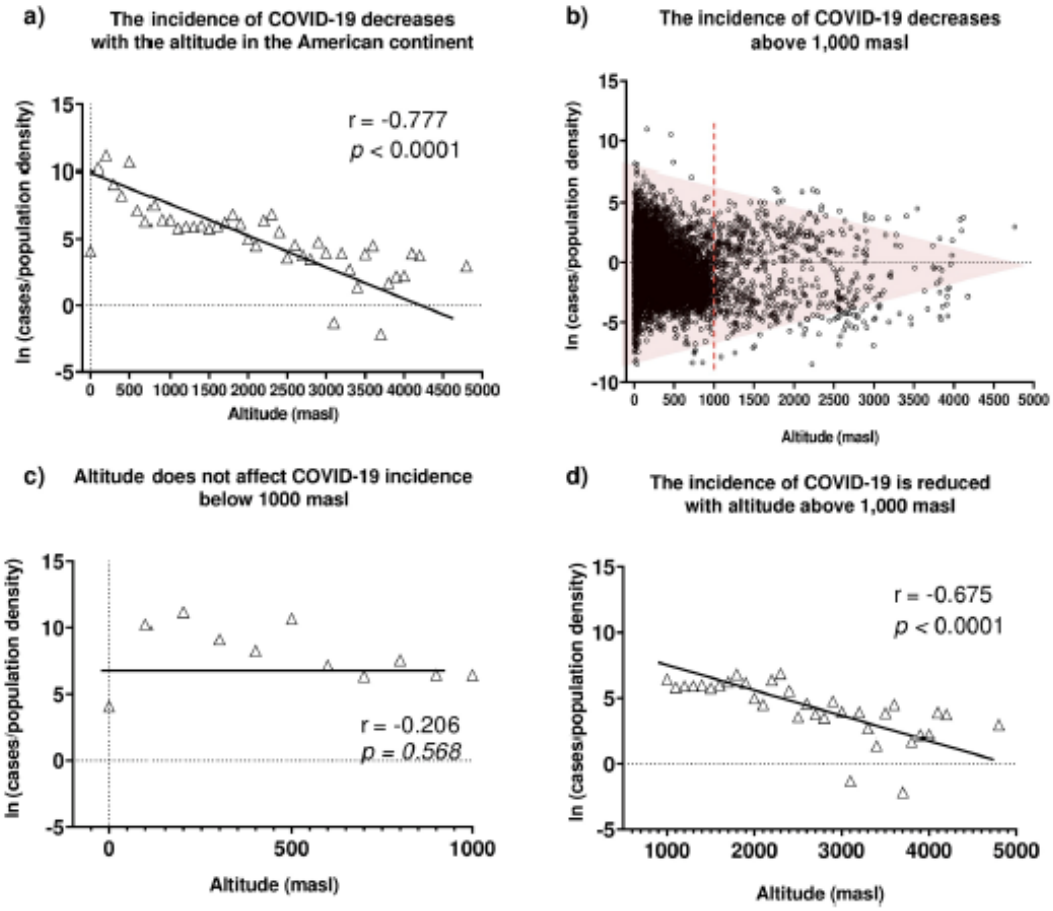

Fig 1. The effect of altitude on the incidence of COVID-19 in the American continent. Epidemiological data were retrieved on May 23. Data on population density were extracted from the dataset created by CIESIN [22] or the corresponding country's national statistics institute on May 23. Data were normalized by the population density of the same location and summed in intervals of 100 m of elevation. Raw, normalized, and adjusted data are available at https://doi.org/10.6084/m9.figshare.12685478. a) Correlation between altitude and the number of positive COVID-19 cases in the American continent grouped in intervals of 100 meters. b) Altitudinal distribution of the of COVID-19 positive cases in the American continent (not grouped by altitude intervals). c) Correlation between altitude and the number of positive COVID-19 cases reported below 1,000 m in the American continent. d) Correlation between altitude and the number of positive COVID-19 cases reported above 1,000 m in the American continent.

	Lowlands (<1,000 masl)			Highlands (>1,000 masl)		
	Probability of transmission (%)	Confidence interval	R_0	Probability of transmission (%)	Confidence interval	R_0
Argentina	3.731	(3.728, 3.733)	2.29	2.038	(2.028, 2.048)	1.25
Bolivia	3.575	(3.572, 3.579)	2.17	2.689	(2.683, 2.696)	1.63
Colombia	3.357	(3.355, 3.36)	2.27	3.511	(3.508, 3.513)	2.38
Ecuador	3.878	(3.877, 3.88)	2.53	3.443	(3.441, 3.445)	2.25
Peru	3.9046	(3.9041, 3.9051)	3.32	2.752	(2.75, 2.754)	2.34

Table 2. COVID-19 probability of transmission and basic reproduction numbers (R0) for highland and lowland populations.

Country	Percentage of Recovered Patients		Death-to-case-ratio	
	Highlands (%)	Lowlands (%)	Highlands (%)	Lowlands (%)
Argentina	57.57	36.05	4.66	4.95
Bolivia	35.73	5.62	5.79	3.84
Colombia	4.05	3.46	36.42	15.7
Ecuador	9.1	2.38	9.56	3.60
Peru	25.77	8.22	3.5	3.70

Table 3. Percentage of recovered and death rates in COVID-19 patients.

ADULTS

SYMPTOMATIC REINFECTION OF SARS-COV-2 WITH SPIKE PROTEIN VARIANT N440K ASSOCIATED WITH IMMUNE ESCAPE

Rani PR, Imran M, Lakshmi JV, Jolly B, Jain A, Surekha A, Senthivel V, Chandrasekhar P, Divakar MK, Srinivasulu D, Bhoyar RC, Vanaja PR, Scaria V, Sivasubbu S.. J Med Virol. 2021 Apr 5. doi: 10.1002/jmv.26997. Online ahead of print.
Level of Evidence: 5 - Case Report

BLUF

A team of microbiologists and physicians from Kurnool Medical College in Andhra Pradesh, India present the case of a 47-year old male public-service employee who tested positive for COVID-19 on July 25, 2020, negative on August 2, and positive again on September 10. Whole genome sequencing showed a total of 15 and 17 genetic variations in the two episodes of infection (Figure 1), with the N440K spike protein variant identified in both infections. Because the prevalence of the N440K variant in the state of Anhra Pradesh was 33% at the time, authors suggest not only that reinfection with variants is possible, but that punctual genetic analysis is crucial to assess potential impact of variants on community transmission patterns.

