

The Daily COVID-19 Literature Surveillance Summary

March 09, 2021



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COVID-19 Daily Literature Surveillance

COVID19LST



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

LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

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

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

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

How to cite the Levels of Evidence Table

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

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

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

EXECUTIVE SUMMARY

Transmission & Prevention

- [Are viral variants and vaccine efficacy linked?](#) An opinion piece penned by a virologist from Weill Cornell Medicine discusses some current issues regarding SARS-CoV-2 variants and COVID-19 vaccine efficacy. The author asserts that caution needs to be taken with vaccine protocols to ensure that improper dosing schedules do not lead to viral variants and resistance and the need for ongoing research into the efficacy of said vaccines in a constantly-evolving viral landscape. The implication being that if care is not taken with these efforts, more vaccine-resistant variants may spring up, worsening the pandemic.

Mental Health & Resilience Needs

- [Retail alcohol and tobacco sales increased during the COVID-19 lockdown.](#) Experts in liver transplantation and preventive medicine from Keck School of Medicine in Los Angeles compared retail purchases of alcohol and tobacco products in the continental United States from April 1 to June 30, 2020 to the same period in 2017-2019. They observed a 34% and 13.2% increase in total weighted sales of alcohol and tobacco, respectively, across all demographic and geographic categories except for households making less than \$20,000. While this aggregated dataset limits inferences on individual behaviors and some of the increase in retail alcohol sales may be explained by restaurant and bar closures, authors suggest health professionals and policymakers recognize and investigate the potential health impacts of increased substance use during the pandemic.

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TRANSMISSION & PREVENTION

APPROACHES FOR OPTIMAL USE OF DIFFERENT COVID-19 VACCINES: ISSUES OF VIRAL VARIANTS AND VACCINE EFFICACY

Moore JP.. JAMA. 2021 Mar 4. doi: 10.1001/jama.2021.3465. Online ahead of print.

Level of Evidence: 5 - Expert Opinion

BLUF

An opinion piece penned by a virologist from Weill Cornell Medicine discusses some current issues regarding SARS-CoV-2 variants and COVID-19 vaccine efficacy. The author asserts that caution needs to be taken with vaccine protocols to ensure that improper dosing schedules do not lead to viral variants and resistance and the need for ongoing research into the efficacy of said vaccines in a constantly-evolving viral landscape. The implication being that if care is not taken with these efforts, more vaccine resistant variants may spring up, worsening the pandemic.

SUMMARY

- The author believes that with current vaccination rates, the USA might be able to return to prepandemic life this coming year
- The author also asserts that what could prevent this return is the spread of viral variants that are resistant to current vaccines
- The B.1.351 and P.1 variants suggest that they arose from selection pressure under neutralizing antibodies, which may prove to be more concerning
- Some current testing showing some resistance of the B.1.351 strain to current vaccines
- The author believes that mandating 2 doses at short intervals as is done in the US is optimal as opposed to the UK where there is no such mandate
- Further research needs to be done in regard to the Johnson and Johnson vaccine as a single less effective dose may promote resistance
- Many vaccine manufacturers are redesigning their vaccine to combat resistance

DEVELOPMENTS IN TRANSMISSION & PREVENTION

INTRAUTERINE VERTICAL SARS-COV-2 INFECTION: A CASE CONFIRMING TRANSPLENTAL TRANSMISSION FOLLOWED BY DIVERGENCE OF THE VIRAL GENOME

Zaigham M, Holmberg A, Karlberg ML, Lindsjö OK, Jokubkiene L, Sandblom J, Strand AS, Andersson O, Hansson SR, Nord DG, Tannenberg P.. BJOG. 2021 Feb 27. doi: 10.1111/1471-0528.16682. Online ahead of print.

Level of Evidence: 5 - Case report

BLUF

A case study conducted at Lund University during late 2020 by the Department of Clinical Sciences focused on the case of a 27-year-old woman at gestational week 34+4 who presented with fever, dry cough, abdominal pain and decreased fetal movements found to be SARS-CoV-2 positive by nasopharyngeal RT-PCR (Figure 2). Because fetal monitoring suggested intrauterine hypoxia, the patient underwent emergency cesarean section with the newborn not breathing spontaneously until 6 minutes of life (Apgars 1, 4, and 8)(Timeline). Because the neonate also tested positive for SARS-CoV-2 (Table 3) and significant placental pathology was observed (Figure 3, see summary), authors suggest vertical transmission is a rare but serious complication of SARS-CoV-2 infection.

SUMMARY

When analyzing the four isolates gathered from the mother and neonate, 11 single-nucleotide polymorphisms (SNP's) and 1 multiple-nucleotide polymorphism's differed.

