

# The Weekly COVID-19 Literature Surveillance Summary

**May 14, 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)
<b>How common is the problem?</b>	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
<b>Is this diagnostic or monitoring test accurate? (Diagnosis)</b>	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
<b>What will happen if we do not add a therapy? (Prognosis)</b>	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
<b>Does this intervention help? (Treatment Benefits)</b>	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
<b>What are the COMMON harms? (Treatment Harms)</b>	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
<b>What are the RARE harms? (Treatment Harms)</b>	Systematic review of randomized trials or n-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
<b>Is this (early detection) test worthwhile? (Screening)</b>	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>

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# EXECUTIVE SUMMARY

## Epidemiology

- [A systematic review of pregnant women with COVID-19 and their neonates](#): Immunology specialists associated with Tehran University of Medical Sciences in Iran conducted a systematic review of 37 articles regarding COVID-19 in pregnant patients. Of the 364 women included in the studies, 25 were asymptomatic, 22 developed pneumonia, and 44 women tested negative for SARS-CoV-2 despite their clinical manifestations. Two mothers died from severe pneumonia and multiple organ dysfunction. The studies also involved a total of 302 neonates, 1 of whom was born dead and 5 had critical conditions. Of the 219 neonates who were tested for SARS-CoV-2 infection, 11 tested positive. These results indicate that the symptoms and prognosis of pregnant women with COVID-19 are similar to that of the general public, but monitoring is crucial for the health of both patients.

## Transmission & Prevention

- [A Systematic Review of Surface Contamination, Stability, and Disinfection Data on SARS-CoV-2 \(Through July 10, 2020\)](#): Researchers associated with Tufts University conducted a systematic review on 78 articles regarding hygiene intervention effectiveness against SARS-CoV-2 transmission. Surface contamination for SARS-CoV-2 RNA was highest in laboratory settings (21%), followed by COVID-19 patient rooms (17%), non-COVID patient rooms (12%), and patient household surfaces (3%). Studies that analyzed surface stability of SARS-CoV-2 indicated a half-life of 2.3-17.9 hours on stainless steel, plastic, and nitrile, which was decreased with increased temperature and humidity. Surface disinfection studies showed a 99% decrease in SARS-CoV-2 detection after using sunlight, UV light, ethanol, hydrogen peroxide, and hypochlorite as disinfectants. These results shed light on the role of fomite transmission of SARS-CoV-2 and efficient disinfection methods to prevent transmission.

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## CLIMATE

### EXPERTS DISCUSS COVID-19-VARIANTS AND VACCINE EFFICACY, IMMUNOSUPPRESSED PATIENTS, AND MORE

JAMA. 2021 Apr 14. doi: 10.1001/jama.2021.5938. Online ahead of print.

Level of Evidence: 5 - Expert Opinion

#### BLUF

In a compilation of interviews, professors and physicians associated with Weill Cornell Medicine, University of Michigan, and Fondazione Policlinico Universitario in Rome, Italy provide their outlook on COVID-19 vaccine doses, accessibility, hesitancy, and variants. They state that the two-dose vaccines have the strongest antibody response and can be more effective against variants, while passive antibody therapy can be helpful to prevent and treat COVID-19 in immunocompromised people who may not benefit from the vaccine. They also suggest walk-in vaccine clinics to bring in those who are less technology-savvy and are less likely to make appointments online. Helmet noninvasive ventilation and high flow nasal oxygen may be used to assist COVID-19 patients with low inspiratory effort.

## GLOBAL

### EXCESS MORTALITY IN THE UNITED STATES IN THE 21ST CENTURY

Preston SH, Vierboom YC.. Proc Natl Acad Sci U S A. 2021 Apr 20;118(16):e2024850118. doi: 10.1073/pnas.2024850118.

Level of Evidence: 5 - Mechanism-based reasoning

#### BLUF

Population specialists associated with University of Pennsylvania and Max Planck Institute for Demographic Research in Rostock, Germany used mortality ratio, excess deaths, and years of life lost to compare age-specific mortality rates in the US compared to a composite of 5 European countries since the year 2000. Analysis of data from the Human Mortality Database revealed that 400,732 excess deaths occurred in the US in 2017, accounting for 13.02 million years of life lost to excess mortality (Table 1). In 2020, COVID-19 alone caused 376,504 deaths, accounting for 4.41 million years of life lost (Table 1), and the authors hypothesize that the lower number of years of life lost is due to the older population primarily affected by COVID-19.

#### ABSTRACT

We use three indexes to identify how age-specific mortality rates in the United States compare to those in a composite of five large European countries since 2000. First, we examine the ratio of age-specific death rates in the United States to those in Europe. These show a sharp deterioration in the US position since 2000. Applying European age-specific death rates in 2017 to the US population, we then show that adverse mortality conditions in the United States resulted in 400,700 excess deaths that year. Finally, we show that these excess deaths entailed a loss of 13.0 My of life. In 2017, excess deaths and years of life lost in the United States represent a larger annual loss of life than that associated with the COVID-19 epidemic in 2020.

#### FIGURES

Table 1. Excess deaths and years of life lost by age group for years 2000 and 2017

Age group, y	Excess deaths			Years of life lost (in 1,000s)		
	2000	2000 with 2017 age-sex distribution	2017	2000	2000 with 2017 age-sex distribution	2017
0	9,653	9,900	9,634	736	755	754
1-14	3,282	3,361	4,010	229	235	286
15-24	10,344	11,575	20,441	581	649	1,170
25-34	11,398	12,763	40,116	539	606	1,973
35-44	24,056	21,543	42,072	915	820	1,700
45-54	32,637	37,785	67,044	968	1,111	2,081
55-64	51,508	90,382	115,589	1,108	1,933	2,695
65-74	65,126	100,817	118,613	970	1,523	1,910
75-84	32,663	35,856	81,002	319	350	844
85+	-14,501	-26,060	-97,788	-48	-85	-390
Total	226,165	297,922	400,732	6,318	7,897	13,023

Source: HMD (12). Note that numbers might not add due to rounding.

Table 1. Excess deaths and years of life lost by age group for years 2000 and 2017

# EPIDEMIOLOGY

## A PHYLOGENETIC WORKFLOW TO RAPIDLY GAIN INSIGHTS INTO THE DISPERSAL HISTORY AND DYNAMICS OF SARS-COV-2 LINEAGES

Dellicour S, Durkin K, Hong SL, Vanmechelen B, Martí-Carreras J, Gill MS, Meex C, Bontems S, André E, Gilbert M, Walker C, Maio N, Faria NR, Hadfield J, Hayette MP, Bours V, Wawina-Bokalanga T, Artesi M, Baele G, Maes P.. Mol Biol Evol. 2021 Apr 13;38(4):1608-1613. doi: 10.1093/molbev/msaa284.

Level of Evidence: 5 - Modeling

### BLUF

Epidemiologists, virologists, and geneticists from the Université Libre de Bruxelles, among others, created a "rapid analytical pipeline" in an attempt to analyze SARS-CoV-2 lineages more rapidly than with typical approaches and applied their method to the pandemic's trajectory in Belgium. They were able to map the dispersion of viral variants and found that lockdowns were associated with a modest decrease in variant dispersal velocity, but that long distance spread of variants continued (Figure 2, 3). Throughout Belgium there was no clearly predominant strain (Figure 1), suggesting the pandemic was driven largely by external introduction attempts. Authors suggest their method of phylogenetic analyses is a useful rapid tool for assessing the impact of intervention measures on the spread of epidemics.

### ABSTRACT

Since the start of the COVID-19 pandemic, an unprecedented number of genomic sequences of SARS-CoV-2 have been generated and shared with the scientific community. The unparalleled volume of available genetic data presents a unique opportunity to gain real-time insights into the virus transmission during the pandemic, but also a daunting computational hurdle if analyzed with gold-standard phylogeographic approaches. To tackle this practical limitation, we here describe and apply a rapid analytical pipeline to analyze the spatiotemporal dispersal history and dynamics of SARS-CoV-2 lineages. As a proof of concept, we focus on the Belgian epidemic, which has had one of the highest spatial densities of available SARS-CoV-2 genomes. Our pipeline has the potential to be quickly applied to other countries or regions, with key benefits in complementing epidemiological analyses in assessing the impact of intervention measures or their progressive easement.

### FIGURES

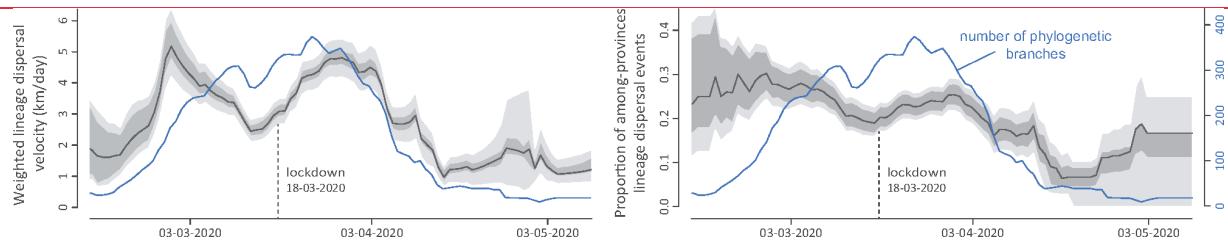


Figure 3. Evolution of viral lineage dispersal dynamics during the Belgian epidemic. These estimates are based on 1,000 trees subsampled from each post burn-in posterior distribution. Except for the number of phylogenetic branches occurring at each time slice, all estimates were smoothed using a 14-days sliding window. Dark gray surrounding polygons represent 95% credible intervals, and light gray surrounding polygons represent 95% credible intervals re-estimated after subsampling 75% of branches in each of the 1,000 posterior trees. The credible interval based on the subsampling procedure is an indication of the robustness of the estimate. In addition, we also report the number of phylogenetic branches occurring per tree at each time slice (blue curve). The number of branches available at each time slice is an additional, yet qualitative, indication of robustness of the estimate for a given time period.

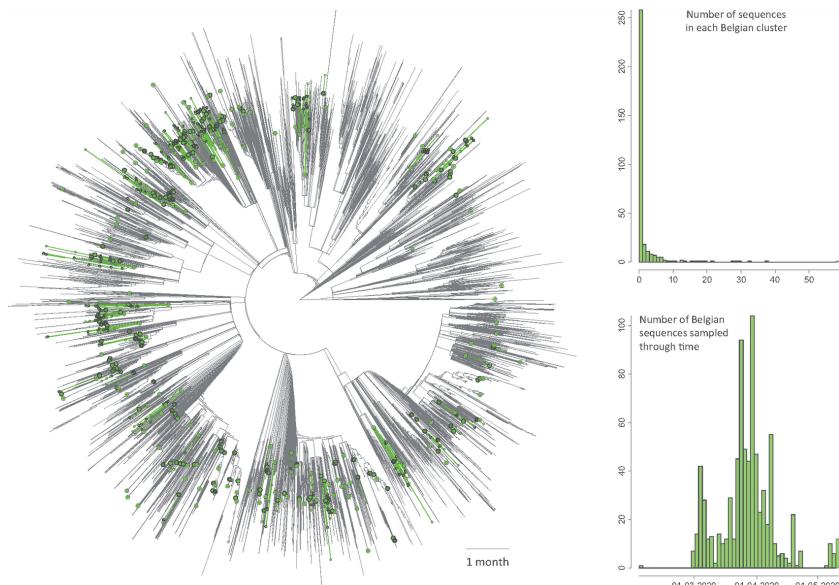


Figure 1. Time-scaled phylogenetic tree in which we identified Belgian clusters. A cluster is here defined as a phylogenetic clade likely corresponding to a distinct introduction into the study area (Belgium). We delineated these clusters by performing a simplistic discrete phylogeographic reconstruction along the time-scaled phylogenetic tree while only considering two potential ancestral locations: “Belgium” and “non-Belgium”. We identified a minimum number of 331 lineage introductions (95% HPD interval = [315–344]), which showcases the relative importance of external introductions considering the number of sequences currently sampled in Belgium ( $n = 740$ ). On the tree, lineages circulating in Belgium are highlighted in green, and green nodes correspond to the most ancestral node of each Belgian cluster (see also supplementary fig. S1, Supplementary Material online for a noncircular visualization of the same tree). Besides the tree, we also report the distribution of cluster sizes (number of sampled sequences in each cluster) as well as the number of sequences sampled through time.