FIGURES

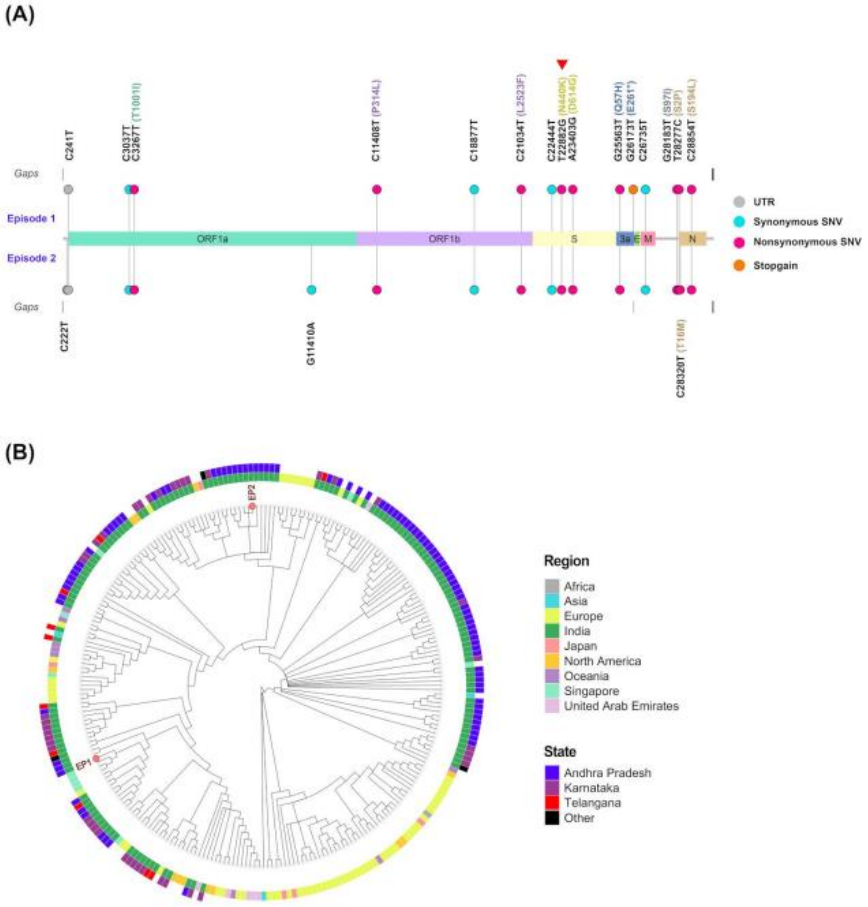

Figure 1 (A) Genetic variants in the genome isolates of the 2 episodes (denoted as Episode 1 and Episode 2) of SARS-CoV-2 infections. The 22882T>G (Spike: N440K) variant is marked with an arrowhead. (B) Phylogenetic context of the virus isolates of the 2 episodes with other global samples having the N440K variant

ABDOMINAL AND TESTICULAR PAIN: AN ATYPICAL PRESENTATION OF COVID-19

Kim J, Thomsen T, Sell N, Goldsmith AJ.. Am J Emerg Med. 2020 Jul;38(7):1542.e1-1542.e3. doi: 10.1016/j.ajem.2020.03.052. Epub 2020 Mar 31.
Level of Evidence: 5 - Case Report

BLUF

In March 2020, emergency physicians from Harvard Medical School in Boston, MA reported a 42-year-old male referred by a PCP to the ED for evaluation of chest, abdominal, and flank pain with tenderness radiating to the groin and testis without any respiratory symptoms, fever, or other typical COVID-19 symptom. He was treated with a diagnosis of pneumonia and possible colitis (Figures 2, 3). Patient tested positive for COVID-19 two days after discharge from the ED. This study suggests using face-mask coverings in hospitals for all patients regardless of symptom presentation and improving communication between healthcare workers could decrease the spread of disease in the community, particularly given that this patient had an unreported fever before the start of other symptoms.

ABSTRACT

The outbreak of a novel coronavirus disease (COVID-19) has been of concern to health care workers (HCW's) in the emergency department (ED) due to potential exposure and transmission. This case report describes a man who was referred to the ED for abdominal and testicular pain who was subsequently found to test positive for COVID-19. Due to the lack of respiratory symptoms, proper protective equipment (PPE) was not donned, and it led to several patients and health care workers being exposed. Given recent new descriptions of patients who present atypically, full PPE for all patients may be considered as community spread increases.

FIGURES

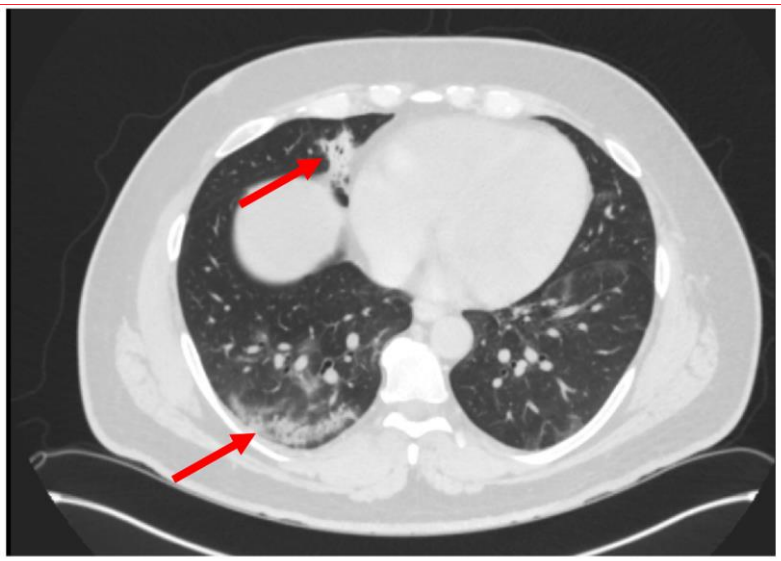

Fig. 2. Computed tomography of patient with GGO in the posterior right lower lobe and consolidation in the right middle lobe (i.e. arrow).