They observed the following in pathologic analysis of the placenta:

- significant perivillous fibrin deposition

- chorangiosis in infected areas
- acute inter-villositis in areas high in detected viral samples

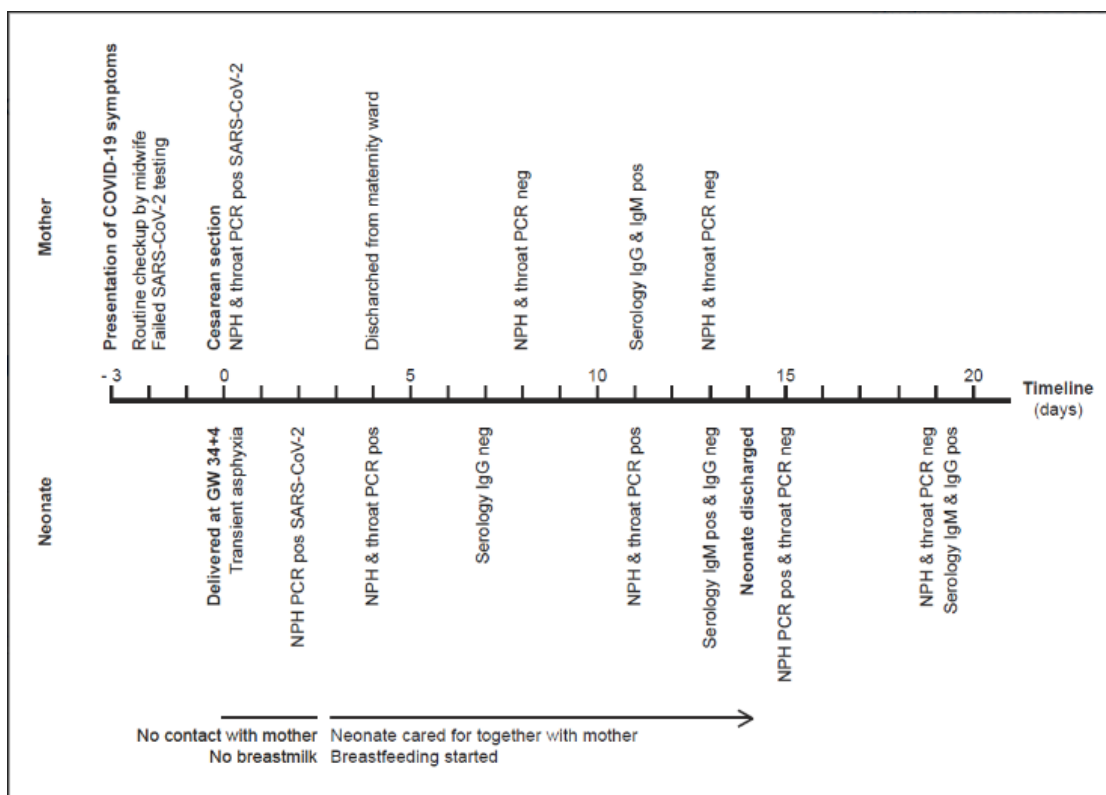
FIGURES

Sample	Time of sampling	Ig class	Result
Serum	Day of delivery	IgM	Weak positive
Serum	Day of delivery	IgG	Negative
Serum	Day 12 postpartum	IgM	Positive
Serum	Day 12 postpartum	IgG	Positive
Breastmilk	Day 35 postpartum	Total Ig	Negative

Neonatal samples

Sample	Time of sampling	Ig class	Result
Serum	DOL 7	IgG	Negative
Serum	DOL 14	IgM	Positive
Serum	DOL 14	IgG	Negative
Serum	DOL 20	IgM	Positive
Serum	DOL 20	IgG	Positive

Table 3: Variant analysis and annotation of whole-genome sequencing data from virus isolates obtained from the mother and placenta at delivery and from the neonate at day of life (DOL) 2 and DOL 5.



Timeline of events for mother and neonate. SARS-CoV-2; severe acute respiratory syndrome coronavirus-2, PCR; Real time reverse transcriptase quantitative polymerase chain reaction, GW; gestational week, NPH; nasopharynx, Ig; Immunoglobulin.