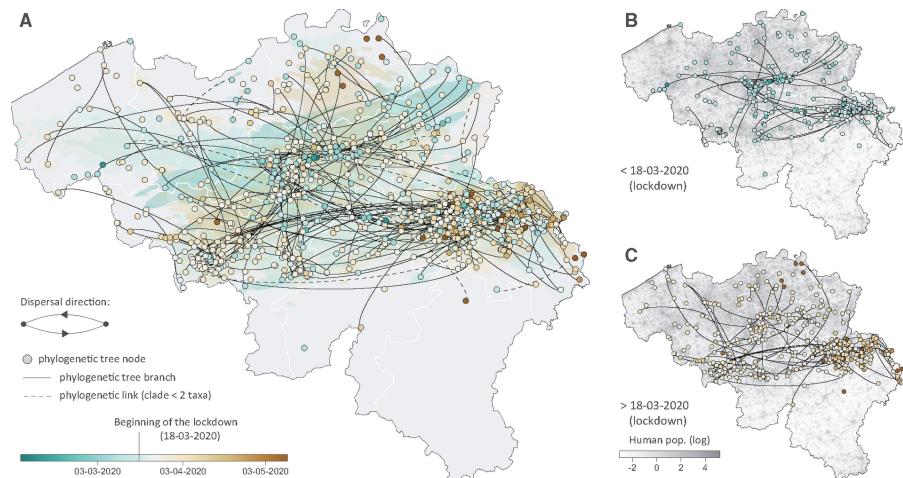


Figure 2. Spatially explicit phylogeographic reconstruction of the dispersal history of SARS-CoV-2 lineages in Belgium. (A) Continuous phylogeographic reconstruction performed along each Belgian clade (cluster) identified by the initial discrete phylogeographic analysis. For each clade, we mapped the maximum clade credibility (MCC) tree and overall 80% highest posterior density (HPD) regions reflecting the uncertainty related to the phylogeographic inference. MCC trees and 80% HPD regions are based on 1,000 trees subsampled from each post burn-in posterior distribution. MCC tree nodes were colored according to their time of occurrence, and 80% HPD regions were computed for successive time layers and then superimposed using the same color scale reflecting time. Continuous phylogeographic reconstructions were only performed along Belgian clades linking at least three sampled sequences for which the geographic origin was known (see the detailed analytical pipeline in Supplementary Information for further detail). Besides the phylogenetic branches of MCC trees obtained by continuous phylogeographic inference, we also mapped sampled sequences belonging to clades linking less than three geo-referenced sequences. Furthermore, when a clade only gathers two geo-referenced sequences, we highlighted the phylogenetic link between these two sequences with a dashed curve connecting them. Subnational province borders are represented by white lines. (B) MCC tree branches occurring before March 18, 2020 (beginning of the lockdown). (C) MCC tree branches occurring after March 18, 2020. See also supplementary figure S2, Supplementary Material online, for a zoomed version of the dispersal history of viral lineages in the Province of Liège, for which we have a particularly dense sampling.

# SYMPTOMS AND CLINICAL PRESENTATION

## ADULTS

### ASTHMA DOES NOT INCREASE COVID-19 MORTALITY AND POOR OUTCOMES: A SYSTEMATIC REVIEW AND META-ANALYSIS

Soeroto AY, Purwiga A, Emmy H Pranggono EHP, Roesli RMA.. Asian Pac J Allergy Immunol. 2021 Apr 18. doi: 10.12932/AP-110920-0955. Online ahead of print.

Level of Evidence: 2 - Systematic review of inception cohort studies

#### BLUF

Pulmonology and internal medicine specialists associated with Hasan Sadikin Hospital, Indonesia conducted a systematic review and meta-analysis of 11 studies (Figure 1) to understand the relationship between asthma and poor outcomes in COVID-19 patients. Results indicated no significant association of asthma with severe COVID ( $p=0.76$ ), mortality ( $p=0.45$ ), or other poor outcomes ( $p=0.28$ ) (Figure 2). These results suggest that asthma is not a risk factor for severe COVID-19, but further research is required to understand the implications of asthma severity and inhaled corticosteroid use in COVID-19.

#### SUMMARY

- Asthma prevalence ranged from 0.9% - 15.8% in COVID-19 patients

#### ABSTRACT

**BACKGROUND:** The Center for Disease Control and Prevention (CDC) has mentioned Coronavirus Disease 2019 (COVID-19) patients with moderate or severe asthma as a high risk group for severe illness. While WHO mentioned only chronic respiratory diseases, not specifically asthma as a risk factor for severe illness. There has been asthma prevalence discrepancy in studies of COVID-19 across the world. **OBJECTIVE:** This meta-analysis aims to investigate the association between asthma and composite poor outcome in patients with coronavirus disease (COVID-19). **METHODS:** We conducted a systematic literature search from PubMed and Embase database. We included all original research articles with adult COVID-19 patients > 18 years old and had information related to asthma as a risk factor. Studies with outcomes consisting of mortality, severe COVID-19, use of mechanical ventilation, ICU admission, and hospital admission were included in this study. The outcomes of interest were divided into severe COVID-19, mortality and other poor outcomes. **RESULTS:** Eleven studies were included in meta-analysis with a total of 6,046 patients. Asthma was not associated with composite poor outcomes with OR = 0.92 (95%CI 0.71-1.19,  $p = 0.61$ , and  $I^2 = 8.49\%$ ). Furthermore, subgroup analysis showed that asthma was not associated with severe COVID ( $p = 0.76$ ), mortality ( $p = 0.45$ ), and other poor outcomes ( $p = 0.28$ ). **CONCLUSIONS:** Our study showed that asthma was not associated with severe COVID-19, mortality, and other poor outcomes in patients with COVID-19.

#### FIGURES

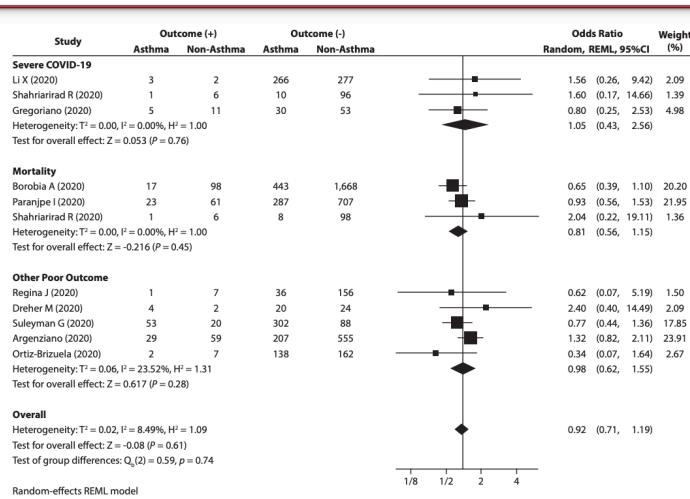


Figure 2.

Figure 2.

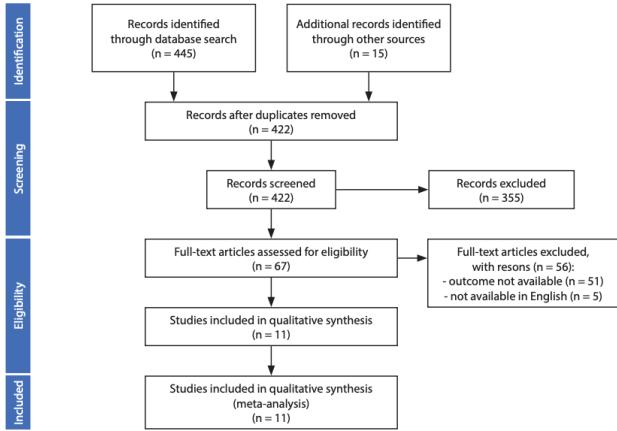


Figure 1.

## PREGNANT PERSONS

### A SYSTEMATIC REVIEW OF PREGNANT WOMEN WITH COVID-19 AND THEIR NEONATES

Mirbeyk M, Saghazadeh A, Rezaei N.. Arch Gynecol Obstet. 2021 Apr 2. doi: 10.1007/s00404-021-06049-z. Online ahead of print.

Level of Evidence: 1 - Systematic review of inception cohort studies

#### BLUF

Immunology specialists associated with Tehran University of Medical Sciences in Iran conducted a systematic review of 37 articles regarding COVID-19 in pregnant patients. Of the 364 women included in the studies, 25 were asymptomatic, 22 developed pneumonia, and 44 women tested negative for SARS-CoV-2 despite their clinical manifestations. Two mothers died from severe pneumonia and multiple organ dysfunction (Table 3). The studies also involved a total of 302 neonates, 1 of whom was born dead and 5 had critical conditions. Of the 219 neonates who were tested for SARS-CoV-2 infection, 11 tested positive. These results indicate that the symptoms and prognosis of pregnant women with COVID-19 are similar to that of the general public, but monitoring is crucial for the health of both patients.

#### SUMMARY

- SARS-CoV-2 infection was tested through nasopharyngeal swabs
- Of the 5 critical neonates, 2 later died

#### ABSTRACT

**BACKGROUND:** In December 2019, a novel coronavirus disease (COVID-19) emerged in Wuhan, China, with an incredible contagion rate. However, the vertical transmission of COVID-19 is uncertain. **OBJECTIVES:** This is a systematic review of published studies concerning pregnant women with confirmed COVID-19 and their neonates. **SEARCH STRATEGY:** We carried out a systematic search in multiple databases, including PubMed, Web of Science, Google Scholar, Scopus, and WHO COVID-19 database using the following keywords: (Coronavirus) OR (novel coronavirus) OR (COVID-19) OR (COVID19) OR (COVID 19) OR (SARS-CoV2) OR (2019-nCoV)) and ((pregnancy) OR (pregnant) OR (vertical transmission) OR (neonate) OR (newborn) OR (placenta) OR (fetus) OR (Fetal)). The search took place in April 2020. **SELECTION CRITERIA:** Original articles published in English were eligible if they included pregnant patients infected with COVID-19 and their newborns. **DATA COLLECTION AND ANALYSES:** The outcomes of interest consisted of clinical manifestations of COVID-19 in pregnant patients with COVID-19 and also the effect of COVID-19 on neonatal and pregnancy outcomes. **MAIN RESULTS:** 37 articles involving 364 pregnant women with COVID-19 and 302 neonates were included. The vast majority of pregnant patients were in their third trimester of pregnancy, and only 45 cases were in the first or second trimester (12.4%). Most mothers described mild to moderate manifestations of COVID-19. Of 364 pregnant women, 25 were asymptomatic at the time of admission. The most common symptoms were fever (62.4%) and cough (45.3%). Two maternal deaths occurred. Some pregnant patients (12.1%) had a negative SARS-CoV-2 test but displayed clinical manifestations and abnormalities in computed tomography (CT) scan related

to COVID-19. Twenty-two (6.0%) pregnant patients developed severe pneumonia. Two maternal deaths occurred from severe pneumonia and multiple organ dysfunction. Studies included a total of 302 neonates from mothers with COVID-19. Of the studies that provided data on the timing of birth, there were 65 (23.6%) preterm neonates. One baby was born dead from a mother who also died from COVID-19. Of the babies born alive from mothers with COVID-19, five newborns faced critical conditions, and two later died. A total of 219 neonates underwent nasopharyngeal specimen collection for SARS-CoV-2, of which 11 tested positive (5%). Seventeen studies examined samples of the placenta, breast milk, umbilical cord, and amniotic fluid, and all tested negative except one amniotic fluid sample. CONCLUSIONS: A systematic review of published studies confirm that the course of COVID-19 in pregnant women resembles that of other populations. However, there is not sufficient evidence to establish an idea that COVID-19 would not complicate pregnancy.