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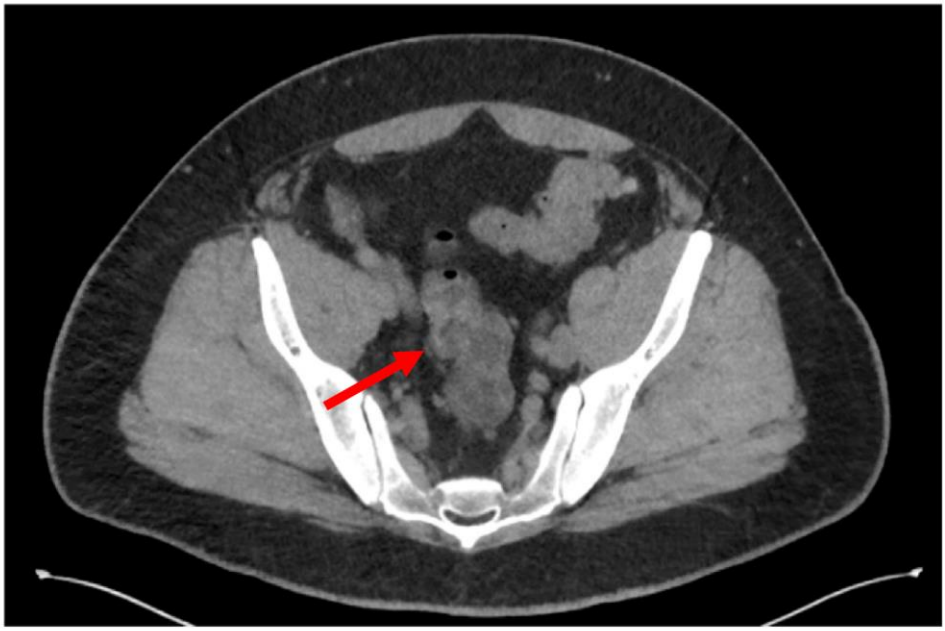


Fig. 3. Computed tomography of patient with mild colonic mural thickening in the sigmoid colon (i.e. arrow).

Fig. 3. Computed tomography of patient with mild colonic mural thickening in the sigmoid colon (i.e. arrow).

THE ROLE OF AUTOPHAGY IN CONTROLLING OF SARS-COV-2 INFECTION: AN OVERVIEW WITH VIROPHAGY-MEDIATED OF MOLECULAR DRUG TARGETS

Sargazi S, Sheervalilou R, Rokni M, Shirvaliloo M, Shahraki O, Rezaei N.. Cell Biol Int. 2021 Apr 5. doi: 10.1002/cbin.11609. Online ahead of print.
Level of Evidence: 5 - Review / Literature Review

BLUF

A team of cellular and molecular biology experts from the Zahedan University in Iran reviewed current literature about the viral mechanisms of SARS-CoV-2 and whether current antiviral medications targeting the autophagy dependent pathway ATG5 (Figures 1, 2) are viable therapeutics. They found current data indicates that corticosteroids, antivirals, and interferons specific for autophagy pathways may mitigate the SARS-CoV-2 replication cycle and suggest further clinical research in this area, specifically into nanoparticle delivery of potential therapeutics.

ABSTRACT

Autophagy-dependent cell death is a prominent mechanism that majorly contributes to homeostasis by maintaining the turnover of organelles under stressful conditions. Several viruses, including coronaviruses, take advantage of cellular autophagy to facilitate their own replication. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a beta-coronavirus that mediates its replication through dependent or independent ATG5 pathway using specific double-membrane vesicles that can be considered as similar to autophagosomes. With due attention to several mutations in NSP6, a non-structural protein with a positive regulatory effect on autophagosome formation, a potential correlation between SARS-CoV-2 pathogenesis mechanisms and autophagy can be expected. Certain medications, albeit limited in number, have been indicated to negatively regulate autophagy flux, potentially in a way similar to the inhibitory effect of beta-CoVs on the process of autophagy. Though, there is no conclusive evidence to support their direct antagonizing effect on CoVs. Off-target accumulation of a major fraction of FDA-approved autophagy modulating drugs may result in adverse effects. Therefore, medications that have modulatory effects on autophagy could be considered as potential lead compounds for the development of new treatments against this virus. This review discusses the role of autophagy/virophagy in controlling of SARS-CoV-2, focusing on the potential therapeutic implications. This article is protected by copyright. All rights reserved.

FIGURES

Fig. 1 represents the lung infection by SARS-CoV-2, followed by autophagy pathway. Entry of SARS-CoV-2 into the lung cells is mainly mediated by the ACE2 receptor, meanwhile the autophagy has also been implicated in the viral replication in the cells, a process partly related to the formation of Double-membrane vesicle in the lung cells.

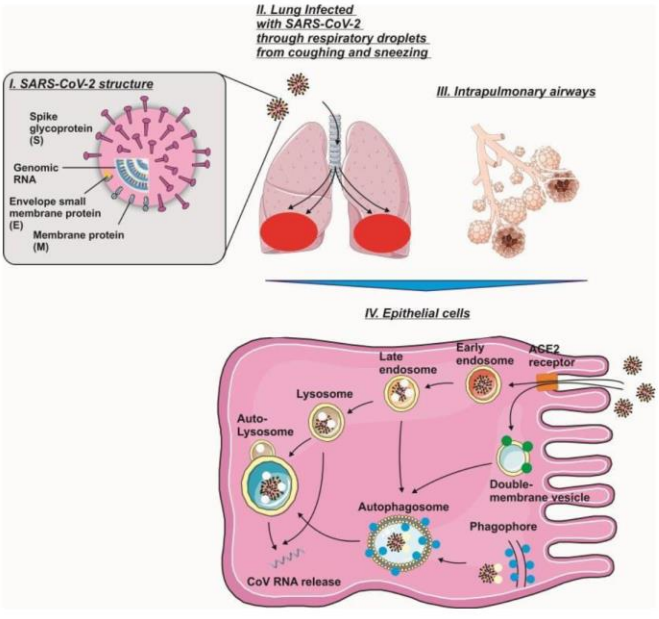
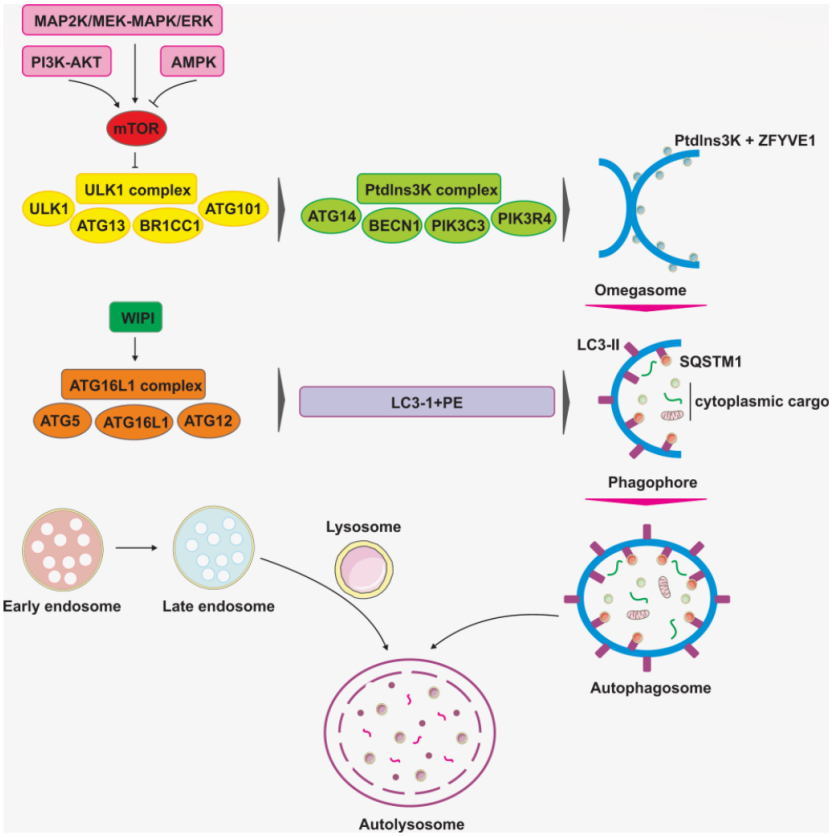


