

The Daily COVID-19 Literature Surveillance Summary

December 02, 2020



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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>

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EXECUTIVE SUMMARY

Climate

- A review by pediatric specialists with The Ruth & Bruce Rappaport Faculty of Medicine in Haifa, Israel discusses the phenomenon known as “vaccine hesitancy” (continued deferment of vaccines despite proven effectiveness and extremely rare adverse effects), and the [barrier it could create for eventual adoption of a COVID-19 vaccine](#), and suggest patient education on vaccine contraindications and lack of evidence supporting adverse reactions or autoimmune disease associations may reduce vaccine hesitancy. Additionally, they suggest thorough vaccine research and multimedia educational campaigning will be needed for the coming COVID-19 vaccines.
- An observational study conducted by academics at the Department of Health and Kinesiology at Texas A&M University analyzed COVID-19 cases between within 817 United States (US) counties and found a positive association between percentage of Black residents and COVID-19 cases that was moderated by explicit and implicit racial attitudes, which persisted in the presence of other control variables (country demographics, subjective well-being, median household income, food security, percent uninsured, and percent unemployed). These data indicate COVID-19 cases are increased with high percent of Black county residents and implicit racial attitudes, suggesting [disproportionate burden among Black US residents](#) and need for increased cultural awareness and sensitivity among healthcare professionals.

Epidemiology

- Physician scientists from Universidad Nacional de Cuyo in Mendoza, Argentina created a Susceptible-Exposed-Infected-Recovered (SEIR) model to explore COVID-19 management policies and found detection and isolation of just 50% of asymptomatic patients infected with SARS-CoV-2 could [significantly reduce hospital bed usage and deaths](#), suggesting that massive screening initiatives including asymptomatic people will facilitate detection and isolation of all SARS-CoV-2 infected people, allowing for pandemic control in lieu of a complete regional shutdown.
- Computer scientists from Greece and Scotland analyzed the ability of Google Trends (COVID-19 related search terms) to predict the trajectory of the COVID-19 outbreak at the state and national level and found a [statistically significant correlation between Google Trends data and COVID-19 cases and deaths](#) by Pearson and Kendall correlation analysis, while prediction analysis by quantile regression predicted the early spread of COVID-19 in several regions. The authors suggest Google Trends can aid epidemic forecasting and allow health care systems to prepare for local outbreaks.
- Indonesian epidemiologists conducted a systematic review and meta-analysis of 14 studies regarding recurrent SARS-CoV-2 RNA positivity (total of 2568 patients) and found [14.8% of recovered COVID-19 patients tested positive by RT-PCR after recovery](#) (95% CI: 11.44–18.19; i²=78%). Average time from last negative to the recurrent positive test was 9.8 days (95% CI: 7.31–12.22; i²=93%) and time from illness onset to re-detectable positive test was 35.4 days (95% CI 32.65–38.24; i²=77%), suggesting that further research is needed to better understand whether individuals with recurrent positivity can transmit SARS-CoV-2 or if recurrent positivity is due to inactive viral shedding.
- A retrospective study conducted by maternal and child health specialists at Tongji Medical College in Wuhan, China assessed clinical characteristics of SARS-CoV-2 among 43,126 individuals in the Hubei Province, including a subset of 1,989 healthcare workers, and found [healthcare workers with SARS-CoV-2 infection had a 0.99% fatality rate with 30.90% reporting fatigue and 19.15% reporting myalgia](#), while 2,026 demographically matched workers of other occupations with SARS-CoV-2 infection had a 2.02% fatality rate with 25.02% reporting fatigue and 13.43% reporting myalgia. This suggests that healthcare workers may have a lower risk of COVID-19 related fatality compared to other occupational groups, but they may also have a higher risk for symptomatic infection.

Transmission & Prevention

- Italian immunologists review the [challenges of SARS-CoV-2 vaccine development in the elderly populations](#) at high risk for COVID-19: elderly populations have relatively poor immune responses due to immunosenescence, comorbidities, and pharmacologic treatments; and increased pro-inflammatory cytokines (IL-6, 8, TNF-alpha) worsen both SARS-CoV-2 prognosis and vaccine efficacy. A systems biology approach considering clinical, socio-economic, immunological factors alongside advanced technologies, adjuvants, and vectors are necessary to develop an effective SARS-CoV-2 vaccine for the elderly.

Mental Health & Resilience Needs

- An international group of psychiatrists summarized guidelines provided by the International Academy of Suicide Research (IASR) on the reported [increase in mental health concerns and suicide attempts after pandemics](#) and they hypothesize that the COVID-19 pandemic might also be followed by similar issues due to several factors, with at-risk populations including the elderly, socially isolated individuals, healthcare professionals, and young children. Recommendations include: videoconferencing for suicide risk assessment rather than teleconferencing, careful attention toward elderly patients in isolation, and increased awareness of mental health concerns during and following the COVID-19 pandemic.

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CLIMATE

GLOBAL

ADHERENCE TO IMMUNIZATION: REBUTTAL OF VACCINE HESITANCY

Etzioni-Friedman T, Etzioni A.. Acta Haematol. 2020 Nov 17:1-5. doi: 10.1159/000511760. Online ahead of print.

Level of Evidence: Other - Expert Opinion

BLUF

A review by pediatric specialists affiliated with The Ruth & Bruce Rappaport Faculty of Medicine in Haifa, Israel discusses the phenomenon known as "vaccine hesitancy" (continued deferment of vaccines despite proven effectiveness and extremely rare adverse effects) and the barrier it could create for eventual adoption of a COVID-19 vaccine. The authors suggest patient education on vaccine contraindications and lack of evidence supporting adverse reactions or autoimmune disease associations may reduce vaccine hesitancy. Additionally, they suggest thorough vaccine research and multimedia educational campaigning will be needed for the coming COVID-19 vaccines.

ABSTRACT

Immunizations have been saving the lives of millions of people since they were first used by Edward Jenner in 1796, and new vaccines are being developed all the time. Hopefully, a new vaccine for coronavirus disease 2019 (COVID-19) will be developed in the near future, and perhaps even one for human immunodeficiency virus. Although the effectiveness of vaccinations has been proven over the years and adverse effects to currently available vaccinations are extremely rare, many people continue to defer immunizations for themselves and their families. According to the World Health Organization (WHO), this phenomenon, known as "vaccine hesitancy," is a major public health problem globally. This review summarizes the unproven adverse effects of various vaccines and stresses the importance of enforcing vaccination policies to minimize vaccine hesitancy. Every effort should be made to improve existing vaccines and to produce new ones, according to carefully designed scientific preclinical and clinical trials. This is particularly important in today's era, in light of the global transparency regarding vaccination development, and the potential for future pandemics such as COVID-19.

DISPARITIES

RACE, EXPLICIT RACIAL ATTITUDES, IMPLICIT RACIAL ATTITUDES, AND COVID-19 CASES AND DEATHS: AN ANALYSIS OF COUNTIES IN THE UNITED STATES

Cunningham GB, Wigfall LT.. PLoS One. 2020 Nov 18;15(11):e0242044. doi: 10.1371/journal.pone.0242044. eCollection 2020.

Level of Evidence: 1 - Local and current random sample surveys (or censuses)

BLUF

An observational study conducted by academics affiliated with the Department of Health and Kinesiology at Texas A&M University analyzed COVID-19 cases between January 22 and August 31, 2020 within 817 United States (US) counties. They discovered a positive association between percentage of Black residents and COVID-19 cases that was moderated by explicit and implicit racial attitudes (Table 4, Figure 1). These results persisted in the presence of other control variables including country demographics, subjective well-being, median household income, food security, percent uninsured, and percent unemployed (Table 2). These data indicate COVID-19 cases are increased with high percent of Black county residents and implicit racial attitudes, suggesting disproportionate burden among Black US residents and need for increased cultural awareness and sensitivity among healthcare professionals.

ABSTRACT

OBJECTIVES: To examine the potential moderating effects of explicit racial attitudes and implicit racial attitudes on the relationship between percent of Black county residents and COVID-19 cases and deaths. METHODS: We collected data from a variety of publicly available sources for 817 counties in the US. (26% of all counties). Cumulative COVID-19 deaths and cases from January 22 to August 31, 2020 were the dependent variables; explicit racial attitudes and implicit racial attitudes served as the moderators; subjective poor or fair health, food insecurity, percent uninsured, percent unemployed, median family income, percent women, percent of Asian county resident, percent of Hispanic county residents, and percent of people 65 or older were controls. RESULTS: The percent of Black county residents was positively associated with COVID-19 cases and deaths at the county level. The relationship between percent of Black residents and COVID-19 cases was moderated by explicit racial attitudes and implicit racial attitudes. CONCLUSIONS: Implicit racial attitudes can take on a shared property at the community level and effectively explain racial disparities. COVID-19 cases are highest when both the percent of Black county residents and implicit racial attitudes are high.

FIGURES

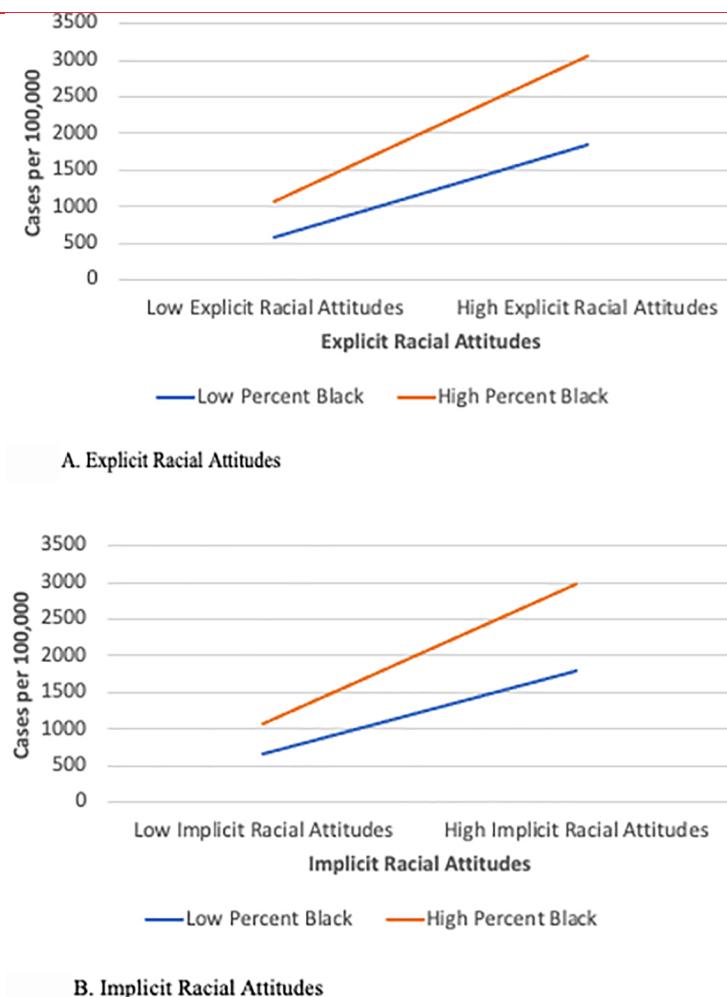


Figure 1. Relationships among percent black county residents, explicit racial attitudes, implicit racial attitudes, and COVID-19 cases per 100,000 residents for January 22, 2020 to August 31, 2020. A. Explicit racial attitudes. B. Implicit racial attitudes.

Table 4. Summary of hypotheses and supplemental analyses.

Prediction	Finding
H1: Explicit racial attitudes will be positively related to COVID-19 cases.	Supported
H2: Explicit racial attitudes will be positively related to COVID-19 deaths.	Not Supported.
H3: Implicit racial attitudes will be positively related to COVID-19 cases.	Supported.
H4: Implicit racial attitudes will be positively related to COVID-19 deaths.	Not Supported.
H5: Explicit racial attitudes will interact with the percent of Black county residents to predict COVID-19 cases.	Supported.
H6: Explicit racial attitudes will interact with the percent of Black county residents to predict COVID-19 deaths.	Not Supported.
H7: Implicit racial attitudes will interact with the percent of Black county residents to predict COVID-19 cases.	Supported.
H8: Implicit racial attitudes will interact with the percent of Black county residents to predict COVID-19 deaths.	Not Supported.

Table 2. Effects of explicit racial attitudes and implicit racial attitudes on COVID-19 cases, January 22, 2020 to August 31, 2020.