## FIGURES

**Table 3** A summary of studies on pregnancy outcomes in pregnant women with COVID-19 included in the systematic review

Article title	Author	Study type	Country	Placental test for nCoV 2019 nucleic acid		Pregnancy complications	Further information
				Result	Method		
Pregnant women with new coronavirus infection: clinical characteristics and placental pathological analysis of three cases	Chen et al.	Case study	China	Negative	RT-PCR	Not reported	Umbilical cord and fetal membranes were tested and went negative
Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia	Zhu et al.	Case study	China	Not reported	Not reported	Premature rupture of membranes (=3), One polyhydramnios, One oligohydramnios	No further samples were examined
Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records	Chen et al.	Case study	China	Not reported	Not reported	Premature rupture of Membranes (=2), Fetal distress (=2)	All amniotic fluid, cord blood, breastmilk samples from six patients were negative (3 cases has unsuccessful sample collection)
Analysis of the pregnancy outcomes in pregnant women with COVID-19 in Hubei Province	Zhang et al.	Case-control	China	Not reported	Not reported	Pre-eclampsia (=1), PROM (=3), Fetal distress (=1), Premature birth (=3), Asphyxia (=1)	No further samples were examined
Clinical manifestations and outcome of SARS-CoV-2 infection during pregnancy	Liu et al.	Case study	China	Not reported	Not reported	Fetal distress (=3), PROM (=1), Stillbirth (=1)	No further samples were examined
Lack of vertical transmission of severe acute respiratory syndrome Coronavirus 2, China	Li et al.	Case report	China	Negative	RT-PCR	Not reported	Serum, urine, feces, amniotic fluid, umbilical cord blood and placenta, and breast milk samples were negative
A case of 2019 Novel Coronavirus in a pregnant woman with preterm delivery	Wang et al.	Case report	China	Negative	RT-PCR	Not reported	Amniotic fluid and cord blood were negative
A case report of neonatal COVID-19 infection in China	Wang et al.	Case report	China	Negative	RT-PCR	Not reported	Cord blood and mother's breast milk were negative
Perinatal transmission of COVID-19-associated SARS-CoV-2: should we worry?	Fan et al.	Case report	China	Negative	RT-PCR	Not reported	Umbilical cord blood, amniotic fluid, vaginal swabs, and mother's breast milk were negative
Clinical analysis of pregnant women with 2019 novel coronavirus pneumonia	Chen et al.	Case series	China	Not reported	Not reported	Pre-eclampsia (=1) Gestational diabetes (=2)	Not reported

**Table 3** (continued)

Article title	Author	Study type	Country	Placental test for nCoV-2019 nucleic acid		Pregnancy complications	Further information
				Result	Method		
Possible vertical transmission of SARS-CoV-2 from an infected mother to her newborn	Dong et al.	Case report	China	Not reported	Not reported	Not reported	Mother's vaginal discharge and breastmilk were negative for COVID-19 PCR test result
Lung ultrasound and computed tomographic findings in a pregnant woman with COVID-19	Kalafat et al.	Case report	Turkey	Negative	RT-PCR	Not reported	Breast milk and cord blood were negative
Coronavirus disease 2019 (COVID-19) during pregnancy: a case series	Liu et al.	Case series	China	Negative	RT-PCR	Gestational hypertension	Breast milk, cord blood, amniotic fluid, neonatal serum, and mothers' vaginal mucosa were negative
Maternal and neonatal outcomes of pregnant women with COVID-19 pneumonia: a case-control study	Li et al.	Case-control	China	Not reported	Not reported	gestational diabetes mellitus (=3) PROM (=1) gestational hypertension (=3), hypothyroidism (=2), pre-eclampsia (=1) Sinus tachycardia (=1) Fetal distress (=2)	Not reported
A pregnant woman with COVID-19 in Central America	Zambrano et al.	Case report	United States, USA	Not reported	Not reported	gestational hypertension and hypothyroidism	Neonate's blood sample was negative
Pregnancy and perinatal outcomes of women with Coronavirus Disease (COVID-19) pneumonia: a preliminary analysis	Liu et al.	Cross-sectional	China	Not reported	Not reported	Placenta previa (=1)	Not reported
Clinical features and obstetric and neonatal outcomes of pregnant patients with COVID-19 in Wuhan, China: a retrospective, single-center, descriptive study	Yu et al.	Retrospective study	China	Not reported	Not reported	Uterine scarring (=3) Hypothyroidism (=1)	Not reported
Neonatal Early-Onset Infection with SARS CoV-2 in 33 Neonates Born to Mothers With COVID-19 in Wuhan, China	Zeng et al.	Cohort study	China	Not reported	Not reported	PROM (=3)	Not reported

**Table 3** (continued)

Article title	Author	Study type	Country	Placental test for nCoV-2019 nucleic acid		Pregnancy complications	Further information
				Result	Method		
Mortality of a pregnant patient diagnosed with COVID-19: A case report with clinical, radiological, and histopathological findings	Karami et al.	Case report	Iran	Not reported	Not reported	Not reported	Not reported
Unlikely SARS-CoV-2 vertical transmission from mother to child: a case report	Peng et al.	Case report	China	Negative	RT-PCR	Not reported	Amniotic fluid, vaginal mucosa, cord blood, and breast milk were all negative
Severe COVID-19 during pregnancy and possible vertical transmission	Alzamora et al.	Case report	The United States, USA	Not reported	Not reported	Diabetes mellitus	Not reported
Preterm delivery in a pregnant woman with critical COVID-19 pneumonia and vertical transmission	Zamanian et al.	Case report	Iran	Not reported	Not reported	Not reported	Cord blood was negative, but Amniotic fluid was positive
Vaginal delivery report of a healthy neonate born to a convalescent mother with COVID-19	Xiong et al.	Case report	China	Negative	RT-PCR	Not reported	Amniotic fluid was negative
Association of COVID-19 infection with pregnancy outcomes in healthcare workers and general women	Khan et al.	Case series	China	Not reported	Not reported	5 women with other complications	Not reported
Impact of COVID-19 infection on pregnancy outcomes and the risk of maternal-to-neonatal intrapartum transmission of COVID-19 during natural birth	Khan et al.	Case report	China	Not reported	Not reported	Not reported	The cord blood sample was negative
Clinical characteristics of 19 neonates born to mothers with COVID-19	Liu et al.	Retrospective study	China	Not reported	Not reported	Not reported	Breast milk sample, amniotic fluid, and cord blood were negative
COVID-19 infection among asymptomatic and symptomatic pregnant women: two weeks of confirmed presentations to an affiliated pair of New York City hospitals	Breslin et al.	Cohort study	The United States, USA	Not reported	Not reported	PROM	Not reported

**Table 3** (continued)

Article title	Author	Study type	Country	Placental test for nCoV-2019 nucleic acid		Pregnancy complications		Further information
				Result	Method			
Clinical features and outcomes of pregnant women suspected of Coronavirus Disease 2019	Yang et al.	Case-control	China	Not reported		Not reported	Not reported	Not reported
Asymptomatic COVID-19 in a pregnant woman with typical chest CT manifestation: a case report	Renbin et al.	Case report	China	Not reported		Not reported	Not reported	Not reported
Chest CT findings in a pregnant patient with 2019 Novel Coronavirus Disease	Liao et al.	Case report	China	Negative	RT-PCR	Not reported		Amniotic fluid and cord blood were negative
Infants born to mothers with a new Coronavirus (COVID-19)	Chen et al.	Case report	China	Not reported		Not reported	Placenta (=1)	Not reported
Anesthetic management for emergent cesarean delivery in a parturient with recent diagnosis of Coronavirus Disease 2019 (COVID-19): a case report	Song et al.	Case report	China	Not reported		Not reported	Not reported	Not reported
Clinical characteristics and risk assessment of newborns born to mothers with COVID-19	Yang et al.	Case series	China	Not reported		Not reported	Not reported	Cord blood and amniotic fluid were negative
COVID-19 in pregnancy: early lessons	Breslin et al.	Case series	The United States, USA	Not reported		Not reported	Type 2 diabetes mellitus (=2)	Not reported
Antibodies in infants born to mothers with COVID-19 pneumonia	Zeng et al.	Case study	China	Not reported		Not reported	Not reported	Not reported
Novel Coronavirus infection in newborn babies under 28 Days in China	Zhang et al.	Case series	China	Not reported		Not reported	Not reported	Not reported
Clinical characteristics of pregnant women with Covid-19 in Wuhan, China	Chen et al.	Retrospective study	China	Not reported		Not reported	Not reported	Breast milk of three mothers were negative for the virus
Total results				All samples examined were negative		RT-PCR		

RT-PCR Reverse transcription-polymerase chain reaction, PROM Premature rupture of membranes

# UNDERSTANDING THE PATHOLOGY

## SHELL DISORDER ANALYSIS PREDICTS GREATER RESILIENCE OF THE SARS-COV-2 (COVID-19) OUTSIDE THE BODY AND IN BODY FLUIDS

Goh GK, Dunker AK, Foster JA, Uversky VN.. *Microb Pathog.* 2020 Jul;144:104177. doi: 10.1016/j.micpath.2020.104177. Epub 2020 Mar 31.

Level of Evidence: 5 - Modeling

### BLUF

Investigators from various computer science and medical departments at institutions in Singapore, United States, and Russia, analyzed the characteristics of SARS-CoV-2 compared to other corona viruses (CoVs) utilizing an artificial intelligence model (PONDR®) validated during the 2012 MERS-CoV outbreak, focusing on the percentage of intrinsic disorder (PID) of viral membrane (M) and nucleocapsid (N). The model analysis represents three statistically identifiable groups (Table 1), with SARS-CoV-2 fitting into group B with intermediate levels of both respiratory and fecal-oral transmission potentials, as well as one of lowest M PID value of all the CoVs (Figure 1), suggesting a hard outer shell providing greater resistance. The authors report this model is a reliable method to understand and explain viral factors contributing to the rapid spread and high transmission rate of SARS-CoV-2 during the pandemic.

