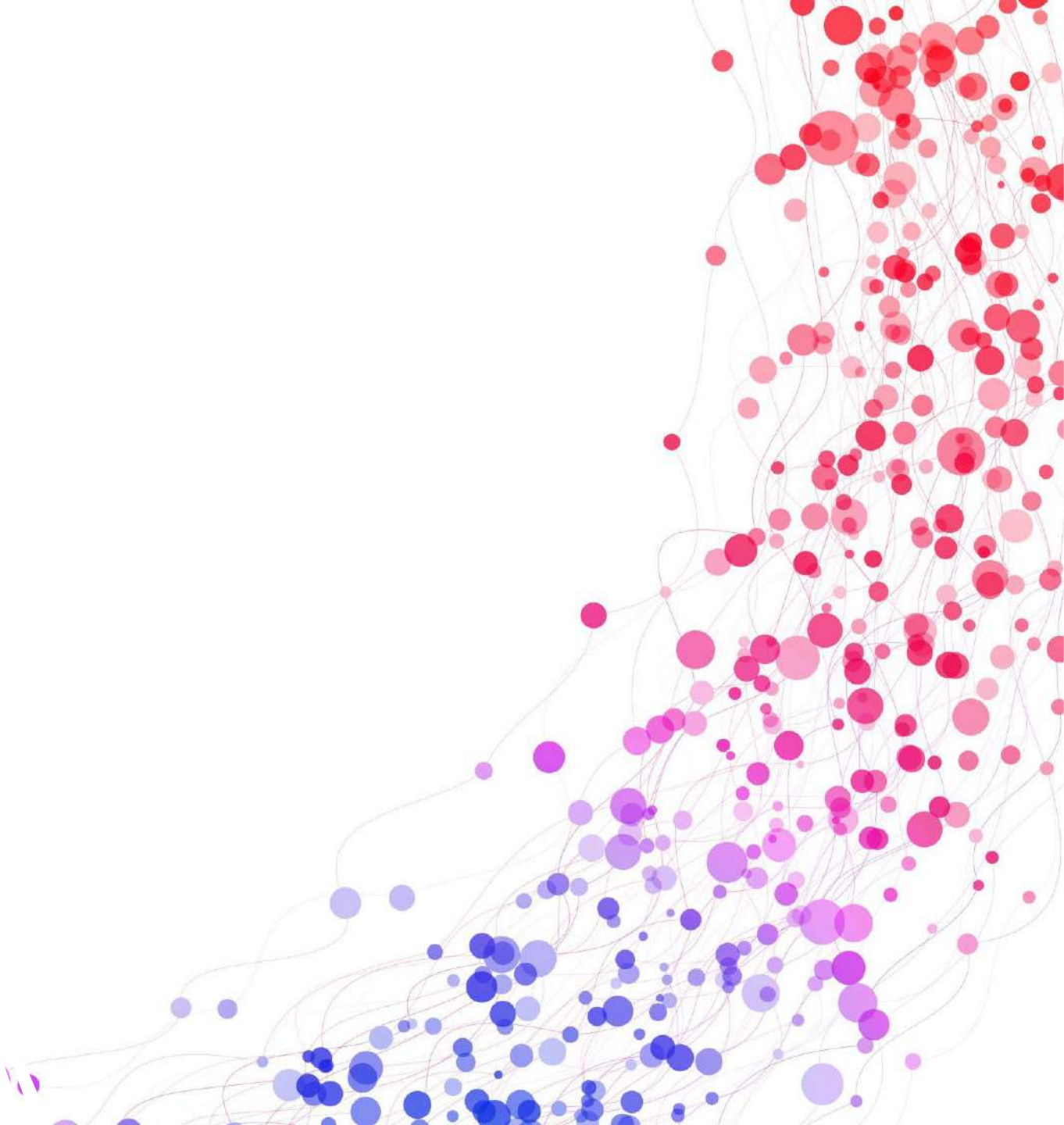
Known Knowns and Known Unknowns: Update on A Pandemic

Jennifer Hanrahan D.O.

Chief, Division of Infectious Diseases

University of Toledo College of Medicine and Life Sciences



Unknowns

There are known knowns; there are things we know we know.

We also know there are known unknowns; that is to say we know there are some things we do not know.

But there are also unknown unknowns—the ones we don't know we don't know.

Objectives

1	2	3
The participant will be able to discuss currently available recommendations for treatment of COVID-19.	The participant will be able to describe uncertainties in treatment of COVID-19.	The participant will be able to counsel individuals regarding vaccination to prevent COVID-19.

Disclosures

- I do not have any financial disclosures.
- If I discuss off-label use of any drug, it will clearly be stated.
- I do not have copyright permissions for the images I am using. This talk is purely for educational purposes. I am not profiting in any way from this talk. I am also not giving permission for reuse of these slides.
- Slides may be used for individual education purposes only.

Asia & Pacific

China identifies new strain of coronavirus as source of pneumonia outbreak

https://www.washingtonpost.com/world/asia_pacific/china-identifies-new-strain-of-coronavirus-as-source-of-pneumonia-outbreak/2020/01/09/f2625650-329f-11ea-971b-43bec3ff9860_story.html

CIDRAP Center for Infectious Disease Research and Policy

News & Perspective | Infectious Disease Topics | Antimicrobial Stewardship | Ongoing Programs

FEATURED NEWS TOPICS Ebola Zika MERS-CoV Chronic Wasting Disease

Wuhan nCoV outbreak quadruples, spreads within China

Filed Under: Coronavirus; Misc Emerging Topics

Lisa Schnirring | News Editor | CIDRAP News | Jan 19, 2020

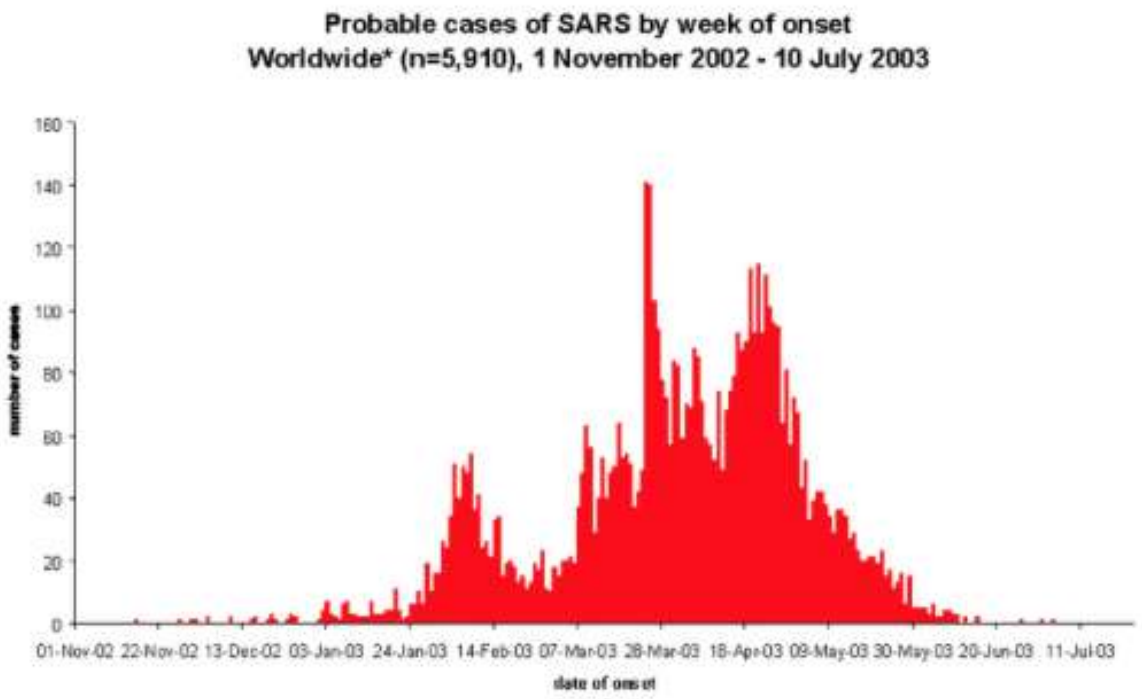
Share Tweet LinkedIn Email Print & PDF

A surge of newly confirmed novel coronavirus (2019-nCoV) cases since Friday in Wuhan has pushed the outbreak total to 198 cases, some of them with no apparent links to the outbreak market, and health officials today announced a case in Shenzhen, China's first outside of Wuhan.

The expansion of the outbreak in China comes during Asia's heavy travel season ahead of the Jan 25 Lunar New Year observance. Meanwhile, the World Health Organization (WHO) said yesterday officials see evidence of limited human-to-human transmission, adding that it's closely watching for signs of sustained spread.

gjp311 / iStock

Epidemic curves - Severe Acute Respiratory Syndrome (SARS)



https://www.who.int/csr/sars/epicurve/epiindex/en/index1.html

Will SARS return?

2019-nCoV

- 440 confirmed cases in China, including 198 in Wuhan, 5 in Beijing and 14 in Guangdong (as of 1/20/2020)
- Most cases have been epidemiologically linked to a large seafood and animal market in Wuhan
- 16 cases have been reported in healthcare workers, demonstrating that there is human-to-human transmission
- A woman in South Korea who traveled to Wuhan, but did not visit any markets or have contact with animals or confirmed cases remains unexplained
- Cases have also been reported in Thailand and Japan
- Many of the cases have been relatively mild, but about 15% are severe; 9 deaths to date
- More severe in people over age 50 and with comorbidities

https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1785/6012472

Clinical Infectious Diseases

IDSA Infectious Diseases Society of America

hivma hiv medicine association

Issues More Content Publish Purchase Advertise About All Clinical Infectious Advanced Search

Article Contents

Abstract

Comments (0)

ACCEPTED MANUSCRIPT

Serologic testing of U.S. blood donations to identify SARS-CoV-2-reactive antibodies: December 2019-January 2020

Sridhar V Basavaraju, MD, Monica E Patton, MD, Kacie Grimm, Mohammed Ata Ur Rasheed, PhD, Sandra Lester, PhD, Lisa Mills, PhD, Megan Stumpf, Brandi Freeman, PhD, Azaibi Tamin, PhD, Jennifer Harcourt, PhD ... Show more

Clinical Infectious Diseases, ciaa1785, https://doi.org/10.1093/cid/ciaa1785

Published: 30 November 2020 **Article history**

PDF Split View Cite Permissions Share

Abstract

Background

SARS-CoV-2, the virus that causes COVID-19 disease, was first identified in Wuhan, China in December 2019, with subsequent worldwide spread. The first U.S. cases were identified in January 2020.

Methods

To determine if SARS-CoV-2 reactive antibodies were present in sera prior to the first identified case in the U.S. on January 19, 2020, residual archived samples from 7,389 routine blood donations collected by the American Red Cross from December 13, 2019 to January 17, 2020, from donors resident in nine states (California, Connecticut, Iowa, Massachusetts, Michigan, Oregon, Rhode Island, Washington, and Wisconsin) were tested at CDC for anti-SARS-CoV-2 antibodies. Specimens reactive by pan-immunoglobulin (pan Ig) enzyme linked immunosorbent assay (ELISA) against the full spike protein were tested by IgG and IgM ELISAs, microneutralization test, Ortho total Ig S1 ELISA, and receptor binding domain / Ace2 blocking activity assay.

Results

Of the 7,389 samples, 106 were reactive by pan Ig. Of these 106 specimens, 90 were available for further testing. Eighty four of 90 had neutralizing activity, 1 had S1 binding activity, and 1 had receptor binding domain / Ace2 blocking activity >50%, suggesting the presence of anti-SARS-CoV-2-reactive antibodies. Donations with reactivity occurred in all nine states.

What Happened?

Science

RESEARCH ARTICLES

Cite as: R. Li *et al.*, *Science*
10.1126/science.abb3221 (2020).

Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV2)

Ruiyun Li[1]*, Sen Pei[2]*†, Bin Chen[3]*, Yimeng Song[4], Tao Zhang[5], Wan Yang[6], Jeffrey Shaman[2]†

[1]MRC Centre for Global Infectious Disease Analysis, Department of Infectious Disease Epidemiology, School of Public Health, Faculty of Medicine, Imperial College London, London W2 1PG, UK. [2]Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, NY 10032, USA. [3]Department of Land, Air and Water Resources, University of California, Davis, Davis, CA 95616, USA. [4]Department of Urban Planning and Design, The University of Hong Kong, Hong Kong. [5]Ministry of Education Key Laboratory for Earth System Modeling, Department of Earth System Science, Tsinghua University, Beijing 10084, P. R. China. [6]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY 10032, USA.

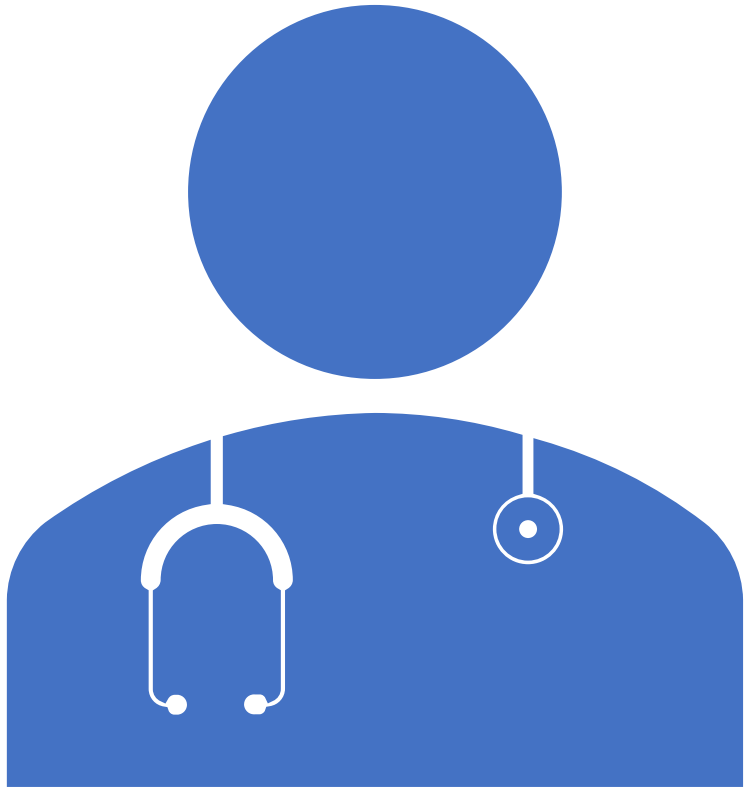
*These authors contributed equally to this work.

†Corresponding author. Email: sp3449@cumc.columbia.edu (S.P.); jls106@cumc.columbia.edu (J.S.)

Estimation of the prevalence and contagiousness of undocumented novel coronavirus (SARS-CoV2) infections is critical for understanding the overall prevalence and pandemic potential of this disease. Here we use observations of reported infection within China, in conjunction with mobility data, a networked dynamic metapopulation model and Bayesian inference, to infer critical epidemiological characteristics associated with SARS-CoV2, including the fraction of undocumented infections and their contagiousness. We estimate 86% of all infections were undocumented (95% CI: [82%–90%]) prior to 23 January 2020 travel restrictions. Per person, the transmission rate of undocumented infections was 55% of documented infections ([46%–62%]), yet, due to their greater numbers, undocumented infections were the infection source for 79% of documented cases. These findings explain the rapid geographic spread of SARS-CoV2 and indicate containment of this virus will be particularly challenging.

Some Unknowns

- When will this be over, or will it ever be over?
- Why are some people at greater risk for severe disease than others?
- Does infection confer long-term immunity?
- How much do fomites contribute to transmission?
- How long are people who are severely ill contagious?
- Will vaccines protect against new variants?
- Will annual vaccination be required?



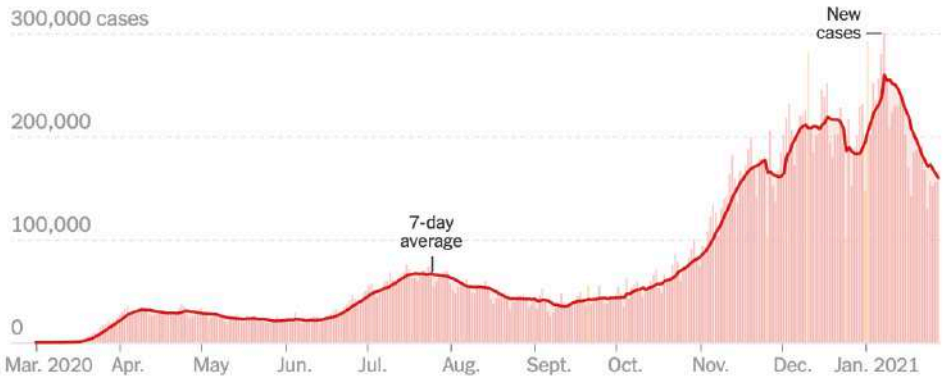
Numbers

U.S.A. World Health

Coronavirus in the U.S.: Latest Map and Case Count

Updated January 29, 2021, 2:09 P.M. E.T.