Variable	Model 1		Model 2		Model 3		Model 4		Model 5	
	B	SE	B	SE	B	SE	B	SE	B	SE
Fair or Poor Health	351.44***	60.54	333.97***	59.18	305.99***	59.12	318.20***	60.11	307.00***	59.87
Uninsured	203.61***	41.50	200.11***	40.53	198.62***	40.18	204.86***	40.94	197.39***	40.77
Unemployed	-13.43	38.17	-12.33	37.27	-14.31	36.95	-20.56	37.67	-22.26	37.46
Food Insecure	-243.43***	52.32	-168.73**	52.42	-186.35***	52.18	-183.77**	53.06	-194.28***	52.86
Log Household Income	49.64	49.20	73.58	48.19	60.12	47.91	57.62	48.56	53.76	48.30
Percent 65 or Older	-42.68	35.13	-45.32	34.30	-46.28	34.01	-41.92	34.65	-36.73	34.49
Percent Female	-204.04***	53.70	-181.55**	52.56	-201.68***	52.37	-225.46***	53.15	-252.86***	53.54
Percent Asian	-3.11	18.05	16.38	17.89	7.07	17.90	6.92	17.92	-0.53	17.97
Percent Hispanic	271.40***	38.16	370.53***	40.40	363.56***	40.10	322.37***	39.09	324.20***	38.87
Percent Black	554.89***	41.30	679.27***	44.84	812.35***	56.28	644.71***	44.77	760.05***	57.26
Explicit Racial Attitudes			506.84***	79.83	432.47***	81.46				
Implicit Racial Attitudes							444.20***	91.79	398.50***	92.37
PB × Explicit					182.21***	47.25				
PB × Implicit									194.32**	60.67

Notes.* $p < .05$.** $p < .01$.*** $p < .001$. PB = Percent Black. Explicit = Explicit Racial Attitudes. Implicit = Implicit Racial Attitudes. Model 1 $\Delta R^2 = .53, p < .001$. Model 2 $\Delta R^2 = .02, p < .001$.Model 3 $\Delta R^2 = .01, p < .001$. Model 4 $\Delta R^2 = .01, p < .001$. Model 5 $\Delta R^2 = .01, p = .001$.**Table 2. Effects of explicit racial attitudes and implicit racial attitudes on COVID-19 cases, January 22, 2020 to August 31, 2020.**

A MODELLING STUDY HIGHLIGHTS THE POWER OF DETECTING AND ISOLATING ASYMPTOMATIC OR VERY MILDLY AFFECTED INDIVIDUALS FOR COVID-19 EPIDEMIC MANAGEMENT

Mayorga L, García Samartino C, Flores G, Masuelli S, Sánchez MV, Mayorga LS, Sánchez CG.. BMC Public Health. 2020 Nov 27;20(1):1809. doi: 10.1186/s12889-020-09843-7.

Level of Evidence: Other - Modeling

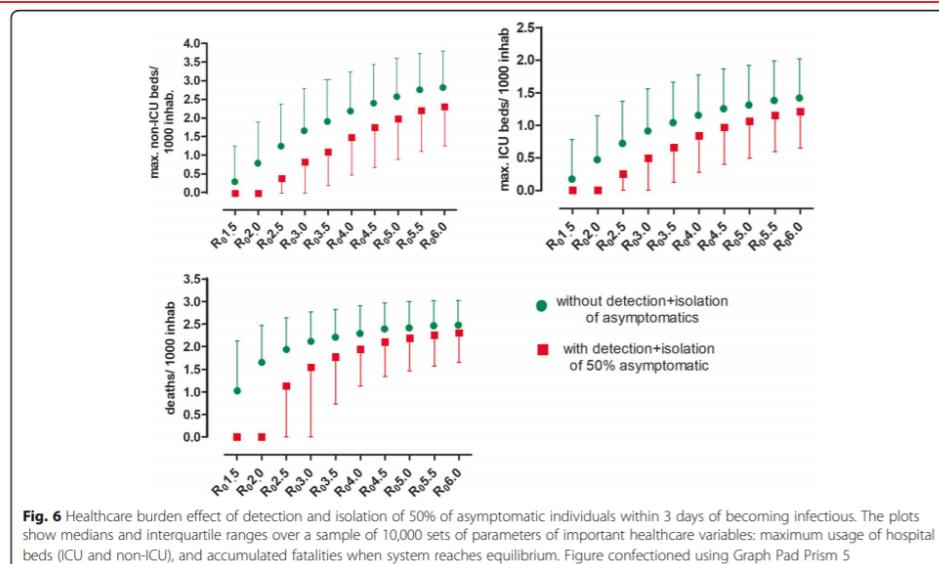
BLUF

Physician scientists from Universidad Nacional de Cuyo in Mendoza, Argentina created a Susceptible-Exposed-Infected-Recovered (SEIR) model (Figure 3) to explore COVID-19 management policies and found detection and isolation of just 50% of asymptomatic patients infected with SARS-CoV-2 could significantly reduce hospital bed usage and deaths (Figure 6). Authors suggest massive screening initiatives including asymptomatic people will facilitate detection and isolation of all SARS-CoV-2 infected people, allowing for pandemic control in lieu of a complete regional shutdown.

ABSTRACT

BACKGROUND: Mathematical modelling of infectious diseases is a powerful tool for the design of management policies and a fundamental part of the arsenal currently deployed to deal with the COVID-19 pandemic. **METHODS:** We present a compartmental model for the disease where symptomatic and asymptomatic individuals move separately. We introduced healthcare burden parameters allowing to infer possible containment and suppression strategies. In addition, the model was scaled up to describe different interconnected areas, giving the possibility to trigger regionalized measures. It was specially adjusted to Mendoza-Argentina's parameters, but is easily adaptable for elsewhere. **RESULTS:** Overall, the simulations we carried out were notably more effective when mitigation measures were not relaxed in between the suppressive actions. Since asymptomatics or very mildly affected patients are the vast majority, we studied the impact of detecting and isolating them. The removal of asymptomatics from the infectious pool remarkably lowered the effective reproduction number, healthcare burden and overall fatality. Furthermore, different suppression triggers regarding ICU occupancy were attempted. The best scenario was found to be the combination of ICU occupancy triggers (on: 50%, off: 30%) with the detection and isolation of asymptomatic individuals. In the ideal assumption that 45% of the asymptomatics could be detected and isolated, there would be no need for complete lockdown, and Mendoza's healthcare system would not collapse. **CONCLUSIONS:** Our model and its analysis inform that the detection and isolation of all infected individuals, without leaving aside the asymptomatic group is the key to surpass this pandemic.

FIGURES



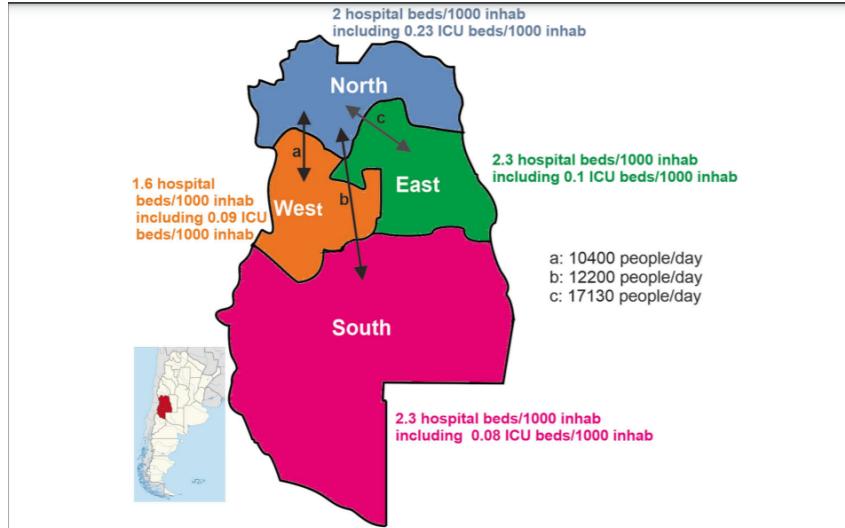


Fig. 3 Mendoza province, located in the Center-West of Argentina (shown in red in the Argentina map). We present the four zones in which we compartmentalized the model detailing hospital beds/1000 inhabitants and daily mean people exchange between regions (a, b, c). Mendoza's map was made by the authors using Corel Draw 2019 demo version, Argentina's map was taken from Wikimedia commons https://commons.wikimedia.org/wiki/File:Provincia_de_Mendoza,_Argentina.png.

COVID-19 PREDICTABILITY IN THE UNITED STATES USING GOOGLE TRENDS TIME SERIES

Mavragani A, Gkillas K.. Sci Rep. 2020 Nov 26;10(1):20693. doi: 10.1038/s41598-020-77275-9.

Level of Evidence: Other - Modeling

BLUF

Computer scientists from Greece and Scotland analyzed the ability of Google Trends (COVID-19 related search terms) to predict the trajectory of the COVID-19 outbreak at the state and national level (Figure 7). They found a statistically significant correlation between Google Trends data and COVID-19 cases and deaths by Pearson and Kendall correlation analysis (Table 3), while prediction analysis by quantile regression predicted the early spread of COVID-19 in several regions (Table 5). The authors suggest Google Trends can aid epidemic forecasting and allow health care systems to prepare for local outbreaks.

ABSTRACT

During the unprecedented situation that all countries around the globe are facing due to the Coronavirus disease 2019 (COVID-19) pandemic, which has also had severe socioeconomic consequences, it is imperative to explore novel approaches to monitoring and forecasting regional outbreaks as they happen or even before they do so. To that end, in this paper, the role of Google query data in the predictability of COVID-19 in the United States at both national and state level is presented. As a preliminary investigation, Pearson and Kendall rank correlations are examined to explore the relationship between Google Trends data and COVID-19 data on cases and deaths. Next, a COVID-19 predictability analysis is performed, with the employed model being a quantile regression that is bias corrected via bootstrap simulation, i.e., a robust regression analysis that is the appropriate statistical approach to taking against the presence of outliers in the sample while also mitigating small sample estimation bias. The results indicate that there are statistically significant correlations between Google Trends and COVID-19 data, while the estimated models exhibit strong COVID-19 predictability. In line with previous work that has suggested that online real-time data are valuable in the monitoring and forecasting of epidemics and outbreaks, it is evident that such infodemiology approaches can assist public health policy makers in addressing the most crucial issues: flattening the curve, allocating health resources, and increasing the effectiveness and preparedness of their respective health care systems.

FIGURES

State	Pearson correlation	Standard error	Wald test ($r=0$)	p-value	State	Pearson correlation	Standard error	Wald test ($r=0$)	p-value
USA	-0.7054***	(0.0536)	[13.1672]	<0.0001	Missouri	-0.2627	(0.1608)	[1.6333]	0.1024
Alabama	-0.6896***	(0.0748)	[9.2185]	<0.0001	Montana	-0.063	(0.1727)	[0.3651]	0.7151
Alaska	-0.1162	(0.1276)	[0.9107]	0.3625	Nebraska	-0.2763*	(0.1503)	[1.8381]	0.0661
Arizona	-0.313**	(0.1292)	[2.4225]	0.0154	Nevada	-0.3452**	(0.1519)	[2.273]	0.0230
Arkansas	0.4282***	(0.1105)	[3.8742]	0.0001	New Hampshire	-0.406***	(0.1432)	[2.8349]	0.0046
California	-0.4123***	(0.1300)	[3.1711]	0.0015	New Jersey	-0.065	(0.2013)	[0.3227]	0.7469
Colorado	0.435**	(0.1761)	[2.4694]	0.0135	New Mexico	-0.1474	(0.1367)	[1.0783]	0.2809
Connecticut	-0.1266	(0.1895)	[0.668]	0.5041	New York	-0.5925***	(0.0790)	[7.5016]	<0.0001
Delaware	0.182	(0.2004)	[0.908]	0.3639	North Carolina	-0.3172**	(0.1561)	[2.032]	0.0421
DC	-0.3464**	(0.1632)	[2.1219]	0.0338	North Dakota	0.2567	(0.1705)	[1.5056]	0.1322
Florida	-0.3171**	(0.1559)	[2.034]	0.0420	Ohio	-0.1645	(0.1979)	[0.8311]	0.4059
Georgia	-0.3467**	(0.1462)	[2.3708]	0.0178	Oklahoma	-0.1703	(0.1713)	[0.9944]	0.3200
Hawaii	-0.1591	(0.1692)	[0.9405]	0.3470	Oregon	0.4605***	(0.1432)	[3.2154]	0.0013
Idaho	0.0614	(0.1436)	[0.4276]	0.6689	Pennsylvania	-0.3645**	(0.1446)	[2.5218]	0.0117
Illinois	0.2501*	(0.1512)	[1.6541]	0.0981	Rhode Island	-0.0366	(0.1805)	[0.2031]	0.8391
Indiana	0.0162	(0.1884)	[0.086]	0.9314	South Carolina	-0.2094	(0.1400)	[1.4958]	0.1347
Iowa	-0.2172	(0.1539)	[1.4112]	0.1582	South Dakota	0.3518*	(0.1920)	[1.8323]	0.0669
Kansas	0.1141	(0.1748)	[0.6531]	0.5137	Tennessee	-0.3878***	(0.1495)	[2.5937]	0.0095
Kentucky	-0.2789*	(0.1663)	[1.677]	0.0935	Texas	0.0223	(0.1931)	[0.1157]	0.9079
Louisiana	-0.2422	(0.1713)	[1.4141]	0.1573	Utah	-0.2135	(0.1448)	[1.4749]	0.1402
Maine	-0.1811	(0.1387)	[1.3062]	0.1915	Vermont	-0.3255**	(0.1549)	[2.1007]	0.0357
Maryland	-0.0385	(0.2045)	[0.1884]	0.8505	Virginia	-0.286**	(0.1414)	[2.0228]	0.0431
Massachusetts	-0.4285***	(0.1421)	[3.0152]	0.0026	Washington	-0.5805***	(0.0835)	[6.9492]	<.0001
Michigan	-0.1045	(0.1757)	[0.5949]	0.5519	West Virginia	0.0033	(0.0426)	[0.0781]	0.9378
Minnesota	-0.3513**	(0.1550)	[2.2657]	0.0235	Wisconsin	-0.3972***	(0.1285)	[3.09]	0.002
Mississippi	0.308	(0.1975)	[1.5599]	0.1188	Wyoming	0.396**	(0.1840)	[2.1524]	0.0314