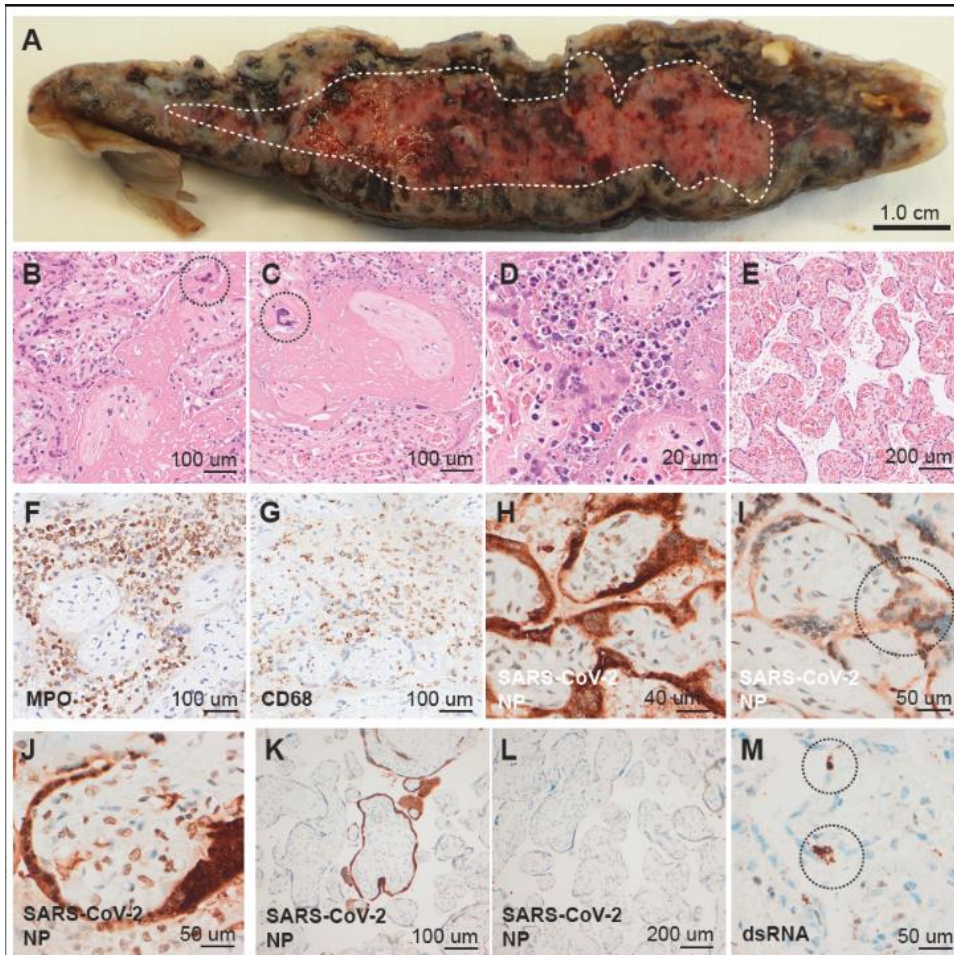


Figure 3. Placental pathology. (A) Transected placenta with confluent accumulation of fibrin demarcated (white broken line) (B-C) Massive intervillous fibrin deposition surrounding denuded villi with extravillous syncytiotrophoblasts (circles) located in the fibrin (D) Acute intervillitis with karyorectic neutrophils in the intervillous space and degeneration of the villous trophoblast layer (E) Representative region of chorangiosis (F-G) Immunohistochemical staining for myeloperoxidase (MPO) and CD68 with positivity in inflammatory cells in areas of intervillitis (H-J) Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) nucleoprotein (NP) detected in nucleus and (circle in I) and cytoplasm in villous trophoblasts and syncytiotrophoblasts as well as in the nucleus of villous stromal cells (J) in areas of intervillitis (K-L) Areas without intervillitis showed absent or focal staining for SARS-CoV-2 nucleoprotein of villi. M. Double stranded RNA (dsRNA) detected in villous trophoblasts and syncytiotrophoblasts (circles).

CARDIOLOGY

ASSOCIATION BETWEEN BLOOD PRESSURE CONTROL AND CORONAVIRUS DISEASE 2019 OUTCOMES IN 45 418 SYMPTOMATIC PATIENTS WITH HYPERTENSION: AN OBSERVATIONAL COHORT STUDY

Sheppard JP, Nicholson BD, Lee J, McGagh D, Sherlock J, Koshari C, Oke J, Jones NR, Hinton W, Armitage L, Van Hecke O, Lay-Flurrie S, Bankhead CR, Liyanage H, Williams J, Ferreira F, Feher MD, Ashworth AJ, Joy MP, de Lusignan S, Hobbs FDR. Hypertension. 2021 Mar 3;77(3):846-855. doi: 10.1161/HYPERTENSIONAHA.120.16472. Epub 2020 Dec 16. Level of Evidence: 3 - Cohort study or control arm of randomized trial

BLUF

Members of the Nuffield Department of Primary Care Health Sciences evaluated COVID-19 outcomes in 45,418 patients between January and August 2020. Of 4,277 diagnosed with COVID-19 (Table 2), those with uncontrolled stage 1 hypertension had lower odds of 28-day mortality compared to those with controlled hypertension (odds ratio, 0.76 [95% CI, 0.62-0.92]) (Figure 1, see summary for definitions). Authors suggest these unexpected findings may be attributable to confounding variables such as socioeconomic factors and duration of disease and recommend further research to understand the role of blood pressure control in prognosis of patients with COVID-19.