Leer en español



	TOTAL REPORTED	ON JAN. 28	14-DAY CHANGE
Cases	25.8 million+	165,264	-34% ↘
Deaths	434,783	3,868	-2% →
Hospitalized		104,303	-15% →

Day with reporting anomaly. Hospitalization data from the Covid Tracking Project; 14-day change trends use 7-day averages.

https://www.nytimes.com/interactive/2020/us/coronavirus-us-cases.html

United States COVID-19 Cases and Deaths by State

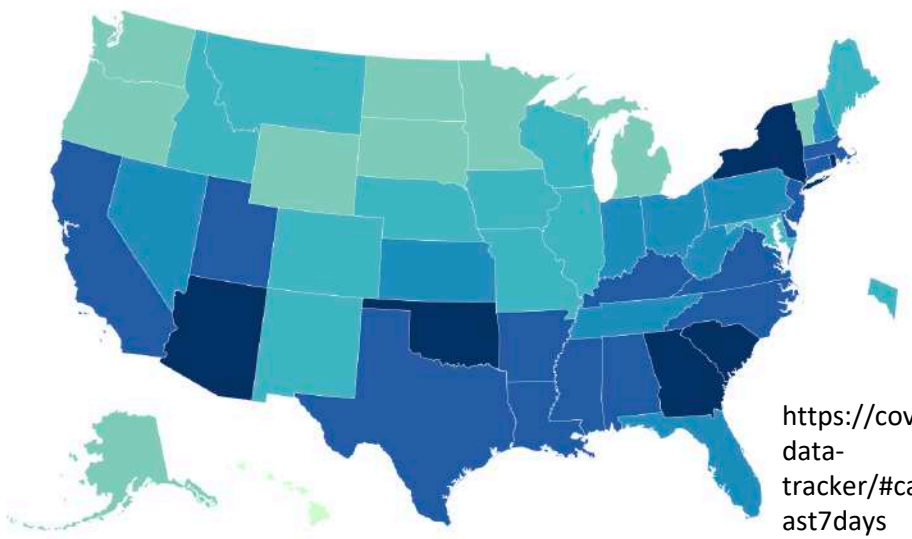
Maps, charts, and data provided by the CDC, updated daily by 8 pm ET†

TOTAL CASES	AVERAGE DAILY CASES PER 100K IN LAST 7 DAYS	TOTAL DEATHS
25,615,268	47.5	431,619
+158,598 New Cases		+3,993 New Deaths

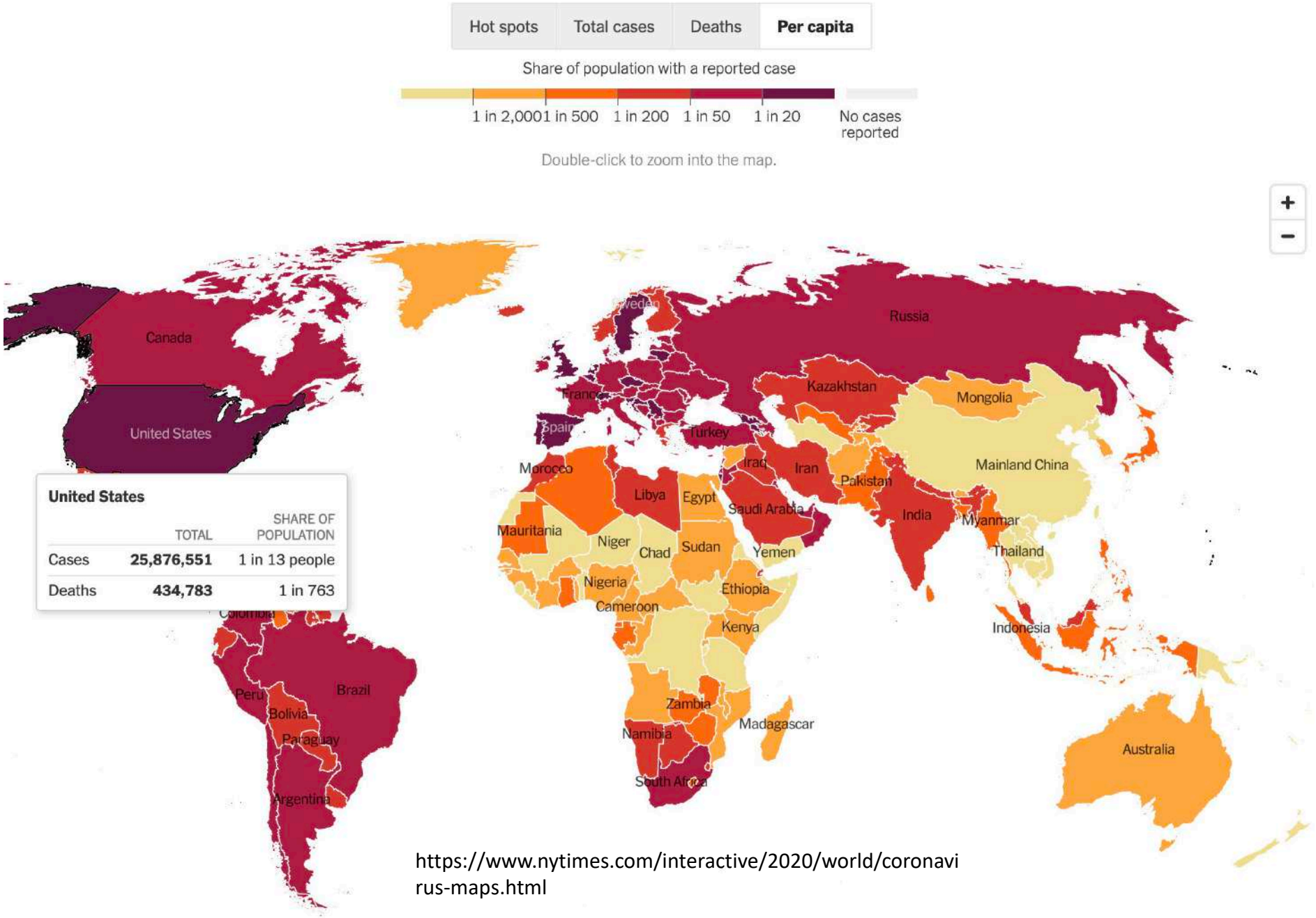
CDC | Updated: Jan 29 2021 2:40PM

View: (•) Cases ( ) Deaths
Time period: (•) Last 7 Days ( ) Since Jan 21, 2020
Metric: ( ) Count (•) Rate per 100,000

US COVID-19 Average Daily Case Rate in Last 7 Days, by State/Territory (cases per 100K)



https://covid.cdc.gov/covid-data-tracker/#cases_casesper100klast7days



https://www.nytimes.com/interactive/2020/world/coronavirus-maps.html

Hot spots | Total cases | **Deaths** | Per capita

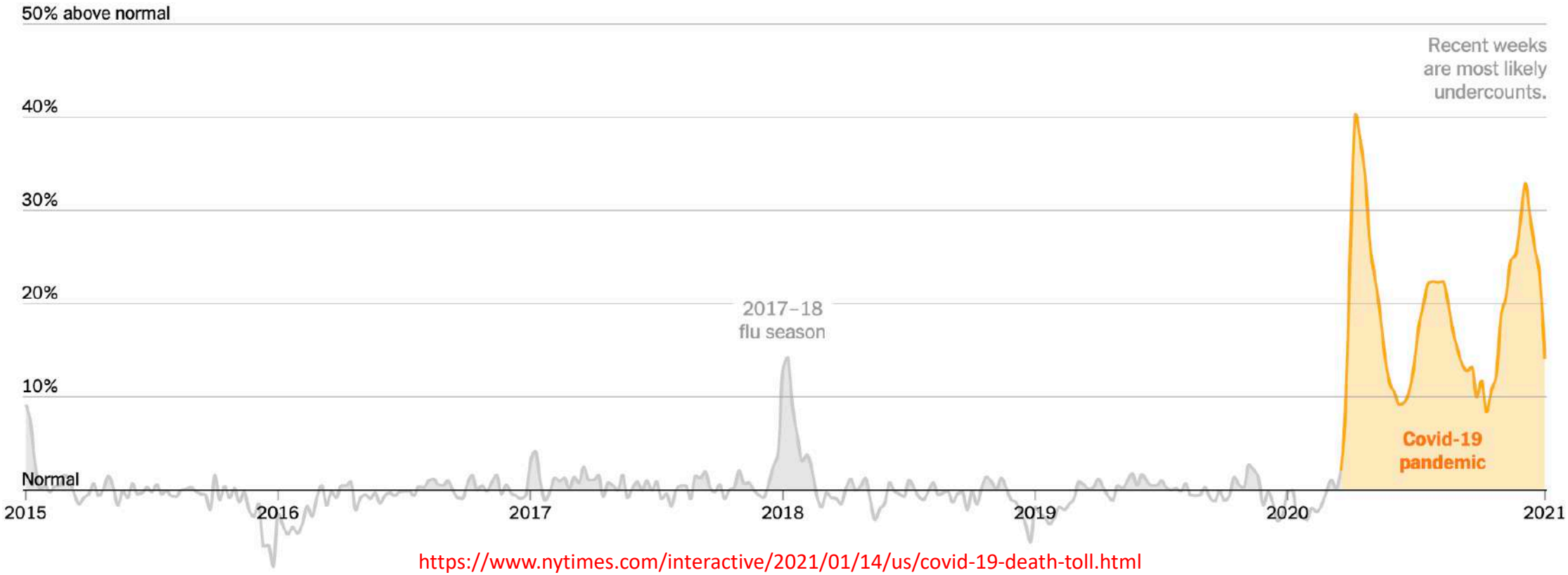
10,000 ○ ● 1,000,000

Double-click to zoom into the map.

446,000 More U.S. Deaths Than Normal Since Covid-19 Struck

By Josh Katz, Denise Lu and Margot Sanger-Katz Updated Jan. 28, 2021

Weekly deaths above and below normal in the U.S. since 2015



https://www.nytimes.com/interactive/2021/01/14/us/covid-19-death-toll.html

CLINICAL ILLNESS

hospitalization-underlying-medical-conditions-lg

OSPITALIZATION RELATED TO UNDERLYING MEDICAL CONDITIONS

FACTORS THAT INCREASE COMMUNITY SPREAD AND INDIVIDUAL RISK


CROWDED SITUATIONS


CLOSE / PHYSICAL CONTACT


ENCLOSED SPACE


DURATION OF EXPOSURE

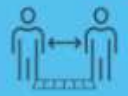
RISK FOR HOSPITALIZATION IF YOU HAVE ANY OF THESE CONDITIONS AND GET COVID-19 COMPARED TO PEOPLE WITHOUT THE CONDITION(S).

*Conditions include asthma, obesity, diabetes, chronic kidney disease, severe obesity, coronary artery disease, history of stroke and COPD.

Data has shown that racial and ethnic minority groups with the referenced conditions are at even higher risk for severe COVID-19 illness. Race and ethnicity are risk markers for other underlying conditions that impact health — including socioeconomic status, access to health care, and increased exposure to the virus due to occupation (e.g., frontline, essential, and critical infrastructure workers).

ACTIONS TO REDUCE RISK OF COVID-19


WEARING A MASK


SOCIAL DISTANCING (6 FT GOAL)


HAND HYGIENE


CLEANING AND DISINFECTION

CDC

ALTHOUGH RISK GENERALLY INCREASES WITH AGE, ALL INDIVIDUALS SHOULD ROUTINELY TAKE ACTIONS TO REDUCE RISK OF INFECTION AND AVOID ACTIVITIES THAT INCREASE COMMUNTY SPREAD.

cdc.gov/coronavirus

Source: Ko JY, Danielson ML, Town M et al. 2020.

CS319360-A 08/08/2020

COVID-19 HOSPITALIZATION AND DEATH BY AGE

FACTORS THAT INCREASE COMMUNITY SPREAD AND INDIVIDUAL RISK


CROWDED SITUATIONS


CLOSE / PHYSICAL CONTACT

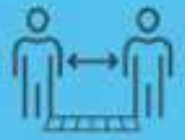

ENCLOSED SPACE


DURATION OF EXPOSURE

Rate ratios compared to 18-29 year olds	0-4 years	5-17 years	18-29 years	30-39 years	40-49 years	50-64 years	65-74 years	75-84 years	85+ years
HOSPITALIZATION[1]	4x lower	9x lower	Comparison Group	2x higher	3x higher	4x higher	5x higher	8x higher	13x higher
DEATH[2]	9x lower	16x lower	Comparison Group	4x higher	10x higher	30x higher	90x higher	220x higher	630x higher

ACTIONS TO REDUCE RISK OF COVID-19


WEARING A MASK


SOCIAL DISTANCING (6 FT GOAL)


HAND HYGIENE


CLEANING AND DISINFECTION

[1] Data source: COVID-NET (https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html, accessed 08/06/20). Numbers are unadjusted rate ratios.

[2] Data source: NCHS Provisional Death Counts (https://www.cdc.gov/nchs/nvss/vsrr/COVID19/index.htm, accessed 08/06/20). Numbers are unadjusted rate ratios.

cdc.gov/coronavirus

CS319360-A 08/10/2020

COVID-19 CASES, HOSPITALIZATION, AND DEATH BY RACE/ETHNICITY

FACTORS THAT INCREASE COMMUNITY SPREAD AND INDIVIDUAL RISK


CROWDED SITUATIONS


CLOSE / PHYSICAL CONTACT


ENCLOSED SPACE

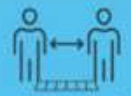

DURATION OF EXPOSURE

Rate ratios compared to White, Non-Hispanic Persons	American Indian or Alaska Native, Non-Hispanic persons	Asian, Non-Hispanic persons	Black or African American, Non-Hispanic persons	Hispanic or Latino persons
CASES[1]	2.8x higher	1.1x higher	2.6x higher	2.8x higher
HOSPITALIZATION[2]	5.3x higher	1.3x higher	4.7x higher	4.6x higher
DEATH[3]	1.4x higher	No Increase	2.1x higher	1.1x higher

Race and ethnicity are risk markers for other underlying conditions that impact health — including socioeconomic status, access to health care, and increased exposure to the virus due to occupation (e.g., frontline, essential, and critical infrastructure workers).

ACTIONS TO REDUCE RISK OF COVID-19


WEARING A MASK


SOCIAL DISTANCING (6 FT GOAL)


HAND HYGIENE


CLEANING AND DISINFECTION

[1] Data source: COVID-19 case-level data reported by state and territorial jurisdictions. Case-level data include about 80% of total reported cases. Numbers are unadjusted rate ratios.

[2] Data source: COVID-NET (https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html, accessed 08/06/20). Numbers are ratios of age-adjusted rates.

[3] Data source: NCHS Provisional Death Counts (https://www.cdc.gov/nchs/nvss/vsrr/COVID19/index.htm, accessed 08/06/20). Numbers are unadjusted rate ratios.

cdc.gov/coronavirus

CS319360-A 08/08/2020

Clinical Course

- Initial symptoms: fever, severe fatigue, headache, anosmia/loss of appetite
- Patients often report development of dry cough/shortness of breath, chest pain
- Profound fatigue and weakness may be present
  Patients may get better and then get worse on days 7-10 (17?)
- On day 10-12, patients may get worse and have increased O2 requirement/intubation
- Patients who are intubated usually require mechanical ventilation for 14 days or more
- 10% will develop secondary infection
- Acute hypoxemic respiratory failure/ARDS is primary reason for ICU admission
- Fever is persistent and may be hectic

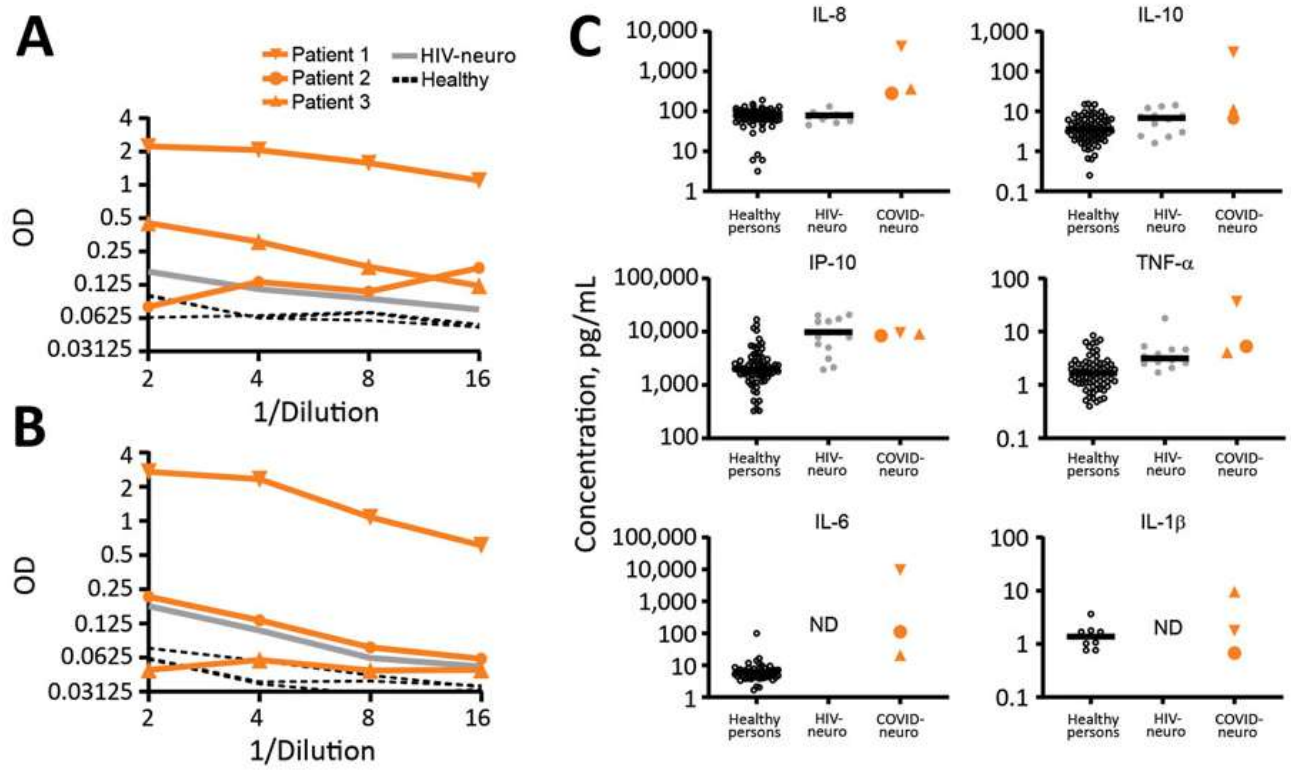
Encephalopathy and Encephalitis Associated with Cerebrospinal Fluid Cytokine Alterations and Coronavirus Disease, Atlanta, Georgia, USA, 2020

Karima Benameur[1]✉, Ankita Agarwal[1], Sara C. Auld, Matthew P. Butters, Andrew S. Webster, Tugba Ozturk, J. Christina Howell, Leda C. Bassit, Alvaro Velasquez, Raymond F. Schinazi, Mark E. Mullins, and William T. Hu

Author affiliations: Emory University School of Medicine, Atlanta, Georgia, USA

Main Article

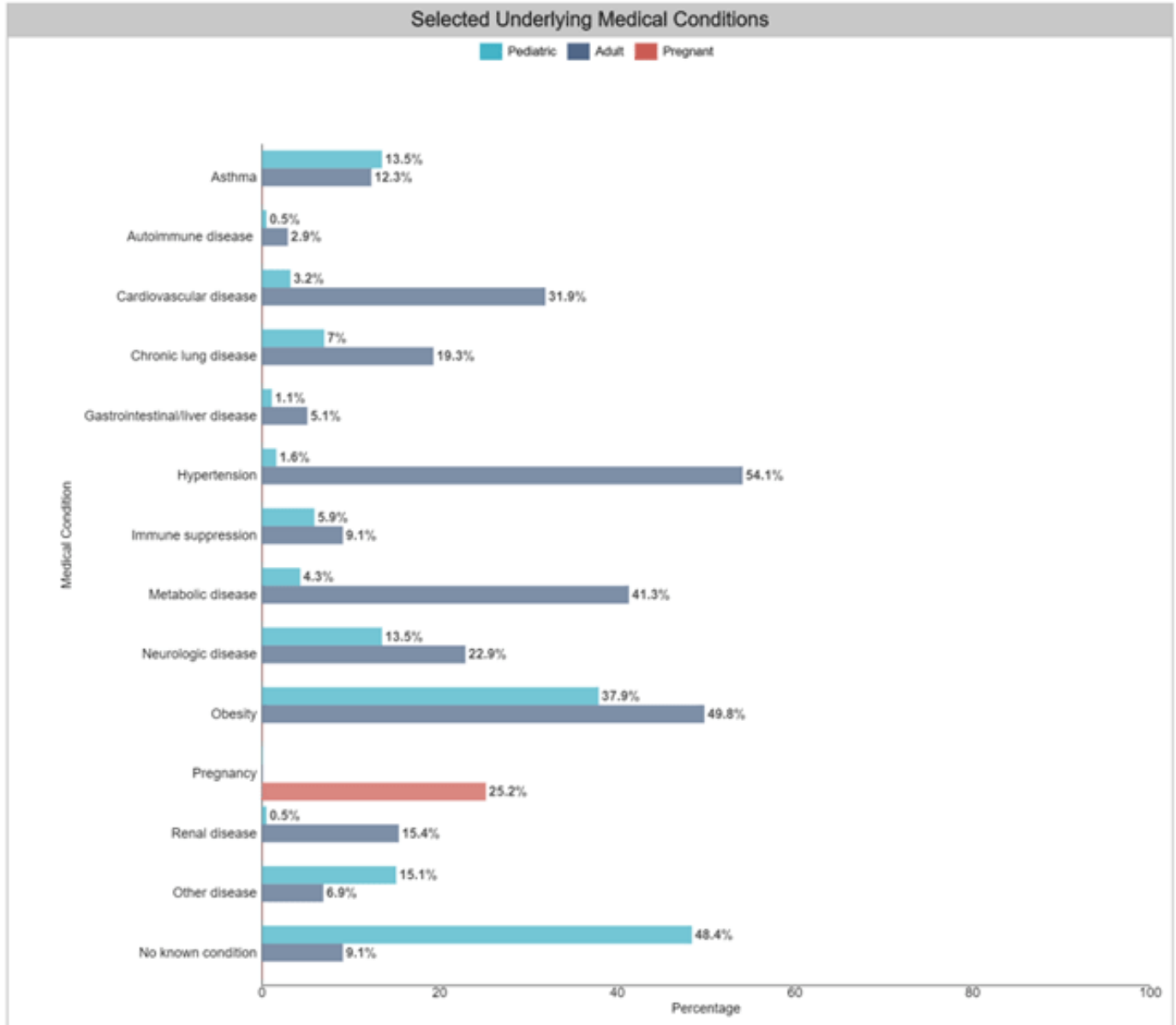
Figure 2



Benameur K, et al. Encephalopathy and encephalitis associated with cerebrospinal fluid cytokine alterations and coronavirus disease, Atlanta, Georgia, USA, 2020. Emerg Infect Dis. 2020 Sep https://doi.org/10.3201/eid2609.202122