Table 3: "Pearson correlation analysis by state. *p<0.1, **p<0.05; ***p<0.01".

	β_0		β_1		β_2				
USA	-0.0509	(0.4339)	[-0.1172]	-0.7506***	(0.2197)	[-3.4173]	-0.0014	(0.0169)	[-0.0831]
AL	0.8944***	(0.2176)	[4.1099]	-0.5961**	(0.1160)	[-5.1383]	-0.0413**	(0.0070)	[-5.8850]
AK	-1.4528***	(0.2003)	[-7.2539]	-0.2449**	(0.1006)	[-2.4341]	0.0663***	(0.0087)	[7.6030]
AZ	-1.4183***	(0.1309)	[-10.8362]	-0.2429**	(0.0817)	[-2.9745]	0.0637***	(0.0049)	[12.8777]
AR	0.2565	(0.4658)	[-0.5507]	0.2785	(0.2531)	[1.1004]	0.0023	(0.0124)	[0.1825]
CA	-1.4274***	(0.0936)	[-15.2521]	-0.1634**	(0.0539)	[-3.0325]	0.0642***	(0.0046)	[13.8481]
CO	-0.9688***	(0.1916)	[-5.0561]	0.3007	(0.2587)	[1.1623]	0.0290***	(0.0074)	[3.9132]
CT	-1.7866***	(0.0654)	[-27.3353]	-0.1645***	(0.0470)	[-3.4989]	0.0782***	(0.0026)	[30.6221]
DE	-2.0415***	(0.4639)	[-4.4003]	-0.2687	(0.2446)	[-1.0987]	0.0715***	(0.0110)	[6.4873]
DC	-1.3077***	(0.1980)	[-6.6064]	-0.1548*	(0.0849)	[-1.8228]	0.0578***	(0.0094)	[6.1513]
FL	-1.5483***	(0.0766)	[-20.2209]	-0.2128**	(0.0431)	[-4.9412]	0.0715***	(0.0024)	[29.3170]
GA	-1.5727***	(0.0808)	[-19.4690]	-0.2047**	(0.0570)	[-3.5898]	0.0721***	(0.0042)	[17.2658]
HI	-1.6732***	(0.0873)	[-19.1647]	-0.2083**	(0.0470)	[-4.4343]	0.0758***	(0.0041)	[18.3027]
ID	-1.8929***	(0.1465)	[-12.9167]	-0.2686***	(0.0663)	[-4.0507]	0.0866***	(0.0067)	[12.8631]
IL	-1.4466***	(0.1404)	[-10.3063]	0.3943***	(0.0707)	[5.5764]	0.0680***	(0.0056)	[12.2022]
IN	-1.4674***	(0.2157)	[-6.8020]	0.0977	(0.1624)	[0.6018]	0.0693***	(0.0065)	[10.7392]
IA	-1.5912***	(0.1402)	[-11.3507]	-0.2957***	(0.0733)	[-4.0346]	0.0732***	(0.0042)	[17.3342]
KS	-1.5579***	(0.2298)	[-6.7799]	0.0463	(0.1101)	[0.4204]	0.0635***	(0.0106)	[5.9774]
KY	-1.5530***	(0.1396)	[-11.1222]	-0.2415***	(0.0599)	[-4.0291]	0.0719***	(0.0062)	[11.5292]
LA	-1.6432***	(0.0602)	[-27.2763]	-0.2050**	(0.0357)	[-5.7381]	0.0751***	(0.0026)	[28.6534]
MD	-1.1066***	(0.2339)	[-4.7306]	0.1135	(0.1008)	[1.1255]	0.0550***	(0.0088)	[6.2834]
MA	-1.6424***	(0.0771)	[-21.3061]	-0.1757**	(0.0538)	[-3.2668]	0.0742***	(0.0034)	[21.8651]
MI	-1.7657***	(0.0813)	[-21.7133]	-0.1884***	(0.0406)	[-4.6375]	0.0800***	(0.0032)	[25.2349]
MN	-1.6085***	(0.0773)	[-20.7963]	-0.2344**	(0.0521)	[-4.4970]	0.0728***	(0.0027)	[26.9966]
MS	-1.3047***	(0.2959)	[-4.4088]	0.1773	(0.1600)	[1.1086]	0.0570***	(0.0082)	[6.9200]
MO	-1.5382***	(0.0883)	[-17.4271]	-0.2326**	(0.0478)	[-4.8610]	0.0718***	(0.0051)	[14.0987]
NE	-1.4875***	(0.1909)	[-7.7908]	-0.2192**	(0.0746)	[-2.9375]	0.0717***	(0.0063)	[11.3935]
NV	-1.6778***	(0.0862)	[-19.4683]	-0.1872**	(0.0348)	[-5.3846]	0.0763***	(0.0037)	[20.4946]
NH	-1.6586***	(0.0723)	[-22.9526]	-0.1515**	(0.0365)	[-4.1562]	0.0741***	(0.0025)	[30.0037]
NJ	-1.8518***	(0.2428)	[-7.6277]	-0.2395	(0.2427)	[-0.9867]	0.0688***	(0.0060)	[11.3949]
NM	-1.2414***	(0.1640)	[-7.5679]	-0.1188	(0.0803)	[-1.4805]	0.0593***	(0.0066)	[8.9371]
NY	-1.2201***	(0.0468)	[-26.0596]	-0.1482**	(0.0562)	[-2.6358]	0.0482***	(0.0043)	[11.2916]
NC	-1.6575***	(0.0953)	[-17.3914]	-0.1613**	(0.0476)	[-3.3848]	0.0722***	(0.0038)	[18.8471]
OH	-1.8408***	(0.1464)	[-12.5751]	-0.1758**	(0.0750)	[-2.3436]	0.0790***	(0.0048)	[16.3817]
OK	-1.7038***	(0.0544)	[-31.2986]	-0.2463***	(0.0318)	[-7.7497]	0.0767***	(0.0026)	[29.5090]
OR	-0.7953***	(0.2019)	[-3.3932]	0.4395***	(0.1362)	[3.2257]	0.0293***	(0.0069)	[4.2697]
PA	-1.3917***	(0.1279)	[-10.8769]	-0.1845*	(0.0758)	[-2.4348]	0.0716***	(0.0041)	[17.5561]
RI	-1.4924***	(0.0752)	[-19.8418]	-0.1461**	(0.0408)	[-3.5844]	0.0588***	(0.0049)	[12.1036]
SC	-1.2889***	(0.0941)	[-13.7030]	-0.1816**	(0.0513)	[-3.5395]	0.0520***	(0.0069)	[7.5216]
SD	-1.1230***	(0.2939)	[-3.8212]	0.2815**	(0.1388)	[2.0277]	0.0537***	(0.0084)	[6.4280]
TN	-1.5098***	(0.0658)	[-22.9294]	-0.2157**	(0.0524)	[-4.1179]	0.0676***	(0.0020)	[33.1730]
TX	-1.4766***	(0.3041)	[-4.8557]	0.2749	(0.1903)	[1.4442]	0.0660***	(0.0077)	[8.5342]
UT	-1.4381***	(0.1399)	[-10.2768]	-0.1586**	(0.0723)	[-2.1944]	0.0720***	(0.0069)	[10.3640]
VT	-1.5359***	(0.1854)	[-8.2848]	-0.2499**	(0.0848)	[-2.9476]	0.0770***	(0.0081)	[9.5352]
VA	-1.5878***	(0.2504)	[-6.3400]	-0.3147**	(0.1021)	[-3.0837]	0.0767***	(0.0106)	[7.2484]
WA	-1.3476***	(0.1540)	[-8.7488]	-0.2236**	(0.1007)	[-2.2212]	0.0660***	(0.0101)	[6.5118]
WI	-1.3407***	(0.0992)	[-13.5142]	-0.2143**	(0.0698)	[-3.0711]	0.0618***	(0.0053)	[11.6287]

Table 5: "Predictability analysis by state. Te numbers in parentheses report the standard errors; the t-statistics are given in brackets. *** ** and * indicate statistical significance at the 0.01, 0.05 and 0.1 levels, respectively. The corresponding critical values are 2.575, 1.96 and 1.645".

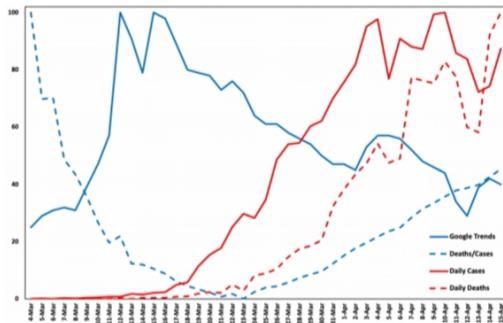


Figure 7: "COVID-19 and Google Trends data from March 4th to April 15th in the US (Microsoft Excel)".

OPTIMAL STRATEGIES FOR VACCINATION AND SOCIAL DISTANCING IN A GAME-THEORETIC EPIDEMIOLOGIC MODEL

Choi W, Shim E.. J Theor Biol. 2020 Nov 21;505:110422. doi: 10.1016/j.jtbi.2020.110422. Epub 2020 Jul 25.

Level of Evidence: Other - Modeling

BLUF

Investigators from the Department of Mathematics in Soongsil University (Korea) created a game-theoretic, epidemiological model for infectious illnesses that takes into account vaccination and social distancing control practices to identify optimal protection strategies. Using generated payoff functions and Nash strategy, they found that social distancing is more likely to be the "dominant strategy" that is adopted by individuals as it may be seen as more efficacious when compared to a possibly less effective vaccine. The authors suggest that this model and its findings may be extended to other infectious diseases in addition to COVID-19 to comprehend individual compliance with specific control practices.

ABSTRACT

For various infectious diseases, vaccination has become a major intervention strategy. However, the importance of social distancing has recently been highlighted during the ongoing COVID-19 pandemic. In the absence of vaccination, or when vaccine efficacy is poor, social distancing may help to curb the spread of new virus strains. However, both vaccination and social distancing are associated with various costs. It is critical to consider these costs in addition to the benefits of these strategies when determining the optimal rates of application of control strategies. We developed a game-theoretic epidemiological model that considers vaccination and social distancing under the assumption that individuals pursue the maximization of payoffs. By using this model, we identified the individually optimal strategy based on the Nash strategy when both strategies are available and when only one strategy is available. Furthermore, we determined the relative costs of control strategies at which individuals preferentially adopt vaccination over social distancing (or vice versa).

SYMPTOMS AND CLINICAL PRESENTATION

RECURRENT SARS-COV-2 RNA POSITIVITY AFTER COVID-19: A SYSTEMATIC REVIEW AND META-ANALYSIS

Azam M, Sulistiana R, Ratnawati M, Fibriana AI, Bahrudin U, Widyaningrum D, Aljunid SM.. Sci Rep. 2020 Nov 26;10(1):20692. doi: 10.1038/s41598-020-77739-y.