SUMMARY

The patient population was put into the following categories:

1. controlled (<130/80 mm Hg)
2. raised (130/80-139/89 mm Hg)
3. stage 1 uncontrolled (140/90-159/99 mm Hg)
4. stage 2 uncontrolled (≥160/100 mm Hg)

ABSTRACT

Hypertension has been identified as a risk factor for COVID-19 and associated adverse outcomes. This study examined the association between pre-infection blood pressure (BP) control and COVID-19 outcomes using data from 460 general practices in England. Eligible patients were adults with hypertension who were tested or diagnosed with COVID-19. BP control was defined by the most recent reading within 24 months of the index date (01/01/2020). BP was defined as controlled (<130/80mmHg), raised (130/80-139/89mmHg), stage 1 uncontrolled (140/90-159/99mmHg) or stage 2 uncontrolled (≥160/100mmHg). The primary outcome was death within 28 days of COVID-19 diagnosis. Secondary outcomes were COVID-19 diagnosis and COVID-19 related hospital admission. Multivariable logistic regression was used to examine the association between BP control and outcomes. Of the 45,418 patients (mean age 67 years; 44.7% male) included, 11,950 (26.3%) had controlled BP. These patients were older, had more co-morbidities and had been diagnosed with hypertension for longer. A total of 4,277 patients (9.4%) were diagnosed with COVID-19 and 877 died within 28 days. Individuals with stage 1 uncontrolled BP had lower odds of COVID-19 death (OR 0.76, 95%CI 0.62-0.92) compared to patients with well-controlled BP. There was no association between BP control and COVID-19 diagnosis or hospitalisation. These findings suggest BP control may be associated with worse COVID-19 outcomes, possibly due to these patients having more advanced atherosclerosis and target organ damage. Such patients may need to consider adhering to stricter social-distancing, to limit the impact of COVID-19 as future waves of the pandemic occur.

FIGURES

Table 2. Patients Being Investigated for COVID and Experiencing Outcomes During Follow-Up

COVID outcome	Total population		BP controlled (<130/80 mm Hg)		BP raised (130/80–139/89 mm Hg)		Stage 1 uncontrolled (140/90–159/99 mm Hg)		Stage 2 uncontrolled (>160/100 mm Hg)	
	Total	%	Total	%	Total	%	Total	%	Total	%
SARS-CoV-2 test negative	41 141	90.6%	10 645	89.1%	15 526	91.2%	12 012	91.2%	2958	90.5%
SARS-CoV-2 test positive	3025	6.7%	939	7.9%	1060	6.2%	806	6.1%	220	6.7%
COVID-19 diagnosis*	1252	2.8%	366	3.1%	439	2.6%	355	2.7%	92	2.8%
COVID-19–related hospital admission†	273	0.6%	86	0.7%	103	0.6%	73	0.6%	11	0.3%
COVID-19–related death‡	877	1.9%	335	2.8%	278	1.6%	200	1.5%	64	2.0%

BP indicates blood pressure; COVID-19, coronavirus disease 2019; and SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

* Based on a diagnostic code.

† Hospital admission within 28 d of positive COVID-19 case or a COVID-19 diagnosis before hospital discharge.

‡ Death within 28 d of a COVID-19 diagnosis.