COVID-19 Laboratory-Confirmed Hospitalizations

Preliminary data as of Jul 04, 2020



Research Letter

ONLINE FIRST FREE

April 15, 2020

Rates of Co-infection Between SARS-CoV-2 and Other Respiratory Pathogens

David Kim, MD, PhD[1]; James Quinn, MD, MS[1]; Benjamin Pinsky, MD, PhD[2]; et al

» Author Affiliations | Article Information

JAMA. Published online April 15, 2020. doi:10.1001/jama.2020.6266

Table 1. Patient Characteristics and Sites of Specimen Collection, by SARS-CoV-2 and Non–SARS-CoV-2 Pathogen Status

Characteristic	SARS-CoV-2 status, No. (%)			
	Negative (n = 1101)		Positive (n = 116)	
	Positive for other respiratory pathogen	Negative for other respiratory pathogen	Positive for other respiratory pathogen	Negative for other respiratory pathogen
No. of samples	294	807	24	92
No. of patients[a]	292	800	23	92
Age, mean (range), y[b]	35.7 (1-95)	45.7 (1-100)	46.9 (14-74)	51.1 (7-83)
Female, No./total (%)[b]	160/292 (54.8)	439/800 (54.9)	12/23 (52.2)	52/92 (56.5)
Site of specimen collection, No./total (%)[c]				
Outpatient clinic	115/294 (39.1)	347/807 (43.0)	11/24 (45.8)	39/92 (42.4)
Emergency department				
Discharged	122/294 (41.5)	301/807 (37.3)	12/24 (50.0)	38/92 (41.3)
Admitted[d]	28/294 (9.5)	109/807 (13.5)	1/24 (4.2)	15/92 (16.3)
Inpatient	29/294 (9.9)	50/807 (6.2)	0/24	0/92

Ongoing Symptoms

6-month consequences of COVID-19 in patients discharged from hospital: a cohort study

Chaolin Huang*, Lixue Huang*, Yeming Wang*, Xia Li*, Lili Ren*, Xiaoying Gu*, Liang Kang*, Li Guo*, Min Liu*, Xing Zhou, Jianfeng Luo, Zhenghui Huang, Shengjin Tu, Yue Zhao, Li Chen, Decui Xu, Yanping Li, Caihong Li, Lu Peng, Yong Li, Wuxiang Xie, Dan Cui, Lianhan Shang, Guohui Fan, Jiuyang Xu, Geng Wang, Ying Wang, Jingchuan Zhong, Chen Wang, Jianwei Wang†, Dingyu Zhang†, Bin Cao†

Summary

Background The long-term health consequences of COVID-19 remain largely unclear. The aim of this study was to describe the long-term health consequences of patients with COVID-19 who have been discharged from hospital and investigate the associated risk factors, in particular disease severity.

Methods We did an ambidirectional cohort study of patients with confirmed COVID-19 who had been discharged from Jin Yin-tan Hospital (Wuhan, China) between Jan 7, 2020, and May 29, 2020. Patients who died before follow-up, patients for whom follow-up would be difficult because of psychotic disorders, dementia, or re-admission to hospital, those who were unable to move freely due to concomitant osteoarthropathy or immobile before or after discharge due to diseases such as stroke or pulmonary embolism, those who declined to participate, those who could not be contacted, and those living outside of Wuhan or in nursing or welfare homes were all excluded. All patients were interviewed with a series of questionnaires for evaluation of symptoms and health-related quality of life, underwent physical examinations and a 6-min walking test, and received blood tests. A stratified sampling procedure was used to sample patients according to their highest seven-category scale during their hospital stay as 3, 4, and 5–6, to receive pulmonary function test, high resolution CT of the chest, and ultrasonography. Enrolled patients who had participated in the Lopinavir Trial for Suppression of SARS-CoV-2 in China received severe acute respiratory syndrome coronavirus 2 antibody tests. Multivariable adjusted linear or logistic regression models were used to evaluate the association between disease severity and long-term health consequences.

Findings In total, 1733 of 2469 discharged patients with COVID-19 were enrolled after 736 were excluded. Patients had a median age of 57·0 (IQR 47·0–65·0) years and 897 (52%) were men. The follow-up study was done from June 16, to Sept 3, 2020, and the median follow-up time after symptom onset was 186·0 (175·0–199·0) days. Fatigue or muscle weakness (63%, 1038 of 1655) and sleep difficulties (26%, 437 of 1655) were the most common symptoms. Anxiety or depression was reported among 23% (367 of 1617) of patients. The proportions of median 6-min walking distance less than the lower limit of the normal range were 24% for those at severity scale 3, 22% for severity scale 4, and 29% for severity scale 5–6. The corresponding proportions of patients with diffusion impairment were 22% for severity scale 3, 29% for scale 4, and 56% for scale 5–6, and median CT scores were 3·0 (IQR 2·0–5·0) for severity scale 3, 4·0 (3·0–5·0) for scale 4, and 5·0 (4·0–6·0) for scale 5–6. After multivariable adjustment, patients showed an odds ratio (OR) 1·61 (95% CI 0·80–3·25) for scale 4 versus scale 3 and 4·60 (1·85–11·48) for scale 5–6 versus scale 3 for diffusion impairment; OR 0·88 (0·66–1·17) for scale 4 versus scale 3 and OR 1·77 (1·05–2·97) for scale 5–6 versus scale 3 for anxiety or depression, and OR 0·74 (0·58–0·96) for scale 4 versus scale 3 and 2·69 (1·46–4·96) for scale 5–6 versus scale 3 for fatigue or muscle weakness. Of 94 patients with blood antibodies tested at follow-up, the seropositivity (96·2% *vs* 58·5%) and median titres (19·0 *vs* 10·0) of the neutralising antibodies were significantly lower compared with at the acute phase. 107 of 822 participants without acute kidney injury and with estimated glomerular filtration rate (eGFR) 90 mL/min per 1·73 m² or more at acute phase had eGFR less than 90 mL/min per 1·73 m² at follow-up.

Published Online January 8, 2021 https://doi.org/10.1016/S0140-6736(20)32656-8

See Online/Comment https://doi.org/10.1016/S0140-6736(21)00039-8

*Contributed equally

†Contributed equally

Medical Department (C Huang MD, L Kang MD, D Zhang MD), and Department of COVID-19 Re-examination Clinic (X Li MD, X Zhou MD, J Luo MD, Z Huang MD, S Tu MD, Y Zhao MD, L Chen MD, D Xu, MD, Ya Li MD, C Li MS, L Peng MS), Jin Yin-tan Hospital, Wuhan, Hubei, China; Wuhan Research Center for Communicable Disease Diagnosis and Treatment (C Huang, X Li, L Kang, X Zhou, J Luo, Z Huang, S Tu, D Zhang), Chinese Academy of Medical Sciences, Wuhan, Hubei, China; Department of Pulmonary and Critical Care Medicine, National Center for Respiratory Medicine, Center of Respiratory Medicine, National Clinical Research Center for Respiratory Diseases (L Huang MD, Ye Wang MD, X Gu PhD, Yo Li MD, D Cui MD, L Shang MD, G Fan MS, Prof C Wang MD, Prof B Cao MD), Institute of Clinical Medical Sciences (X Gu, G Fan), and Department of Radiology (M Liu MD), China-Japan Friendship Hospital, Beijing, China; Institute of Respiratory Medicine (L Huang, Ye Wang, X Gu, Yo Li, D Cui, L Shang,

- Fatigue or muscle weakness (63%, 1038 of 1655) and sleep difficulties (26%, 437 of 1655) were the most common symptoms.
- Anxiety or depression was reported among 23% (367 of 1617) of patients.
- The proportions of median 6-min walking distance less than the lower limit of the normal range were 24% for those at severity scale 3, 22% for severity scale 4, and 29% for severity scale 5–6, and there were corresponding abnormalities in diffusion.
- Results may be different in U.S. where there is more underlying medical illness

Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): a multicentre cohort study

Brenda T Pun, Rafael Badenes*, Gabriel Heras La Calle, Onur M Orun, Wencong Chen, Rameela Raman, Beata-Gabriela K Simpson, Stephanie Wilson-Linville, Borja Hinojal Olmedillo, Ana Vallejo de la Cueva, Mathieu van der Jagt, Rosalia Navarro Casado, Pilar Leal Sanz, Günseli Orhun, Carolina Ferrer Gómez, Karla Núñez Vázquez, Patricia Piñeiro Otero, Fabio Silvio Taccone, Elena Gallego Curto, Anselmo Caricato, Hilde Woien, Guillaume Lacave, Hallis R O'Neal Jr, Sarah J Peterson, Nathan E Brummel, Timothy D Girard, E Wesley Ely, Pratik P Pandharipande, for the COVID-19 Intensive Care International Study Group†*

Summary

Background To date, 750 000 patients with COVID-19 worldwide have required mechanical ventilation and thus are at high risk of acute brain dysfunction (coma and delirium). We aimed to investigate the prevalence of delirium and coma, and risk factors for delirium in critically ill patients with COVID-19, to aid the development of strategies to mitigate delirium and associated sequelae.

Methods This multicentre cohort study included 69 adult intensive care units (ICUs), across 14 countries. We included all patients (aged ≥18 years) admitted to participating ICUs with severe acute respiratory syndrome coronavirus 2 infection before April 28, 2020. Patients who were moribund or had life-support measures withdrawn within 24 h of ICU admission, prisoners, patients with pre-existing mental illness, neurodegenerative disorders, congenital or acquired brain damage, hepatic coma, drug overdose, suicide attempt, or those who were blind or deaf were excluded. We collected de-identified data from electronic health records on patient demographics, delirium and coma assessments, and management strategies for a 21-day period. Additional data on ventilator support, ICU length of stay, and vital status was collected for a 28-day period. The primary outcome was to determine the prevalence of delirium and coma and to investigate any associated risk factors associated with development of delirium the next day. We also investigated predictors of number of days alive without delirium or coma. These outcomes were investigated using multivariable regression.

Findings Between Jan 20 and April 28, 2020, 4530 patients with COVID-19 were admitted to 69 ICUs, of whom 2088 patients were included in the study cohort. The median age of patients was 64 years (IQR 54 to 71) with a median Simplified Acute Physiology Score (SAPS) II of 40·0 (30·0 to 53·0). 1397 (66·9%) of 2088 patients were invasively mechanically ventilated on the day of ICU admission and 1827 (87·5%) were invasively mechanical ventilated at some point during hospitalisation. Infusion with sedatives while on mechanical ventilation was common: 1337 (64·0%) of 2088 patients were given benzodiazepines for a median of 7·0 days (4·0 to 12·0) and 1481 (70·9%) were given propofol for a median of 7·0 days (4·0 to 11·0). Median Richmond Agitation–Sedation Scale score while on invasive mechanical ventilation was –4 (–5 to –3). 1704 (81·6%) of 2088 patients were comatose for a median of 10·0 days (6·0 to 15·0) and 1147 (54·9%) were delirious for a median of 3·0 days (2·0 to 6·0). Mechanical ventilation, use of restraints, and benzodiazepine, opioid, and vasopressor infusions, and antipsychotics were each associated with a higher risk of delirium the next day (all p≤0·04), whereas family visitation (in person or virtual) was associated with a lower risk of delirium (p<0·0001). During the 21-day study period, patients were alive without delirium or coma for a median of 5·0 days (0·0 to 14·0). At baseline, older age, higher SAPS II scores, male sex, smoking or alcohol abuse, use of vasopressors on day 1, and invasive mechanical ventilation on day 1 were independently associated with fewer days alive and free of delirium and coma (all p<0·01). 601 (28·8%) of 2088 patients died within 28 days of admission, with most of those deaths occurring in the ICU.

Interpretation Acute brain dysfunction was highly prevalent and prolonged in critically ill patients with COVID-19. Benzodiazepine use and lack of family visitation were identified as modifiable risk factors for delirium, and thus these data present an opportunity to reduce acute brain dysfunction in patients with COVID-19.

Lancet Respir Med 2021

Published Online January 8, 2021 https://doi.org/10.1016/S2213-2600(20)30552-X

See Online/Comment https://doi.org/10.1016/S2213-2600(20)30570-1

For the French translation of the abstract see Online for appendix 1

For the Spanish translation of the abstract see Online for appendix 2

*Joint first authors

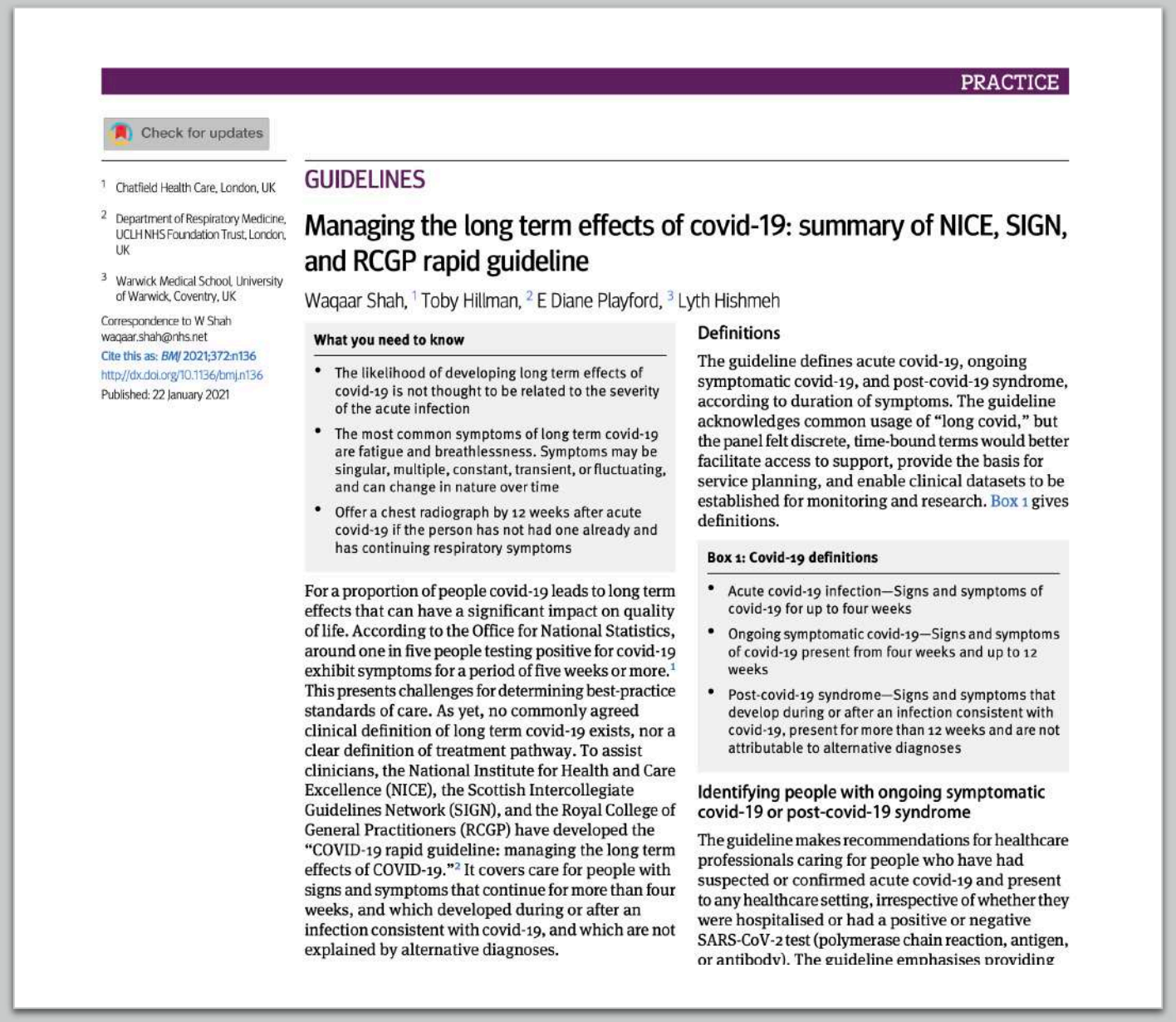
†Members listed in appendix 3

Critical Illness, Brain Dysfunction, and Survivorship Center (B T Pun DNP, O M Orun MS, W Chen PhD, R Raman PhD, B-G K Simpson MPH, S Wilson-Linville BSN, N E Brummel MD, T D Girard MD, Prof E W Ely MD, Prof P P Pandharipande MD), **Center for Health Services Research** (R Raman, Prof E W Ely, Prof P P Pandharipande), **Department of Anesthesiology, Division of Anesthesiology Critical Care Medicine** (Prof P P Pandharipande), **Department of Medicine, Division of Allergy, Pulmonary, and Critical Care Medicine** (B T Pun, B-G K Simpson, S Wilson-Linville, Prof E W Ely), **and Department of Biostatistics** (O M Orun, W Chen, R Raman), **Vanderbilt University Medical Center, Nashville, TN, USA; Geriatric**

- Between Jan 20 and April 28, 2020, 4530 patients with COVID-19 were admitted to 69 ICUs, from 14 countries of whom 2088 patients were included in the study cohort.
- The median age of patients was 64 years
- 67% were invasively mechanically ventilated on the day of ICU admission and 1827 (87·5%) were invasively mechanical ventilated at some point during hospitalisation.
- Infusion with sedatives while on mechanical ventilation was common: 1337 (64·0%) of 2088 patients were given benzodiazepines for a median of 7·0 days (4·0 to 12·0) and 1481 (70·9%) were given propofol for a median of 7·0 days (4·0 to 11·0).
- Mechanical ventilation, use of restraints, and benzodiazepine, opioid, and vasopressor infusions, and antipsychotics were each associated with a higher risk of delirium the next day (all p≤0·04),
- family visitation (in person or virtual) was associated with a lower risk of delirium (p<0·0001).
- During the 21-day study period, patients were alive without delirium or coma for a median of 5·0 days (0·0 to 14·0). At baseline, older age, higher SAPS II scores, male sex, smoking or alcohol abuse, use of vasopressors on day 1, and invasive mechanical ventilation on day 1 were independently associated with fewer days alive and free of delirium and coma (all p<0·01). 601 (28·8%) of 2088 patients died within 28 days of admission, with most of those deaths occurring in the ICU.