Fig. 2 represents autophagy involved genes. Autophagy is included three protein complexes: ULK1 complex, including of ULK1, ATG13, RB1CC1 and ATG101; PtdIns3K complex, including of the ATG14, BECN1, PIK3R4/VPS15 and PIK3C3/VPS34 and ATG16L1 complex, including of ATG16L1, ATG5 and ATG12. During Starvation and stress the cell is in an emergency condition, when the mTOR protein is inactivated, allowing ULK1 complex formation, then activation of the PtdIns3K complex, at the result products the PtdIns3P-rich areas on the surface of the omegasome. WIPI proteins realize this process and recruit the ATG16L1 complex and facilitate lipidation of LC3-I to make LC3-II. Expansion of the phagophore through membrane addition sequesters some of the cytoplasm and upon closure forms the autophagosome. After formation autophagosome from phagophore, autophagosomes are fused with lysosomes to make the autolysosomes, where the cargo is digested (Bello-Perez, Sola, Novoa, Klionsky, & Falco, 2020).



INVESTIGATION OF SARS-COV-2 RNA IN MILK PRODUCED BY WOMEN WITH COVID-19 AND FOLLOW-UP OF THEIR INFANTS: A PRELIMINARY STUDY

Kilic T, Kilic S, Kırıcı Berber N, Gunduz A, Ersoy Y.. Int J Clin Pract. 2021 Mar 24:e14175. doi: 10.1111/ijcp.14175. Online ahead of print.

Level of Evidence: 3 - Local non-random sample

BLUF

A prospective observational study conducted by pulmonary medicine and pediatric researchers from Inonu University in Malatya, Turkey investigated the presence of SARS-CoV-2 in the whole human milk of 15 lactating women with COVID-19. The infants of these women were followed for 14 days and received COVID-19 swab tests. They found SARS-CoV-2 RNA in 4 mothers' milk, 3 of whom were breastfeeding. Six infants (including all four from the breastmilk-positive mothers) had positive throat swab (RT-qPCR) with mild symptoms and good clinical outcomes (Table 1). The authors note that the RNA found in breastmilk does not confirm the presence of viable virus and that respiratory transmission from mother to child is the more likely route of transmission in these cases.

ABSTRACT

OBJECTIVES: Studies have shown that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is primarily transmitted from person to person via airborne droplets.It is unclear whether it can be shed into human milk and transmitted to a child via breastfeeding.We investigated the presence of SARS-CoV-2 RNA in human milk samples of 15 mothers with coronavirus disease 19(COVID-19) and in the throat swab samples of their infants. METHODS: This is a prospective observational study in which breast milk samples were collected from 15 mothers with COVID-19.The presence of SARS-CoV-2 RNA in the whole human milk samples of the patients was investigated using RT-qPCR. All of the infants underwent a clinical follow-up during their 14-day isolation and their throat swab samples were tested for SARS-CoV-2 RNA. RESULTS: Of 15 mothers with COVID-19,SARS-CoV-2 RNA was detected in milk samples from 4 mothers. The throat swab samples from these mothers'infants were found to be positive for SARS-CoV-2 RNA.Three of the four mothers were breastfeeding. In addition, during the 14-day isolation,all but three of the mothers breastfed their infants. Of the 12 breastfed infants,while the test for SARS-CoV-2 RNA in throat swab samples was negative in six of the infants, the other six infants,who had mild COVID-19 symptoms,tested positive for SARS-CoV-2 RNA.Clinical outcomes of all mothers and infants were uneventful. CONCLUSION: To our knowledge, this is the first case series with the largest number of cases with SARS-CoV-2 RNA positivity in human milk samples of mothers with COVID-19. However, we believe that the benefits of breastfeeding may outweigh the risk of SARS-CoV-2 infection in infants.

FIGURES

Table 1. Clinical Characteristics of the Mothers with SARS-CoV-2 Confirmed by RT-qPCR and Their Infants.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12	Case 13	Case 14	Case 15
Age(year)	24	26	26	28y	34	25	27	33	44	27	27	32	29	30	31
Signs of infection	Sore throat, fatigue, light cough	Cough, fatigue	Sore throat, cought	sore throat, cought	Fever, cought	Fatigue, headache	Shortness of breath, fever	Hedache, myalgia	Fever, arthralgia	Fever	myalgia	Hedache, arthralgia	Fevere	Cought, hedache	Myalgia cought
Coexisting conditions	No	Bipolar disorder	No	No	No	No	No	No	No	No	No	No	No	Psoriasis	Gestatic diabetes hypothy ism
CT scan finding	No	No	ND	No	No	ND	No	No	ND	ND	ND	ND	ND	ND	Yes
Contact with patients	No	Yes	Yes	No	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Throat swab RT-qPCR	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive
Throat swab RT-qPCR results	30.21[b]	32.04[b]	35.31[b]	29.04[b]	28.01[b]	27.90[b]	31.05[b]	24.09[b]	24.08[b]	29.09[b]	28.12[b]	27.02[b]	24.02[b]	32.47[b]	20.07[b]
Human milk RT-qPCR	**Positive**	Negative [a]	Negative [a]	Negative [a]	Negative [a]	Negative [a]	Negative [a]	Negative [a]	Negative [a]	Negative [a]	**Positive**	**Positive**	**Positive**	Negative [a]	Negativ
Human milk RT-qPCR results	38,04[b]										32.02[b]	29.12[b]	26.12[b]		
Mother–infant contact															
Immediate separation	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	Yes
Breastfeeding	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Mode of delivery	vaginal	Caesarean	Vaginal	Vaginal	Vaginal	Vaginal	Caesarean	Vaginal	Vaginal	Vaginal	Caesarean	Caesarean	Vaginal	Vaginal	Caesare
Hospital stay days	7	6	Not hospitalized	6	Not hospitalized	Not hospitalized	Not hospitalized	Not hospitalized	5	Not hospitalized	Not hospitalized	5	5	Not hospitalized	10
Any severe complications	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Treatment															
Supportive treatment	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hydroxychloroq	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No