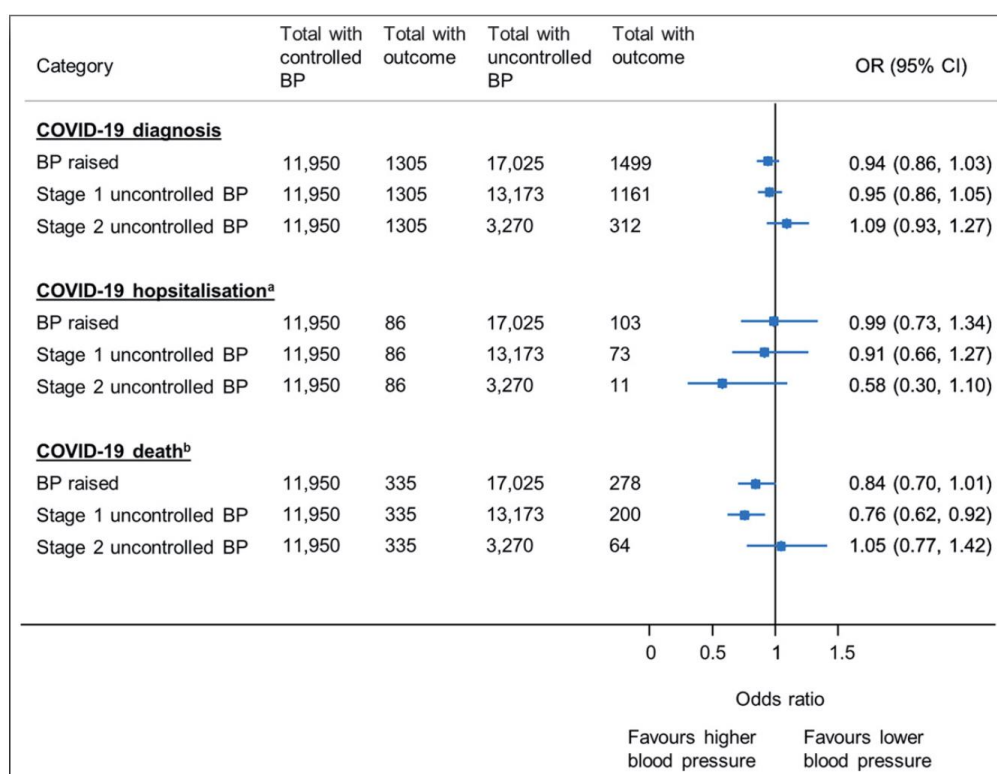


Figure 1. Primary analysis showing the association between blood pressure (BP) control and coronavirus disease 2019 (COVID-19) diagnosis, COVID-19–related hospitalization and death. Models adjusted for age, sex, ethnicity, deprivation, household size, body mass index, smoking status, COVID-19 shielding status, date of suspected COVID-19 diagnosis, diabetes, chronic kidney disease, previous stroke, previous transient ischemic attack, previous myocardial infarction, chronic lung disease, asthma, chronic obstructive pulmonary disease, cancer, antihypertensive, and statin prescription. OR indicates odds ratio. ^aHospital admission within 28 d of positive COVID-19 case or a COVID-19 diagnosis before hospital discharge. ^bDeath within 28 d of a COVID-19 diagnosis.

R&D: DIAGNOSIS & TREATMENTS

CURRENT DIAGNOSTICS

SALIVA FOR DETECTION OF SARS-COV-2

Markewitz RDH, Wandinger KP, Junker R. N Engl J Med. 2021 Feb 3;384(9):10.1056/NEJMc2032165#sa1. doi: 10.1056/NEJMc2032165. Online ahead of print.

Level of Evidence: 5 - Expert Opinion

BLUF

In this letter to the editor, the authors from University Hospital Schleswig-Holstein in Kiel, Germany, critique a recently published study that used saliva samples in the detection of SARS-CoV-2 by RT-PCR. However, a standard curve from a previous study was used without additional paralleled amplification of each PCR cycle, suggesting the possibility of unreliable results and the authors call for further attention to detail when reporting results that may be misleading.

DEVELOPMENTS IN TREATMENTS

EFFECT OF IVERMECTIN ON TIME TO RESOLUTION OF SYMPTOMS AMONG ADULTS WITH MILD COVID-19: A RANDOMIZED CLINICAL TRIAL

López-Medina E, López P, Hurtado IC, Dávalos DM, Ramirez O, Martínez E, Díazgranados JA, Oñate JM, Chavarriaga H, Herrera S, Parra B, Libreros G, Jaramillo R, Avendaño AC, Toro DF, Torres M, Lesmes MC, Rios CA, Caicedo I. JAMA. 2021 Mar 4. doi: 10.1001/jama.2021.3071. Online ahead of print.

Level of Evidence: 2 - Randomized trial or observational study with dramatic effect

BLUF

Researchers from various academic and medical institutions in Columbia conducted a double-blinded, randomized trial at a single center (Centro de Estudios en Infectología Pediátrica, Cali, Columbia) of 398 patients with mild COVID-19 confirmed by PCR from July 15, 2020 through December 21, 2020, allocating 200 of them with treatment of Ivermectin and the remaining 198 with a placebo. The primary outcome revealed 85% of the Ivermectin treated group versus 75% of the placebo treated group had complete resolution of symptoms within 21 days (Figure 2), with the median time to resolution 10 days vs. 12 days ($p=0.53$), respectively. However, neither of these results were statistically significant, suggesting the use of Ivermectin in COVID-19 patients with mild symptoms is not an effective treatment option.