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

BLUF

Indonesian epidemiologists conducted a systematic review and meta-analysis of 14 studies regarding recurrent SARS-CoV-2 RNA positivity (total of 2568 patients) and found 14.8% of recovered COVID-19 patients tested positive by RT-PCR after recovery (95%CI: 11.44–18.19; $i^2=78\%$)(Figure 2). Average time from last negative to the recurrent positive test was 9.8 days (95% CI: 7.31–12.22; $i^2=93\%$) and time from illness onset to re-detectable positive test was 35.4 days (95% CI 32.65–38.24; $i^2=77\%$)(Figure 3). Authors suggest further research is needed to better understand whether individuals with recurrent positivity can transmit SARS-CoV-2 or if recurrent positivity is due to inactive viral shedding.

ABSTRACT

Present study aimed to estimate the incidence of recurrent SARS-CoV-2 RNA positivity after recovery from COVID-19 and to determine the factors associated with recurrent positivity. We searched the PubMed, MedRxiv, BioRxiv, the Cochrane Library, ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry for studies published to June 12, 2020. Studies were reviewed to determine the risk of bias. A random-effects model was used to pool results. Heterogeneity was assessed using I². Fourteen studies of 2568 individuals were included. The incidence of recurrent SARS-CoV-2 positivity was 14.8% (95% confidence interval [CI] 11.44-18.19%). The pooled estimate of the interval from disease onset to recurrence was 35.4 days (95% CI 32.65-38.24 days), and from the last negative to the recurrent positive result was 9.8 days (95% CI 7.31-12.22 days). Patients with younger age and a longer initial illness were more likely to experience recurrent SARS-CoV-2 positivity, while patients with diabetes, severe disease, and a low lymphocyte count were less likely to experience. Present study concluded that the incidence of recurrent SARS-CoV-2 positivity was 14.8% suggesting further studies must be conducted to elucidate the possibility of infectious individuals with prolonged or recurrent RNA positivity.

FIGURES

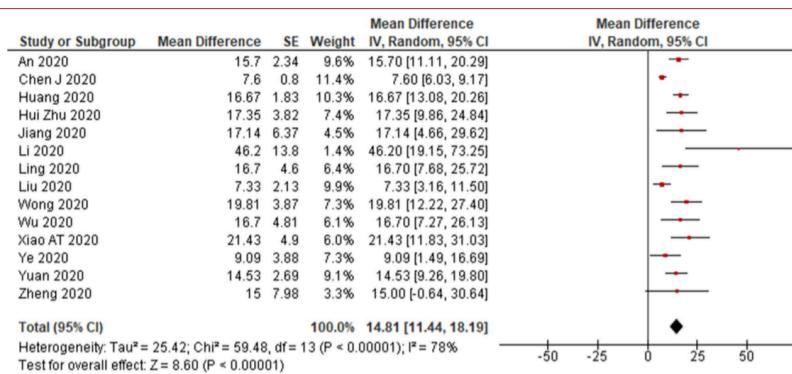
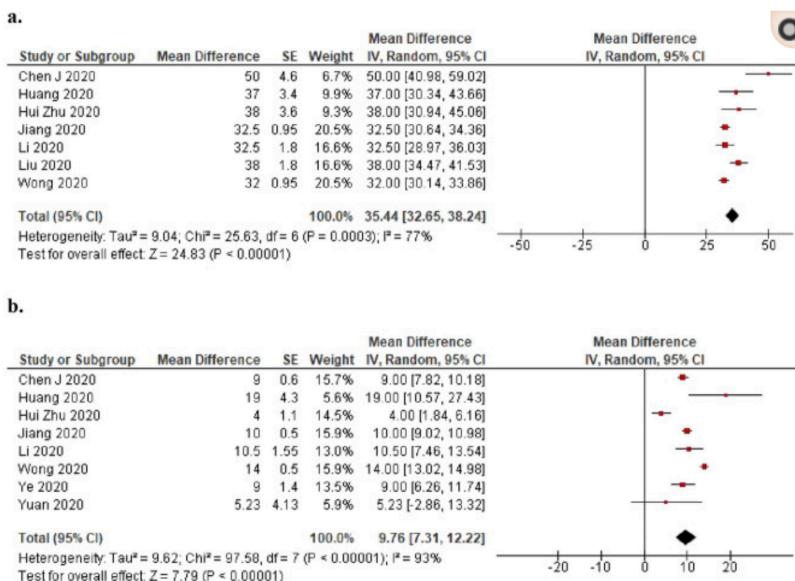


Figure 2. A meta-analysis of the pooled estimated incidence of recurrent SARS-CoV-2 RNA positivity.

Figure 3



(a) A meta-analysis of the pooled estimated interval from onset to recurrent SARS-CoV-2 RNA positivity (days) and (b) A meta-analysis of the pooled estimated interval from last negative to recurrent SARS-CoV-2 RNA positivity (days).

EPIDEMIOLOGICAL AND CLINICAL CHARACTERISTICS OF SARS-COV-2 INFECTION AMONG HEALTHCARE WORKERS IN HUBEI PROVINCE OF CHINA

Wu M, Xie C, Wu R, Shu Y, Wang L, Li M, Wang Y.. Infect Control Hosp Epidemiol. 2020 Nov 18:1-20. doi:

10.1017/ice.2020.1321. Online ahead of print.

Level of Evidence: 3 - Local non-random sample

BLUF

A retrospective cohort-control study conducted by maternal and child health specialists at Tongji Medical College in Wuhan, China assessed clinical characteristics of SARS-CoV-2 among individuals in the Hubei Province (n=43,126; Table S1), including a subset of healthcare workers (n=1,989; Table 1). They found healthcare workers with SARS-CoV-2 infection had a 0.99% fatality rate with 30.90% reporting fatigue and 19.15% reporting myalgia, while demographically matched workers of other occupations with SARS-CoV-2 infection (n=2,026) had a 2.02% fatality rate with 25.02% reporting fatigue and 13.43% reporting myalgia (Table 2). Authors suggest that healthcare workers may have a lower risk of COVID-19 related fatality compared to other occupational groups, but they may also have a higher risk for symptomatic infection.

ABSTRACT

OBJECTIVE: To evaluate the epidemiological and clinical characteristics of SARS-CoV-2 infection among healthcare workers in Hubei Province, China. **DESIGN:** Retrospective cohort study. **SETTING:** Hubei Provincial Center for Disease Control and Prevention. **PARTICIPANTS:** The participants in this study are cases identified by epidemiological investigation in Hubei Province, as of February 27, 2020, and were followed-up until March 7, 2020. A total of 1,989 healthcare workers and 41,137 other occupational cases were included for analysis. **METHODS:** We used descriptive statistics to summarize patient characteristics. **RESULTS:** Of the total 1,989 laboratory-confirmed healthcare workers, there were 297 (14.93%) severe or critical cases, 73 (3.67%) asymptomatic infections, and 18 healthcare workers died of COVID-19. This gave a case fatality rate of 0.9%. The proportion of severe or critical cases decreased from the beginning to the end of the outbreak (from 21.29% to 3.52%), while the proportion of asymptomatic cases increased from 0.0% to 47.18%. Nearly half of healthcare workers with confirmed COVID-19 reported no known contact with COVID-19 patients (969 [48.72%]). Fever and cough were the most common symptoms at disease onset in both healthcare workers and other occupational cases, however, healthcare workers had higher rates of fatigue (30.90% vs 25.02%, P<0.001) and myalgia (19.15% vs 13.43%, P<0.001). Additionally, compared with other occupational groups, healthcare workers were associated with a lower risk of death after adjustment for potential confounders (OR: 0.50; 95% CI: 0.30-0.79). **CONCLUSIONS:** Compared with COVID-19 cases in other occupational groups, healthcare workers with COVID-19 have half the risk of death, although they have been shown to have higher rates of fatigue and myalgia.

FIGURES

	before 2020/01/23 (n=587)	01/24-02/03 (n=974)	02/04-02/13 (n=286)	02/14-02/27 (n=142)
Age, years	38.08(31.34-47.66)	38.76(30.61-49.31)	37.18(29.52-46.89)	33.82(27.34-44.41)
20-29	111(18.91)	217(22.28)	79(27.62)	57(40.14)
30-39	218(37.14)	302(31.01)	84(29.37)	38(26.76)
40-49	136(23.17)	223(22.9)	76(26.57)	23(16.2)
50-59	90(15.33)	154(15.81)	26(9.09)	19(13.38)
60+	32(5.45)	78(8.01)	21(7.34)	5(3.52)
Sex, male, No. (%)	230(39.18)	324(33.26)	74(25.87)	39(27.46)
Contact with confirmed patients, No. (%)	277(47.19)	515(52.87)	146(51.05)	82(57.75)
Clinical severity, No. (%)				
asymptomatic	0(0.00)	0(0.00)	6(2.10)	67(47.18)
mild	198(33.73)	487(50.00)	149(52.10)	37(26.06)
common	264(44.97)	342(35.11)	109(38.11)	33(23.24)
Severe or critical	125(21.29)	145(14.89)	22(7.69)	5(3.52)
Wuhan city, No. (%)	445(75.81)	635(65.20)	190(66.43)	68(47.89)
Signs and symptoms, No. (%)				
fever	278(76.16)	341(71.04)	62(65.26)	8(10.96)
<37.5°C	20(7.22)	34(10.03)	6(9.68)	2(25)
37.5-37.9°C	84(30.32)	143(42.18)	38(61.29)	5(62.5)
38.0-38.4°C	69(24.91)	78(23.01)	6(9.68)	0(0)
38.5-38.9°C	71(25.63)	61(17.99)	9(14.52)	0(0)
39.0°C+	33(11.91)	23(6.78)	3(4.84)	1(12.5)
missing	310	635	224	134
cough	194(53.15)	258(53.75)	47(49.47)	13(17.81)
fatigue	156(42.74)	137(28.54)	16(16.84)	4(5.48)
myalgia	88(24.11)	98(20.42)	6(6.32)	2(2.74)
headache	61(16.71)	77(16.04)	7(7.37)	1(1.37)
chest tightness	36(9.86)	63(13.12)	5(5.26)	5(6.85)
sore throat	37(10.14)	38(7.92)	7(7.37)	2(2.74)
chills	49(13.42)	52(10.83)	6(6.32)	1(1.37)
diarrhea	34(9.32)	30(6.25)	7(7.37)	1(1.37)
polypnea	35(9.59)	27(5.62)	1(1.05)	1(1.37)
dyspnoea	20(5.48)	30(6.25)	1(1.05)	0(0)
arthragia	28(7.67)	27(5.62)	0(0)	0(0)
nasal obstruction	18(4.93)	20(4.17)	2(2.11)	1(1.37)
nasal discharge	20(5.48)	27(5.62)	1(1.05)	2(2.74)
vomit	13(3.56)	15(3.12)	2(2.11)	1(1.37)
WBC,<9.5, No. (%)	208(94.98)	245(98)	57(96.61)	24(100)
Lymphocytes,<1.0, No. (%)	93(42.47)	102(40.8)	19(32.2)	1(4.17)
CT image, No. (%)	303(85.35)	413(85.51)	72(75.79)	30(41.1)
Death, No. (%)	6(1.02)	12(1.23)	0(0)	0(0)

Table 1. Characters of 1989 healthcare workers

	Other occupational cases (n=2026)	Healthcare workers (n=1013)	P
Age, years	39.27(30.48-49.23)	39.06(30.84-48.89)	0.764
20-29	465(22.95)	221(21.82)	
30-39	594(29.32)	318(31.39)	
40-49	511(25.22)	246(24.28)	
50-59	318(15.7)	159(15.7)	
60+	138(6.81)	69(6.81)	
Sex, male, No. (%)	793(39.14)	369(36.43)	0.158
Contact with confirmed patients, No. (%)	472(23.3)	472(46.59)	<0.001
Severe or Critical, No. (%)	287(14.17)	151(14.91)	0.622
Wuhan city, No. (%)	734(36.23)	367(36.23)	1.000
Signs and symptoms, No. (%)			
fever	1583(78.13)	689(68.02)	<0.001
<37.5 °C	121(7.71)	62(9.04)	0.727
37.5-37.9°C	607(38.66)	270(39.36)	
38.0-38.4 °C	364(23.18)	153(22.3)	
38.5-38.9 °C	321(20.45)	141(20.55)	
39.0 °C+	157(10)	60(8.75)	
missing	456	327	
cough	1095(54.05)	512(50.54)	0.074
fatigue	507(25.02)	313(30.9)	<0.001
myalgia	272(13.43)	194(19.15)	<0.001
headache	261(12.88)	146(14.41)	0.267
chest tightness	237(11.7)	109(10.76)	0.480
sore throat	145(7.16)	84(8.29)	0.296
chills	164(8.09)	108(10.66)	0.023
diarrhea	135(6.66)	72(7.11)	0.703
polypnea	161(7.95)	64(6.32)	0.123
dyspnoea	149(7.35)	51(5.03)	0.019
arthragia	78(3.85)	55(5.43)	0.056
nasal obstruction	95(4.69)	41(4.05)	0.476
nasal discharge	100(4.94)	50(4.94)	1.000
vomit	65(3.21)	31(3.06)	0.912
WBC,<9.5, No. (%)	1250(95.2)	534(96.74)	0.173
Lymphocytes, <1.0, No. (%)	454(34.58)	215(38.95)	0.081
CT image, No. (%)	1661(83.09)	812(81.2)	0.332
Death, No. (%)	41(2.02)	10(0.99)	0.052

Table 2. The comparison of clinical characteristics between healthcare workers and the matched cases in other occupation.