Long COVID

- https://www.bmj.com/content/bmj/372/bmj.n136.full.pdf



PRACTICE

Check for updates

1 Chatfield Health Care, London, UK

2 Department of Respiratory Medicine, UCLH NHS Foundation Trust, London, UK

3 Warwick Medical School, University of Warwick, Coventry, UK

Correspondence to W Shah
waqaar.shah@nhs.net

Cite this as: *BMJ* 2021;372:n136
http://dx.doi.org/10.1136/bmj.n136
Published: 22 January 2021

GUIDELINES

Managing the long term effects of covid-19: summary of NICE, SIGN, and RCGP rapid guideline

Waqaar Shah, [1] Toby Hillman, [2] E Diane Playford, [3] Lyth Hishmeh

What you need to know

- The likelihood of developing long term effects of covid-19 is not thought to be related to the severity of the acute infection
- The most common symptoms of long term covid-19 are fatigue and breathlessness. Symptoms may be singular, multiple, constant, transient, or fluctuating, and can change in nature over time
- Offer a chest radiograph by 12 weeks after acute covid-19 if the person has not had one already and has continuing respiratory symptoms

For a proportion of people covid-19 leads to long term effects that can have a significant impact on quality of life. According to the Office for National Statistics, around one in five people testing positive for covid-19 exhibit symptoms for a period of five weeks or more.[1] This presents challenges for determining best-practice standards of care. As yet, no commonly agreed clinical definition of long term covid-19 exists, nor a clear definition of treatment pathway. To assist clinicians, the National Institute for Health and Care Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN), and the Royal College of General Practitioners (RCGP) have developed the "COVID-19 rapid guideline: managing the long term effects of COVID-19."[2] It covers care for people with signs and symptoms that continue for more than four weeks, and which developed during or after an infection consistent with covid-19, and which are not explained by alternative diagnoses.

Definitions

The guideline defines acute covid-19, ongoing symptomatic covid-19, and post-covid-19 syndrome, according to duration of symptoms. The guideline acknowledges common usage of "long covid," but the panel felt discrete, time-bound terms would better facilitate access to support, provide the basis for service planning, and enable clinical datasets to be established for monitoring and research. Box 1 gives definitions.

Box 1: Covid-19 definitions

- Acute covid-19 infection—Signs and symptoms of covid-19 for up to four weeks
- Ongoing symptomatic covid-19—Signs and symptoms of covid-19 present from four weeks and up to 12 weeks
- Post-covid-19 syndrome—Signs and symptoms that develop during or after an infection consistent with covid-19, present for more than 12 weeks and are not attributable to alternative diagnoses

Identifying people with ongoing symptomatic covid-19 or post-covid-19 syndrome

The guideline makes recommendations for healthcare professionals caring for people who have had suspected or confirmed acute covid-19 and present to any healthcare setting, irrespective of whether they were hospitalised or had a positive or negative SARS-CoV-2 test (polymerase chain reaction, antigen, or antibody). The guideline emphasises providing

Annals of Internal Medicine

OBSERVATION: BRIEF RESEARCH REPORT

COVID-19 Symptoms: Longitudinal Evolution and Persistence in Outpatient Settings

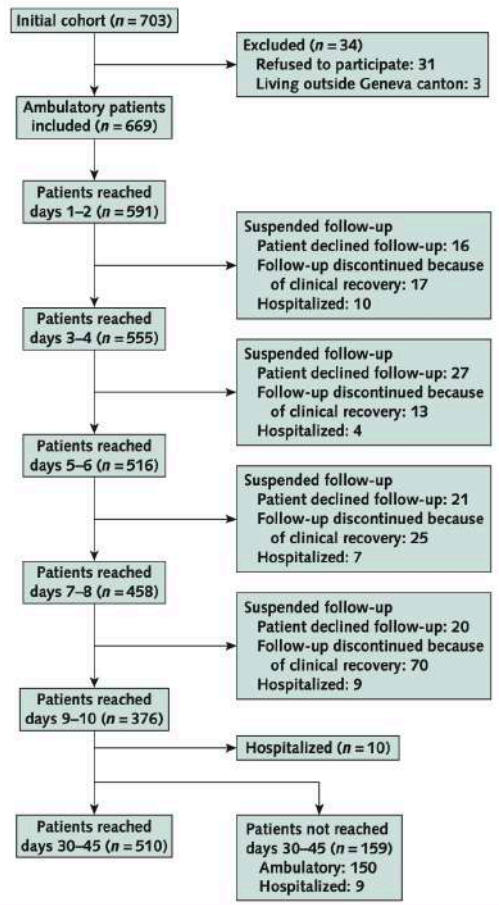
Background: Coronavirus disease 2019 (COVID-19) has spread, causing a worldwide pandemic, and prolonged effects are emerging (1,2). The term "long COVID" describes illness in persons who continue to report lasting effects after infection (3,4). To date, little information exists about outpatient settings in this novel disease where 81% of cases are reportedly on the mild end of the spectrum (5). Informing patients and physicians about COVID-19 symptom evolution may help them recognize the time course of the disease, legitimize patients' concerns, and reassure them when possible. Messages around potentially persisting symptoms could also assist in reinforcing public health measures to avoid the spread of infection.

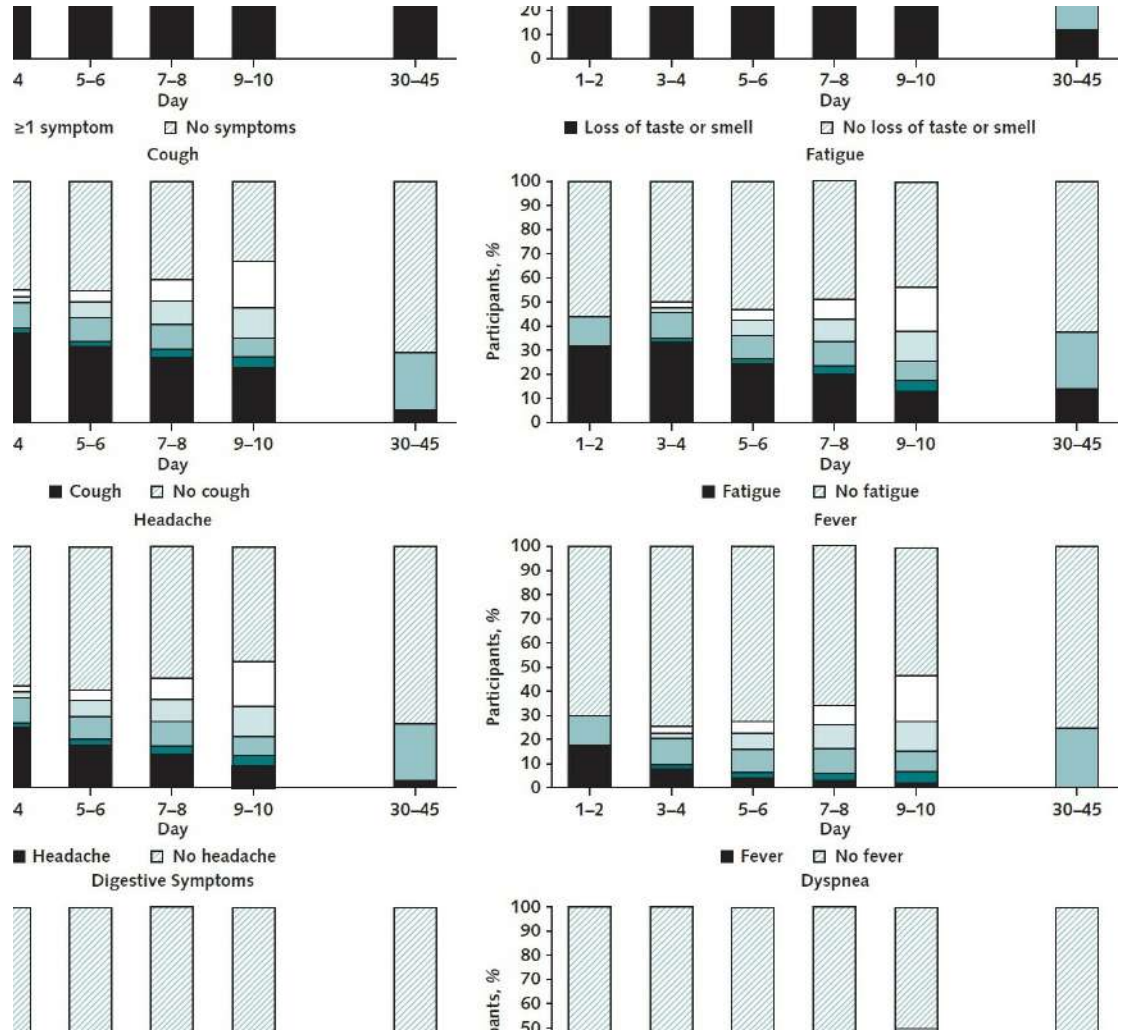
Objective: To describe COVID-19 symptom evolution and persistence in an outpatient setting in Geneva, Switzerland, from day 1 through day 30 to 45 after diagnosis.

Methods: From 18 March to 15 May 2020, the Geneva University Hospitals (sole and largest public hospital in Geneva) was 1 of 5 available testing centers and served more than 50% of patients with COVID-19 in the Geneva canton. Only symptomatic persons were tested during that period. Because many practices were closed, persons who were not hospitalized at baseline could benefit from remote follow-up with an ambulatory care center (a process called COVICARE) in case their primary care physician was unavailable for follow-up care (a full description is available atwww.covicare24.com). Exclusion criteria were refusal to provide consent and administrative reasons (living outside the Geneva canton).

Most patients were called every 48 hours for the first 10 days with a standardized interview inquiring about self-reported symptoms (**Supplement**, available at Annals.org). Follow-up during the 10 days was suspended if patients declined follow-up, clinically recovered, or were hospitalized (**Figure 1**). Participants were called every 24 hours if they reported deteriorating clinical symptoms; those who were

Figure 1. Study flow diagram.





https://www.acpjournals.org/doi/10.7326/M20-5926

Diagnostic Testing

Types of Tests for SARS-CoV-2

- RT-PCR-based tests
  - NP, OP, nasal, saliva
- Antigen tests
- Antibody tests
- Viral culture (not available except through special labs)

Rapid Antigen Testing for SARS-CoV-2

- Antigen tests are immunoassays that detect presence of a specific viral antigen, which implies current viral infection.
- Antigen tests are currently authorized to be performed on nasopharyngeal or nasal swab specimens
- No age restrictions
- Antigen tests are relatively inexpensive and can be used at the point-of-care.
- Currently authorized devices return results in approximately 15 minutes and are generally less expensive than PCR
- Rapid antigen tests perform best in early stages of infection with SARS-CoV-2 when viral load is highest.
- They also may be useful in diagnostic testing situations in which the person has a known exposure to a confirmed case of COVID-19

Table 2. Summary of Some Differences between RT-PCR Tests and Antigen Tests

	RT-PCR Tests	Antigen Tests
Intended Use	Detect current infection	Detect current infection
Analyte Detected	Viral RNA	Viral Antigens
Specimen Type(s)	Nasal Swab, Sputum, Saliva	Nasal Swab
Sensitivity	High	Moderate
Specificity	High	High
Test Complexity	Varies	Relatively easy to use
Authorized for Use at the Point-of-Care	Most devices are not, some devices are	Yes
Turnaround Time	Ranges from 15 minutes to >2 days	Approximately 15 minutes
Cost/Test	Moderate	Low

Table 3. Relationship between pre-test probability and the likelihood of positive and negative predictive values

Pretest Probability*	Negative Predictive Value**	Positive Predictive Value**	Impact on Test Results
Low	High	Low	Increased likelihood of False Positives Increased likelihood of True Negatives
High	Low	High	Increased likelihood of True Positives Increased likelihood of False Negatives

*Sensitivity and specificity of tests are generally stable and not affected by pretest probability.

**Predictive values are affected by pretest probability.

Antigen Test Recommendations

- Currently, the two rapid antigen tests that have received EUAs from FDA are limited to ***diagnostic testing*** on symptomatic persons within the first five days of symptom onset
- CDC recommends confirming negative antigen test results with an RT-PCR test when the pretest probability is relatively high, especially if the patient is symptomatic or has a known exposure to a person confirmed to have COVID-19.
- When used for ***screening testing*** in congregate settings, test results for SARS-CoV-2 should be considered presumptive. Confirmatory nucleic acid testing following a ***positive*** antigen test may not be necessary when the pretest probability is high, especially if the person is symptomatic or has a known exposure. When the pretest probability is low, those persons who receive a positive antigen test should isolate until they can be confirmed by RT-PCR.

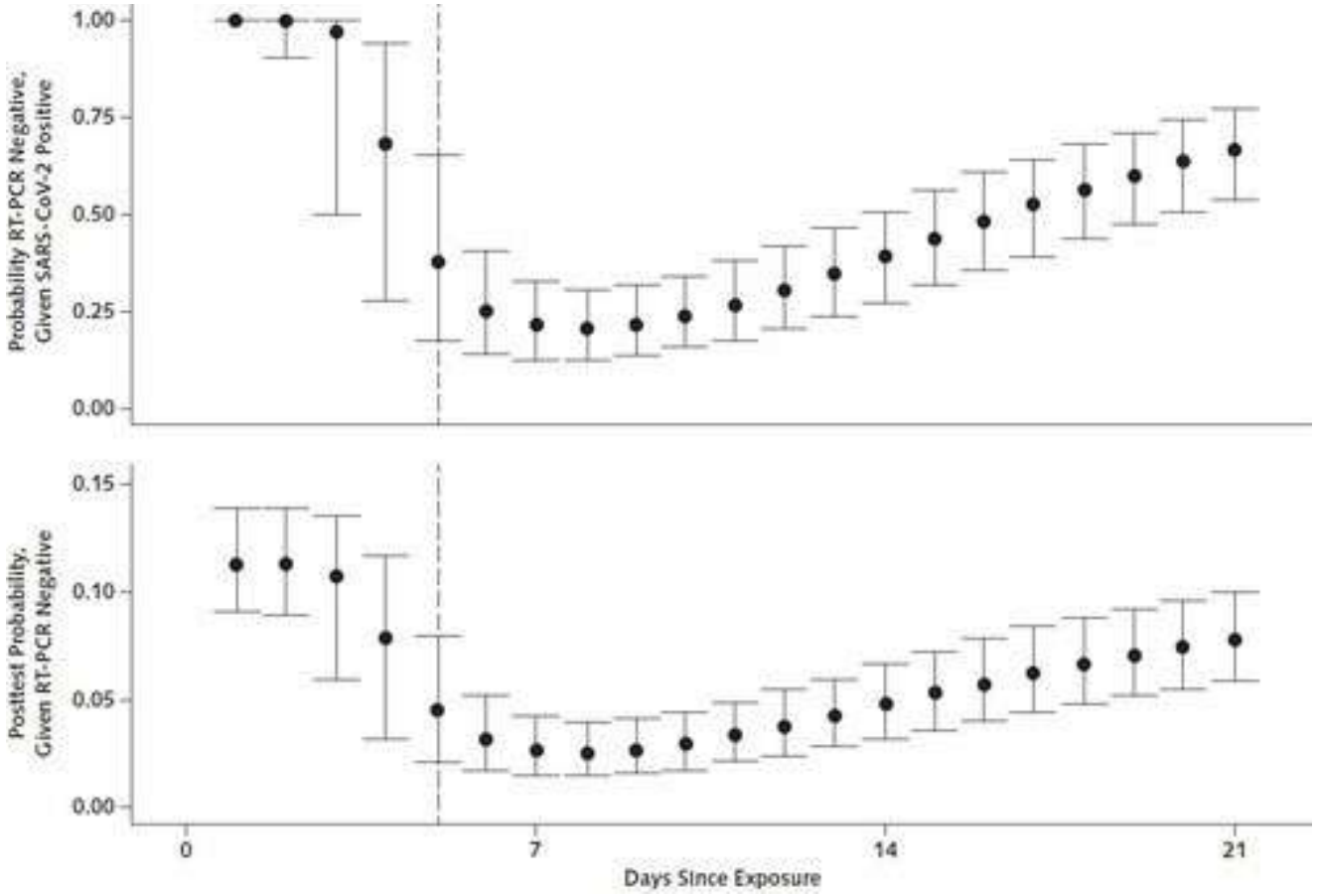
Antigen Testing for SARS COV-2

- The “gold standard” for clinical diagnostic detection of SARS-CoV-2 remains RT-PCR.
- It may be necessary to confirm a rapid antigen test result with PCR, especially if the result of the antigen test is inconsistent with the clinical context. When confirming an antigen test result with a RT-PCR test, it is important that the time interval between the two sample collections is less than two days, and there have not been any opportunities for new exposures between the two tests.
- If more than two days separates the two tests, or there have been opportunities for new exposures between the two tests, the nucleic acid test should be considered a separate test.
- The sensitivity of rapid antigen tests is generally lower than RT-PCR. The first two antigen tests that have received FDA EUAs demonstrate sensitivity of 84% and 97% compared to RT-PCR.
- Studies have shown that antigen levels in some patients who have been symptomatic for > five days may drop below the limit of detection of the test. This may result in a negative test result, while a more sensitive test, such as RT-PCR, may return a positive result.

Variation in False-Negative Rate of Reverse Transcriptase Polymerase Chain Reaction–Based SARS-CoV-2 Tests by Time Since Exposure

Over the 4 days of infection before the typical time of symptom onset (day 5), the probability of a false-negative result in an infected person decreases from 100% (95% CI, 100% to 100%) on day 1 to 67% (CI, 27% to 94%) on day 4. On the day of symptom onset, the median false-negative rate was 38% (CI, 18% to 65%). This decreased to 20% (CI, 12% to 30%) on day 8 (3 days after symptom onset) then began to increase again, from 21% (CI, 13% to 31%) on day 9 to 66% (CI, 54% to 77%) on day 21.

Annals of Internal Medicine®



https://doi.org/10.7326/M20-1495

Annals of Internal Medicine

Prevalence of Asymptomatic SARS-CoV-2 Infection

A Narrative Review

Daniel P. Oran, AM, and Eric J. Topol, MD

Table. Summary of SARS-CoV-2 Testing Studies

Cohort	Tested, *n*	SARS-CoV-2 Positive, *n* (%)	Positive but Asymptomatic, *n* (%)	Notes*
Iceland residents (6)	13 080	100 (0.8)	43 (43.0)	R
Vo', Italy, residents (7)	5155	102 (2.0)	43 (42.2)	R, L
Diamond Princess cruise ship passengers and crew (8)	3711	712 (19.2)	331 (46.5)	–
Boston homeless shelter occupants (9)	408	147 (36.0)	129 (87.8)	–
New York City obstetric patients (11)	214	33 (15.4)	29 (87.9)	L
U.S.S. *Theodore Roosevelt* aircraft carrier crew (12)	4954	856 (17.3)	~500 (58.4)	E
Japanese citizens evacuated from Wuhan, China (2)	565	13 (2.3)	4 (30.8)	L
Greek citizens evacuated from the United Kingdom, Spain, and Turkey (14)†	783	40 (5.1)	35 (87.5)	L
Charles de Gaulle aircraft carrier crew (13)	1760	1046 (59.4)	~500 (47.8)	E
Los Angeles homeless shelter occupants (10)	178	43 (24.2)	27 (62.8)	–
King County, Washington, nursing facility residents (15)	76	48 (63.2)	3 (6.3)	L
Arkansas, North Carolina, Ohio, and Virginia inmates (16)	4693	3277 (69.8)	3146 (96.0)	–
New Jersey university and hospital employees (17)	829	41 (4.9)	27 (65.9)	–
Indiana residents (18)	4611	78 (1.7)	35 (44.8)	R
Argentine cruise ship passengers and crew (19)	217	128 (59.0)	104 (81.3)	–
San Francisco residents (29)	4160	74 (1.8)	39 (52.7)	–

E = estimated from incomplete source data; L = longitudinal data collected; R = representative sample.
* A dash indicates that the study did not have a representative sample, collected no longitudinal data, and did not require estimation of missing data.
† Clarified via e-mail communication with coauthor.