FIGURES

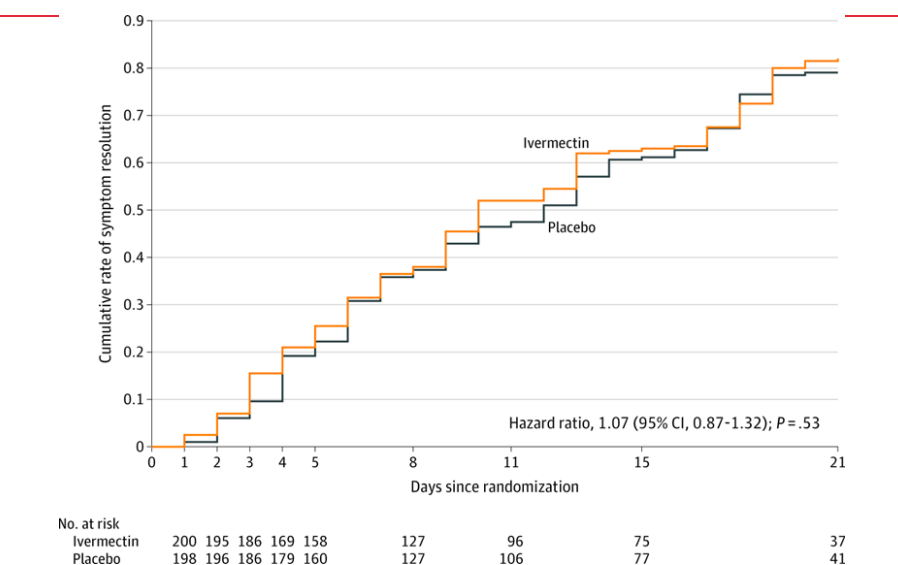


Figure 2. Time to Resolution of Symptoms in the Primary Analysis Population.

MENTAL HEALTH & RESILIENCE NEEDS

IMPACT ON PUBLIC MENTAL HEALTH

RETAIL ALCOHOL AND TOBACCO SALES DURING COVID-19

Lee BP, Dodge JL, Leventhal A, Terrault NA.. Ann Intern Med. 2021 Mar 2. doi: 10.7326/M20-7271. Online ahead of print.
Level of Evidence: 1 - Local and current random sample surveys (or censuses)

BLUF

Experts in liver transplantation and preventive medicine from Keck School of Medicine in Los Angeles compared retail purchases of alcohol and tobacco products in the continental United States from April 1 to June 30, 2020 to the same period in 2017-2019 (see summary). They observed a 34% and 13.2% increase in total weighted sales of alcohol and tobacco, respectively, across all demographic and geographic categories except for households making less than \$20,000 (Table, Figure). While this aggregated dataset limits inferences on individual behaviors, and some of the increase in retail alcohol sales may be explained by restaurant and bar closures, authors suggest health professionals and policymakers recognize and investigate the potential health impacts of increased substance use during the pandemic.

SUMMARY

Data was extracted from a longitudinal household cohort of retail and e-commerce purchase data collected by the Nielsen National Consumer Panel. Investigators focused on retail purchases of the following products:

1. alcohol: wine, liquor, beer, and cider
2. tobacco: e-cigarettes, cigars, and smokeless tobacco