### ABSTRACT

The coronavirus (CoV) family consists of viruses that infects a variety of animals including humans with various levels of respiratory and fecal-oral transmission levels depending on the behavior of the viruses' natural hosts and optimal viral fitness. A model to classify and predict the levels of respective respiratory and fecal-oral transmission potentials of the various viruses was built before the outbreak of MERS-CoV using AI and empirically-based molecular tools to predict the disorder level of proteins. Using the percentages of intrinsic disorder (PID) of the nucleocapsid (N) and membrane (M) proteins of CoV, the model easily clustered the viruses into three groups with the SARS-CoV (M PID = 8%, N PID = 50%) falling into Category B, in which viruses have intermediate levels of both respiratory and fecal-oral transmission potentials. Later, MERS-CoV (M PID = 9%, N PID = 44%) was found to be in Category C, which consists of viruses with lower respiratory transmission potential but with higher fecal-oral transmission capabilities. Based on the peculiarities of disorder distribution, the SARS-CoV-2 (M PID = 6%, N PID = 48%) has to be placed in Category B. Our data show however, that the SARS-CoV-2 is very strange with one of the hardest protective outer shell, (M PID = 6%) among coronaviruses. This means that it might be expected to be highly resilient in saliva or other body fluids and outside the body. An infected body is likelier to shed greater numbers of viral particles since the latter is more resistant to antimicrobial enzymes in body fluids. These particles are also likelier to remain active longer. These factors could account for the greater contagiousness of the SARS-CoV-2 and have implications for efforts to prevent its spread.

### FIGURES

Table 1

Categorization of coronaviruses by shell disorder to predict levels of Respiratory and Fecal-oral transmission (Statistical Analyses:Two-Way ANOVA,  $p < 0.00$ ), (Regression analysis of category as dependent variable with M and N PIDs as independent variables:  $p < 0.001$ ,  $r^2 = 0.83$ , Regression analysis with only N PID as an independent variable:  $p < .001$ ,  $r^2 = 0.77$ ).

Shell Disorder Category	Coronavirus	M PID % (UniProt/Genbank Accession Code) <sup>a</sup>	N PID % (UniProt/Genbank Accession Code) <sup>b</sup>	Remarks
A	HCoV-229E IBV(Avian)	23(P15422) 10(P69606)	56(P15130) 56(Q8JM16)	Higher Levels of Respiratory Transmission Lower Levels of Fecal-oral Transmission
B	Bovine PEDV(Porcine) Canine(Resp.) HGCV-OC43 SARS-CoV HCoV-NL63 Bat-HKU4 “SARS-CoV-2” <sup>c</sup> Bat-HKU5	7.4(P69704) 8(P59771) 6.5(A3EXD6) 7(Q4VID2) 8(P59596) 11(Q6Q1R9) 16(A3EXA0) 6(QHD43419.1) <sup>d</sup> 11.5(A3EXD6) 11(A3EXD6)	53(Q8V432) 51(Q07499) 51(A3E2F7) 51(P33469) 50(P59595) 49(Q6Q1R8) 48(A3EXA1) 48(QHD43423.2) <sup>d</sup> 47(Q3LZX4) 47(A3EXD7) <sup>b</sup>	Intermediate Levels of Respiratory and Fecal-oral Transmission
C	MHV(Murine) MERS-CoV TGEV(Porcine) Canine(Ent.) HCoV-HKU1	8(Q9JEB4) 9(K0BV37) 14(P09175) 8(B8RR2) 4(Q14EA7)	46(Po3416) 44(K0BVN3) 43(P04134) 40(Q04700) 37(Q0ZME3)	Lower Levels of Respiratory Transmission Higher Levels of Fecal-oral Transmission

<sup>a</sup> M PID refers to the percentage of intrinsic disorder (PID) of the membrane protein (M). PID is measured by the number of residues predicted to be disordered divided by the total number of disorder. M PID predicts how long the virus can remain outside the body. M is considered to be one of the outer shell.

<sup>b</sup> N protein refers to the nucleocapsid protein, which is an inner shell protein.

<sup>c</sup> SARS-CoV-2 (COVID).

<sup>d</sup> Genbank accession code, <https://www.ncbi.nlm.nih.gov/nucleotide/MN908947>.

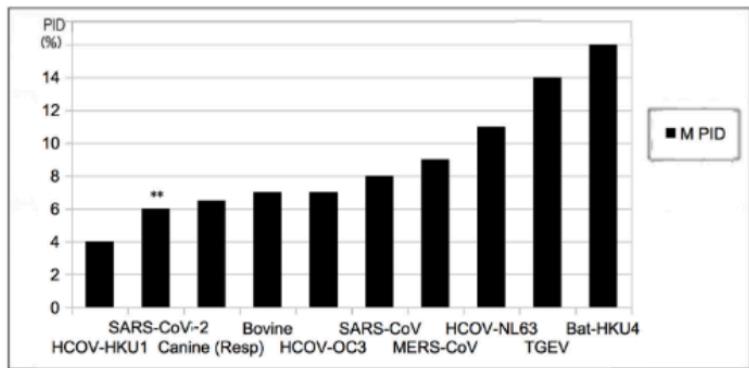


Figure 1. Level of disorder (PID ie Percentage of Intrinsic Disorder) for the M protein. M PID for SARS-CoV-2 (\*\*) is among the lowest in its family, which is indicative of its hard outer shell.

# TRANSMISSION & PREVENTION

## SARS-COV-2 PRESENCE IN THE SALIVA, TEARS, AND CERUMEN OF COVID-19 PATIENTS

Hanege FM, Kocoglu E, Kalcioglu MT, Celik S, Cag Y, Esen F, Bayindir E, Pence S, Alp Mese E, Agalar C.. Laryngoscope. 2021 May;131(5):E1677-E1682. doi: 10.1002/lary.29218. Epub 2020 Nov 19.

Level of Evidence: 3 - Local non-random sample

### BLUF

A multidisciplinary team of researchers from Istanbul Medeniyet University, Turkey conducted a cross-sectional study on SARS-CoV-2 RNA extraction from saliva, tear, and cerumen samples of 38 COVID-19 patients. 76.3% of saliva samples, 56% of tear samples, and 39.5% of cerumen samples had positive RT-PCR tests (Table 2), and viral load was significantly higher in nasopharyngeal-oropharyngeal and saliva samples compared to tear and cerumen samples (Figure 1). These results suggest the presence of SARS-CoV-2 in bodily secretions, requiring adequate precautions and protective equipment in procedures involving saliva, tears, or cerumen.

### SUMMARY

- COVID-19 was confirmed in these patients through a positive RT-PCR test of nasopharyngeal-oropharyngeal swab samples.

### ABSTRACT

**OBJECTIVES:** The emergence of a new coronavirus strain (SARS-CoV-2) in December 2019 from China led to a global pandemic. The lack of herd immunity against this virus and the possibility of viral spread from asymptomatic individuals is still a major challenge for the prevention of viral transmission. The aim of this study was to evaluate the presence of the virus in different bodily secretions as a potential source of viral spread among patients infected with SARS-CoV-2. **METHODS:** The study included 38 COVID-19 patients with a positive real time polymerase chain reaction (RT-PCR) test result for SARS-CoV-2, obtained from the combined nasopharyngeal-oropharyngeal swab samples. Saliva, tear and cerumen samples were taken from the patients within 72 hours of the first RT-PCR test. SARS-CoV-2 N1 and N2 gene regions were studied with single-step RT-PCR in all samples. **RESULTS:** Among the studied samples, the highest positivity rate was in saliva (76.3%) followed by tears (55.3%) and cerumen (39.5%). Viral load in saliva was also significantly higher compared to tears and cerumen ( $p<0.001$ ), while there was no significant difference between tears and cerumen. Higher viral load in combined nasopharyngeal-oropharyngeal swab samples was associated with higher viral load in tears, but not in saliva or cerumen. Half of the saliva, tear and cerumen samples obtained from asymptomatic patients contained SARS-CoV-2 genome. **CONCLUSION:** The virus was detected in the saliva, tears and cerumen samples of both symptomatic and asymptomatic patients. The potential role of these bodily fluids on viral spread needs to be studied.

### FIGURES

TABLE II.  
RT-PCR Positivity Rates and Viral Load in Different Bodily Secretions.

	Positivity Rate, % (n)	Ct Value (Mean $\pm$ SD)	Ct Value (95% CI)
Naso/oropharynx	100 (38)	27.98 $\pm$ 4.29	26.57–29.39
Saliva	76.3 (29)	30.97 $\pm$ 1.56	30.37–31.56
Tears	55.3 (21)	35.39 $\pm$ 1.01	34.93–35.85
Cerumen	39.5 (15)	35.14 $\pm$ 1.03	34.57–35.71

CI = confidence interval; Ct = threshold cycle; RT-PCR = real time polymerase chain reaction; SD = standard deviation.

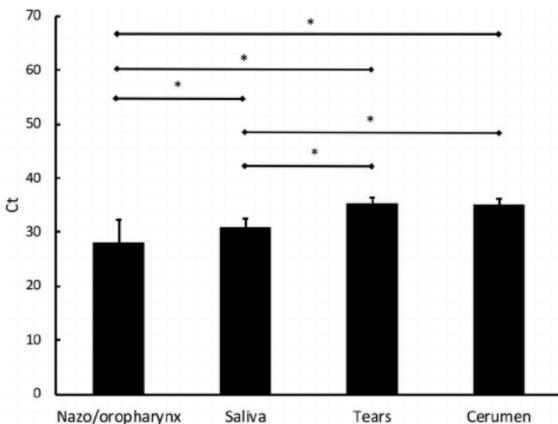


Fig. 1. Relative concentrations of SARS-CoV-2 virus in four different bodily secretions. Viral load was significantly higher in combined nasopharyngeal-oropharyngeal swabs compared to the other samples, which was shown by a significantly lower Cycle threshold (Ct) value in real time polymerase chain reaction. The viral load was also significantly higher in the saliva compared to tears and cerumen, while there was no significant difference between tear and cerumen samples. P < 0.001.

## DEVELOPMENTS IN TRANSMISSION & PREVENTION

### A SYSTEMATIC REVIEW OF SURFACE CONTAMINATION, STABILITY, AND DISINFECTION DATA ON SARS-COV-2 (THROUGH JULY 10, 2020)

Bedrosian N, Mitchell E, Rohm E, Rothe M, Kelly C, String G, Lantagne D.. Environ Sci Technol. 2021 Apr 6;55(7):4162-4173.  
doi: 10.1021/acs.est.0c05651. Epub 2020 Nov 23.

Level of Evidence: 1 - Systematic review of randomized trials or n-of-1 trials

#### BLUF

Researchers associated with Tufts University conducted a systematic review on 78 articles regarding hygiene intervention effectiveness against SARS-CoV-2 transmission. Surface contamination for SARS-CoV-2 RNA was highest in laboratory settings (21%), followed by COVID-19 patient rooms (17%), non-COVID patient rooms (12%), and patient household surfaces (3%) (Table 1). Studies that analyzed surface stability of SARS-CoV-2 indicated a half-life of 2.3-17.9 hours on stainless steel, plastic, and nitrile, which was decreased with increased temperature and humidity (Table 3). Surface disinfection studies showed a 99% decrease in SARS-CoV-2 detection after using sunlight, UV light, ethanol, hydrogen peroxide, and hypochlorite as disinfectants (Table 4). These results shed light on the role of fomite transmission of SARS-CoV-2 and efficient disinfection methods to prevent transmission.