How does SARS-CoV-2 spread?

The airborne lifetime of small speech droplets and their potential importance in SARS-CoV-2 transmission

Valentyn Stadnytskyi[a], Christina E. Bax[b], Adriaan Bax[a,1], and Philip Anfinrud[a,1]

[a]Laboratory of Chemical Physics, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD 20892-0520; and [b]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104

Edited by Axel T. Brunger, Stanford University, Stanford, CA, and approved May 4, 2020 (received for review April 10, 2020)

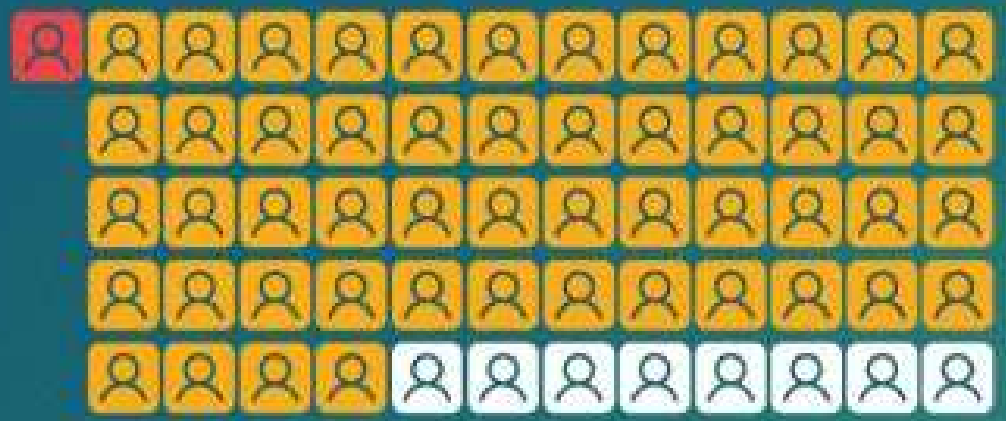
Speech droplets generated by asymptomatic carriers of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are increasingly considered to be a likely mode of disease transmission. Highly sensitive laser light scattering observations have revealed that loud speech can emit thousands of oral fluid droplets per second. In a closed, stagnant air environment, they disappear from the window of view with time constants in the range of 8 to 14 min, which corresponds to droplet nuclei of *ca.* 4 μm diameter, or 12- to 21-μm droplets prior to dehydration. These observations confirm that there is a substantial probability that normal speaking causes airborne virus transmission in confined environments.

COVID-19 | speech droplet | independent action hypothesis | respiratory disease | disease transmission

The amount by which a droplet shrinks upon dehydration depends on the fraction of nonvolatile matter in the oral fluid, which includes electrolytes, sugars, enzymes, DNA, and remnants of dehydrated epithelial and white blood cells. Whereas pure saliva contains 99.5% water when exiting the salivary glands, the weight fraction of nonvolatile matter in oral fluid falls in the 1 to 5% range. Presumably, this wide range results from differential degrees of dehydration of the oral cavity during normal breathing and speaking and from decreased salivary gland activity with age. Given a nonvolatile weight fraction in the 1 to 5% range and an assumed density of 1.3 $g \cdot mL^{-1}$ for that fraction, dehydration causes the diameter of an emitted droplet to shrink to about 20 to 34% of its original size, thereby slowing down the speed at which it falls (1, 13). For example, if a droplet

https://www.pnas.org/content/pnas/early/2020/05/12/2006874117.full.pdf

After choir practice with one symptomatic person, 87% of group developed COVID-19

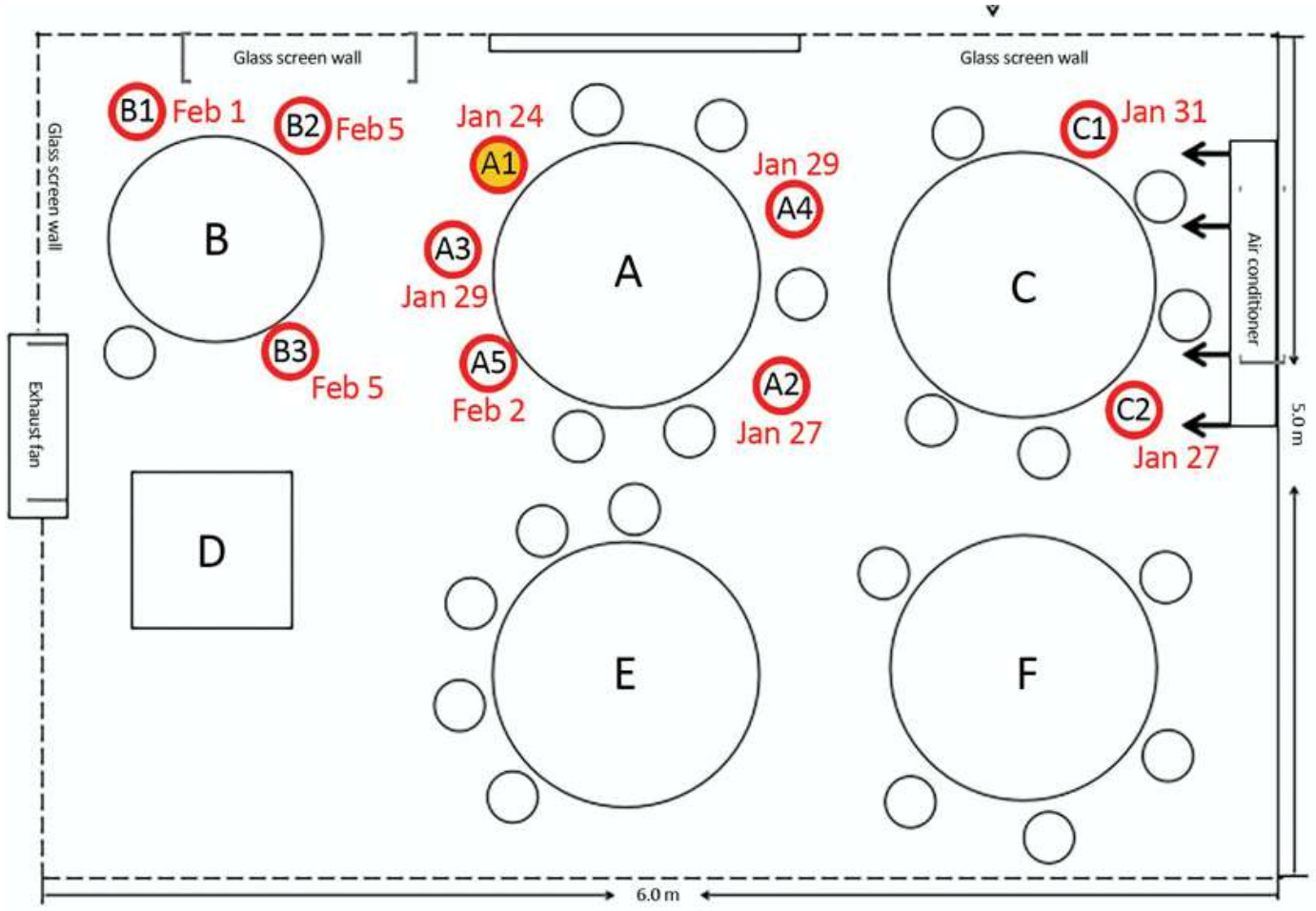


Index case · 32 confirmed and 20 probable cases · unaffected person

COVID-19 spreads easily

- Avoid groups
- Stay at least 6 feet apart
- Wear face coverings

CDC.GOV bit.ly/MMWR51220 MMWR



Authors Conclusion:
Virus transmission in this outbreak cannot be explained by droplet transmission alone. Larger respiratory droplets (>5 μm) remain in the air for only a short time and travel only short distances, generally <1 m (2,3). The distances between patient A1 and persons at other tables, especially those at table C, were all >1 m. However, strong airflow from the air conditioner could have propagated droplets from table C to table A, then to table B, and then back to table C (Figure).

Lu J, Gu J, Li K, Xu C, Su W, Lai Z, et al. COVID-19 outbreak associated with air conditioning in restaurant, Guangzhou, China, 2020. Emerg Infect Dis. 2020 Jul [*date cited*]. https://doi.org/10.3201/eid2607.200764

Wellcome Open Research

Wellcome Open Research 2020, 5:83 Last updated: 11 JUN 2020

Check for updates

RESEARCH ARTICLE

REVISED What settings have been linked to SARS-CoV-2 transmission clusters? [version 2; peer review: 1 approved]

Quentin J. Leclerc [1,2], Naomi M. Fuller [1,2], Lisa E. Knight[3], CMMID COVID-19 Working Group, Sebastian Funk [1,2], Gwenan M. Knight [1,2]

[1]Department of Infectious Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, UK
[2]Centre for Mathematical Modelling of Infectious Diseases, London School of Hygiene & Tropical Medicine, London, UK
[3]GP registrar, Brecon Surgery, Gwent Deanery, UK

v2 **First published:** 01 May 2020, **5**:83
https://doi.org/10.12688/wellcomeopenres.15889.1
Latest published: 05 Jun 2020, **5**:83
https://doi.org/10.12688/wellcomeopenres.15889.2

Abstract

Background: Concern about the health impact of novel coronavirus SARS-CoV-2 has resulted in widespread enforced reductions in people's movement ("lockdowns"). However, there are increasing concerns about the severe economic and wider societal consequences of these measures. Some countries have begun to lift some of the rules on physical distancing in a stepwise manner, with differences in what these "exit strategies" entail and their timeframes. The aim of this work was to inform such exit strategies by exploring the types of indoor and outdoor settings where transmission of SARS-CoV-2 has been reported to occur and result in clusters of cases. Identifying potential settings that result in transmission clusters allows these to be kept under close surveillance and/or to remain closed as part of strategies that aim to avoid a resurgence in transmission following the lifting of lockdown measures.
Methods: We performed a systematic review of available literature and media reports to find settings reported in peer reviewed articles and media with these characteristics. These sources are curated and made available in an editable online database.

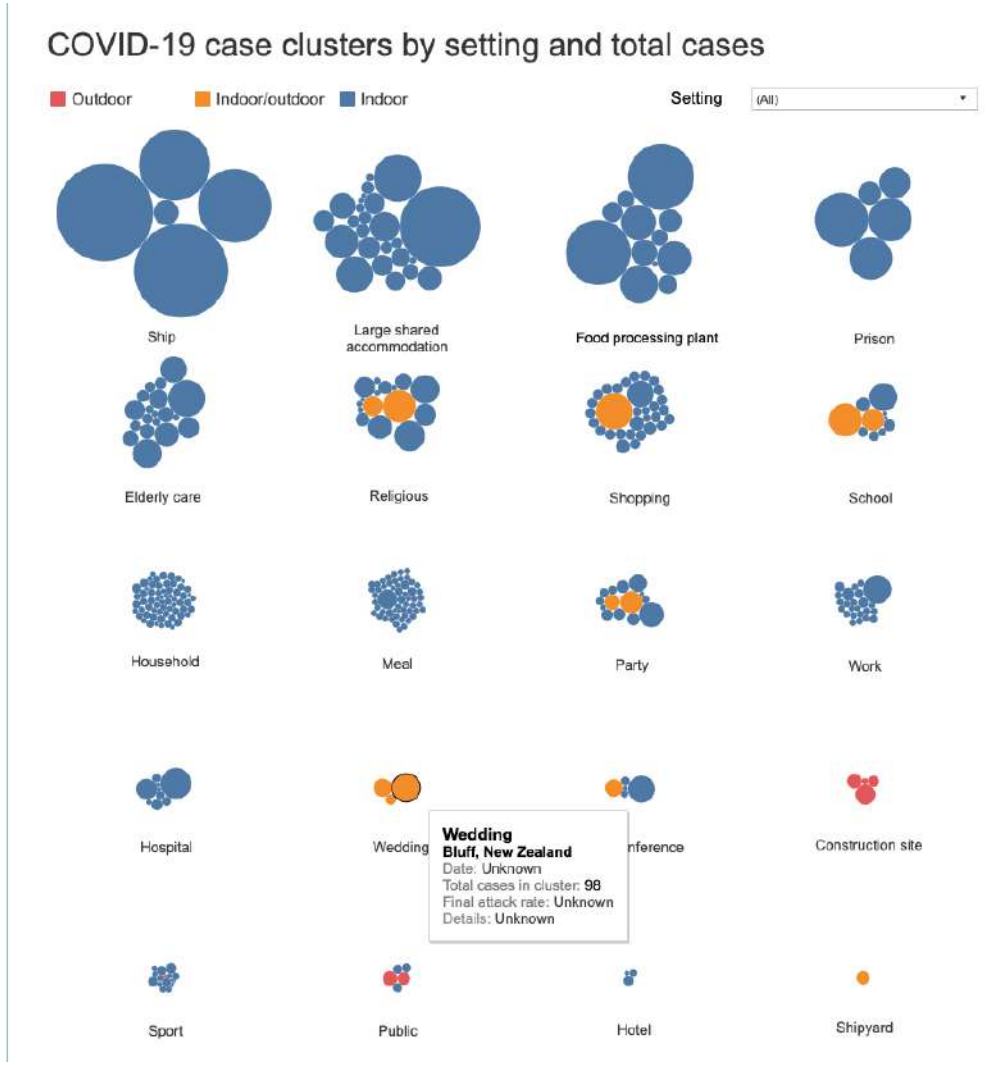
Open Peer Review

Reviewer Status ✔

	Invited Reviewers
	1
version 2 (revision) 05 Jun 2020	✔ report
version 1 01 May 2020	? report

1 **Joël Mossong**, Laboratoire National de Santé, Dudelange, Luxembourg

Any reports and responses or comments on the article can be found at the end of the article.



Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis

*Derek K Chu, Elie A Akl, Stephanie Duda, Karla Solo, Sally Yaacoub, Holger J Schünemann, on behalf of the COVID-19 Systematic Urgent Review Group Effort (SURGE) study authors**

Summary

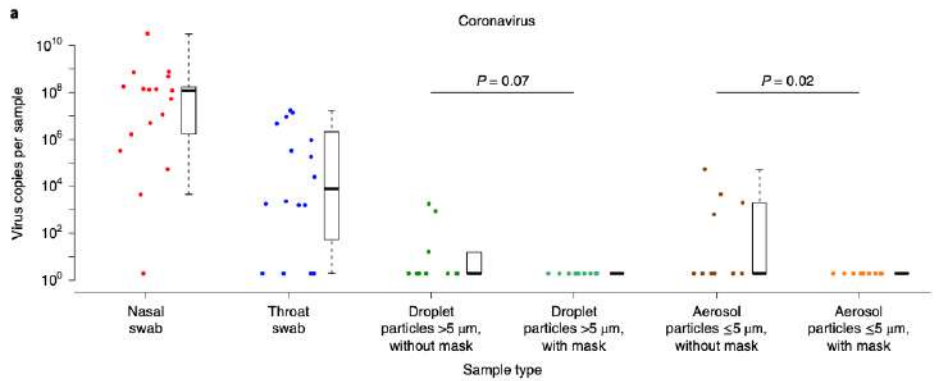
Background Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes COVID-19 and is spread person-to-person through close contact. We aimed to investigate the effects of physical distance, face masks, and eye protection on virus transmission in health-care and non-health-care (eg, community) settings.

Methods We did a systematic review and meta-analysis to investigate the optimum distance for avoiding person-to-person virus transmission and to assess the use of face masks and eye protection to prevent transmission of viruses. We obtained data for SARS-CoV-2 and the betacoronaviruses that cause severe acute respiratory syndrome, and

Published Online
June 1, 2020
https://doi.org/10.1016/S0140-6736(20)31142-9

See Online/Comment
https://doi.org/10.1016/S0140-6736(20)31183-1

*Study authors are listed in the



nature medicine

BRIEF COMMUNICATION

https://doi.org/10.1038/s41591-020-0843-2

Check for updates

Respiratory virus shedding in exhaled breath and efficacy of face masks

Nancy H. L. Leung[1], Daniel K. W. Chu[1], Eunice Y. C. Shiu[1], Kwok-Hung Chan[2], James J. McDevitt[3], Benien J. P. Hau[1,4], Hui-Ling Yen[1], Yuguo Li[5], Dennis K. M. Ip[1], J. S. Malik Peiris[1], Wing-Hong Seto[1,6], Gabriel M. Leung[1], Donald K. Milton[7,8] and Benjamin J. Cowling[1,8] ✉

We identified seasonal human coronaviruses, influenza viruses and rhinoviruses in exhaled breath and coughs of children and adults with acute respiratory illness. Surgical face masks significantly reduced detection of influenza virus RNA in respiratory droplets and coronavirus RNA in aerosols, with a trend toward reduced detection of coronavirus RNA in respiratory droplets. Our results indicate that surgical face masks could prevent transmission of human coronaviruses and influenza viruses from symptomatic individuals.

Respiratory virus infections cause a broad and overlapping spectrum of symptoms collectively referred to as acute respiratory virus illnesses (ARIs) or more commonly the 'common cold'. Although mostly mild, these ARIs can sometimes cause severe disease and medically attended ARIs and determining the potential efficacy of surgical face masks to prevent respiratory virus transmission.

Results

We screened 3,363 individuals in two study phases, ultimately enrolling 246 individuals who provided exhaled breath samples (Extended Data Fig. 1). Among these 246 participants, 122 (50%) participants were randomized to not wearing a face mask during the first exhaled breath collection and 124 (50%) participants were randomized to wearing a face mask. Overall, 49 (20%) voluntarily provided a second exhaled breath collection of the alternate type.

Infections by at least one respiratory virus were confirmed by reverse transcription PCR (RT–PCR) in 123 of 246 (50%) partici-

JAMA Network Open

Original Investigation | Infectious Diseases

Association of Social Distancing, Population Density, and Temperature With the Instantaneous Reproduction Number of SARS-CoV-2 in Counties Across the United States

David Rubin, MD, MSCE; Jing Huang, PhD; Brian T. Fisher, DO, MPH, MSCE; Antonio Gasparrini, PhD, MSc; Vicky Tam, MA; Lihai Song, MS; Xi Wang, PhD; Jason Kaufman, MSt; Kate Fitzpatrick, BS; Arushi Jain, BS; Heather Griffis, PhD, MS; Koby Crammer, PhD; Jeffrey Morris, PhD; Gregory Tasian, MD, MSc, MSCE

Abstract

IMPORTANCE Local variation in the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) across the United States has not been well studied.

OBJECTIVE To examine the association of county-level factors with variation in the SARS-CoV-2 reproduction number over time.

DESIGN, SETTING, AND PARTICIPANTS This cohort study included 211 counties, representing state capitals and cities with at least 100 000 residents and including 178 892 208 US residents, in 46 states and the District of Columbia between February 25, 2020, and April 23, 2020.

EXPOSURES Social distancing, measured by percentage change in visits to nonessential businesses; population density; and daily wet-bulb temperatures.