Table1 part 1

uine															
Azithromycin	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No
Antiviral agent (Favipiravir)	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	Yes
Intensive care unit	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Infant	**Infant 1**	**Infant 2**	**Infant 3**	**Infant 4**	**Infant 5**	**Infant 6**	**Infant 7**	**Infant 8**	**Infant 9**	**Infant 10**	**Infant 11**	**Infant 12**	**Infant 13**	**Infant 14**	**Infant (a twin**
Age(day)	22	36	120	34	180	150	300	150	2	24	16	34	120	185	1
Sign of infection	Fever	No	No	Fever	No	No	Stuffy nose	No	No	No	Fever	Fever	Fever	Fever	respirat distress moanin
CT scan finding	ND	ND	ND	No finding	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Coexisting condition	No	No	No	Diabetes mellitus	No	No	No	No	No	No	No	No	No	No	No
Throat swab RT-qPCR	Positive	Negative [a]	Negative [a]	Positive	Negative [a]	Negative [a]	Positive	Negative [a]	Negative [a]	Negative [a]	Positive	Positive	Positive	Positive	Positive
Throat swab RT-qPCR results	31.05[b]			29.05[b]			30.07[b]				25.08[b]	28.42[b]	25.57[b]	25.09[b]	21.63[b] 15.32[b]
Hospital stay days	7	Not hospitalized	Not hospitalized	7	Not hospitalized	Not hospitalized	Not hospitalized	Not Hospitalized	5	Not Hospitalized	5	5	5	Not hospitalized	20
Any severe complications	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Treatment															
Supportive treatment	Yes	No	No	Yes	No	No	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes
Specific treatment for Covid-19	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Intensive care unit	No	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes

ND: Not done. *Human milk collection was performed with manual expression. [a] Two RT-qPCR specimens examined at 24-hour intervals are negative. [b]Cycle threshold values.

Table 1 part 2

TRANSMISSION OF SARS-COV-2 INFECTION AMONG CHILDREN IN SUMMER SCHOOLS APPLYING STRINGENT CONTROL MEASURES IN BARCELONA, SPAIN

Jordan I, de Sevilla MF, Fumado V, Bassat Q, Bonet-Carne E, Fortuny C, Garcia-Miquel A, Jou C, Adroher C, Casas MM, Girona-Alarcon M, Garcia MH, Tomas GP, Ajanovic S, Arias S, Balanza N, Baro B, Millat-Martinez P, Varo R, Alonso S, Álvarez-Lacalle E, López D, Claverol J, Cubells M, Brotons P, Codina A, Cuadras D, Bruijning-Verhagen P, Faust S, Munro A, Muñoz-Almagro C, Català M, Prats C, Garcia-Garcia JJ, Gratacós E.. Clin Infect Dis. 2021 Mar 12:ciab227. doi: 10.1093/cid/ciab227. Online ahead of print.

Level of Evidence: 3 - Local non-random sample

BLUF

Epidemiologists from Barcelona University evaluated SARS-CoV-2 transmission rates in 1,905 children attending summer schools with strict preventive measures for 5 weeks between June and July of 2020 compared to general population transmission rates in the same period (Table 5). They found reproduction number was lower in children attending summer school (normalized reproduction rate [Re]=1.3) compared to the general population (Re=1.9)(Table 1, see summary). Authors conclude risk for SARS-CoV-2 transmission in schools is low and schools can be opened safely with strict preventive measures in place.

SUMMARY

For comparison of reproduction number in children attending summer school (8 hours during weekdays) with general population (theoretically during a longer period/day; i.e 24h), authors normalized Re according to the following parameters:
A) 40 hours a week in the summer school
B) 168 hours in a week (general population)

ABSTRACT

BACKGROUND: Understanding the role of children in SARS-CoV-2 transmission is critical to guide decision-making for schools in the pandemic. We aimed to describe the transmission of SARS-CoV-2 among children and adult staff in summer schools.
METHODS: During July 2020 we prospectively recruited children and adult staff attending summer schools in Barcelona who had SARS-CoV-2 infection. Primary SARS-CoV-2 infections were identified through: (1) surveillance program in 22 summer schools' of 1905 participants, involving weekly saliva sampling for SARS-CoV-2 RT-PCR during 2-5 weeks; (2)cases identified through the Catalonian Health Surveillance System of children diagnosed with SARS-CoV-2 infection by nasopharyngeal RT-

PCR. All centres followed prevention protocols: bubble groups, hand washing, facemasks and conducting activities mostly outdoors. Contacts of a primary case within the same bubble were evaluated by nasopharyngeal RT-PCR. Secondary attack rates and effective reproduction number in summer schools(R*) were calculated. RESULTS: Among the over 2000 repeatedly screened participants, 30children and 9adults were identified as primary cases. A total of 253 close contacts of these primary cases were studied (median 9 (IQR 5-10) for each primary case), among which twelve new cases (4.7%) were positive for SARS-CoV-2. The R* was 0.3, whereas the contemporary rate in the general population from the same areas in Barcelona was 1.9. CONCLUSIONS: The transmission rate of SARS-CoV-2 infection among children attending school-like facilities under strict prevention measures was lower than that reported for the general population. This suggests that under preventive measures schools are unlikely amplifiers of SARS-CoV-2 transmission and supports current recommendations for school opening.

FIGURES

Table 5: Summer schools characteristics, according to the confirmation of transmission in their premises.