#### ABSTRACT

We conducted a systematic review of hygiene intervention effectiveness against SARS-CoV-2, including developing inclusion criteria, conducting the search, selecting articles for inclusion, and summarizing included articles. Overall, 96 268 articles were screened and 78 articles met inclusion criteria with outcomes in surface contamination, stability, and disinfection. Surface contamination was assessed on 3343 surfaces using presence/absence methods. Laboratories had the highest percent positive surfaces (21%, n = 83), followed by patient-room healthcare facility surfaces (17%, n = 1170), non-COVID-patient-room healthcare facility surfaces (12%, n = 1429), and household surfaces (3%, n = 161). Surface stability was assessed using infectivity, SARS-CoV-2 survived on stainless steel, plastic, and nitrile for half-life 2.3-17.9 h. Half-life decreased with temperature and humidity increases, and was unvaried by surface type. Ten surface disinfection tests with SARS-CoV-2, and 15 tests with surrogates, indicated sunlight, ultraviolet light, ethanol, hydrogen peroxide, and hypochlorite attain 99.9% reduction. Overall there was (1) an inability to align SARS-CoV-2 contaminated surfaces with survivability data and effective surface disinfection methods for these surfaces; (2) a knowledge gap on fomite contribution to SARS-COV-2 transmission; (3) a need for testing method standardization to ensure data comparability; and (4) a need for research on hygiene interventions besides surfaces, particularly handwashing, to continue developing recommendations for interrupting SARS-CoV-2 transmission.

## FIGURES

**Table 1. Percent Surface Contamination by Setting**

setting	percent contamination	positive samples/total samples
<b>Healthcare</b>	14.3%	371/2599
patient room	16.8%	197/1170
non-COVID-patient room	12.2%	174/1429
<b>Household</b>	2.5%	4/161
<b>Non-household Accommodations</b>	14%	76/537
<b>Other Shared</b>	16%	37/228
laboratory	21%	17/83
outdoor	14%	20/145

**Table 3. Surface Stability Data using SARS-CoV-2 with >3 Samples/Surface and Half-Life End Point**

surface type	n	humidity	temperature (°C)	half-life (hours)	study reference
stainless steel	14 total (11 with half-life)	30–40	4	12.9	<a href="#">55,57,58,62</a>
		30–40	RT	9.1	<a href="#">63</a>
		30–40	30	17.9	
		20	24	15.33	
		40	24	11.52	
		60	24	9.15	
		80	24	8.33	
		40	28	6.11	
		20	35	7.33	
		40	35	7.52	
		60	35	2.26	
ABS plastic	8 (8 with half-life)	20	24	15.33	<a href="#">62</a>
		40	24	11.52	
		60	24	9.15	
		80	24	8.33	
		40	28	6.11	
		20	35	7.33	
		40	35	7.52	
		60	35	2.26	
nitrile gloves	5 (4 with half-life)	20	24	15.33	<a href="#">58,62</a>
		60	35	2.26	
		20	24	15.33	
		60	35	2.26	

**Table 4. Surface Disinfection Data from Studies using SARS-CoV-2 on Surfaces**

disinfectant	n	surface type	concentration	contact time	log reduction	reference
simulated sunlight	2	stainless steel	1 sun	60 min	>4	<a href="#">86</a>
			1 sun	180 min	>4	
deep-UV LED irradiation	5	Petri dish	280 nm $\pm$ 5 nm	1 sec	0.9	<a href="#">76</a>
				10 sec	3.1	
				20 sec	>3.3	
				30 sec	>3.3	
				60 sec	>3.3	
UV-C irradiation from PX-UV device	3	chamber slides	280 nm $\pm$ 200 nm	1 min	3.56	<a href="#">72</a>
				2 min	>4.54	
				5 min	>4.12	

# EFFECTIVENESS OF PFIZER-BIONTECH AND MODERNA VACCINES AGAINST COVID-19 AMONG HOSPITALIZED ADULTS AGED $\geq 65$ YEARS - UNITED STATES, JANUARY-MARCH 2021

Tenforde MW, Olson SM, Self WH, Talbot HK, Lindsell CJ, Steingrub JS, Shapiro NI, Ginde AA, Douin DJ, Prekken ME, Brown SM, Peltan ID, Gong MN, Mohamed A, Khan A, Exline MC, Files DC, Gibbs KW, Stubblefield WB, Casey JD, Rice TW, Grijalva CG, Hager DN, Shehu A, Qadir N, Chang SY, Wilson JG, Gaglani M, Murthy K, Calhoun N, Monto AS, Martin ET, Malani A, Zimmerman RK, Silveira FP, Middleton DB, Zhu Y, Wyatt D, Stephenson M, Baughman A, Womack KN, Hart KW, Kobayashi M, Verani JR, Patel MM; IVY Network; HAIVEN Investigators.. MMWR Morb Mortal Wkly Rep. 2021 May 7;70(18):674-679. doi: 10.15585/mmwr.mm7018e1.

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

## BLUF

A team from the IVY Network and HAIVEN Investigators evaluated the effectiveness of vaccination with Pfizer-BioNTech or Moderna vaccines against hospitalization in adults 65 and older in 24 hospitals across 14 US states (187 case-patients and 230 controls). The adjusted effectiveness of full vaccination was 94% (95% confidence interval [CI] = 49%-99%) and partial vaccination 64% (95% CI = 28%-82%) (Figure). Though limited by the small sample size and wide confidence intervals, authors suggest administration of these mRNA vaccines may reduce severe prognostic outcomes in the elderly population.

## ABSTRACT

Adults aged  $\geq 65$  years are at increased risk for severe outcomes from COVID-19 and were identified as a priority group to receive the first COVID-19 vaccines approved for use under an Emergency Use Authorization (EUA) in the United States (1-3). In an evaluation at 24 hospitals in 14 states,\* the effectiveness of partial or full vaccination with Pfizer-BioNTech or Moderna vaccines against COVID-19-associated hospitalization was assessed among adults aged  $\geq 65$  years. Among 417 hospitalized adults aged  $\geq 65$  years (including 187 case-patients and 230 controls), the median age was 73 years, 48% were female, 73% were non-Hispanic White, 17% were non-Hispanic Black, 6% were Hispanic, and 4% lived in a long-term care facility. Adjusted vaccine effectiveness (VE) against COVID-19-associated hospitalization among adults aged  $\geq 65$  years was estimated to be 94% (95% confidence interval [CI] = 49%-99%) for full vaccination and 64% (95% CI = 28%-82%) for partial vaccination. These findings are consistent with efficacy determined from clinical trials in the subgroup of adults aged  $\geq 65$  years (4,5). This multisite U.S. evaluation under real-world conditions suggests that vaccination provided protection against COVID-19-associated hospitalization among adults aged  $\geq 65$  years. Vaccination is a critical tool for reducing severe COVID-19 in groups at high risk.

## FIGURES

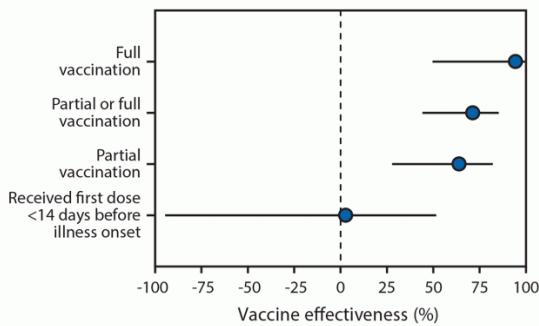


Figure. Adjusted\* vaccine effectiveness (with 95% confidence intervals) against COVID-19 among hospitalized† adults aged  $\geq 65$  years, by vaccination status§ — 24 medical centers in 14 states, January–March 2021

# **COMPREHENSIVE ASSESSMENT OF HUMORAL RESPONSE AFTER PFIZER BNT162B2 mRNA COVID-19 VACCINATION: A THREE-CASE SERIES**

Danese E, Montagnana M, Salvagno GL, Peserico D, Pighi L, De Nitto S, Henry BM, Porru S, Lippi G.. Clin Chem Lab Med. 2021 Apr 12. doi: 10.1515/cclm-2021-0339. Online ahead of print.

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

## **BLUF**

A case-series at the University Hospital of Verona, Italy examined the post-vaccination immune response in 3 healthcare workers who received the BNT162b2 mRNA Covid-19 Pfizer Vaccine. Serum anti-SARS-CoV-2 antibodies, anti-S1 IgA, and IgM increased 7-11 days after the first vaccine dose (Figure 1), total Ig anti-RBD (receptor binding domain), anti-S1/S2, and anti-RBD IgG increased 91-368 fold from day 11 to 21; after the second dose, total Ig anti-RBD increased an additional 30-fold, while anti-S1/S2 and anti-RBD IgG increased 8-fold (Figure 2). This information provides a timeline for the immune response following administration of the NT162b2 mRNA Covid-19 Pfizer vaccine, which can help in modification of vaccine formulas and administration plans.

## **ABSTRACT**

**OBJECTIVES:** Since universal vaccination is a pillar against coronavirus disease 2019 (COVID-19), monitoring anti-SARS-CoV-2 neutralizing antibodies is essential for deciphering post-vaccination immune response. **METHODS:** Three healthcare workers received 30 mug BNT162b2 mRNA Covid-19 Pfizer Vaccine, followed by a second identical dose, 21 days afterwards. Venous blood was drawn at baseline and at serial intervals, up to 63 days afterwards, for assessing total immunoglobulins (Ig) anti-RBD (receptor binding domain), anti-S1/S2 and anti-RBD IgG, anti-RBD and anti-N/S1 IgM, and anti-S1 IgA. **RESULTS:** All subjects were SARS-CoV-2 seronegative at baseline. Total Ig anti-RBD, anti-S1/S2 and anti-RBD IgG levels increased between 91 and 368 folds until 21 days after the first vaccine dose, then reached a plateau. The levels raised further after the second dose (by ~30-, ~8- and ~8-fold, respectively), peaking at day 35, but then slightly declining and stabilizing ~50 days after the first vaccine dose. Anti-S1 IgA levels increased between 7 and 11 days after the first dose, slightly declined before the second dose, after which levels augmented by ~24-fold from baseline. The anti-RBD and anti-N/S1 IgM kinetics were similar to that of anti-S1 IgA, though displaying substantially weaker increases and modest peaks, only 4- to 7-fold higher than baseline. Highly significant inter-correlation was noted between total Ig anti-RBD, anti-S1/S2 and anti-RBD IgG (all  $r=0.99$ ), whilst other anti-SARS-CoV-2 antibodies displayed lower, though still significant, correlations. Serum spike protein concentration was undetectable at all-time points. **CONCLUSIONS:** BNT162b2 mRNA vaccination generates a robust humoral immune response, especially involving anti-SARS-CoV-2 IgG and IgA, magnified by the second vaccine dose.