MAIN OUTCOMES AND MEASURES Instantaneous reproduction number (R_t), or cases generated by each incident case at a given time, estimated from daily case incidence data.

RESULTS The 211 counties contained 178 892 208 of 326 289 971 US residents (54.8%). Median (interquartile range) population density was 1022.7 (471.2-1846.0) people per square mile. The mean (SD) peak reduction in visits to nonessential business between April 6 and April 19, as the country was sheltering in place, was 68.7% (7.9%). Median (interquartile range) daily wet-bulb temperatures were 7.5 (3.8-12.8) °C. Median (interquartile range) case incidence and fatality rates per 100 000 people were approximately 10 times higher for the top decile of densely populated counties (1185.2 [313.2-1891.2] cases; 43.7 [10.4-106.7] deaths) than for counties in the lowest density quartile (121.4 [87.8-175.4] cases; 4.2 [1.9-8.0] deaths). Mean (SD) R_t in the first 2 weeks was 5.7 (2.5) in the top decile compared with 3.1 (1.2) in the lowest quartile. In multivariable analysis, a 50% decrease in visits to nonessential businesses was associated with a 45% decrease in R_t (95% CI, 43%-49%). From a relative R_t at 0 °C of 2.13 (95% CI, 1.89-2.40), relative R_t decreased to a minimum as temperatures warmed to 11 °C, increased between 11 and 20 °C (1.61; 95% CI, 1.42-1.84) and then declined again at temperatures greater than 20 °C. With a 70% reduction in visits to nonessential business, 202 counties (95.7%) were estimated to fall below a threshold R_t of 1.0, including 17 of 21 counties (81.0%) in the top density decile and 52 of 53 counties (98.1%) in the lowest density quartile.[2]

Key Points

Question How is the instantaneous reproduction number of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) associated with social distancing, wet-bulb temperature, and population density in counties across the United States?

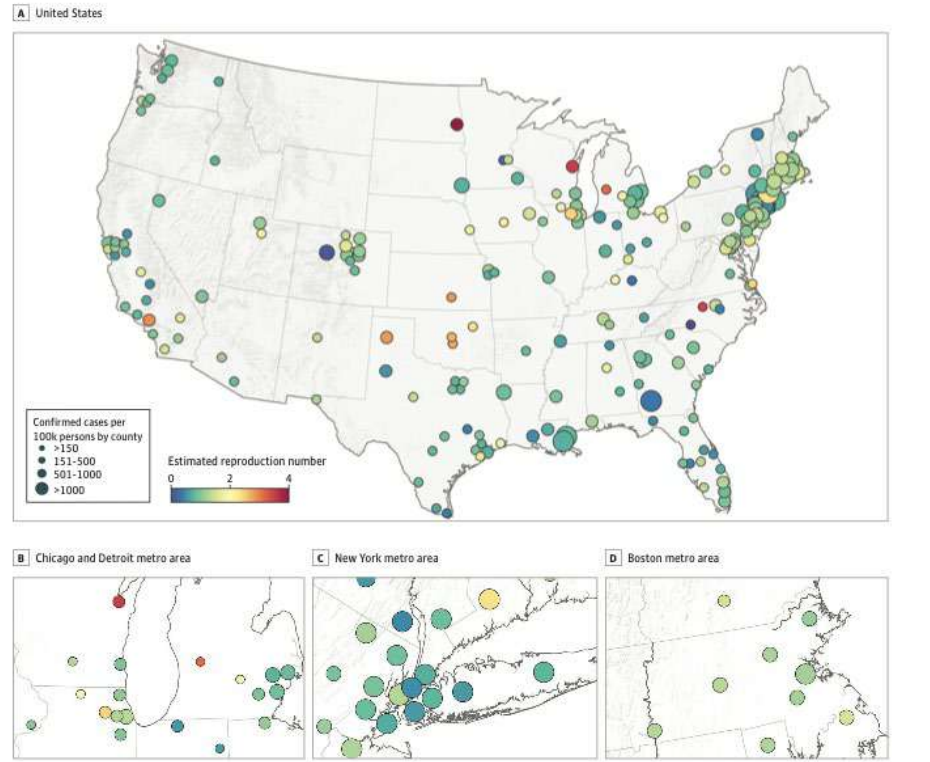
Findings In this cohort study of 211 counties in 46 states, social distancing, temperate weather, and lower population density were associated with a decrease in the instantaneous reproduction number of SARS-CoV-2. Of these county-specific factors, social distancing appeared to have the most substantial association with a reduction in SARS-CoV-2 transmission.

Meaning In this study, the instantaneous reproduction number of SARS-CoV-2 varied substantially among counties; the associations between the reproduction number and county-specific factors could inform policies to reduce SARS-CoV-2 transmission in selective and heterogeneous communities.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Figure 1. Location and Estimated Instantaneous Reproduction Number of Severe Acute Respiratory Syndrome Coronavirus 2 as of April 26, 2020, in 211 Counties in the United States



When is SARS-CoV-2 most contagious?

JAMA Internal Medicine | Original Investigation

Contact Tracing Assessment of COVID-19 Transmission Dynamics in Taiwan and Risk at Different Exposure Periods Before and After Symptom Onset

Hao-Yuan Cheng, MD, MSc; Shu-Wan Jian, DVM, MPH; Ding-Ping Liu, PhD; Ta-Chou Ng, BSc; Wan-Ting Huang, MD; Hsien-Ho Lin, MD, ScD; for the Taiwan COVID-19 Outbreak Investigation Team

IMPORTANCE The dynamics of coronavirus disease 2019 (COVID-19) transmissibility are yet to be fully understood. Better understanding of the transmission dynamics is important for the development and evaluation of effective control policies.

OBJECTIVE To delineate the transmission dynamics of COVID-19 and evaluate the transmission risk at different exposure window periods before and after symptom onset.

DESIGN, SETTING, AND PARTICIPANTS This prospective case-ascertained study in Taiwan included laboratory-confirmed cases of COVID-19 and their contacts. The study period was from January 15 to March 18, 2020. All close contacts were quarantined at home for 14 days after their last exposure to the index case. During the quarantine period, any relevant symptoms (fever, cough, or other respiratory symptoms) of contacts triggered a COVID-19 test. The final follow-up date was April 2, 2020.

MAIN OUTCOMES AND MEASURES Secondary clinical attack rate (considering symptomatic cases only) for different exposure time windows of the index cases and for different exposure settings (such as household, family, and health care).

RESULTS We enrolled 100 confirmed patients, with a median age of 44 years (range, 11-88 years), including 56 men and 44 women. Among their 2761 close contacts, there were 22 paired index-secondary cases. The overall secondary clinical attack rate was 0.7% (95% CI, 0.4%-1.0%). The attack rate was higher among the 1818 contacts whose exposure to index cases started within 5 days of symptom onset (1.0% [95% CI, 0.6%-1.6%]) compared with those who were exposed later (0 cases from 852 contacts; 95% CI, 0%-0.4%). The 299 contacts with exclusive presymptomatic exposures were also at risk (attack rate, 0.7% [95% CI, 0.2%-2.4%]). The attack rate was higher among household (4.6% [95% CI, 2.3%-9.3%]) and nonhousehold (5.3% [95% CI, 2.1%-12.8%]) family contacts than that in health care or other settings. The attack rates were higher among those aged 40 to 59 years (1.1% [95% CI, 0.6%-2.1%]) and those aged 60 years and older (0.9% [95% CI, 0.3%-2.6%]).

CONCLUSIONS AND RELEVANCE In this study, high transmissibility of COVID-19 before and

Medications/Treatments

Overview of COVID-19 Treatment Guidelines (Summary Table)

Overview of IDSA COVID-19 Treatment Guidelines

Version 3.5.1 – December 2, 2020

		Setting and severity of illness			
		Ambulatory care: *mild-to-moderate disease*	***Hospitalized:*** *mild-to-moderate disease without need for suppl. oxygen*	***Hospitalized:*** *severe but non-critical disease (spO_2 <94% on room air)*	***Hospitalized:*** *critical disease (e.g., in ICU needing MV, or septic shock, ECMO)*
1	*Hydroxy-chloroquine (HCQ)**	NA	**Recommend against use** ⊕⊕⊕◯	**Recommend against use** ⊕⊕⊕◯	**Recommend against use** ⊕⊕⊕◯
2	*HCQ* + azithromycin*	NA	**Recommend against use** ⊕⊕◯◯	**Recommend against use** ⊕⊕◯◯	**Recommend against use** ⊕⊕◯◯
3	*Lopinavir + ritonavir*	NA	**Recommend against use** ⊕⊕⊕◯	**Recommend against use** ⊕⊕⊕◯	**Recommend against use** ⊕⊕⊕◯
4-6	*Corticosteroids*	NA	**Suggest against use** ⊕◯◯◯	**Suggest use** ⊕⊕⊕◯ R: If dexamethasone is unavailable, equivalent total daily doses of alternative glucocorticoids may be used.**	**Recommend use** ⊕⊕⊕◯ R: If dexamethasone is unavailable, equivalent total daily doses of alternative glucocorticoids may be used.**
7	*Tocilizumab*	NA	**Suggest against routine use** ⊕⊕◯◯	**Suggest against routine use** ⊕⊕◯◯	**Suggest against routine use** ⊕⊕◯◯
8	*Convalescent plasma*	NA	Recommended only in the context of a clinical trial (knowledge gap)	Recommended only in the context of a clinical trial (knowledge gap)	Recommended only in the context of a clinical trial (knowledge gap)
9-11	*Remdesivir*	NA	**Suggest against routine use** ⊕◯◯◯	**Suggest use** ⊕⊕◯◯ R: In patients on mechanical ventilation or ECMO, the duration of treatment is 10 days.	**Suggest use** ⊕⊕⊕◯ R: For consideration in contingency or crisis capacity settings (i.e., limited remdesivir supply): Remdesivir appears to demonstrate the most benefit in those with severe COVID-19 on supplemental oxygen rather than in patients on mechanical ventilation or ECMO.
12	*Famotidine*	NA	**Suggests against use except in a clinical trial** ⊕◯◯◯	**Suggests against use except in a clinical trial** ⊕◯◯◯	**Suggests against use except in a clinical trial** ⊕◯◯◯
13	*Bamlanivimab*	**Suggest against routine use** ⊕◯◯◯ R: In patients at increased risk*** bamlanivimab is a reasonable treatment option if, after informed decision-making, the patient puts a high value on the uncertain benefits and a low value on uncertain adverse events.	NA	NA	NA

https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

- Per Paul Sax:
- My take-home view? The clinical trials data for ivermectin look stronger than they ever did for hydroxychloroquine, but we're not quite yet at the "practice changing" level. Results from at least 5 randomized clinical trials are expected soon that might further inform the decision. NIH treatment guidelines **still recommend against use of ivermectin for treatment of COVID-19,** a recommendation I support pending further data — we shouldn't have to wait long.

NEJM Journal Watch

Renew | Subscribe | MY ACCOUNT

SPECIALTIES & TOPICS | NEWS | BLOGS | CME | SPECIAL FEATURES | ARCHIVE/PDFs

HIV and ID Observations

An ongoing dialogue on HIV/AIDS, infectious diseases, all matters medical, and some not so medical.

January 4th, 2021

Ivermectin for COVID-19 — Breakthrough Treatment or Hydroxychloroquine Redux?

It's an indisputable fact that we need better treatments for COVID-19.

This is particularly true in the outpatient setting. Let's count how many we have today, hmm, this shouldn't take long. That would be *zero* — the same number we had over a year ago, when the disease first emerged in China.

Something safe, easy to take as a pill, and inexpensive. Something that isn't a **costly bioengineered molecule** that requires lengthy infusions, given within a short time after diagnosis, to a highly contagious person.

Enter ivermectin — and let the controversy begin.

Yes, ivermectin — the drug licensed for use against strongyloides and other parasites, and probably best known to primary providers for its off-label use for scabies and head lice, and for pet owners as a common de-worming agent.

Sulphur-crested Cockatoo. Anonymous, ca. 1600.

Of course upon hearing about this "repurposed" antiparasitic drug, many will develop a weary feeling of déjà vu.

Didn't we make this mistake with hydroxychloroquine? Wasn't excess enthusiasm for this treatment a dismal chapter in our clinical and research approach to this new disease? Enthusiasm that led to wasteful, duplicative clinical trials, flawed observational studies, and irrational prescribing with arguably more harm than benefit? Harms that included not just side effects, but also drug shortages and pointless stockpiling?

Yes to all of the above.

Note that the harm done by the hydroxychloroquine controversy continues to this day. I know investigators who led well-done, fully powered clinical trials with negative results who were, and continue to be, viciously attacked in emails and on social media. Accusations typically charge that they succumbed to pressure from big

Paul E. Sax, MD

Contributing Editor

NEJM JOURNAL WATCH INFECTIOUS DISEASES

Biography | Disclosures | Summaries

Learn more about *HIV and ID Observations*.

FREE PDF COLLECTION

Guideline Watch 2020

ACCESS NOW →

ADVERTISEMENT

MOST READ | MOST COMMENTED

Ivermectin for COVID-19 — Breakthrough Treatment or Hydroxychloroquine Redux?

Bamlanivimab for COVID-19 — Hard to Pronounce, Even Harder to Give

Common Questions About the Shingles Vaccine — Answered Here!

Brush with Greatness — Rochelle Walensky to Head CDC

With Vaccine Rollout, a Mixture of Gratitude, Envy, and Cautious Hope

Stay Informed with Quick, Concise, Evidence-Based Information

INCLUDES FULL ACCESS TO PDF ARCHIVE

The COVID-19 Treatment Guidelines Panel's Statement on the Use of Ivermectin for the Treatment of COVID-19

Last Updated: January 14, 2021

Recommendation

- The COVID-19 Treatment Guidelines Panel (the Panel) has determined that currently there are insufficient data to recommend either for or against the use of ivermectin for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin for the treatment of COVID-19.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults

R. Libster, G. Pérez Marc, D. Wappner, S. Coviello, A. Bianchi, V. Braem, I. Esteban, M.T. Caballero, C. Wood, M. Berrueta, A. Rondan, G. Lescano, P. Cruz, Y. Ritou, V. Fernández Viña, D. Álvarez Paggi, S. Esperante, A. Ferreti, G. Ofman, Á. Ciganda, R. Rodriguez, J. Lantos, R. Valentini, N. Itcovici, A. Hintze, M.L. Oyarvide, C. Etchegaray, A. Neira, I. Name, J. Alfonso, R. López Castelo, G. Caruso, S. Rapelius, F. Alvez, F. Etchenique, F. Dimase, D. Alvarez, S.S. Aranda, C. Sánchez Yanotti, J. De Luca, S. Jares Baglivo, S. Laudanno, F. Nowogrodzki, R. Larrea, M. Silveyra, G. Leberzstein, A. Debonis, J. Molinos, M. González, E. Perez, N. Kreplak, S. Pastor Argüello, L. Gibbons, F. Althabe, E. Bergel, and F.P. Polack, for the Fundación INFANT–COVID-19 Group*

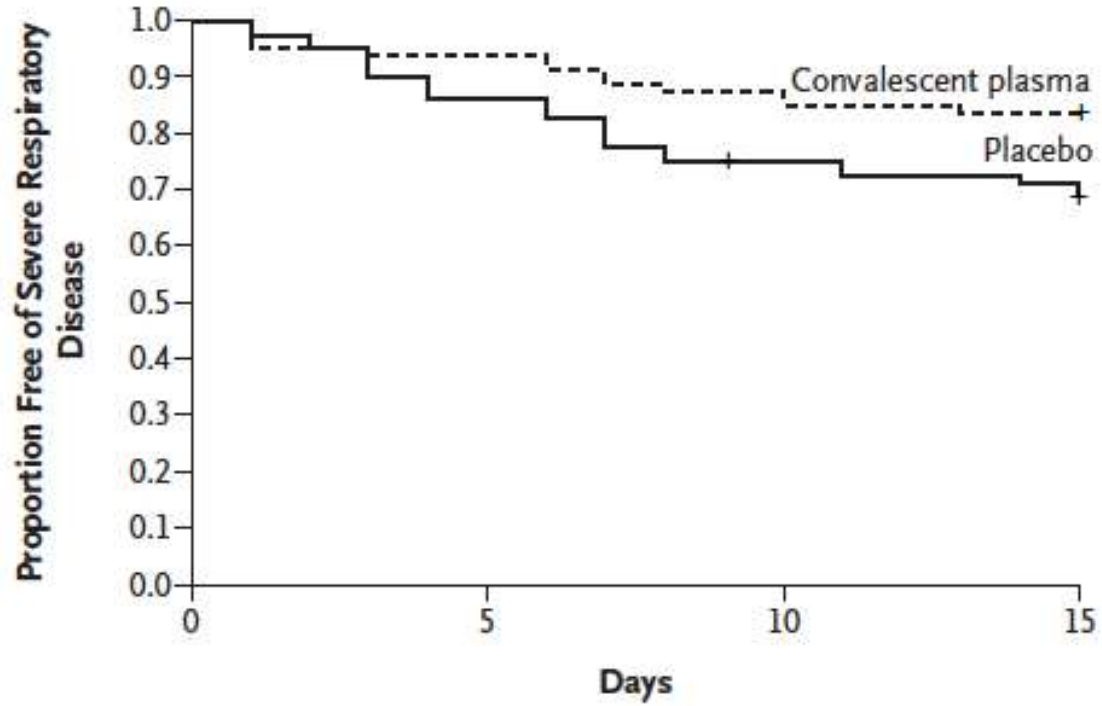


Figure 1. Time to the Development of Severe Respiratory Disease Due to Coronavirus Disease 2019, According to Trial Group in the Intention-to-Treat Analysis.

Shown are Kaplan–Meier estimates of the time from the intervention (administration of convalescent plasma or placebo) to the development of severe respiratory disease. The tick marks on the curves represent the interquartile range in the Kaplan–Meier time-to-event analysis in the convalescent plasma and placebo groups.

Table 2. Trial End Points in the Intention-to-Treat Population.*

End Point	Convalescent Plasma (N=80)	Placebo (N=80)	Relative Risk (95% CI)
	no./total no. (%)		
Primary end point: severe respiratory disease	13/80 (16)	25/80 (31)	0.52 (0.29–0.94)
Secondary end points			
Life-threatening respiratory disease	4/80 (5)	10/80 (12)	0.40 (0.13–1.22)
Oxygen supplementation at an F_{IO_2} of 100%	4/80 (5)	6/80 (8)	0.67 (0.20–2.27)
Noninvasive ventilation	1/80 (1)	6/80 (8)	0.17 (0.02–1.35)
Admission to intensive care unit	2/80 (2)	6/80 (8)	0.33 (0.07–1.60)
Mechanical ventilation	2/80 (2)	4/80 (5)	0.50 (0.09–2.65)
Critical systemic illness	5/80 (6)	6/80 (8)	0.83 (0.27–2.62)
Acute respiratory failure	2/80 (2)	5/80 (6)	0.40 (0.08–2.00)
Shock	2/80 (2)	1/80 (1)	2.00 (0.19–21.6)
Multiple organ dysfunction syndrome	3/80 (4)	5/80 (6)	0.60 (0.15–2.43)
Death from Covid-19	2/80 (2)	4/80 (5)	0.50 (0.09–2.65)
Life-threatening respiratory disease, critical systemic illness, or death, alone or in combination	7/80 (9)	12/80 (15)	0.58 (0.24–1.41)

* CI denotes confidence interval, and F_{IO_2} fraction of inspired oxygen.