FIGURES

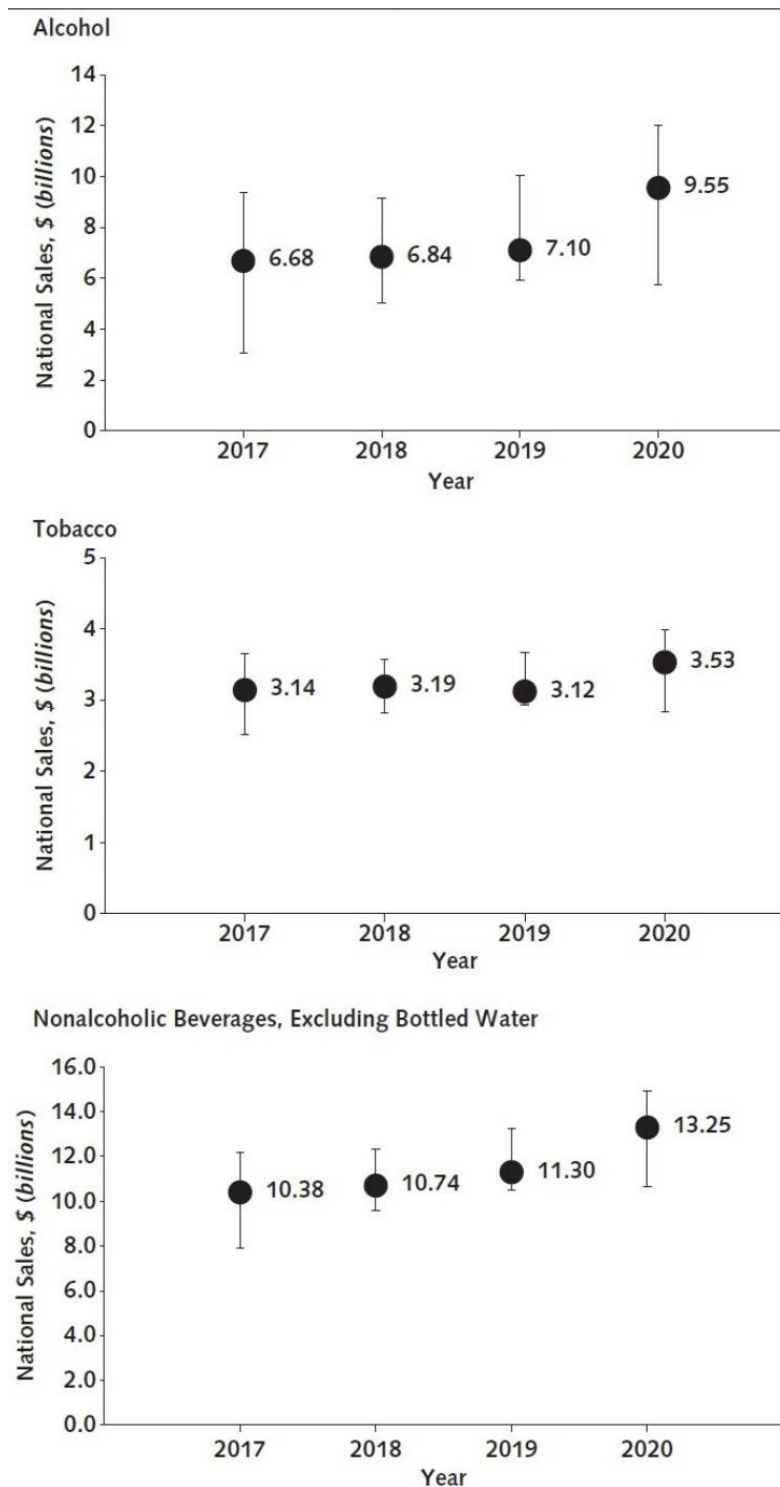


Figure. Weighted national estimates of retail sales.

Point estimates (circles) with 95% CIs (error bars). Top. Alcohol. Middle. Tobacco. Bottom. Nonalcoholic beverages, excluding bottled water.

Table. Observed National Estimates of Alcohol Sales During 1 April to 30 June in 2019 and 2020*