	Survivors (n=41,052)	Deaths (n=2074)	Case fatality rate (%)	P
Age, year	52.35(39.66-63.64)	70.67(62.95-78.62)	--	<0.001
20-29	3963	11	0.28	
30-39	6497	31	0.47	
40-49	7595	71	0.93	
50-59	9486	258	2.65	
60+	13511	1703	11.19	
Sex, No.				<0.001
male	20385	1323	6.09	
female	20667	751	3.51	
Severe or Critical, No.				<0.001
no	34062	621	1.79	
yes	6990	1453	17.21	
Wuhan city, No. (%)				<0.001
no	15784	578	3.53	
yes	25268	1496	5.59	
The date of symptom onset, No.				<0.001
before 2020/01/23	7999	664	7.66	
01/24-02/03	20724	1074	4.93	
02/04-02/13	8319	278	3.23	
02/14-02/27	4010	58	1.43	
Healthcare workers, No.				<0.001
no	39081	2056	5.0	
yes	1971	18	0.9	

Table S1. The crude fatality rate of SARS-CoV-2 infections among subgroup population (n=43,126).

DENDRITIC CELLS IN COVID-19 IMMUNOPATHOGENESIS: INSIGHTS FOR A POSSIBLE ROLE IN DETERMINING DISEASE OUTCOME

Borges RC, Hohmann MS, Borghi SM.. Int Rev Immunol. 2020 Nov 16:1-18. doi: 10.1080/08830185.2020.1844195. Online ahead of print.

Level of Evidence: Other - Review / Literature Review

BLUF

A review conducted by pathologists from University of Sao Paulo and Londrina State University in Brazil assessed the role of dendritic cells in curtailing COVID-19 infection through adaptive immune response priming. They found dendritic cell function was negatively affected by many drugs being tested for treatment of COVID-19 (Table 1). Additionally, elderly populations (age >65 years) may be more susceptible to infection due to dysfunctional dendritic cell changes (Figure 1), chronic lung diseases, and decreased lung adaptability. The review literature suggests dendritic cell dysfunction may play a critical role in susceptibility to SARS-CoV-2 infection due to a disconnect between innate and adaptive immunity, and the authors urge for further research to fill knowledge gaps regarding pathophysiological mechanisms of COVID-19.

ABSTRACT

SARS-CoV-2 is the causative agent of the COVID-19 pandemic. This novel coronavirus emerged in China, quickly spreading to more than 200 countries worldwide. Although most patients are only mildly ill or even asymptomatic, some develop severe pneumonia and become critically ill. One of the biggest unanswered questions is why some develop severe disease, whilst others do not. Insight on the interaction between SARS-CoV-2 and the immune system and the contribution of dysfunctional immune responses to disease progression will be instrumental to the understanding of COVID-19 pathogenesis, risk factors for worst outcome, and rational design of effective therapies and vaccines. In this review we have gathered the knowledge available thus far on the epidemiology of SARS-CoV-2 infection, focusing on the susceptibility of older individuals, SARS-CoV-2-host cell interaction during infection and the immune response directed at SARS-CoV-2. Dendritic cells act as crucial messengers linking innate and adaptative immunity against viral infections. Thus, this review also brings a focused discussion on the role of dendritic cells and their immune functions during SARS-CoV-2 infection and how immune evasion strategies of SARS-CoV-2 and advancing age mediate dendritic cell dysfunctions that contribute to COVID-19 pathogenesis and increased susceptibility to worst outcomes. This review brings to light the hypothesis that concomitant occurrence of dendritic cell dysfunction/cytopathic effects induced by SARS-CoV-2 and/or aging may influence disease outcome in the elderly. Lastly, a detailed discussion on the effects and mechanisms of action of drugs currently being tested for COVID-19 on the function of dendritic cells is also provided.

FIGURES

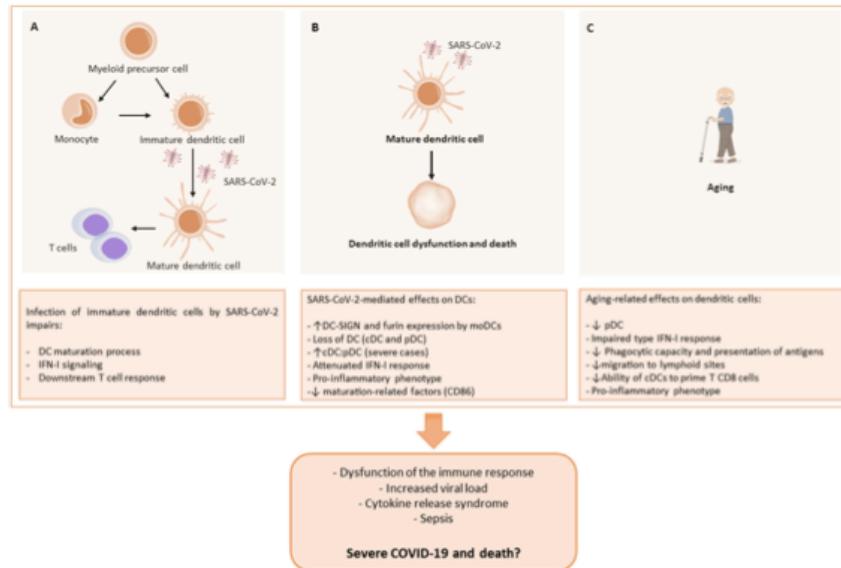


Figure 1. Schematic diagram of the proposed mechanism of dendritic cells dysfunction in COVID-19. (A) During hematopoiesis, myeloid precursor cells can generate monocytes or immature dendritic cells. Under specific cytokine stimulation such as GM-CSF and IL-4 monocytes can also differentiate into immature dendritic cells; under Flt3L stimulus steady-state dendritic cells develop. Following antigen stimulation, immature dendritic are activated to become mature dendritic cells. SARS-CoV-2 infection may occur in immature dendritic cells impairing maturation process, and consequently declining IFN-I signaling and T cell response. (B) SARS-CoV-2 infection of mature dendritic cells increases DC-SIGN and furin expressions, making these cells even more permissible to infection. Additionally, reduction in the number of dendritic cells (affecting CD11b β and CD123 β populations as well as the CD11b β :CD123 β ratio), expression of co-stimulatory molecules, added to defective STAT1-dependent type I IFN response and switch to a pro-inflammatory phenotype are observed [69, 71]. These effects negatively impact the development of the adaptive responses, leading to reduced and dysfunctional T cells and reduced viral clearance, culminating in COVID-19. (C) Advancing age also negatively impact dendritic cell numbers (reductions in plasmacytic dendritic cells) and function (impaired IFN-I response, phagocytic capacity, migration to lymphoid organs, presentation of antigens and ability to prime T CD8 cells) added to switch to a pro-inflammatory phenotype. These concomitant events mediated by SARS-CoV-2 infection (A and B) and aging (C) may converge to promote dendritic cell dysfunction and/or death, resulting in increased viral loads, cytokine release syndrome, and sepsis. Thus, the dysfunction and death of dendritic cells can be decisive events in the development of severe infection and worst outcome in COVID-19, contributing to complications and/or deaths. DCs1/4dendritic cells; cDC1/4conventional dendritic cell (CD11b β); pDC 1/4plasmacytic dendritic cell (CD123 β).

Table 1. Effects of drugs currently being tested for COVID-19 on dendritic cells structure, phenotype and functions.

Drug	Effects on dendritic cells	Model/species	Reference
Remdesivir	Not yet known		
Chloroquine	a) Reduced molecules related to antigen presentation; b) Inhibit the activation of plasmacytic dendritic cells; c) STAT1-dependent induction of tolerogenic dendritic cells	<i>In vitro</i> ; a) Experimental autoimmune encephalomyelitis/mice; b) HIV-infected rhesus macaque; c) Experimental autoimmune encephalomyelitis/mice	[133, 147, 148]
Hydroxychloroquine	Impaired ability of plasmacytic dendritic cells to produce IFN- α /TNF- α	<i>In vitro</i> ; Systemic lupus erythematosus subjects	[149]
Ritonavir	a) Failure of dendritic cells maturation, reduced response to antigens and weak priming of NK cells; b) Atypical phenotype of mature dendritic cells, reduced T cell stimulatory capacity and increased vulnerability to NK cell	a and b) <i>In vitro</i> (human monocyte-derived dendritic cells)	[151, 152]
Ivermectin	Major effects upon dendritic cells functions; toxicity was observed with high dose stimulation	<i>In vitro</i> ; Atopic dermatitis/mice	[155]
Human recombinant soluble ACE2 (APN01)	Not yet known		
Tocilizumab	Induction of inflammatory phenotype of dendritic cells with enhanced expression of mIL-6R α and secretion of soluble form of the receptor gp130	<i>In vitro</i> (human monocyte-derived dendritic cells)	[165]

STAT1: Signal transducer and activator of transcription 1; NK: natural killer; mIL-6R α : membrane-bound IL-6 receptor α .

Table 1. Effects of drugs currently being tested for COVID-19 on dendritic cells structure, phenotype and functions.

ADULTS

ATYPICAL PRESENTATION OF COVID-19; AN OBSERVATIONAL RETROSPECTIVE STUDY

Haghghi-Morad M, Alavi Darazam I, Bahrami-Moltagh H, Amerifar M, Zamani N, Hassanian-Moghaddam H.. BMC Infect Dis. 2020 Nov 23;20(1):870. doi: 10.1186/s12879-020-05617-z.

Level of Evidence: 4 - Case-series

BLUF

An interdisciplinary group of Iranian physicians conducted a retrospective review of 662 patients with a final diagnosis of COVID-19 (via RT-PCR, chest CT findings, or progression of clinical symptoms) at Loghman Hakim Hospital between February 20 and May 11, 2020. They focused on 19 patients who presented without a chief complaint of fever, dyspnea, and/or cough. Of these atypical presentations, 17 were male with the most common chief complaints being overdose (n=7), methanol poisoning (n=2), and unknown loss of consciousness (n=3)(Table 1). Because first RT-PCR has limited sensitivity and was positive in only eight of these atypically presenting patients (42%), the authors suggest atypical presentation of COVID-19 should be considered in patients presenting with substance overdose and other toxicologic etiologies.

ABSTRACT

BACKGROUND: COVID-19 infection may present with atypical signs and symptoms and false negative polymerase chain reaction (PCR) tests predisposing healthy people and health care workers to infection. The aim of the current study is to evaluate the features of atypical presentations in COVID-19 infection in a referral center in Tehran, Iran. **METHODS:** Hospital database of inpatients admitted to Loghman Hakim hospital between February 20th and May 11th, 2020 was reviewed and all patients with final diagnosis of COVID-19 infection were evaluated for their presenting symptoms. Patients with chief complaints of "fever", "dyspnea", and/or "cough" as typical presentations of COVID-19 were excluded and those with other clinical presentations were included. **RESULTS:** Nineteen patients were included with a mean age of 51 ± 19 years, of whom, 17 were males (89%). Median [IQR] Glasgow coma scale (GCS) was 14 [13, 15]. Almost 10 had referred with chief complaint of methanol poisoning and overdose on substances of abuse. Only 8 cases (42%) had positive COVID-19 test. Nine (47%) needed invasive mechanical ventilation, of whom, two had positive COVID-19 test results ($p = ns$). Eight patients (42%) died with three of them having positive PCRs. **CONCLUSIONS:** In patients referring to emergency departments with chief complaint of poisoning (especially poisonings that can result in dyspnea including substances of abuse and toxic alcohols), gastrointestinal, and constitutional respiratory symptoms, attention should be given not to miss possible cases of COVID-19.