Variable	All campuses (n=41)	Campuses where contagion occurred (n=7)	Campuses with no contagion (n=34)	p
Number of children/day	76 (55-120)	60 (42.00-67)	88.5 (57.75-120)	0.0890
Number of adult staff/day	13.5 (10-20)	10 (9-13)	15 (11-20)	0.2224
Number of caregivers/day	12 (9-15)	9 (7.5-12)	12 (9-15)	0.4449
Ratio children/caregiver	10 (9-10)	10 (7-10)	10 (9-10)	0.4853
Indoors surface area	685 (347-1312.5)	600 (350-670)	756 (359-1375)	0.5368
Outdoors surface area (m^2)	525 (220-2125)	93 (21-145)	838 (240-2500)	0.0036
Number of communal use toilets o	6 (5-12)	4 (2-9)	6.5 (5-12)	0.1802
Activities conducted outdoors (%)	70 (60-80)	60 (35-77.5)	70 (67-80)	0.2702
Compulsory use of masks indoors	35 (85.4%)	7 (100%)	28 (82.4%)	0.229
Assessed compliance with indoors mask wearing (0-10 scale)	8 (7-9)	8 (7.5-8.5)	8 (7-9)	0.9
Compulsory use of masks outdoors	24 (60%)	4 (66.7%)	20 (58.8%)	0.7176
Assessed compliance with indoors mask wearing (0-10 scale)	8 (6-9)	9 (7.5-9.75)	8 (6-9)	0.2738
Handwashing frequency/day ≥5 times/day	26 (63.4%)	1 (14.3%)	25 (73.5%)	0.0030
<5 times/day	15 (36.6%)	6 (85.7%)	9(26.5%)	
Presence of hydroalcoholic gel dispensers on site	40 (100)	7 (100)	33 (100)	-

Table 1. Overall PCR screening results, per week (includes children and staff) and calculated incidence from the RP1.

Type of PCR screening test		Week 1	Week 2	Week 3	Week 4	Week 5	TOTAL Week 1-5
Saliva	Total	531	1600	1473	1094	542	5240
n (%)	Positive	1 (0.2)	3 (0.2)	1 (0.07)	4 (0.4)	3 (0.6)	12 (0.2)
	Negative	524 (98.7)	1589 (99.3)	1471 (99.9)	1090 (99.6)	538 (99.3)	5212 (97.7)
	I	1 (0.2)	0 (0)	1(0.07)	0 (0)	1 (0.2)	3 (0.06)
	NA	5 (0.9)	8 (0.5)	0 (0)	0 (0)	0 (0)	13 (0.2)
Nasopharyngeal*	Total	181	136	131	92	40	580
n (%)	Positive	2 (1.1)	1 (0.7)	1(0.8)	1(1.1)	0 (0)	5 (0.9)
	Negative	177 (97.8)	133 (97.8)	130 (99.2)	89 (96.7)	40 (100)	569 (98.1)
	I	1 (0.5)	1(0.7)	0 (0)	2 (2.2)	0 (0)	4 (0.7)
	NA	1 (0.5)	1(0.7)	0 (0)	0 (0)	0 (0)	2 (0.3)
Calculated Summer-Camps overall Incidence for 100,000		187.97	187.50	67.89	365.63	553.51	630.00

RP1: Recruitment Pathway 1. I: indeterminate. NA: Cannot be assessed.

* Nasopharyngeal samples were done paired with saliva samples for saliva verification

TRANSMISSIBILITY AND VIRAL REPLICATION OF SARS-COV-2 IN IMMUNOCOMPROMISED PATIENTS

Beran A, Zink E, Mhanna M, Abugharbyeh A, Hanrahan J, Duggan J, Assaly R.. J Med Virol. 2021 Mar 30. doi: 10.1002/jmv.26970. Online ahead of print.
Level of Evidence: 5 - Review / Literature Review

BLUF

Internists, infectious disease physicians, and a pulmonologist from the University of Toledo summarized the findings of 21 studies reporting data on the infectiousness and shedding of SARS-CoV-2 in a total of 69 immunocompromised patients. They found that all patients had positive RT-PCR for > 3 weeks (median 50.5 days, IQR 35-74 days). Though RT-PCR cannot differentiate between viable and dead virus, authors suggest immunocompromised patients may transmit SARS-CoV-2 for prolonged periods and emphasize the importance of isolation precautions and follow-up in this population.

ABSTRACT

Most of the available data are for the immunocompetent population, and the duration of live-virus shedding and transmissibility is well-understood in this population. However, the date regarding infectiousness and shedding of SARS-CoV-2 in the immunocompromised patients is scarce, with no specific guidelines regarding the isolation precautions of these patients. We summarized the findings of all the available studies published until now regarding transmissibility and replication of SARS-CoV-2 in immunosuppressed patients. Studies that reported data regarding viral shedding and replication from respiratory samples (oropharynx or nasopharynx) in immunosuppressed adults with COVID-19 were included. A total of 21 studies, including 69 patients (mean age 52.2 years, and 62.3% males) were included. All patients had persistently positive RT-PCR for > 3 weeks, with median duration of 50.5 days (Interquartile range [IQR] 35-74 days. Five studies[3-7] (including nine patients) reported positive viral cultures with median time of 26 days (IQR 19-94.5). Two studies[7, 8] (including eight patients) reported detecting sub-genomic RNA (sg-RNA) with median duration of 59 days (IQR 29-78). Our review emphasizes the prolonged RT-PCR positivity and viral replication of SAR-CoV-2 in the immunosuppressed population. Our review highlights the importance of close follow-up and prolonged isolation precautions in immunosuppressed patients with persistently positive SARS-CoV-2 RT-PCR. Since viral culture may not be readily available, it may be reasonable to employ sg-RNA as an additional tool for detecting the infectious virus. Further studies with larger sample sizes are needed to evaluate the SARS-CoV-2 shedding and sg-RNA correlation to viral cultures in immunocompromised patients. This article is protected by copyright. All rights reserved.

COVID-19 INFECTION COMPLICATED BY ACUTE ST-ELEVATION MYOCARDIAL INFARCTION

Fu T, Mamaliga G, Pierce JD, Gilkeson R, Gupta A.. Clin Imaging. 2021 Mar 24;78:117-120. doi: 10.1016/j.clinimag.2021.03.010. Online ahead of print.
Level of Evidence: 5 - Case Report

BLUF

Researchers from Case Western Reserve University, OH present a case of a 62-year-old male with a history of hypertension and coronary artery disease who was admitted with COVID-19 who, on day 3 of admission, had a posterior wall ST-elevation myocardial infarction due to occlusion of the left circumflex artery which was treated with a drug eluting stent. On day 6, he went into cardiac arrest, was placed on ECMO, and several days later had a pacemaker placed due to recurrent episodes atrial fibrillation and asystole. This case emphasizes the nature and severity of possible cardiovascular effects of COVID-19 infection, especially in patients with pre-existing risk factors.