## FIGURES

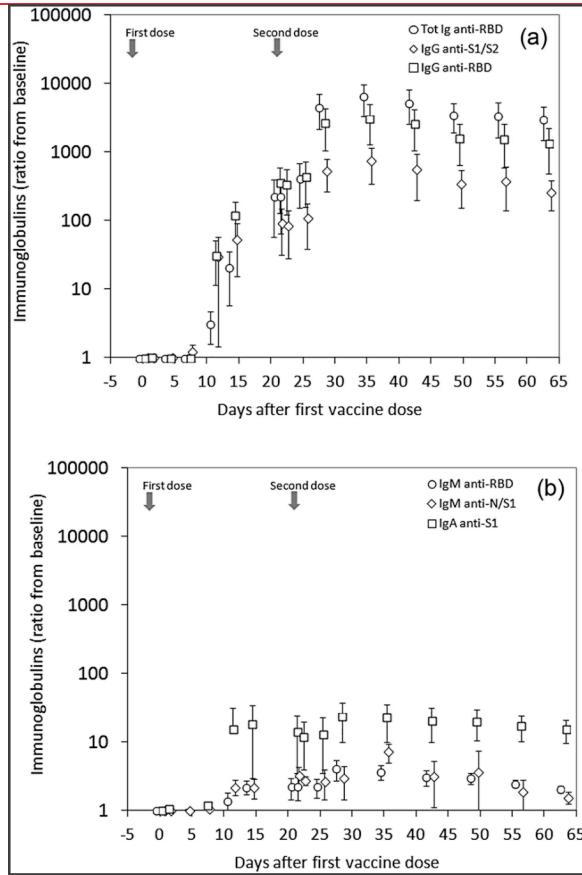


Figure 1: Overall kinetics of anti-SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) antibodies following BNT162b2 mRNA Covid-19 vaccination. Values are shown as mean  $\pm$  standard deviation. Ig, immunoglobulin; N, nucleocapsid; RBD, receptor binding domain; S, spike protein; Tot, total.

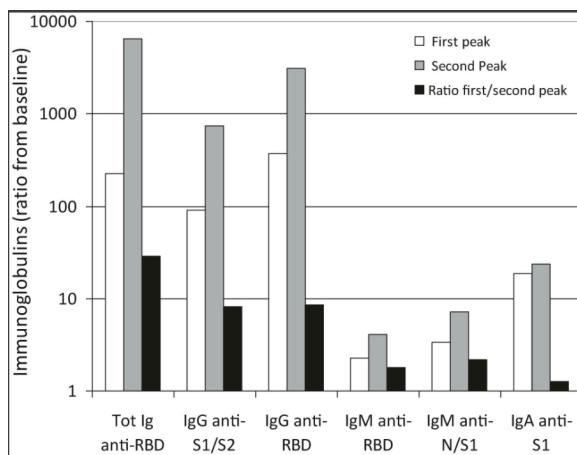


Figure 2: Peak values of anti-SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) antibodies observe after the first and second dose administration of BNT162b2 mRNA Covid-19 vaccine. The day of the peak is reported in the text. Ig, immunoglobulin; N, nucleocapsid; RBD, receptor binding domain; S, spike protein; Tot, total.

## PREVENTION IN THE COMMUNITY

### COVID-19 AND PHYSICAL ACTIVITY IN SEDENTARY INDIVIDUALS: DIFFERENCES IN METABOLIC, CARDIOVASCULAR, AND RESPIRATORY RESPONSES DURING AEROBIC EXERCISE PERFORMED WITH AND WITHOUT A SURGICAL FACE MASKS

Umutlu G, Acar NE, Sinar DS, Akarsu G, Güven E, Yildirim İ.. J Sports Med Phys Fitness. 2021 Apr 22. doi: 10.23736/S0022-4707.21.12313-8. Online ahead of print.

Level of Evidence: 3 - Local non-random sample

#### BLUF

Sports and education specialists from Mersin University, Turkey examined the metabolic, cardiovascular, and pulmonary effects of wearing a surgical face mask (SFM) during incremental walking in 14 sedentary people. Results showed that use of a SFM lead to a 17.27% greater energy expenditure after 10 minutes of walking compared to no mask (NM) (Figure 4b), heart rate was significantly increased at 112 bpm with a SFM compared to 105 bpm with NM ( $p=0.032$ ) (Figure 2a), and a significantly lower VO<sub>2</sub>, VCO<sub>2</sub>, and Ve were also observed with a SFM ( $p<0.001$ ) (Figure 3c,d). These results suggest that SFM use may have negative impacts on otherwise healthy behaviors like exercise in sedentary individuals.

#### SUMMARY

- Incremental walking procedure including walking on a treadmill. Speed started at 4.5 km/h and was increased by 0.5 km/h every 10 mins for a total of 40 mins of walking.
- SFM used was a disposable 3-ply ear-loop face mask (CRC-Elm 5)
- A Masterscreen CPX metabolic cart was used to measure metabolic (VO<sub>2</sub>, VCO<sub>2</sub>, RER, EE), cardiovascular (HR, O<sub>2</sub> pulse), and pulmonary gas exchange (VO<sub>2</sub>, VCO<sub>2</sub>, VE)
- A significant increase in systolic and diastolic BP was also noted with SFM use.

#### ABSTRACT

**BACKGROUND:** The Coronavirus-19 (COVID-19) impairs metabolic, cardiovascular, and pulmonary functions in human metabolism, and wearing face masks is recommended for the prevention of contracting or exposing others to cardio-respiratory infections. Since the effect of wearing a surgical face mask (SFM) on cardiopulmonary exercise capacity has not been systematically reported we aimed to determine the effects of wearing SFM during an incremental walking test on metabolic, cardiovascular, and pulmonary gas exchange responses in sedentary individuals. **METHODS:** The evaluations were performed using a repeated measures study design. Seven sedentary males (age:40years, height:178cm, weight:88kg, BMI:28kg/m<sup>2</sup>, VO<sub>2</sub>max:32.7+-3.9ml/kg/min) and 7 sedentary female participants (age:34years, height:169cm, weight:62kg, BMI:22kg/m<sup>2</sup>, VO<sub>2</sub>max:32.1+-6.8 ml/kg/min) volunteered to participate in the current study. Anthropometric parameters were measured using a Bioelectrical impedance analysis prior to each testing session. The measures of lung function assessed by spirometry, breathing pattern, maximal exercise capacity with-and-without mask were measured with a breath-by-breath automated exercise metabolic system during incremental Bruce protocol on a treadmill with two consecutive sessions with 48-h intervals. Blood pressure values (systolic and diastolic pressure) of the individuals were taken and recorded within 1 minute at the end of every ten minutes, without speed changes. **RESULTS:** VO<sub>2</sub>, VCO<sub>2</sub>, and VE were significantly lower during exercise performed with SFM ( $p<0.001$ ). Heart rate, systolic and diastolic blood pressure were also found significantly higher during exercise performed with SFM ( $p<0.01$ ). **CONCLUSIONS:** Wearing a SFM during incremental walking predispose a decrease in oxygen delivery while increasing pulmonary ventilation in sedentary individuals. Thus, it could be speculated that surgical face masks have a negative impact on oxygen delivery during exercise which results in decreased exercise performance due to the restricted ventilatory conditions.

## FIGURES

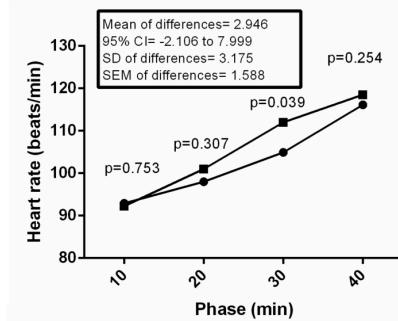


Figure 2a. Comparison of HR during an incremental walking test performed with a surgical mask and wearing no mask.

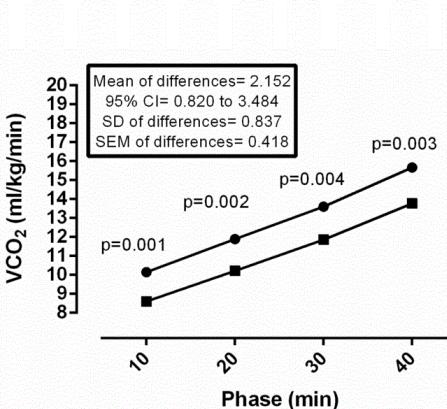
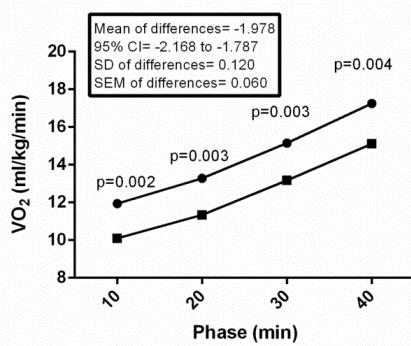


Figure 3c,d. Comparison of (c) VO<sub>2</sub> and (d) VCO<sub>2</sub> parameters during incremental walking test performed with a surgical mask and wearing no mask.

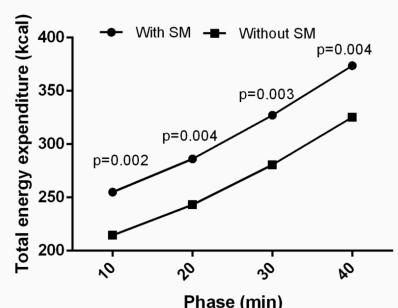


Figure 4b. Energy expenditure induced by incremental walking test performed with surgical mask and wearing no mask.

# EVALUATING THE EFFECTS OF SHELTER-IN-PLACE POLICIES DURING THE COVID-19 PANDEMIC

Berry CR, Fowler A, Glazer T, Handel-Meyer S, MacMillen A.. Proc Natl Acad Sci U S A. 2021 Apr 13;118(15):e2019706118.  
doi: 10.1073/pnas.2019706118.

Level of Evidence: 5 - Modeling

## BLUF

Researchers from University of Chicago, IL conduct a computational analysis to estimate the effects of shelter-in-place (SIP) orders on the number of nationwide COVID-19 cases, COVID-related deaths, mobility, and unemployment. No significant decreases in the number of cases, deaths, or unemployment was seen immediately after implementation of SIP, but unemployment increased when SIP was in place for 10+ days (Figure 2). Mobility did decrease by 0.7% on average but returned to trend after 1 week of SIP (Table 1). The authors emphasize that behavioral changes before the SIP orders were placed significantly reduced the spread of COVID-19 but the SIP orders themselves may have had little effect.

## ABSTRACT

We estimate the effects of shelter-in-place (SIP) orders during the first wave of the COVID-19 pandemic. We do not find detectable effects of these policies on disease spread or deaths. We find small but measurable effects on mobility that dissipate over time. And we find small, delayed effects on unemployment. We conduct additional analyses that separately assess the effects of expanding versus withdrawing SIP orders and test whether there are spillover effects in other states. Our results are consistent with prior studies showing that SIP orders have accounted for a relatively small share of the mobility trends and economic disruptions associated with the pandemic. We reanalyze two prior studies purporting to show that SIP orders caused large reductions in disease prevalence, and show that those results are not reliable. Our results do not imply that social distancing behavior by individuals, as distinct from SIP policy, is ineffective.

## FIGURES

**Table 1. Effects of SIP policies on COVID-19, mobility, and unemployment**

	DV = cases	Deaths	Mobility	Unemployment
Shelter in Place	3.804 (2.786)	0.328 (0.174)	-0.007** (0.002)	0.475 (0.266)
Controls for lagged DV	X	X	X	X
State FE	X	X	X	X
Day FE	X	X	X	X
Observations	4,150	4,150	4,200	600
R-squared	0.676	0.696	0.953	0.909

State-clustered SEs are in parentheses; \*\* $P < 0.01$ . Shelter in place is measured as the proportion of a state's residents under a SIP order on a given day. Cases and deaths are coded as new cases or new deaths per million residents. Mobility is measured as the proportional change in distance traveled. Unemployment is the insured unemployment rate. For cases, deaths, and mobility, we include 14 controls for the lagged dependent variable for each of the preceding 14 d, and, for unemployment, which is measured weekly, we include two controls for the lagged dependent variable from 7 and 14 d prior. DV, dependent variable; FE, fixed effects. X indicates they were included in the regression.