FIGURES

Table 1 On-arrival signs and symptoms of the patients with atypical COVID-19 disease (n = 19)

	Variable	n (%)
Admitting service	Toxicology department	10 (52)
	General ED	6 (32)
	Covid ED	3 (16)
Cause of admission	Substance abuse	7 (37)
	Unknown LOC	3 (16)
	Methanol poisoning	2 (11)
	Other poisonings	2 (11)
	GI bleeding	1 (5)
	DVT	1 (5)
	Convulsion	1 (5)
	Flank pain	1 (5)
	Dyspnea	5 (26)
	Cough	4 (21)
Sign/symptom ^a	Tachycardia	3 (16)
	Weakness	3 (16)
	Vomiting	2 (11)
	Abdominal pain	2 (11)
	Convulsion	2 (11)
	Diarrhea	1 (5)
	Restlessness	1 (5)
	Sputum	1 (5)
	Myalgia	1 (5)
	Paresis	1 (5)

^aSubject to be more than 100% as some patients had more than one sign/symptom

UNDERSTANDING THE PATHOLOGY

ALCOHOL MISUSE MAY INCREASE THE SEVERITY OF COVID-19 INFECTIONS

Abbasi-Oshaghi E, Mirzaei F, Khodadadi I.. Disaster Med Public Health Prep. 2020 Nov 18:1-4. doi: 10.1017/dmp.2020.452.
Online ahead of print.

Level of Evidence: Other - Expert Opinion

BLUF

A letter to the editor by biochemists and anatomists at Hamadan University of Medical Sciences, Iran highlights how alcohol misuse (both acute and chronic) might exacerbate COVID-19 infections by upregulating lung injury biomarkers (TGF- β 1), proinflammatory markers (IL-6, TNF- α) and downregulating antioxidants, lung immune effector cells, and vitamin levels. Authors suggest alcohol misuse has potential to increase susceptibility to and severity of SARS-CoV-2 infection, therefore individuals should exercise caution when using alcohol during the current pandemic.

TRANSMISSION & PREVENTION

TRENDS IN COUNTY-LEVEL COVID-19 INCIDENCE IN COUNTIES WITH AND WITHOUT A MASK MANDATE - KANSAS, JUNE 1-AUGUST 23, 2020

Van Dyke ME, Rogers TM, Pevzner E, Satterwhite CL, Shah HB, Beckman WJ, Ahmed F, Hunt DC, Rule J.. MMWR Morb Mortal Wkly Rep. 2020 Nov 27;69(47):1777-1781. doi: 10.15585/mmwr.mm6947e2.

Level of Evidence: 3 - Local non-random sample

BLUF

Epidemic Intelligence Service Officers from the Centers for Disease Control in the United States compare the incidence of COVID-19 in counties with (n=24) and without (n=81) mask mandate in Kansas from June 1 to August 23, 2020 before and after the governor's executive order on July 3. They found COVID-19 incidence increased in counties without a mask mandate (6 to 12 cases/million, 100% increase) while incidence decreased in those with a mandate (17 to 16 cases/million; 6% decrease)(Table, Figure), suggesting mask mandates could mitigate SARS-CoV-2 transmission.

ABSTRACT

Wearing masks is a CDC-recommended* approach to reduce the spread of SARS-CoV-2, the virus that causes coronavirus disease 2019 (COVID-19), by reducing the spread of respiratory droplets into the air when a person coughs, sneezes, or talks and by reducing the inhalation of these droplets by the wearer. On July 2, 2020, the governor of Kansas issued an executive order (state mandate), effective July 3, requiring masks or other face coverings in public spaces. CDC and the Kansas Department of Health and Environment analyzed trends in county-level COVID-19 incidence before (June 1-July 2) and after (July 3-August 23) the governor's executive order among counties that ultimately had a mask mandate in place and those that did not. As of August 11, 24 of Kansas's 105 counties did not opt out of the state mandate or adopted their own mask mandate shortly before or after the state mandate was issued; 81 counties opted out of the state mandate, as permitted by state law, and did not adopt their own mask mandate. After the governor's executive order, COVID-19 incidence (calculated as the 7-day rolling average number of new daily cases per 100,000 population) decreased (mean decrease of 0.08 cases per 100,000 per day; net decrease of 6%) among counties with a mask mandate (mandated counties) but continued to increase (mean increase of 0.11 cases per 100,000 per day; net increase of 100%) among counties without a mask mandate (nonmandated counties). The decrease in cases among mandated counties and the continued increase in cases in nonmandated counties adds to the evidence supporting the importance of wearing masks and implementing policies requiring their use to mitigate the spread of SARS-CoV-2 (1-6). Community-level mitigation strategies emphasizing wearing masks, maintaining physical distance, staying at home when ill, and enhancing hygiene practices can help reduce transmission of SARS-CoV-2.

FIGURES

Characteristic	Before executive order	Executive order effective [§]	After executive order	% Change in incidence [¶]	
	June 1–June 7	July 3–9	August 17–23	June 1–7 versus July 3–9	July 3–9 versus August 17–23
Mandated counties (N = 24)*,**					
No. of daily cases ^{††}	60	333	310	N/A	N/A
Incidence ^{§§}	3	17	16	467	-6
Nonmandated counties (N = 81)^{†,***}					
No. of daily cases ^{††}	40	59	118	N/A	N/A
Incidence ^{§§}	4	6	12	50	100

Abbreviations: COVID-19 = coronavirus disease 2019; mandated = counties with a mask mandate; N/A = not applicable; nonmandated = counties without a mask mandate.

* Counties that as of August 11 did not opt out of the state mandate or adopted their own mask mandate shortly before or after the state mandate include Allen, Atchison, Bourbon, Crawford, Dickinson, Douglas, Franklin, Geary, Gove, Harvey, Jewell, Johnson, Mitchell, Montgomery, Morris, Pratt, Reno, Republic, Saline, Scott, Sedgwick, Shawnee, Stanton and Wyandotte. Total population in mask-mandated counties = 1,960,703 based on 2019 U.S. Census Bureau data.

† Counties that took no official action to opt out of the state mask mandate or adopted their own mask mandate shortly before or after the state mandate were considered to have a mask mandate in place. Counties were considered to not have a mask mandate in place if they took official action to opt out of the state mask mandate and did not adopt their own mask mandate or if their official action used only the language of guidance (e.g., "should" or "recommend"). Total population in non-mask-mandated counties = 952,611 based on 2019 U.S. Census Bureau data.

‡ Week of governor's executive order (effective July 3, 2020).

¶ Change in incidence = [(incidence in period – incidence in previous period)/incidence in previous period] X 100.

** Data on county orders were collected through point-in-time surveys of local health department and other county officials and were supplemented with online searches for published orders and announcements on social media and local news sites. Text in the county orders was analyzed to determine whether mask mandates were in place as of August 11, 2020.

†† Seven-day rolling average number of new daily cases.

§§ Seven-day rolling average number of new daily cases per 100,000 population.

Table: "Confirmed COVID-19 infection 7-day rolling average case counts, rates, and percentage changes, by mask mandate status*,† and period — Kansas, June 1–August 23, 2020".

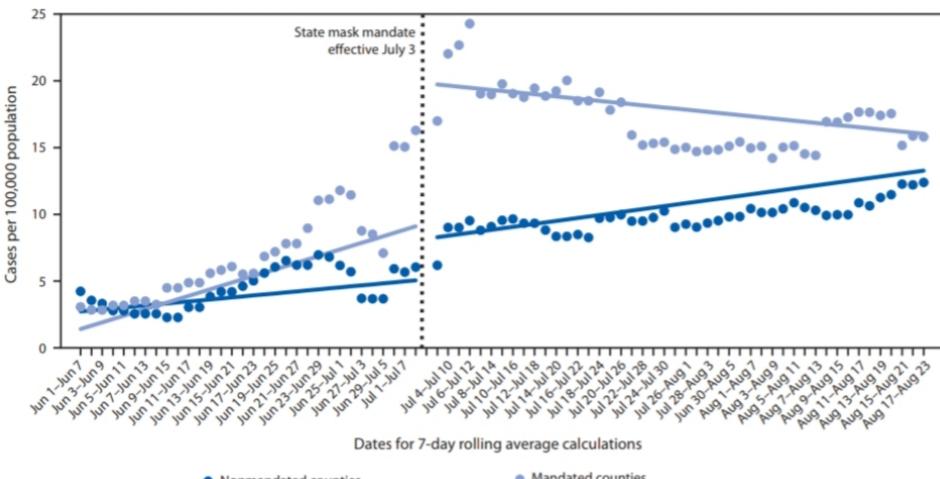


Figure: " Trends* in 7-day rolling average of new daily COVID-19 cases per 100,000 population among mask-mandated† and non-mask-mandated counties before (June 1–July 2)§ and after (July 3–August 23)¶ the governor's executive order requiring masks — Kansas, June 1–August 23, 2020".

DEVELOPMENTS IN TRANSMISSION & PREVENTION

SHELTER FROM THE CYTOKINE STORM: PITFALLS AND PROSPECTS IN THE DEVELOPMENT OF SARS-COV-2 VACCINES FOR AN ELDERLY POPULATION

Giabattini A, Garagnani P, Santoro F, Rappuoli R, Franceschi C, Medaglini D.. Semin Immunopathol. 2020 Nov 6. doi: 10.1007/s00281-020-00821-0. Online ahead of print.

Level of Evidence: Other - Expert Opinion

BLUF

Italian immunologists review the challenges of SARS-CoV-2 vaccine development in the elderly populations at high risk for COVID-19. They argue elderly populations have relatively poor immune responses due to immunosenescence, comorbidities, and pharmacologic treatments (Figures 3, 5) and that increased pro-inflammatory cytokines (IL-6, 8, TNF-alpha) worsen both SARS-CoV-2 prognosis and vaccine efficacy (Figure 2). Authors suggest a systems biology approach considering clinical, socio-economic, immunological factors alongside advanced technologies, adjuvants, and vectors are necessary to develop an effective SARS-CoV-2 vaccine for the elderly.

ABSTRACT

The SARS-CoV-2 pandemic urgently calls for the development of effective preventive tools. COVID-19 hits greatly the elder and more fragile fraction of the population boosting the evergreen issue of the vaccination of older people. The development of a vaccine against SARS-CoV-2 tailored for the elderly population faces the challenge of the poor immune responsiveness of the older population due to immunosenescence, comorbidities, and pharmacological treatments. Moreover, it is likely that the inflammatory phenotype associated with age could both influence vaccination efficacy and exacerbate the risk of COVID-19-related "cytokine storm syndrome" with an overlap between the factors which impact vaccination effectiveness and those that boost virulence and worsen the prognosis of SARS-CoV-2 infection. The complex and still unclear immunopathological mechanisms of SARS-CoV-2 infection, together with the progressive age-related decline of immune responses, and the lack of clear correlates of protection, make the design of vaccination strategies for older people extremely challenging. In the ongoing effort in vaccine development, different SARS-CoV-2 vaccine candidates have been developed, tested in pre-clinical and clinical studies and are undergoing clinical testing, but only a small fraction of these are currently being tested in the older fraction of the population. Recent advances in systems biology integrating clinical, immunologic, and omics data can help to identify stable and robust markers of vaccine response and move towards a better understanding of SARS-CoV-2 vaccine responses in the elderly.