SUMMARY

- Laboratory studies showed low hemoglobin, creatinine of 1.41 mg/dL, mildly elevated LFTs, and INR 1.6.
- Initial chest X-ray showed new multifocal bilateral infiltrates
- Initial chest CT showed extensive peripheral basal lung predominant consolidations and ground glass opacities, indicating COVID-19 pneumonia
- SARS-CoV-2 infection was confirmed through RT-PCR testing

ABSTRACT

Clinicians should be aware of the potential for cardiovascular involvement in COVID-19 infection. Coronavirus disease-2019 (COVID-19) is a viral illness caused by severe acute respiratory syndrome-coronavirus-2. While it primarily causes a respiratory illness, a number of important cardiovascular implications have been reported. We describe a patient presenting with COVID-19 whose hospital course was complicated by ST elevation myocardial infarction requiring percutaneous coronary intervention. The goal is to help clinicians gain awareness of the possibility of cardiovascular disease in COVID-19 infection, and maintain a high index of suspicion particularly for patients with risk factors or a prior history of cardiovascular disease.

INTERNATIONAL COMMITTEE OF THE RED CROSS (ICRC): GENERAL GUIDANCE FOR THE MANAGEMENT OF THE DEAD RELATED TO COVID-19

Finegan O, Fonseca S, Guyomarc'h P, Morcillo Mendez MD, Rodriguez Gonzalez J, Tidball-Binz M, Winter KA; ICRC Advisory Group on the Management of COVID-19 Related Fatalities.. Forensic Sci Int. 2020 Mar 31;2:129-137. doi: 10.1016/j.fsisyn.2020.03.007. eCollection 2020.
Level of Evidence: 5 - Guidelines and Recommendations

BLUF

In March 2020, the International Committee of the Red Cross Advisory Group on the Management of COVID-19 Related Fatalities presented guidelines for handling human remains infected with SARS-CoV-2. They provide guidance regarding the management of human remains (Table 1), handling non-identified bodies, policies for temporary holding areas, procedures for decontamination and disposal of remains, and preparing a mass fatality response plan (see summary). Authors suggest following these recommendations will minimize transmission and maintain a safe working environment for employees.

SUMMARY

The Management of Human Remains
- Provide specific training for the staff handling bodily remains
- From recovery to storage to final disposal, ensure exhaustive documentation and traceability
- Body Handlers, those handling human remains, must use the following Personal Protective Equipment: Gloves, Face Masks, Eye protection, Respirators

In the Case of Non-identified Bodies
- Due to the complexity and difficulty identifying remains which may have decomposed beyond recognition, it is recommended that, if unlikely to yield results, examination of identity should be withdrawn if the time it takes poses a high risk of infectious probability for the body handler.

In Temporary Holding Areas
- The following ought to be routinely disinfected: the body bags upon arrival, the original body bag with remains, the outer bag following identification, post-mortem procedures, the two layers of gloves used
- Bags with bodies identified to be positive for COVID-19 must be clearly labelled

In Disposal of Remains
- Cremation of unidentified individuals ought to be avoided, with burial in single graves the preferred method of disposal
- If final disposal takes place off-site, human remains ought to be placed in a second outer body bag
- Due to the release of inhaled vapor, decontamination of the bodies is not advisable

Components of the Mass Fatality Response Plan (MFRP)
- It is essential that local capacity for a mass fatality event is constructed well ahead of time
- All agencies involved must maintain permanent and effective lines of communication
- Proper communication ought to be conducted with the public, particularly with families of the deceased

ABSTRACT

Based on its forensic capacity and experience gained worldwide from the management of the dead in emergencies, including epidemics, the International Committee of the Red Cross has been asked by the authorities and other relevant stakeholders in some of its operational contexts to advise on the management of the dead from COVID-19 infection, for which it has prepared the following guidance. This includes advice on the handling of COVID-19 fatalities and a set of considerations for managers faced with the need to plan for adequately responding to a possible surge in fatalities caused by COVID-19.

FIGURES

Table 1

Transmission based precautions (TBPs): Personal protective equipment (PPE) for care of deceased during COVID-19 pandemic. Table adapted from guidance developed by Department of Health and Social Care, Public Health Wales, Public Health Agency (PHA) Northern Ireland, Health Protection Scotland and Public Health England [7].

	Low risk Procedures*: Admission of deceased Preparation for viewing Release of deceased	Medium risk Procedures**: Rolling deceased Undressing deceased Significant manual handling	High risk Procedures: Autopsy and other invasive procedures
Disposable gloves	Yes	Yes	Yes
Disposable plastic apron	Yes	Yes	Yes
Disposable gown	No	No	Yes
Fluid-resistant (Type IIR) surgical mask (FRSM)	Yes	No	No
Filtering face piece (FFP)***	No	FFP2 or FFP3	FFP3
Disposable eye protection	Yes	Yes	Yes
Protective footwear (e.g. rubber boots which can be disinfected after use)	Yes	Yes	Yes

*If procedure likely to cause droplet contact, use medium risk procedure.

**If procedure likely to generate aerosols, use high risk procedure. ***ECDC (European Centre for Disease Prevention and Control) recommends the use of FFP3 masks for performing aerosol-generating procedures [15]. In case of shortage of Class 3 respirators, the use of Class 2 respirators (e.g. FFP2) may be considered, on a case by case basis and after assessing the risks of the procedures required.

ESCAPE OF SARS-COV-2 501Y.V2 FROM NEUTRALIZATION BY CONVALESCENT PLASMA

Cele S, Gazy I, Jackson L, Hwa SH, Tegally H, Lustig G, Giandhari J, Pillay S, Wilkinson E, Naidoo Y, Karim F, Ganga Y, Khan K, Bernstein M, Balazs AB, Gosnell BI, Hanekom W, Moosa MS; NGS-SA; COMMIT-KZN Team, Lessells RJ, de Oliveira T, Sigal A.. Nature. 2021 Mar 29. doi: 10.1038/s41586-021-03471-w. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Investigators from various academic and medical institutions in South Africa, Israel, London, United States, and Germany collected and analyzed plasma from patients positive for SARS-CoV-2 501Y.V2 variant with K417N, E484K, and N501Y mutations in the spike receptor binding domain (RBD), then compared viral growth response verses non-variant strains using a live neutralizing assay (LVNA). The results revealed the strongest neutralization of both the variant and non-variant strains of SARS-CoV-2 when treated with plasma elicited by E484K mutation (Figure 2), suggesting the possibility of novel treatments and targets with adequate protection from variant strains, a concern with the current vaccines.