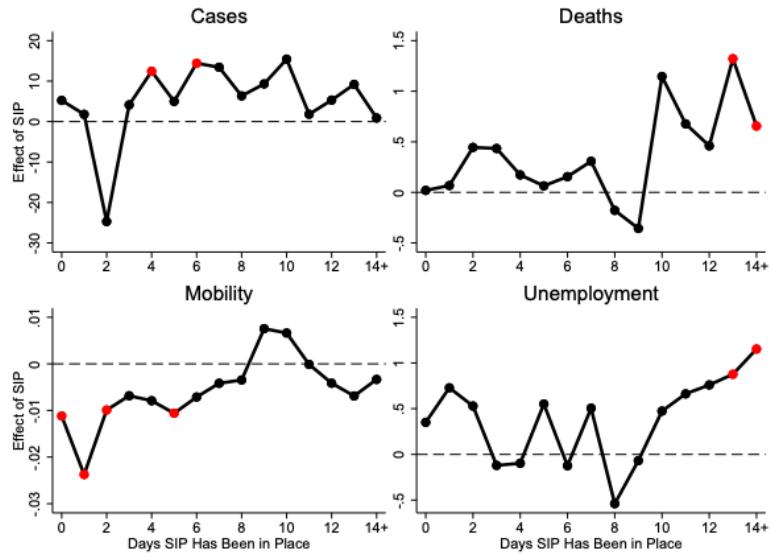


Figure 2. Effects of SIP policies over time. The figure shows the estimated effects of having a SIP policy in place for 0 d to 14+ d in a row. Estimates that are statistically distinguishable from zero ( $P < 0.05$ ) are red. We regressed the outcome of interest on state fixed effects, day fixed effects, lags of the dependent variable, our SIP policy variable, and 14 lags of the SIP policy variable. To estimate the effect of 2 d of SIP policies, for example, we add the coefficients associated with the SIP policy variable, the 1-d lag, and the 2-d lag, and we conduct an F test of the null hypothesis that this sum is equal to zero. Complete results for these regressions are shown in column 7 of SI Appendix, Tables S1–S4.

### NEUTRALIZING RESPONSE AGAINST VARIANTS AFTER SARS-COV-2 INFECTION AND ONE DOSE OF BNT162B2

Lustig Y, Nemet I, Klier L, Zuckerman N, Yishai R, Alroy-Preis S, Mendelson E, Mandelboim M.. N Engl J Med. 2021 Apr 7. doi: 10.1056/NEJMc2104036. Online ahead of print.

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

#### BLUF

Researchers associated with the Ministry of Health, Israel studied whether 1 dose of the BNT162b2 vaccine increases neutralizing activity against B.1.1.7, B.1.351, and P.1 variants in 6 healthcare workers previously infected with the B.1 original SARS-CoV-2 virus. After infection, serum samples had neutralization activity against the B.1, B.1.1.7 and P.1 variants with geometric mean titers of 456, 256, and 71 respectively. Before vaccination, geometric mean titers were 81, 40, 36, and 7 for the B.1, B.1.1.7, P.1, and B.1.351 variants respectively. After vaccination with the BNT162b2 vaccine, geometric mean titers were 9195, 8192, 2896, and 1625 for the B.1, B.1.1.7, P.1, and B.1.351 variants respectively (Figure 1). This suggests that 1 dose of the BNT162b2 vaccine significantly increases neutralizing activity against SARS-CoV-2 variants.

#### FIGURES

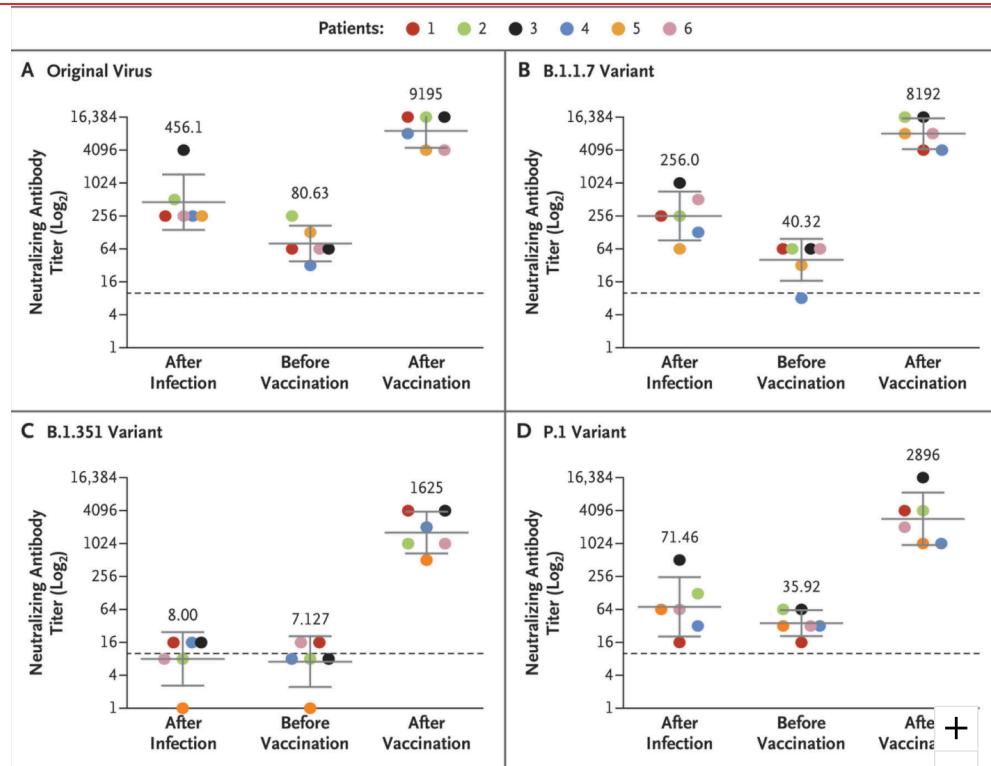


Figure 1. Neutralizing Response against the Original Virus and Variants after SARS-CoV-2 Infection and One Dose of the BNT162b2 Vaccine.

Serum samples from six patients previously infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), obtained 1 to 12 weeks after natural infection, immediately before receiving one dose of the BNT162b2 vaccine, and 1 to 2 weeks after vaccination, were tested with a microneutralization assay for the neutralizing response against sublineage B.1 of the original virus (Panel A), the B.1.1.7 variant first identified in the United Kingdom (Panel B), the B.1.351 variant first identified in South Africa (Panel C), and the P.1 variant first identified in Brazil (Panel D). Dashed lines indicate the cutoff titer. Solid lines and numbers indicate the geometric mean titer, and I bars show the 95% confidence interval.

# DEVELOPMENTS IN TREATMENTS

## ANTIRETROVIRALS FOR PROPHYLAXIS AGAINST COVID-19: A COMPREHENSIVE LITERATURE REVIEW

Alavian G, Kolahdouzan K, Mortezaee M, Torabi ZS.. J Clin Pharmacol. 2021 May;61(5):581-590. doi: 10.1002/jcph.1788. Epub 2020 Dec 6.

Level of Evidence: 5 - Review / Literature Review

### BLUF

A literature review conducted by researchers affiliated with the Tehran University of Medical Sciences and Shahid Beheshti University of Medical Sciences examined 176 studies published between June - October 23, 2020 in the PubMed, Google Scholar, and Medline databases investigating the use for antiretroviral therapy in pre- or post-exposure prophylaxis against COVID-19 infection (Figure 1). The authors found no definitive current evidence to support the role of antiretroviral therapies, however there are multiple ongoing studies looking at the role of protease inhibitors, Tenofovir, and emtricitabine (Table 1). The results of this literature review and current studies could be invaluable for patients with HIV/AIDS or a contraindication to receiving the COVID-19 vaccines.

### ABSTRACT

Although people living with human immunodeficiency virus(PLWH) and other comorbidities are expected to experience griefer 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

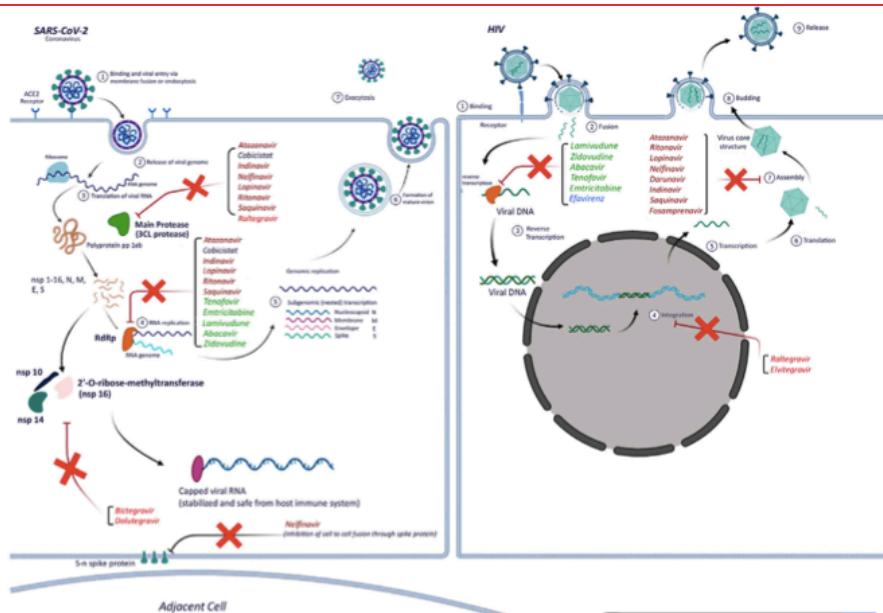


Figure 1. Mechanism of action of antiretroviral drugs through the life cycle of HIV and SARS-CoV-2 viruses. This figure was created using BioRender.com.

**Table I.** Ongoing Studies on Effectiveness of Antiretrovirals for Prophylaxis of COVID-19

Study	Study Type	Prophylaxis Mode	Country	(Expected) Publication Date	Intervention
COVID-19 Ring-Based Prevention Trial With Lopinavir/Ritonavir (CORIPREV-LR)	RCT	PEP	Canada	March 2022 Ongoing	LPV/r (400/100 mg Q12h × 14 days) versus no treatment
Treatment of Non-severe Confirmed Cases of COVID-19 and Chemoprophylaxis of Their Contacts as Prevention Strategy: A Cluster Randomized Clinical Trial (PEP CoV-2)	RCT	PEP	Spain	Unknown	DRV/c (800/150 mg QD) versus HCQ (200 mg QD)
Impact of Long-Term Protease Inhibitors in Patients Living With HIV on the Incidence of COVID-19 (COVIP)	Cohort	PrEP	France	July 2021 Ongoing	Protease inhibitors (dosage not specified)
Randomized Clinical Trial for the Prevention of SARS-CoV-2 Infection (COVID-19) in Healthcare Personnel (EPICOS)	RCT	PrEP	Spain	December 2020 Ongoing	TDF/FTC (245/200 mg QD), HCQ (200 mg QD), TDF/FTC (245/200 mg QD) plus HCQ (200 mg QD), and placebo
TAF/FTC for Pre-exposure Prophylaxis of COVID-19 in Healthcare Workers (CovIPrep Study)	RCT	PrEP	Argentina	November 2020 Ongoing	FTC/TAF (200/25 mg QD) versus placebo
Chemoprophylaxis of SARS-CoV-2 Infection (COVID-19) in Exposed Healthcare Workers (COVIDAXIS)	RCT	PrEP	France	November 2020 Ongoing	HCQ (400 mg Q12h for 2 doses, then 200 mg Q12h) or LPV/r (400/100 mg Q12h) versus placebo
Daily Regimen of Tenofovir/Emtricitabine as Prevention for COVID-19 in Health Care Personnel in Colombia	RCT	PrEP	Colombia	April 2021 Ongoing	TDF/FTC (300/200 mg QD) plus PPE versus placebo plus PPE

DRV/c, darunavir/cobicistat; FTC, emtricitabine; HCQ, hydroxychloroquine; LPV/r, lopinavir/ritonavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PEP, postexposure prophylaxis; PPE, personal protective equipment; PrEP, preexposure prophylaxis; Q12h, every 12 hours; QD, every day; RCT, randomized, controlled trial.