Medical News & Perspectives | QUICK UPTAKES

Sorting Out Whether Vitamin D Deficiency Raises COVID-19 Risk

Rita Rubin, MA

One of the risk factors du jour for coronavirus disease 2019 (COVID-19) has been vitamin D deficiency.

Even Anthony Fauci, MD, has said he takes a vitamin D supplement. Vitamin D "does have an impact on your susceptibility to infection," Fauci, director of the National Institute of Allergy and Infectious Diseases, told actress Jennifer Garner in a September interview. "I would not mind recommending—and I take it myself—taking vitamin D supplements."

Most people get some vitamin D from sunlight exposure, although individuals in the US get the nutrient mainly from fortified foods, such as milk, orange juice, and breakfast cereals.

At higher latitudes, people with more melanin content in their skin have lower blood levels of vitamin D because their skin doesn't produce as much in response to sunlight. A recent article in the *Journal of the National Medical Association* speculated that vitamin D deficiency "is likely a significant factor" behind disproportionately high COVID-19 cases and deaths among US Black and Latino populations.

An analysis of data from 4962 participants in the National Health and Nutrition Examination Survey found that 1981 (39.92%) were vitamin D deficient, defined as a blood level lower than 20 ng/mL (<50 nmol/L). Vitamin D deficiency was greater in certain subpopulations of screening in asymptomatic adults for any reason.

"Vitamin D might be helpful in that there is evidence it can attenuate immune responses," which could prevent the "cytokine storms" seen in some patients with COVID-19, A. Catharine Ross, PhD, chair of nutrition sciences at Penn State, wrote in an email. "On the other hand, attenuation might not be beneficial in terms of helping the antibody response."

Mixed Signals

Research findings about vitamin D and COVID-19 have been mixed *and* sparse:

- A study of 77 frail elderly patients hospitalized with COVID-19 in France con

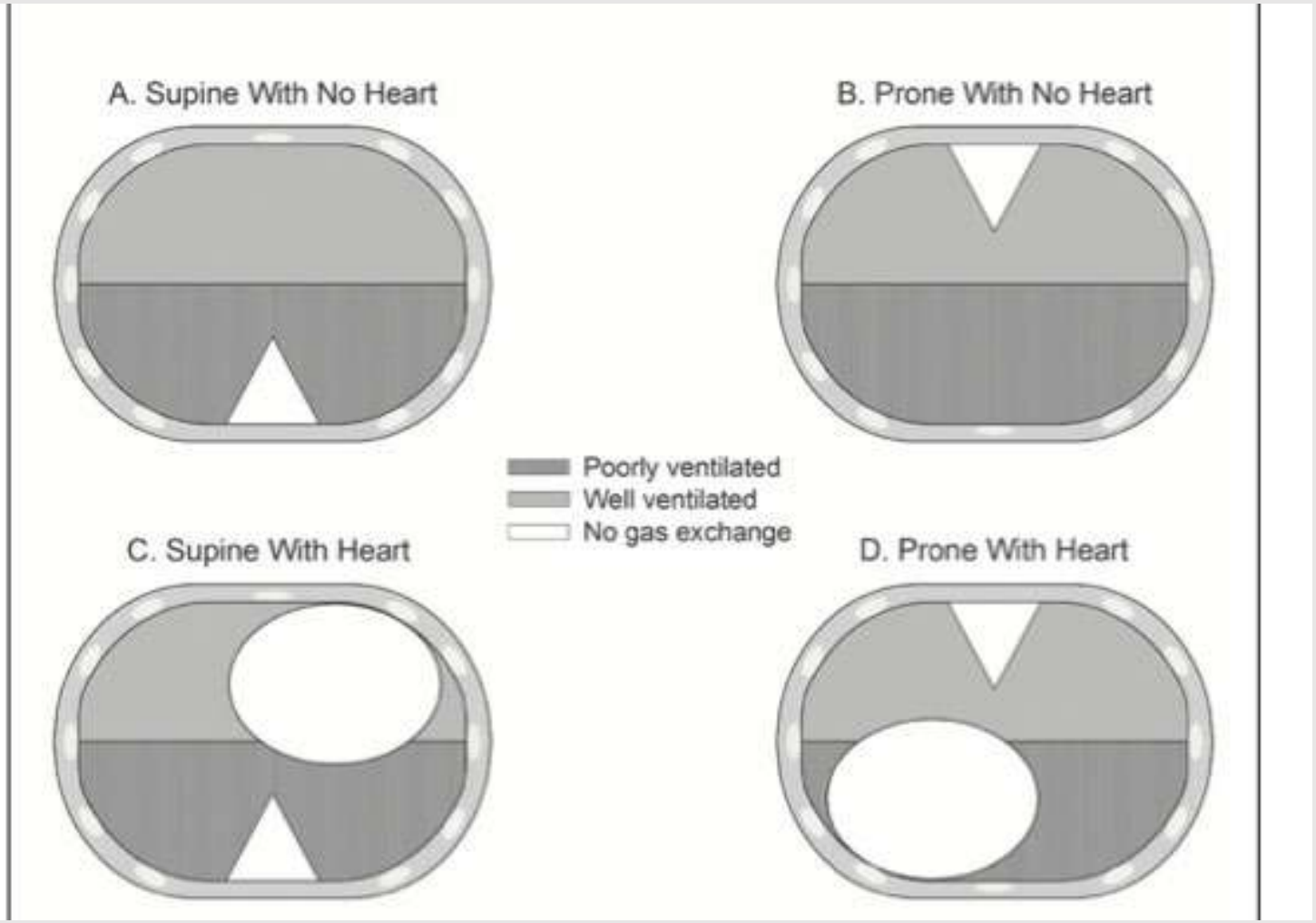
journal the same day as their study, the researchers in Italy concluded that poor vitamin D status appears to be linked to an increased risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, but age, sex, and comorbidities seem to play a more important role in COVID-19 severity and mortality. Nine days later, a different group of Italian researchers published an observational study of 324 patients with COVID-19 that found taking vitamin D supplements was not linked to risk of hospitalization but was associated with a higher risk of dying if hospitalized.

- A recent study in *JAMA Network Open* by University of Chicago researchers linked vitamin D deficiency with a greater likelihood of testing positive for SARS-CoV-2. However, an earlier study of UK Biobank participants found no such connection. The Chicago researchers noted that vitamin D levels examined in the UK study predated COVID-19 diagnoses by at least a decade, so they could have changed by the time SARS-CoV-2 testing took place.

Behind the Headlines

Some of the evidence about vitamin D and COVID-19 doesn't pass the smell test, according to a July letter to the editor of the *British Journal of Nutrition*.

https://jamanetwork.com/journals/jama/fullarticle/2775003?resultClick=1



Can Respir J Vol 21 No 4 July/August 2014

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4173887/pdf/crj-21-4-213.pdf

Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19

16 June 2020

Statement from the Chief Investigators of the Randomised Evaluation of COVid-19 thERapY (RECOVERY) Trial on dexamethasone, 16 June 2020

Dexamethasone

- In March 2020, the RECOVERY (Randomised Evaluation of COVid-19 thERapY) trial was established as a randomised clinical trial to test a range of potential treatments for COVID-19, including low-dose dexamethasone (a steroid treatment). Over 11,500 patients have been enrolled from over 175 NHS hospitals in the UK.
- On 8 June, recruitment to the dexamethasone arm was halted since, in the view of the trial Steering Committee, sufficient patients had been enrolled to establish whether or not the drug had a meaningful benefit.
- A total of 2104 patients were randomised to receive dexamethasone 6 mg once per day (either by mouth or by intravenous injection) for ten days and were compared with 4321 patients randomised to usual care alone. Among the patients who received usual care alone, 28-day mortality was highest in those who required ventilation (41%), intermediate in those patients who required oxygen only (25%), and lowest among those who did not require any respiratory intervention (13%).
- Dexamethasone reduced deaths by one-third in ventilated patients (rate ratio 0.65 [95% confidence interval 0.48 to 0.88]; p=0.0003) and by one fifth in other patients receiving oxygen only (0.80 [0.67 to 0.96]; p=0.0021). There was no benefit among those patients who did not require respiratory support (1.22 [0.86 to 1.75]; p=0.14).
- Based on these results, 1 death would be prevented by treatment of around 8 ventilated patients or around 25 patients requiring oxygen alone.
- Given the public health importance of these results, we are now working to publish the full details as soon as possible.

https://www.recoverytrial.net/news/low-cost-dexamethasone-reduces-death-by-up-to-one-third-in-hospitalised-patients-with-severe-respiratory-complications-of-covid-19

ORIGINAL ARTICLE

Remdesivir for the Treatment of Covid-19 — Preliminary Report

J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, and H.C. Lane, for the ACTT-1 Study Group Members*

ABSTRACT

BACKGROUND

Although several therapeutic agents have been evaluated for the treatment of coronavirus disease 2019 (Covid-19), none have yet been shown to be efficacious.

METHODS

We conducted a double-blind, randomized, placebo-controlled trial of intravenous remdesivir in adults hospitalized with Covid-19 with evidence of lower respiratory tract involvement. Patients were randomly assigned to receive either remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days) or placebo for up to 10 days. The primary outcome was the time to recovery, defined by either discharge from the hospital or hospitalization for infection-control purposes only.

RESULTS

A total of 1063 patients underwent randomization. The data and safety monitoring board recommended early unblinding of the results on the basis of findings from an analysis that showed shortened time to recovery in the remdesivir group. Preliminary results from the 1059 patients (538 assigned to remdesivir and 521 to placebo) with data available after randomization indicated that those who received remdesivir had a median recovery time of 11 days (95% confidence interval [CI], 9 to 12), as compared with 15 days (95% CI, 13 to 19) in those who received placebo (rate ratio for recovery, 1.32; 95% CI, 1.12 to 1.55; P<0.001). The Kaplan-Meier estimates of mortality by 14 days were 7.1% with remdesivir and 11.9% with placebo (hazard ratio for death, 0.70; 95% CI, 0.47 to 1.04). Serious adverse events were reported for 114 of the 541 patients in the remdesivir group who underwent randomization (21.1%) and 141 of the 522 patients in the placebo group who underwent randomization (27.0%).

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Beigel at the National Institute of Allergy and Infectious Diseases, National Institutes of Health, 5601 Fishers Ln., Rm. 7E60, MSC 9826, Rockville, MD 20892-9826, or at jbeigel@niaid.nih.gov.

*A complete list of members of the ACTT-1 Study Group is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on May 22, 2020, at NEJM.org.

DOI: 10.1056/NEJMoa2007764

Remdesivir

- Shortened time to clinical improvement by 4 days
- Patients improved in terms of oxygen requirements
- No statistically significant difference in mortality rate

INTERNATIONAL JOURNAL OF INFECTIOUS DISEASES

INTERNATIONAL SOCIETY FOR INFECTIOUS DISEASES

FULL LENGTH ARTICLE | ARTICLES IN PRESS

Treatment with Hydroxychloroquine, Azithromycin, and Combination in Patients Hospitalized with COVID-19

Samia Arshad • Paul Kilgore • Zohra S. Chaudhry • ... William O'Neill • Marcus Zervos

Again, Hydroxychloroquine

- Observational study of patients admitted to Henry Ford System between March-May
- Patient were given HCQ, Azithromycin., Both or Neither
- 2541 patient hospitalized, Median age 64
- Overall in-hospital mortality was 18.1%
- Mortality by treatment: hydroxychloroquine + azithromycin, 157/783 20.1%
- hydroxychloroquine alone, 162/1202 13.5%
- azithromycin alone, 33/147 22.4%
- and neither drug, 108/409 26.4%
- Hydroxychloroquine provided a 66% hazard ratio reduction, and hydroxychloroquine + azithromycin 71% compared to neither treatment ($p < 0.001$).

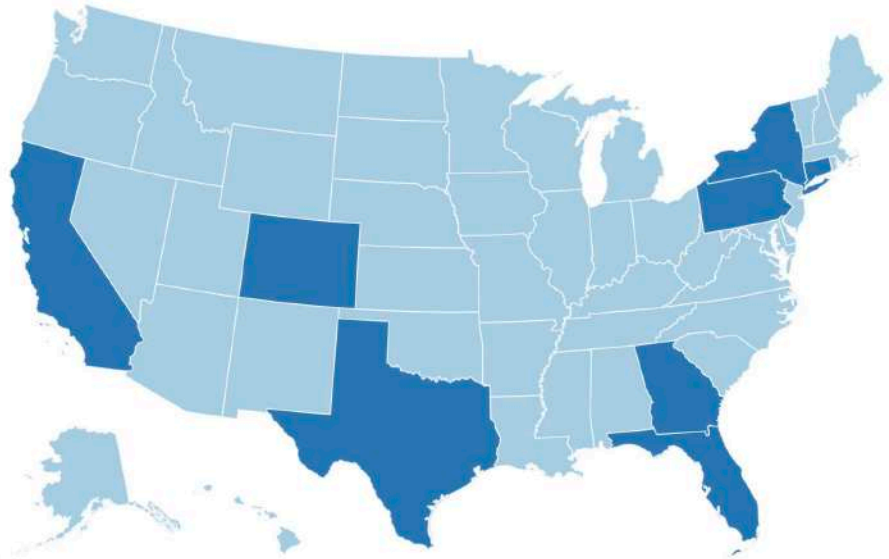
Variant Strains

YOUR HEALTH

US COVID-19 Cases Caused by Variants

Updated Jan. 8, 2021 Languages Print

B.1.1.7 Lineage Cases in the United States*† Total Cases: 63



Territories AS GU MH FM MP PW PR VI

CDC

VIEWPOINT

Genetic Variants of SARS-CoV-2—What Do They Mean?

Adam S. Lauring, MD, PhD
Division of Infectious Diseases, Department of Internal Medicine and Department of Microbiology and Immunology, University of Michigan, Ann Arbor.

Emma B. Hodcroft, PhD
Institute of Social and Preventive Medicine, University of Bern, Switzerland.

Multimedia

Over the course of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, the clinical, scientific, and public health communities have had to respond to new viral genetic variants. Each one has triggered a flurry of media attention, a range of reactions from the scientific community, and calls from governments to either "stay calm" or pursue immediate countermeasures. While many scientists were initially skeptical about the significance of the D614G alteration, the emergence of the new "UK variant"—lineage B.1.1.7—has raised widespread concern. Understanding which variants are concerning, and why, requires an appreciation of virus evolution and the genomic epidemiology of SARS-CoV-2.

Mutations, Variants, and Spread

Mutations arise as a natural by-product of viral replication.[1] RNA viruses typically have higher mutation rates than DNA viruses. Coronaviruses, however, make fewer mutations than most RNA viruses because they encode an enzyme that corrects some of the errors made during replication. In most cases, the fate of a newly arising mutation is determined by natural selection. Those that confer a competitive advantage with respect to viral replication, transmission, or escape from immunity will increase in frequency, and those that reduce viral fitness tend to be culled from the population of circulating viruses. However, mutations can also increase and decrease in frequency due to chance events. For example, a "founder effect" occurs

> Understanding which variants are concerning, and why, requires an appreciation of virus evolution and the genomic epidemiology of SARS-CoV-2.

speaking, a variant is a *strain* when it has a demonstrably different phenotype (eg, a difference in antigenicity, transmissibility, or virulence).

Evaluation of a new SARS-CoV-2 variant should include assessment of the following questions: Did the variant achieve prominence through natural selection or chance events? If the evidence suggests natural selection, which mutation(s) are being selected? What is the adaptive benefit of these mutations? What effect do these mutations have on transmissibility and spread, antigenicity, or virulence?

Spike D614G

The D614G mutation in the spike glycoprotein of SARS-CoV-2 was first detected at a significant level in early March 2020 and spread to global dominance over the next month.[2] The mutation initially appeared to arise independently and simultaneously sweep across multiple geographic regions. This apparent convergent evolution was suggestive of natural selection and an adaptive benefit of D614G. However, subsequent sequencing efforts identified the D614G mutation in viruses in several Chinese provinces in late January. This raised the possibility that global dispersal of this mutation could have resulted from chance founder events, in which viruses harboring 614G just happened to initiate the majority of early transmission events in multiple locations.

This plausible null hypothesis led many in the evolution community to doubt that the D614G mutation was adaptive, despite in vitro data showing its effects on receptor binding. A recent population genetic and phylodynamic analysis of more than 25 000 sequences from the UK found that viruses bearing 614G did appear to spread faster and seed larger phylogenetic clusters than viruses with 614D.[3] The effect size was modest, and the varying models did not always achieve

https://jamanetwork.com/journals/jama/fullarticle/2775006

Estimated transmissibility and severity of novel SARS-CoV-2 Variant of Concern 202012/01 in England

Status: Paper under peer review | First online: 23-12-2020 | Last update: 31-12-2020

Authors: *Nicholas Davies*, Rosanna C Barnard[1], Christopher I Jarvis[1], Adam J Kucharski[1], James D Munday[1], Carl A.B. Pearson[1], Timothy W Russell[1], Damien C Tully[1], Sam Abbott, Amy Gimma, William Waites, Kerry LM Wong, Kevin van Zandvoort, CMMID COVID-19 working group, Rosalind M Eggo, Sebastian Funk, Mark Jit, Katherine E Atkins & W John Edmunds.*

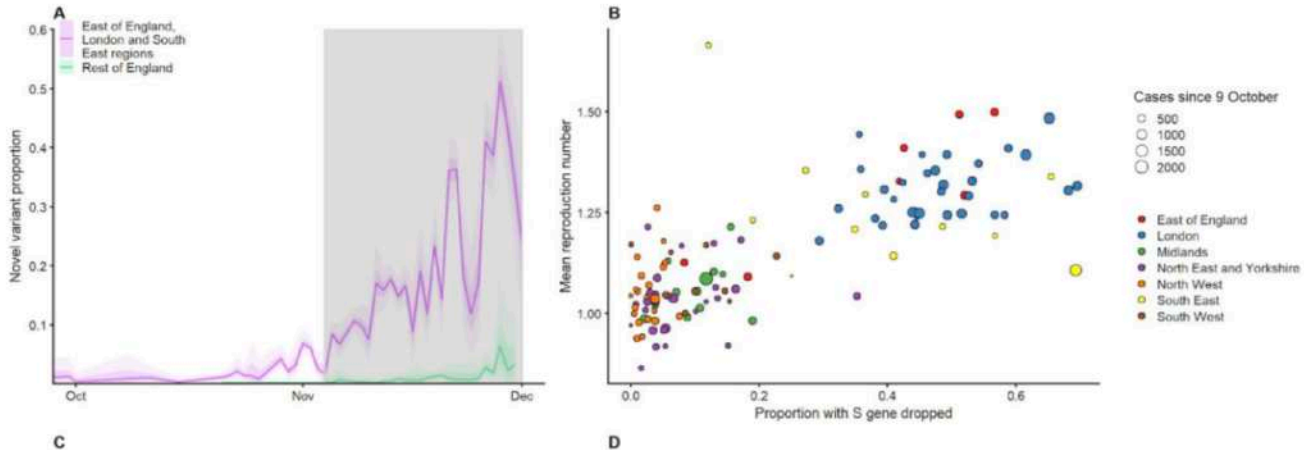
* corresponding author 1 contributed equally

This study has not yet been peer reviewed.

We have updated our analysis on 31 December 2020 with a brief report here.