FIGURES

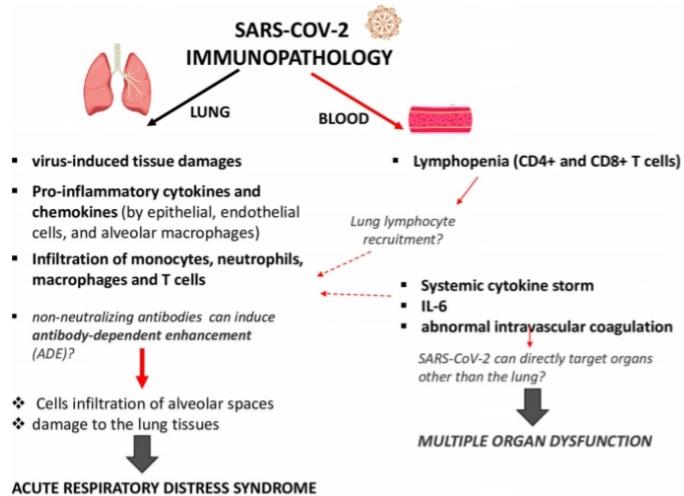


Figure 2: "Possible mechanisms of SARS-CoV-2 immunopathology. Systemic and local (lung) immune responses and their pathological role, following SARS-CoV-2 entry into the host are schematically represented. Induction of innate immune responses is a crucial step in the pathophysiology of COVID-19 disease, contributing to hyperinflammation and tissue damage during the later stages of the disease. Infiltration of immune cells in the lungs causes overproduction of proinflammatory cytokines, which eventually damages the lung infrastructure, accumulation of macrophages in the air spaces and diffuse alveolar damage leading to acute respiratory distress syndrome (ARDS). Furthermore, elevated levels of circulating proinflammatory cytokines can cause septic shock and multi-organ dysfunction. Together with the hyperinflammatory response, overt disseminated intravascular coagulation has been reported and a significant lymphopenia, mainly related to CD4+ T and CD8+ T cells, has been observed, possibly due to pulmonary recruitment of lymphocytes from the blood. A possible immunopathological role can be mediated by non-neutralizing antibodies produced by B cells, which may enhance SARS-CoV-2 infection through antibody-dependent enhancement (ADE), further exacerbating organ damage".

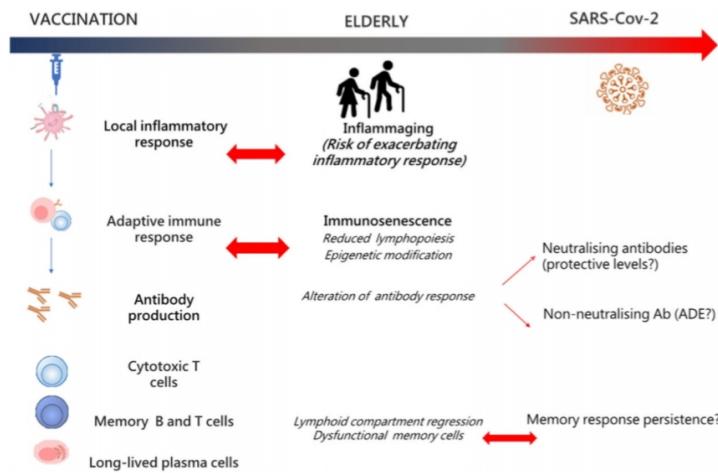


Figure 3: "Challenges for the development of a SARS-CoV-2 vaccine for elderly people. Schematic interconnection between the main immune mechanisms elicited by the vaccination process, with the peculiarity of the elderly immune system—affected by both inflammaging and immunosenescence—and the still undefined correlates of protection from SARS-CoV-2 infection. The complex and still unclear immunopathological mechanisms of SARS-CoV-2 infection, together with the progressive age-related decline of innate and adaptive immune responses, and the lack of a clear correlate of protection make the design of vaccination strategies for older people extremely challenging".

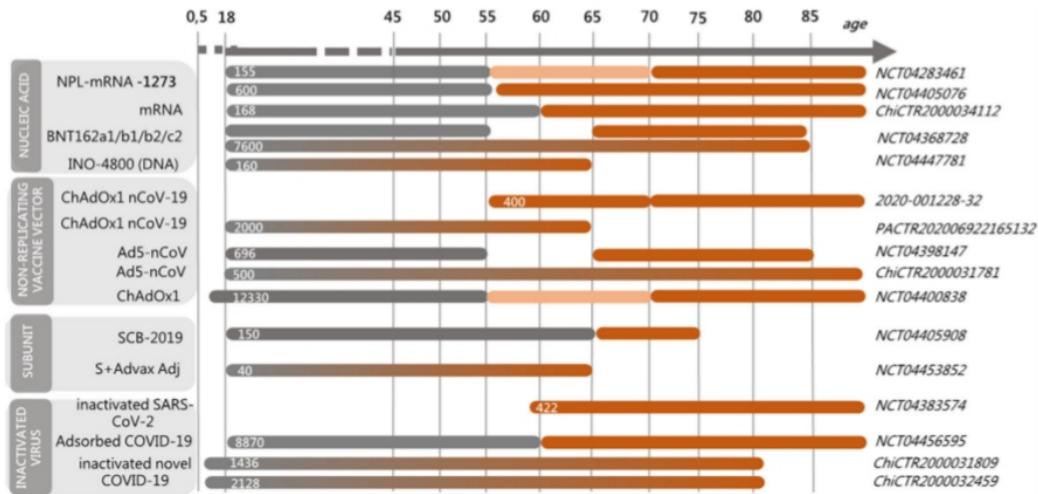


Figure 5: "Ongoing clinical trials of COVID-19 vaccines specifically including the elderly population. Schematic representation of clinical studies specifically including older people in the selection criteria of volunteers. The platform used for each clinical trial is shown on the left. The identifier number of the clinical trial and the number of volunteers included (in brackets) are reported on the right. Bars represent the partition of volunteers according to the age range. Data are updated to 8th July 2020".

MANAGEMENT

CLINICAL STUDIES ASSESSING THE EFFICACY, EFFECTIVENESS, AND SAFETY OF REMDESIVIR IN MANAGEMENT OF COVID-19: A SCOPING REVIEW

Pimentel J, Laurie C, Cockcroft A, Andersson N.. Br J Clin Pharmacol. 2020 Nov 27. doi: 10.1111/bcp.14677. Online ahead of print.

Level of Evidence: Other - Review / Literature Review

BLUF

Family medicine physicians from McGill University in Montreal, Canada conducted a scoping review of the literature surrounding the safety, efficacy, and effectiveness of the anti-viral medication remdesivir to treat COVID-19. They reviewed 23 clinical trial registrations and 17 empirical studies (46,508 total participants). From these studies, two randomized-controlled trials reported improved clinical status and a shorter median recovery time in patients who received remdesivir (Table 1) and two observational studies demonstrated mortality benefit for patients receiving remdesivir. Authors conclude existing literature suggests remdesivir may improve COVID-19 outcomes, and suggest that forthcoming results of the 23 ongoing clinical trials will allow for more definitive analysis.

ABSTRACT

AIM: Remdesivir is one of the repurposed drugs under investigation to treat patients with COVID-19. Clinicians and decision-makers need a summary of the most recent evidence. This scoping review maps the evidence on the efficacy, effectiveness, and safety of remdesivir for patients with COVID-19, up to September 14th, 2020. **METHODS:** Our scoping review searched Pubmed, Embase (Ovid), Scopus, and 17 primary trial registries for empirical publications or active registered clinical trials for data on the efficacy, effectiveness, or safety of remdesivir for COVID-19 or SARS-CoV-2. We conducted a narrative synthesis of the included publications. **RESULTS:** 17 empirical studies and 23 clinical trial registrations (n=40) accumulated 46,508 participants. We found four published randomised controlled trials accumulating 2,293 patients. Two trials reported shorter median recovery time and better clinical status among patients who received remdesivir compared with the control groups. Observational studies report an association between remdesivir treatment and decreased mortality, as well as increased survival. The most common adverse reaction was hepatic impairment, although the trials reported a similar proportion of adverse events in the intervention and control groups. **CONCLUSION:** Remdesivir might shorten the time to clinical improvement among hospitalized adults with severe COVID-19. Trial data report a similar proportion of adverse events in treated and control groups. The results of the 23 registered active trials, including more than 30,000 participants, will shed light on the efficacy and safety of the antiviral. The findings of the remaining clinical trials expected to report results in 2020 will allow a quantitative synthesis of available evidence.

FIGURES

Table 1. Characteristics of the trials included in our study

Authors	Type of study	Patients randomised	Inclusion criteria	Intervention	Control	Randomization	Primary outcome	Main findings	Reported adverse events
Olender SA, Perez KK, Go AS, Balani B, Price-Haywood EG, Shah NS, et al.	Comparison of interim data from a phase 3, randomized, open-label study, with a retrospective cohort study	1130	Hospitalized patients with SARS-CoV-2 confirmed infection, SaO ₂ <95% on room air or requiring supplemental oxygen, with pulmonary infiltrates	200 mg loading dose on day 1, followed by 100 mg daily for up to 4 or 9 additional days (plus SC)	Standard-of-care treatment according to local clinical practice	NA	Proportion of patients with recovery on day 14 based on a 7-point clinical status ordinal scale	Compared with 59.0% in the control group, 74.4% of patients in the remdesivir group had recovered by day 14 (aOR 2.03: 95% CI 1.34–3.08, p<0.001). Compared with 12.5% in the control group, 7.6% of patients in the remdesivir group died by day 14 (aOR 0.38, 95% CI: 0.22–0.68, p=0.001).	Not reported
Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al.	Double-blind, randomized, placebo-controlled trial	1063	Adults with SARS-CoV-2 infection, SaO ₂ <95% on room air or requiring supplemental oxygen, with pulmonary infiltrates	200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days	1:1, stratified by study site and disease severity at enrollment	Matching placebo	Time to recovery (discharge from the hospital or hospitalization for infection control)	Median recovery time was 11 days (95% CI 9–12) for patients in the remdesivir group, compared to 15 days (95% CI, 13–19) for patients in the placebo group (RRR 1.32; 95% CI, 1.12–1.55; p<0.001).	114/541 (21.1%) patients in the remdesivir group and 141/522 (27.0%) in the control group had serious adverse events.

Spinner CD, Gottlieb RL, Criner GJ, Arribas JR, Cattelan AM, Soriano Viladomiu A, et al.	Three-arm randomized, open-label trial	596	Hospitalized patients with RT-PCR confirmed SARS-CoV-2 infection and moderate pneumonia (room air $\text{SaO}_2 >94\%$ and pulmonary infiltrates)	Intravenous remdesivir 200mg on day 1 followed by 100mg/d. Arm 1: 10-day course of remdesivir; Arm 2: 5-day course of remdesivir	Standard care	1:1; not stratified	Clinical status on day 11 (7-point ordinal scale)	The odds of a better clinical status distribution was higher among patients in the 5-day remdesivir group compared to those receiving standard care (OR 1.65; 95% CI, 1.09-2.48; $p = 0.02$). The clinical status distribution between the 10-day remdesivir and standard care groups was not significantly different on day 11 ($p = 0.18$).	The most frequent adverse events were nausea (10% vs 3%), hypokalemia (6% vs 2%), and headache (5% vs 3%) among patients in the remdesivir compared to the standard care group.
Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, et al.	Randomized, open-label, phase 3 trial	397	Hospitalized patients with confirmed SARS-CoV-2 infection, at least 12 years old, $\text{SaO}_2 <95\%$ on ambient air, and pneumonia	200 mg loading dose on day 1, followed by 100 mg daily for 4 additional days	200 mg loading dose on day 1, follow ed by 100 mg daily for 9 additional days	1:1; not stratified	Clinical status on day 14 (7-point ordinal scale)	At day 14, the distribution in clinical status among patients in the 10-day group was similar to that among patients in the 5-day group ($p = 0.14$).	Common adverse events were similar in both groups (70% in 5-day and 74% in 10-day); included nausea (9%), worsening respiratory failure (8%), elevated alanine aminotransferase level (7%), and constipation (7%).

Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al.	Randomized, double-blind, placebo-controlled, multicentre trial	237	Hospitalized patients with confirmed SARS-CoV-2 infection, >17 years old, interval from symptom onset to enrolment <13 days, room air $\text{SaO}_2 <95\%$ or a ratio of arterial oxygen to inspired oxygen < 301 mm, and pneumonia	200 mg loading dose on day 1, followed by 100 mg daily for 9 additional days	Placebo infusion	2:1; stratified according to the level of respiratory support	Time to clinical improvement up to day 28 (six-point ordinal scale)	There was no statistically significant difference in time to clinical improvement between arms (HR 1.23, 95% CI 0.87–1.75). Among treated patients with symptom duration <11 days, there was a numerical reduction in time to clinical improvement (HR 1.52, 0.95–2.43).	There were 102/155 (66%) adverse events reported in remdesivir patients and 50/78 (64%) reported in placebo patients.
Shih WJ, Shen X, Zhang P, Xie T	Re-analysis of Wang paper	NA	NA	NA	NA	NA	Time to recovery (reaching the clinical status with point=2 or 1 in the 6-category scale)	On day 28, the response rate for the remdesivir group with baseline status=3 (moderately severe category) was 85%, and for the placebo group, the response rate was 70% (OR=2.38, $p=0.0012$). The response rate was 43% for the remdesivir group compared to 33% for the placebo group on day 14 (OR=1.53, $p=0.0022$).	NA

SaO_2 = oxygen saturation, mg= milligrams, NA= not applicable, aOR= adjusted odds ratio, CI= confidence interval, RRR= rate ratio for recovery, RT-PCR= reverse transcription polymerase chain reaction, OR= odds ratio, HR= hazard ratio

Table 1, continued

R&D: DIAGNOSIS & TREATMENTS

DEVELOPMENTS IN DIAGNOSTICS

CURRENT METHODS FOR DIAGNOSIS OF HUMAN CORONAVIRUSES: PROS AND CONS

Benzigar MR, Bhattacharjee R, Baharfar M, Liu G.. Anal Bioanal Chem. 2020 Nov 20. doi: 10.1007/s00216-020-03046-0.
Online ahead of print.