Ongoing studies on the effectiveness of antiretrovirals for prophylaxis of COVID-19.

Table 1. Ongoing Studies on Effectiveness of Antiretrovirals for Prophylaxis of COVID-19

DRV/c, darunavir/cobicistat; FTC, emtricitabine; HCQ, hydroxychloroquine; LPV/r, lopinavir/ritonavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PEP, postexposure prophylaxis; PPE, personal protective equipment; PrEP, preexposure prophylaxis; Q12h, every 12 hours; QD, every day; RCT, randomized, controlled trial.

Ongoing studies on the effectiveness of antiretrovirals for prophylaxis of COVID-19.

## SILENCING OF SARS-COV-2 WITH MODIFIED SIRNA-PEPTIDE DENDRIMER FORMULATION

Khaitov M, Nikanova A, Shilovskiy I, Kozhikhova K, Kofiadi I, Vishnyakova L, Nikolsky A, Gattinger P, Kovchina V, Barvinskaya E, Yumashev K, Smirnov V, Maerle A, Kozlov I, Shatilov A, Timofeeva A, Andreev S, Koloskova O, Kuznetsova N, Vasina D, Nikiforova M, Rybalkin S, Sergeev I, Trofimov D, Martynov A, Berzin I, Gushchin V, Kovalchuk A, Borisevich S, Valenta R, Khaitov R, Skvortsova V.. Allergy. 2021 Apr 10. doi: 10.1111/all.14850. Online ahead of print.

Level of Evidence: 5 - Mechanism-based reasoning

### BLUF

Immunology and microbiology specialists from Russia and Austria tested 13 siRNAs to determine the most potent in silencing SARS-CoV-2 gene expression (Table 1). SiN-4, siR-7, and siR-11 all significantly decreased the level of luminescence by 80%+ in HEp-2 cells, and siR-7 showed a significant decrease in vRNA concentrations in Vero E6 cells infected with siRNA/Lipofectamine 3000 and SARS-CoV-2 (Figure 2). LNA-modified siR-7 (siR-7-EM) had a significantly longer half-life compared to unmodified siR-7, and siR-7-EM combined with KK-46 peptide dendrimer (siR-7-EM/KK-46) had anti-SARS-CoV-2 effects in vitro and in vivo in Syrian hamsters (Figure 4), suggesting its possible use in the treatment of COVID-19 in humans.

### SUMMARY

- Elaboration of anti-SARS-CoV-2 effects seen in vivo: siR-7-EM/KK-46 showed decreased progeny virus production and lung inflammation in comparison to untreated SARS-CoV-2-infected hamsters.

- 2mg/kg daily of siR-7-EM/KK-46 optimally decreased viral titers and lung inflammation in Syrian hamsters after 6 days

## ABSTRACT

**BACKGROUND:** First vaccines for prevention of Coronavirus disease 2019 (COVID-19) are becoming available but there is a huge and unmet need for specific forms of treatment. In this study we aimed to evaluate the anti-SARS-CoV-2 effect of siRNA both in vitro and in vivo. **METHODS:** To identify the most effective molecule out of a panel of 15 in silico designed siRNAs, an in vitro screening system based on vectors expressing SARS-CoV-2 genes fused with the firefly luciferase reporter gene and SARS-CoV-2-infected cells was used. The most potent siRNA, siR-7, was modified by Locked nucleic acids (LNAs) to obtain siR-7-EM with increased stability and was formulated with the peptide dendrimer KK-46 for enhancing cellular uptake to allow topical application by inhalation of the final formulation - siR-7-EM/KK-46. Using the Syrian Hamster model for SARS-CoV-2 infection the antiviral capacity of siR-7-EM/KK-46 complex was evaluated. **RESULTS:** We identified the siRNA, siR-7, targeting SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) as the most efficient siRNA inhibiting viral replication in vitro. Moreover, we showed that LNA-modification and complexation with the designed peptide dendrimer enhanced the antiviral capacity of siR-7 in vitro. We demonstrated significant reduction of virus titer and lung inflammation in animals exposed to inhalation of siR-7-EM/KK-46 in vivo. **CONCLUSIONS:** Thus, we developed a therapeutic strategy for COVID-19 based on inhalation of a modified siRNA-peptide dendrimer formulation. The developed medication is intended for inhalation treatment of COVID-19 patients.

## FIGURES

№	siRNA name	The suppression of luciferase activity (%, N=4, Mean±SD) in comparison with:		
		plasmid		nonspecific siGFP
1	siLuc	pRdRp-full	82.9±6.2	79.3±10.2
1a	siLuc	pVAX-N-IRES-LUC	75.2±10.9	72.4±9.1
2	siN-2	pVAX-N-IRES-LUC	42.3±27.4	36.4±20.7
3	siN-3	pVAX-N-IRES-LUC	64.6±17.3	60.8±14.7
4	siN-4	pVAX-N-IRES-LUC	81.2±9.2	78.8±10.05
5	siN-5	pVAX-N-IRES-LUC	64.7±13.4	60.4±6.1
6	siR-7	pRdRp-full	91.3±3.2	89.2±4.9
7	siR-8	pRdRp-full	47.2±28.3	56.6±22.01
8	siR-9	pRdRp-full	67.6±7.9	61.7±14.6
9	siR-10	pRdRp-full	70.6±19.3	64.6±22.9
10	siR-11	pRdRp-full	84.5±8.6	81.3±10.6
11	siR-12	pRdRp-full	56.8±23.5	48.01±28.9
12	siR-13	pRdRp-full	77.9±8.8	73.4±12.2
13	siR-14	pRdRp-full	47.3±22.4	36.3±31.06
14	siR-15	pRdRp-full	71.1±11.3	65.03±17.4

Table 1. The suppression of luciferase activity by siRNA in Hep-2 cells consecutively transfected with plasmid coding SARS-CoV-2 genes fused with firefly luciferase gene and specific or nonspecific siRNAs.

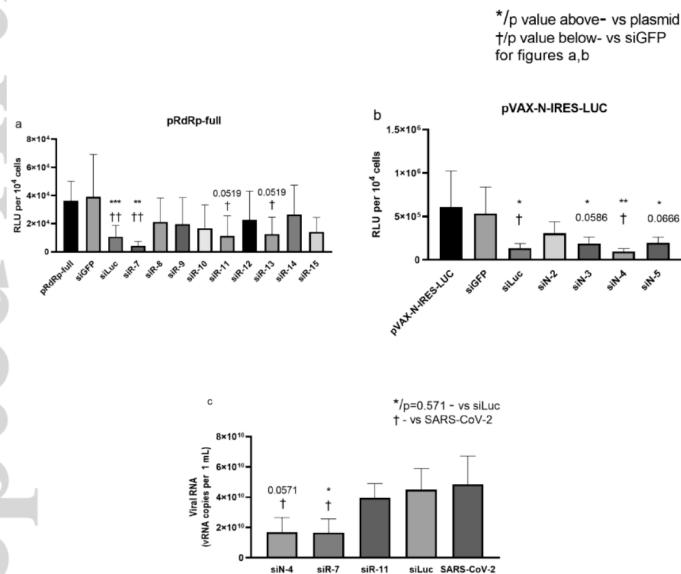


Figure 2. Properties of designed siRNA(a-c) Inhibition of gene expression with synthetic siRNA. Hep-2 cells were transfected with each of the plasmids coding SARS-CoV-2 genes fused with firefly luciferase gene (pRdRp-full) (a) or pVAX-N-IRES-LUC (b) followed by transfection with SARS-CoV-2-specific or control siRNA. siLuc and siGFP were used as positive and negative controls, respectively. LipofectamineTM 3000 was used as vehicle for both pDNA and siRNA. After 24h cells were harvested and luciferase activity was determined. Data are expressed as relative light units (RLU) per  $10^4$  cells. Footnotes: \*/† or adjusted p value above/below represents the difference compared to cells transfected with plasmid only/non-specific siGFP, respectively. \*†P<0.05, \*\*††P<0.01, \*\*\*P<0.001.

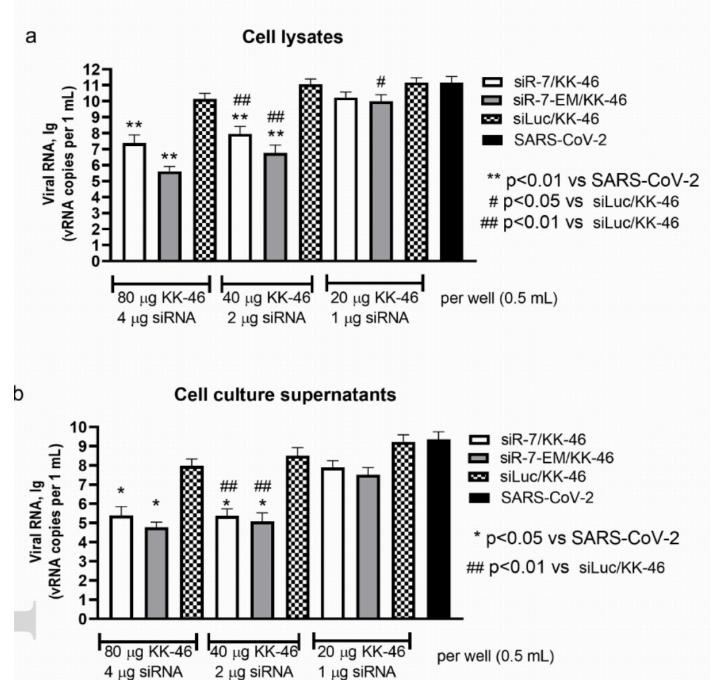


Figure 4. Inhibition of SARS-CoV-2 reproduction with unmodified or LNA-modified siR-7/ peptide dendrimer KK-46 complexes in vitro. Vero E6 cells were transfected with unmodified siR-7 or LNA-modified siR-7-EM-peptide dendrimer KK-46 complexes at three concentrations (x-axes). Media with complexes were removed four hours after transfection and cells were infected with SARS-CoV-2 at MOI 0.0001. After 48 hours supernatants and cells were harvested. Viral load was determined by qRT-PCR in cells lysates (a) and supernatants (b). The results are expressed as viral RNA copies per mL. Differences between multiple groups were estimated using a Kruskal-Wallis test followed by post-hoc testing (if the Kruskal-Wallis was significant) using un-paired Mann-Whitney U tests. Bars show medians of five independent experiments + SDs.

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