ABSTRACT

SARS-CoV-2 variants of concern (VOC) have arisen independently at multiple locations [1, 2] and may reduce the efficacy of current vaccines targeting the spike glycoprotein [3]. Here, using a live virus neutralization assay (LVNA), we compared neutralization of a non-VOC variant versus the 501Y.V2 variant using plasma collected from adults hospitalized with COVID-19 from two South African infection waves, with the second wave dominated by 501Y.V2 infections. Sequencing demonstrated that infections in first wave plasma donors were with viruses harbouring none of the 501Y.V2-defining mutations, except for one with the E484K mutation in the receptor binding domain. 501Y.V2 virus was effectively neutralized by plasma from second wave infections and first wave virus was effectively neutralized by first wave plasma. In cross-neutralization, 501Y.V2 virus was poorly neutralized by first wave plasma, with a 15.1-fold drop relative to 501Y.V2 neutralization by second wave plasma across participants. In contrast, second wave plasma cross-neutralization of first wave virus was more effective, showing only a 2.3-fold decline relative to first wave plasma neutralization of first wave virus. While we only tested one plasma elicited by E484K alone, this potently neutralized both variants. The observed effective neutralization of first wave virus by 501Y.V2 infection elicited plasma provides preliminary evidence that vaccines based on VOC sequences could retain activity against other circulating SARS-CoV-2 lineages.

FIGURES

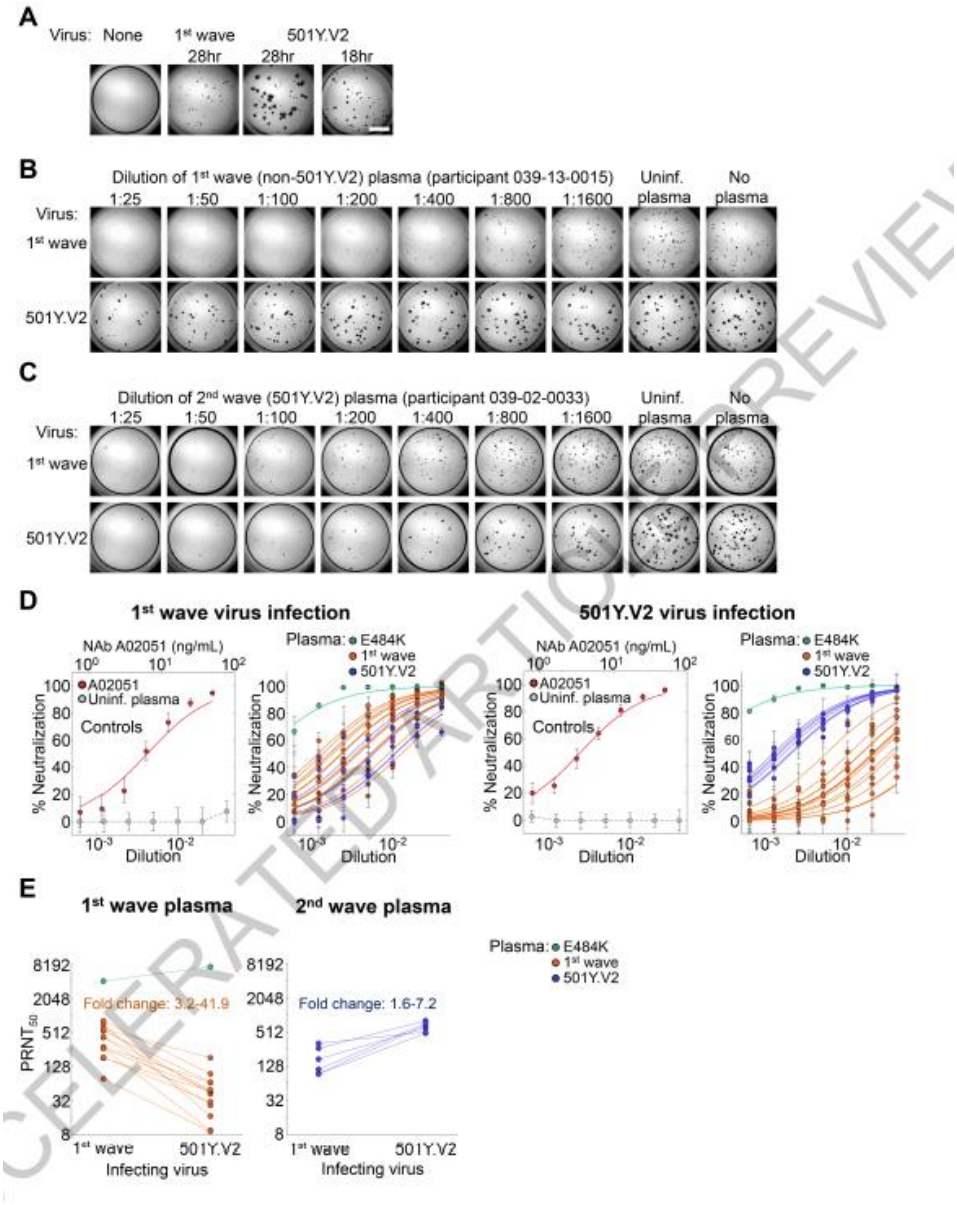


Figure 2. Neutralization of first South African infection wave and 501Y.V2 variants by convalescent plasma elicited by first wave and 501Y.V2 infections. (A) Focus formation by first wave versus 501Y.V2 virus. To obtain similar focus size, 501Y.V2 incubation time was reduced to 18 hours. Scale bar 2mm. A representative focus forming assay using plasma from first wave infected participant 039-13-0015 (B) or 501Y.V2 infected participant 039-02-0033 (C). Columns are plasma dilutions, ranging from 1:25 to 1:1600, a plasma pool from 3 uninfected individuals, and a no plasma control. (D) Quantified neutralization per participant. Bright red points are neutralization by A02051 NAb, grey points neutralization by uninfected plasma, green points neutralization by E484K mutant virus elicited plasma, red points neutralization by plasma from participants infected by first wave, non-501Y.V2 variants, and blue points are neutralization by plasma from 501Y.V2 infected participants. Mean and s.e. of 3-4 independent experiments per participant convalescent plasma from the first (n = 14) or second (n = 6) infection wave or 10 independent experiments for controls. Solid lines of the corresponding colour are fitted values using a sigmoidal equation. First plot shows neutralization of first wave virus by A02051 (PRNT50 = 6.5 ng/mL, 95% confidence intervals of 3.9–9.1 ng/mL) and uninfected plasma. Second plot is neutralization of first wave virus by plasma from convalescent participants. Third plot is neutralization of the 501Y.V2 by A02051 (PRNT50 = 3.5 ng/mL (2.9–4.1 ng/mL)) and uninfected plasma. Forth plot is neutralization of 501Y.V2 virus by plasma from convalescent participants. (E) Decline in PRNT50 in cross-neutralization. Left plot is first wave plasma neutralization of first wave versus 501Y.V2 virus, right plot is second wave plasma neutralization of 501Y.V2 versus first wave virus. Fold-change decline ranged from 3.2–41.9 for first wave plasma, and 1.6–7.2 for second wave plasma. Fold-change elicited by E484K was excluded.

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