Level of Evidence: 3 - Review / Literature Review

BLUF

Investigators affiliated with the University of New South Wales review benefits and disadvantages of diagnostic protocols for human coronaviruses, including more readily used methods (real time RT-PCR, CT scanning, etc.), and less commonly known methods (High-throughput gene sequencing, CASPR/Cas, etc; Table 2). They found that the current gold standard real time RT-PCR is beneficial in that it has high sensitivity and is able to be widely used, however its disadvantages include false-positive results and risk to healthcare workers performing sample collection. Additionally, the diagnostic tool of antibody-based serology detection is not useful for early diagnosis of COVID-19 but may have potential for investigating the acquired immunity of recovered COVID-19 patients (Figure 3). The authors believe that this review can assist researchers in the development of advanced diagnostic methods to improve the accuracy of testing and improve control of human coronavirus transmission.

SUMMARY

This review discusses the pros/cons of the following diagnostic modalities for human coronaviruses:

Current Well-Known Methods:

- Real-time reverse transcription polymerase chain reaction (RT-PCR; Figure 1)
- Serologic method
- CT scanning

Less Commonly Used Methods (Early/Emerging):

- High-throughput gene sequencing (HTGS)
- Loop-Mediated Isothermal Methods (LAMP)
- CRISPR/Cas-based methods
- Antibody-based Serology Detection (Figure 3)
- Enzyme-linked Immunosorbent Assay
- Lateral Flow Immunochromatographic Assays
- Antigen detection-based methods

ABSTRACT

The current global fight against coronavirus disease (COVID-19) to flatten the transmission curve is put forth by the World Health Organization (WHO) as there is no immediate diagnosis or cure for COVID-19 so far. In order to stop the spread, researchers worldwide are working around the clock aiming to develop reliable tools for early diagnosis of severe acute respiratory syndrome (SARS-CoV-2) understanding the infection path and mechanisms. Currently, nucleic acid-based molecular diagnosis (real-time reverse transcription polymerase chain reaction (RT-PCR) test) is considered the gold standard for early diagnosis of SARS-CoV-2. Antibody-based serology detection is ineffective for the purpose of early diagnosis, but a potential tool for serosurveys, providing people with immune certificates for clearance from COVID-19 infection. Meanwhile, there are various blooming methods developed these days. In this review, we summarise different types of coronavirus discovered which can be transmitted between human beings. Methods used for diagnosis of the discovered human coronavirus (SARS, MERS, COVID-19) including nucleic acid detection, gene sequencing, antibody detection, antigen detection, and clinical diagnosis are presented. Their merits, demerits and prospects are discussed which can help the researchers to develop new generation of advanced diagnostic tools for accurate and effective control of human coronavirus transmission in the communities and hospitals.

FIGURES

Detection methods	Assay time	Specificity	Accuracy	Advantages	Disadvantages	References
Nucleic acid detection	4 to 6 h	95%	Poor accuracy, the exact percentage is not revealed	High sensitivity, possibility of large-scale operation	Professional technicians needed, difficult data analysis, expensive, less accuracy, false-negative or false-positive results	[140, 141]
Gene sequencing	Unknown	Poor sensitivity	Poor accuracy	Finding the evaluation of virus, identification of mutation,	Experts and trained personnel needed, time consuming, costly, and complex data analysis. Laboratory and clinical differences	[142]
Antibody detection	15 min	90.63%	88.66%	Easy handling, no requirement of expert	Long window period, difficulty in early diagnosis, detection only after post infection from 3 to 6 days for IgM and 8 days for IgG	[143]
Antigen detection	15 to 30 min	Poor sensitivity	Poor accuracy	Easy handling	Not reliable	[15]
Clinical diagnosis	2 days	Not specified	Not applicable	Finding the disease through imaging	Requirement of experts and trained personnel, difficulties in early detection	[144]

Table 2. Comparison of performance of different methods for coronavirus diagnosis

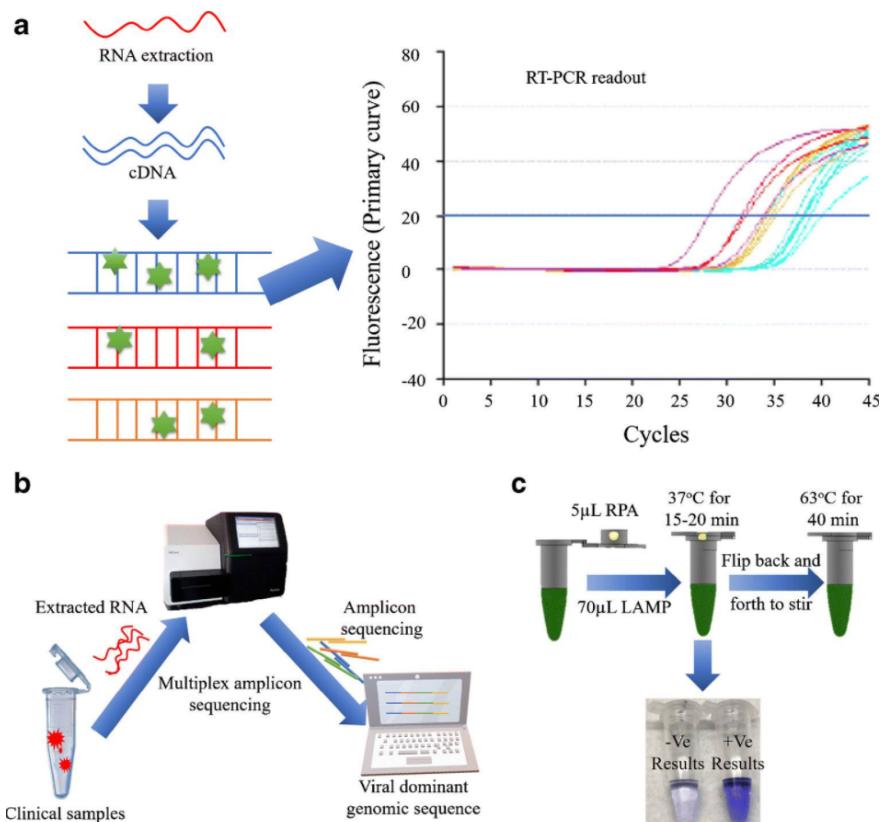


Figure 1 Schematic representation for the promising techniques generally used to detect SARS-CoV-2: (a) RT-PCR method is carried out from the reverse transcription of viral RNA into cDNA which is then amplified using specific primers. The amplification process is confirmed from the fluorescent signal indicating the total number of copies in target sequence. (b) Whole genomic sequencing is a complete gene sequencing method which is complicated and not helpful for urgent and large-scale detection. Generally, the viral RNA is extracted from the specimen going through multiplex amplicon sequencing to identify the nucleic acid [58]. Redrawn with permission. (c) Combined method of LAMP and COVID-19 Penn-RAMP: The Penn-RAMP contains two processes of isothermal amplification, first the RPA was carried out at 37 °C at the cap of the tube and then the LAMP at 63 °C within the tube. The LAMP reaction mixture was added with the LCV dye and the ratio between RPA and LAMP was 1:9. This was incubated at 38 °C for 15–20 min followed by flipping for thorough mixing moving towards second time incubation in a thermal cycler for 40 min at 63 °C. LCV dye helped by producing dark violet signal in the presence of dsDNA and colourless in the absence of dsDNA. This method was found to have high potential as it reduced false negatives [59]. Re-produced, permission has taken under the CC-BY-NC-ND 4.0 International license)

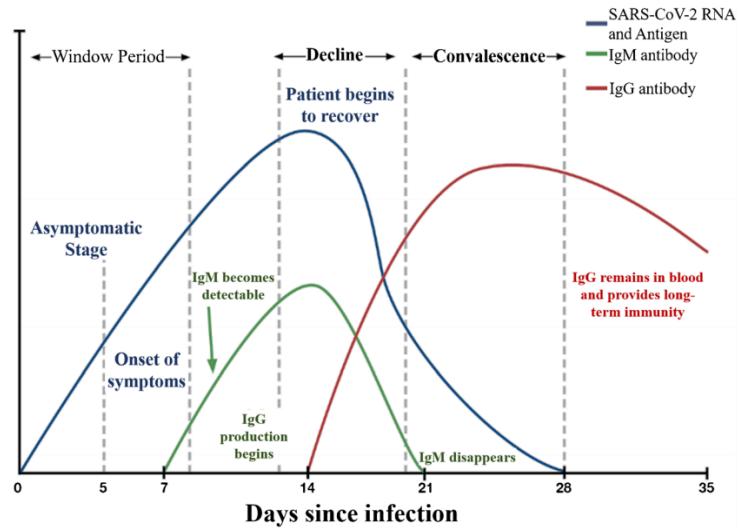


Figure 3 Comparative relation theoretically between different levels of SARS-CoV-2 RNA and antigen, IgM and IgG during the different infection days showing three main phases such as window period, decline phase, and convalescence phase. In the window period, the onset of symptoms takes place within a week of contact with viral source. Secondly, the IgM shows up and the production of IgG takes place until it disappears in 21 days of infection. Thirdly, in the recovery, the IgG remains in the blood. This suggests that the serological examination could be done 3 days after the symptoms or a week after the infection [114]. Reproduced with permission

MENTAL HEALTH & RESILIENCE NEEDS

IMPACT ON PUBLIC MENTAL HEALTH

SUICIDE IN THE TIME OF COVID-19: REVIEW AND RECOMMENDATIONS

Zalsman G, Stanley B, Szanto K, Clarke DE, Carli V, Mehlum L.. Arch Suicide Res. 2020 Nov 17:1-6. doi:

10.1080/13811118.2020.1830242. Online ahead of print.

Level of Evidence: Other - Guidelines and Recommendations

BLUF

An international group of psychiatrists summarized guidelines provided by the International Academy of Suicide Research (IASR) on the reported increase in mental health concerns and suicide attempts after pandemics. They hypothesize that the COVID-19 pandemic might also be followed by similar issues due to several factors (see summary), with at-risk populations including the elderly, socially isolated individuals, healthcare professionals, and young children. Their recommendations include: videoconferencing for suicide risk assessment rather than teleconferencing, careful attention toward elderly patients in isolation, and increased awareness of mental health concerns during and following the COVID-19 pandemic.

SUMMARY

Proposed factors influencing increased mental health concerns and suicide attempts as a result of the COVID-19 pandemic:

- Reduced access to care for populations with mental health issues
- Decreased hospitalization/psychiatric referral rates due to fear of infection
- Increased alcohol use/abuse
- Lack of income and higher rates of economic hardships
- Grief due to loss of loved ones during the pandemic
- Issues arising in familial relationships due to prolonged isolation together
- Anxiety regarding what the future will entail

ABSTRACT

The coronavirus (COVID-19) pandemic presents us with unusual challenges to the global health system and economics. The pandemic may not have an immediate impact on suicide rates, however, given that it is likely to result in a confluence of risk factors for suicide and economic crisis, it is highly possibly that it will lead to increases in suicide rates in the long-run. Elderly persons are more likely to live alone, be socially isolated during COVID-19 and have physical health problems, which are risk factors for suicide. Young children and health professionals may also be population at risk. Isolation, quarantine and the economic crisis that follows may impact mental health significantly. The International Academy of Suicide Research (IASR) is an organization dedicated to promote high standards of research and scholarship in the field of suicidal behaviour to support efforts to prevent suicide globally. This IASR's board position paper gives recommendations for suicide research during the COVID-10 pandemic. Clinical research has to be modified due to COVID-19 shutdown.

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