Characteristic	All Households, n (%)†		Alcohol				
	2019	2020	2019		2020		Relative Change in Sales,%
			Households, n‡	Sales (95% CI), \$ (billions)\$	Households, n‡	Sales (95% CI), \$ (billions)\$	
Total	73 202 (100)	71 502 (100)	28 378	7.10 (5.9–10.0)	31 296	9.55 (5.7–12.0)	+34.4
Household demographics							
Annual household income							
<\$20 000	6591 (13.5)	7043 (13.2)	1750	0.60 (0.6–0.6)	2094	0.59 (0.5–0.6)	−0.8
\$20 000–\$29 999	6939 (10.5)	6816 (9.6)	2050	0.47 (0.4–0.6)	2369	0.57 (0.3–0.7)	+21.9
\$30 000–\$39 999	7812 (8.9)	7437 (8.5)	2679	0.51 (0.4–0.6)	2879	0.58 (0.4–0.7)	+15.3
\$40 000–\$49 999	7939 (8.3)	7564 (8.1)	2919	0.48 (0.4–0.7)	3066	0.61 (0.4–0.8)	+27.1
\$50 000–\$69 999	13 059 (13.7)	12 356 (13.5)	5137	0.91 (0.8–1.2)	5397	1.16 (0.8–1.4)	+27.6
\$70 000–\$99 999	15 711 (15.5)	15 113 (15.6)	6717	1.21 (1.0–1.8)	7337	1.65 (1.0–2.1)	+36.3
≥\$100 000	15 151 (29.6)	15 174 (31.5)	7126	2.93 (2.3–4.5)	8155	4.38 (2.3–5.7)	+49.4
Members in household							
1	17 116 (27.2)	17 553 (27.3)	5542	1.54 (1.3–2.2)	6374	2.02 (1.2–2.5)	+31.0
2	28 718 (32.4)	28 780 (32.4)	12 704	3.11 (2.7–4.2)	13 936	4.00 (2.6–4.9)	+28.9
3–4	20 698 (29.3)	18 973 (29.3)	7900	1.86 (1.5–2.8)	8526	2.68 (1.4–3.5)	+43.9
≥5	6671 (11.0)	6195 (11.1)	2232	0.59 (0.5–0.9)	2460	0.84 (0.5–1.1)	+42.5
Children aged <18 y							
Yes	19 488 (31.0)	17 350 (30.7)	6893	1.70 (1.3–2.7)	7399	2.50 (1.3–3.3)	+47.0
No	53 714 (69.0)	54 152 (69.3)	21 485	5.41 (4.6–7.4)	23 898	7.05 (4.5–8.7)	+30.3
Head of household demographics							
Age							
<35 y	7553 (14.6)	6294 (14.3)	2670	0.72 (0.6–1.1)	2621	1.03 (0.5–1.4)	+43.1
35–44 y	12 856 (15.3)	12 073 (15.3)	4660	0.90 (0.7–1.4)	5236	1.32 (0.8–1.7)	+46.6
45–54 y	13 970 (16.3)	13 779 (16.3)	5559	1.19 (0.9–1.8)	6351	1.66 (0.8–2.2)	+40.0
55–64 y	16 747 (17.0)	16 790 (17.2)	6963	1.45 (1.3–1.9)	7742	1.87 (1.3–2.2)	+29.2
>64 y	15 453 (16.0)	15 876 (16.0)	6008	1.04 (0.7–1.5)	6611	1.39 (0.8–1.8)	+33.7
Employed	39 386 (46.8)	38 395 (47.5)	15 565	3.22 (2.6–4.9)	17 675	4.66 (2.5–6.0)	+44.9
Full time	26 526 (32.4)	25 749 (32.8)	10 708	2.27 (1.8–3.5)	12 166	3.32 (1.7–4.3)	+46.1
Part time	12 860 (14.4)	12 646 (14.7)	4857	0.95 (0.8–1.4)	5509	1.35 (0.8–1.7)	+41.9
No	27 190 (32.3)	26 417 (31.6)	10 294	2.08 (1.8–2.7)	10 886	2.62 (1.8–3.2)	+25.8
Highest education							
High school graduate	14 502 (25.3)	14 270 (24.4)	5217	1.73 (1.6–2.1)	5866	2.12 (1.6–2.4)	+22.0
Some college	20 002 (24.6)	19 620 (24.4)	7730	1.62 (1.3–2.3)	8645	2.24 (1.2–2.9)	+38.0
College graduate	30 848 (26.6)	29 590 (27.3)	12 526	1.77 (1.3–3.0)	13 609	2.74 (1.2–3.7)	+55.2
Race							
White¶	55 921 (74.6)	55 921 (74.3)	22 915	5.66 (4.7–8.0)	24 751	7.57 (4.5–9.5)	+33.7
African American	8208 (12.6)	8421 (12.6)	2895	0.64 (0.5–1.0)	3624	0.92 (0.5–1.2)	+42.3
Asian	3057 (4.5)	3039 (4.8)	994	0.23 (0.2–0.4)	1113	0.35 (0.2–0.5)	+54.6
Hispanic	4782 (13.3)	5964 (13.8)	2394	0.96 (0.8–1.4)	2850	1.34 (0.8–1.7)	+39.7
Other	4154 (8.3)	4122 (8.3)	1575	0.57 (0.5–0.7)	1808	0.71 (0.5–0.8)	+24.5
Geography demographics							
County size**							
A	27 517 (40.9)	27 005 (40.8)	10 961	3.08 (2.6–4.4)	12 176	4.19 (2.5–5.3)	+35.9
B	23 794 (30.7)	23 071 (30.9)	9552	2.27 (1.9–3.2)	10 360	3.07 (1.8–3.9)	+35.5
C	11 793 (14.9)	11 505 (14.9)	4430	0.98 (0.8–1.3)	4888	1.30 (0.8–1.6)	+32.0
D	10 098 (13.5)	9922 (13.4)	3435	0.77 (0.7–1.0)	3872	0.99 (0.6–1.2)	+28.1
Geographic region							
East	12 481 (17.6)	12 051 (17.5)	3833	0.78 (0.6–1.2)	4197	1.14 (0.6–1.5)	+45.0
Central	18 398 (21.7)	18 005 (21.7)	7538	1.52 (1.2–2.2)	8436	2.08 (1.2–2.6)	+37.2
South	28 314 (38.7)	27 775 (38.9)	11 090	2.74 (2.4–3.6)	12 307	3.55 (2.4–4.3)	+29.7
West	14 010 (21.9)	13 670 (22.0)	5918	2.07 (1.7–3.0)	6356	2.78 (1.6–3.6)	+34.5

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