A novel SARS-CoV-2 variant, VOC 202012/01, emerged in southeast England in November 2020 and appears to be rapidly spreading towards fixation. We fitted a two-strain mathematical model of SARS-CoV-2 transmission to observed COVID-19 hospital admissions, hospital and ICU bed occupancy, and deaths; SARS-CoV-2 PCR prevalence and seroprevalence; and the relative frequency of VOC 202012/01 in the three most heavily affected NHS England regions (South East, East of England, and London). We estimate that VOC 202012/01 is 56% more transmissible (95% credible interval across three regions 50-74%) than preexisting variants of SARS-CoV-2. We were unable to find clear evidence that VOC 202012/01 results in greater or lesser severity of disease than preexisting variants. Nevertheless, the increase in transmissibility is likely to lead to a large increase in incidence, with COVID-19 hospitalisations and deaths projected to reach higher levels in 2021 than were observed in 2020, even if regional tiered restrictions implemented before 19 December are maintained. Our estimates suggest that control measures of a similar stringency to the national lockdown implemented in England in November 2020 are unlikely to reduce the effective reproduction number Rt to less than 1, unless primary schools, secondary schools, and universities are also closed. We project that large resurgences of the virus are likely to occur following easing of control measures. It may be necessary to greatly accelerate vaccine roll-out to have an appreciable impact in suppressing the resulting disease burden.

Read the full preprint here.



What we do not know

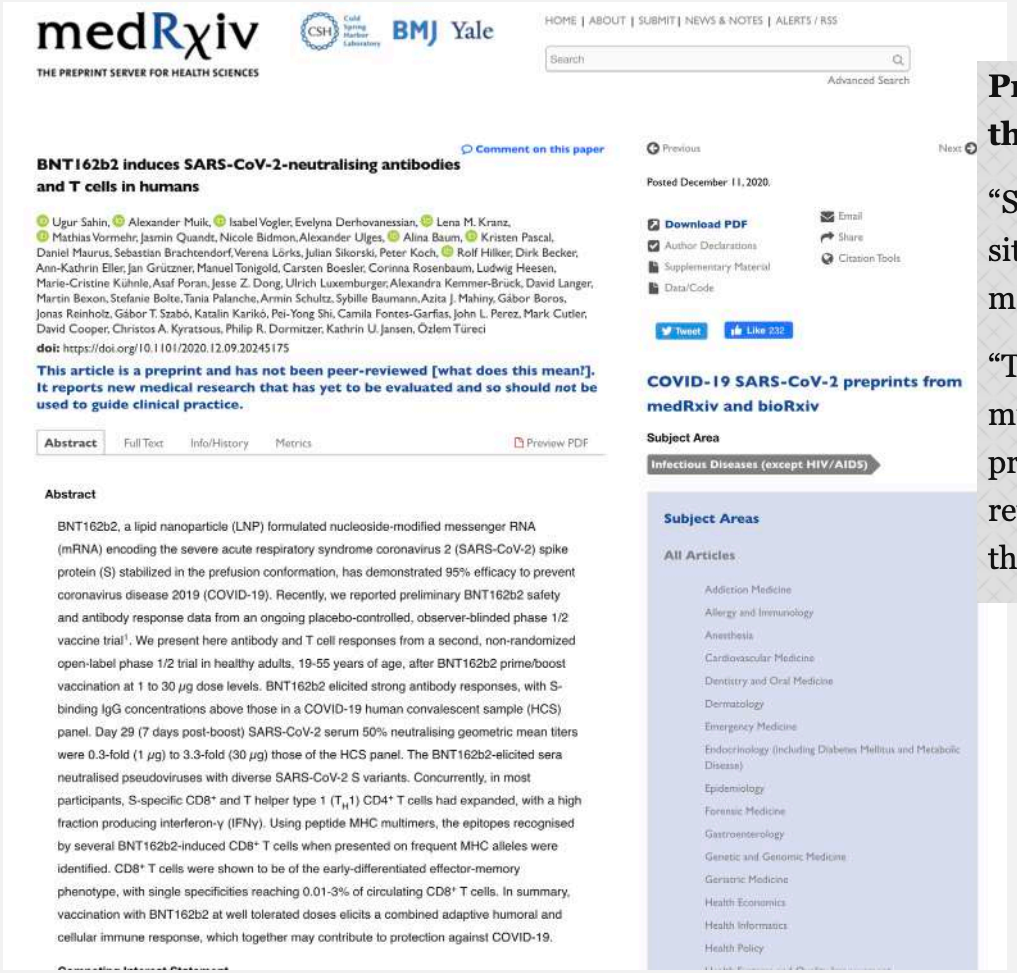
Scientists are working to learn more about these variants, and more studies are needed to understand:

- How widely these new variants have spread
- How the new variants differ
- How the disease caused by these new variants differs from the disease caused by other variants that are currently circulating

What it means

Public health officials are studying these variants quickly to learn more to control their spread. They want to understand whether the variants:

- Spread more easily from person to person
- Cause milder or more severe disease in people
- Are detected by currently available viral tests
- Respond to medicines currently being used to treat people for COVID-19
- Change the effectiveness of COVID-19 vaccines. There is no evidence that this is occurring, and most experts believe this is unlikely to occur because of the nature of the immune response to the virus.



medRxiv
THE PREPRINT SERVER FOR HEALTH SCIENCES

BMJ Yale

HOME | ABOUT | SUBMIT | NEWS & NOTES | ALERTS / RSS

Search

Advanced Search

Comment on this paper

BNT162b2 induces SARS-CoV-2-neutralising antibodies and T cells in humans

Ugur Sahin, Alexander Muik, Isabel Vogler, Evelyna Derhovanessian, Lena M. Kranz, Mathias Vormehr, Jasmin Quandt, Nicole Bidmon, Alexander Ulges, Alina Baum, Kristen Pascal, Daniel Maurus, Sebastian Brachtendorf, Verena Lörks, Julian Sikorski, Peter Koch, Rolf Hilker, Dirk Becker, Ann-Kathrin Eller, Jan Grützner, Manuel Tonigold, Carsten Boesler, Corinna Rosenbaum, Ludwig Heesen, Marie-Cristine Kühnle, Asaf Poran, Jesse Z. Dong, Ulrich Luxemburger, Alexandra Kemmer-Brück, David Langer, Martin Bexon, Stefanie Bolte, Tania Palanche, Armin Schultz, Sybille Baumann, Azita J. Mahiny, Gábor Boros, Jonas Reinholz, Gábor T. Szabó, Katalin Karikó, Pei-Yong Shi, Camila Fontes-Garfias, John L. Perez, Mark Cutler, David Cooper, Christos A. Kyratsous, Philip R. Dormitzer, Kathrin U. Jansen, Özlem Türeci

doi: https://doi.org/10.1101/2020.12.09.20245175

This article is a preprint and has not been peer-reviewed [what does this mean?]. It reports new medical research that has yet to be evaluated and so should *not* be used to guide clinical practice.

Abstract | Full Text | Info/History | Metrics | Preview PDF

Abstract

BNT162b2, a lipid nanoparticle (LNP) formulated nucleoside-modified messenger RNA (mRNA) encoding the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein (S) stabilized in the prefusion conformation, has demonstrated 95% efficacy to prevent coronavirus disease 2019 (COVID-19). Recently, we reported preliminary BNT162b2 safety and antibody response data from an ongoing placebo-controlled, observer-blinded phase 1/2 vaccine trial[1]. We present here antibody and T cell responses from a second, non-randomized open-label phase 1/2 trial in healthy adults, 19-55 years of age, after BNT162b2 prime/boost vaccination at 1 to 30 μg dose levels. BNT162b2 elicited strong antibody responses, with S-binding IgG concentrations above those in a COVID-19 human convalescent sample (HCS) panel. Day 29 (7 days post-boost) SARS-CoV-2 serum 50% neutralising geometric mean titers were 0.3-fold (1 μg) to 3.3-fold (30 μg) those of the HCS panel. The BNT162b2-elicited sera neutralised pseudoviruses with diverse SARS-CoV-2 S variants. Concurrently, in most participants, S-specific $CD8^+$ and T helper type 1 (T_H1) $CD4^+$ T cells had expanded, with a high fraction producing interferon-γ (IFNγ). Using peptide MHC multimers, the epitopes recognised by several BNT162b2-induced $CD8^+$ T cells when presented on frequent MHC alleles were identified. $CD8^+$ T cells were shown to be of the early-differentiated effector-memory phenotype, with single specificities reaching 0.01-3% of circulating $CD8^+$ T cells. In summary, vaccination with BNT162b2 at well tolerated doses elicits a combined adaptive humoral and cellular immune response, which together may contribute to protection against COVID-19.

Previous | Next

Posted December 11, 2020.

Download PDF | Email | Share | Author Declarations | Citation Tools | Supplementary Material | Data/Code

Tweet | Like 232

COVID-19 SARS-CoV-2 preprints from medRxiv and bioRxiv

Subject Area

Infectious Diseases (except HIV/AIDS)

Subject Areas

All Articles

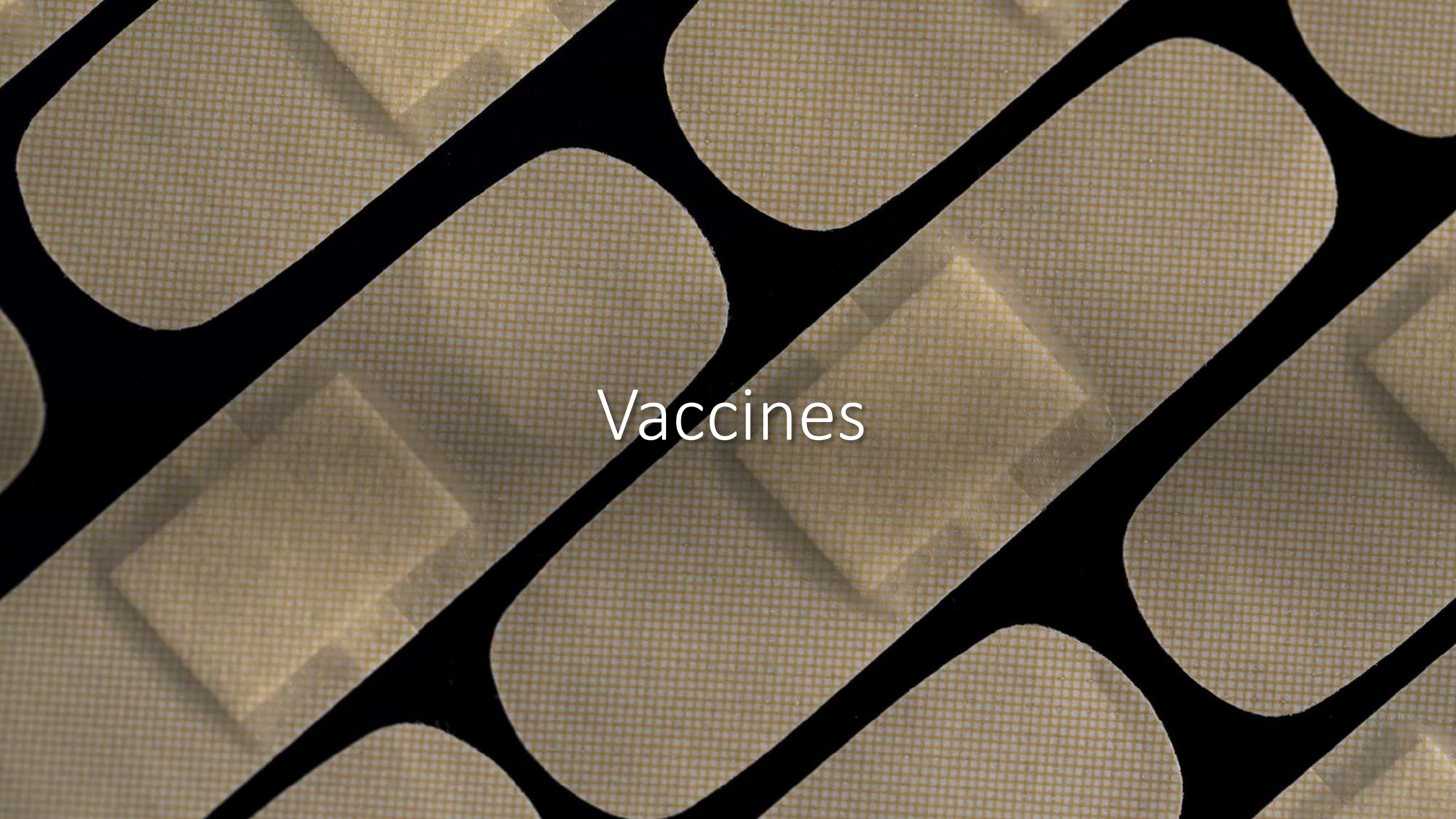
Addiction Medicine
Allergy and Immunology
Anesthesia
Cardiovascular Medicine
Dentistry and Oral Medicine
Dermatology
Emergency Medicine
Endocrinology (including Diabetes Mellitus and Metabolic Disease)
Epidemiology
Forensic Medicine
Gastroenterology
Genetic and Genomic Medicine
Geriatric Medicine
Health Economics
Health Informatics
Health Policy

Prof Eleanor Riley, Professor of Immunology and Infectious Disease at the University of Edinburgh, said:

"So far, so good. There will be other new mutants and we will need to monitor the situation carefully by repeating this type of study on new variants as they appear. It may be necessary to tweak the vaccine over time.

"To inject a little optimism into the discussion: there is a limit to the number of mutations the virus can accumulate and still be able to bind to the receptor. We probably have enough structural data now to be able to predict which mutations will retain receptor binding but may evade antibodies. So we may be able to get ahead of the virus by preparing vaccine constructs that would cover this eventuality."

https://www.medrxiv.org/content/10.1101/2020.12.09.20245175v1


Vaccines

Groups who should be offered vaccination next (1b and 1c)

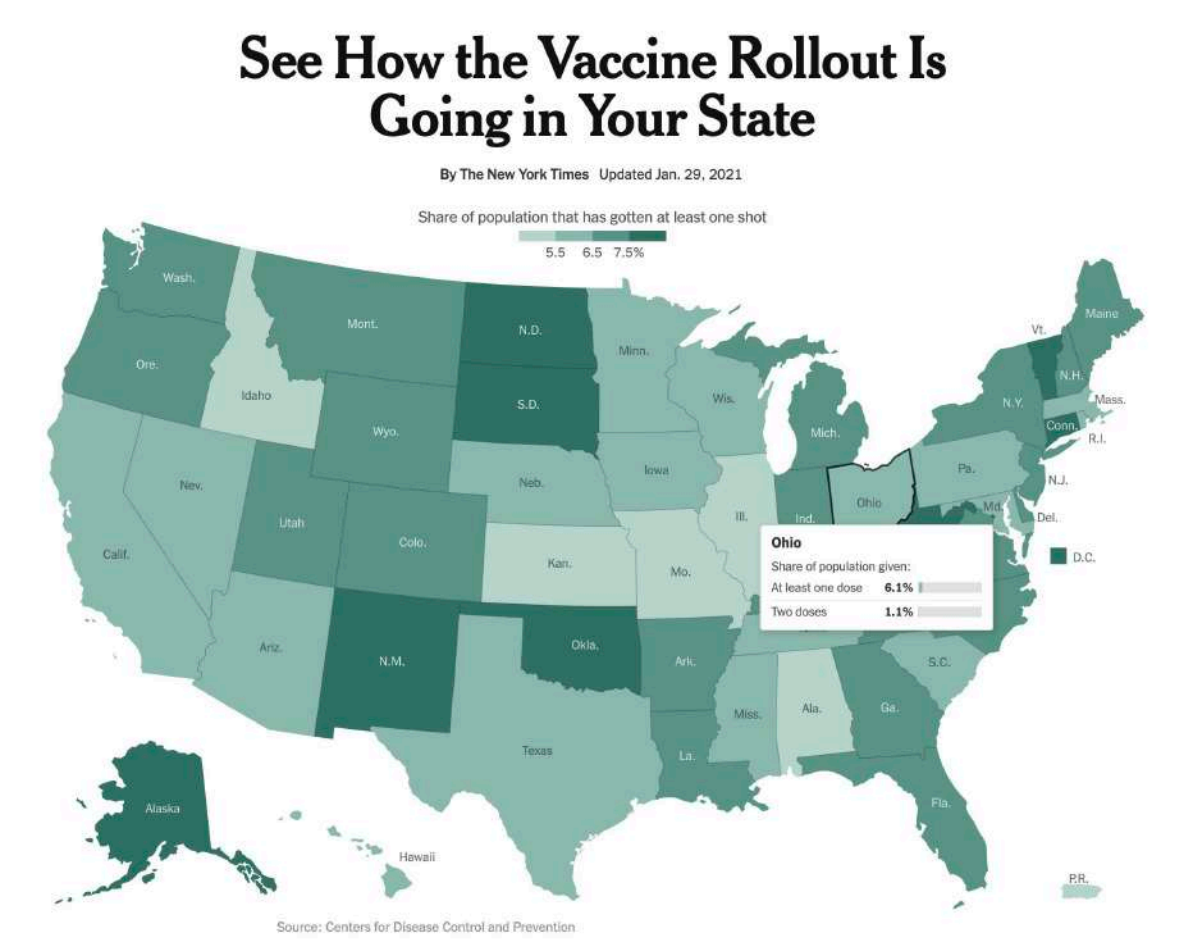
CDC recommends that in Phase 1b and Phase 1c, which may overlap, vaccination should be offered to people in the following groups. CDC made this recommendation on December 22, 2020.

Phase 1b

- **Frontline essential workers** such as fire fighters, police officers, corrections officers, food and agricultural workers, United States Postal Service workers, manufacturing workers, grocery store workers, public transit workers, and those who work in the educational sector (teachers, support staff, and daycare workers.)
- **People aged 75 years and older** because they are at high risk of hospitalization, illness, and death from COVID-19. People aged 75 years and older who are also residents of long-term care facilities should be offered vaccination in Phase 1a.

Phase 1c

- **People aged 65—74 years** because they are at high risk of hospitalization, illness, and death from COVID-19. People aged 65—74 years who are also residents of long-term care facilities should be offered vaccination in Phase 1a.
- **People aged 16—64 years with underlying medical conditions** which increase the risk of serious, life-threatening complications from COVID-19.
- **Other essential workers**, such as people who work in transportation and logistics, food service, housing construction and finance, information technology, communications, energy, law, media, public safety, and public health.



https://www.nytimes.com/interactive/2020/us/covid-19-vaccine-doses.html

COVID-19 Vaccinations in the United States

Overall US COVID-19 Vaccine Distribution and Administration; Maps, charts, and data provided by the CDC, updated daily by 8 pm ET†

Total Doses Distributed	Total Doses Administered	Number of People Receiving 1 or More Doses	Number of People Receiving 2 Doses
49,216,500	27,884,661	22,858,318	4,780,888

CDC | Data as of: Jan 29 2021 6:00am ET | Posted: Jan 29 2021 2:40PM ET

View:
- (●) Total Doses Administered
- ( ) People Receiving 1 or More Doses
- ( ) People Receiving 2 Doses
- ( ) Total Doses Distributed

Metric:
- ( ) Count
- (●) Rate per 100,000

https://covid.cdc.gov/covid-data-tracker/#vaccinations

RESEARCH SUMMARY

Efficacy and Safety of mRNA-1273 SARS-CoV-2 Vaccine

L.R. Baden, et al. DOI: 10.1056/NEJMoa2035389

CLINICAL PROBLEM

The Covid-19 pandemic continues and expands. Additional data regarding vaccines to prevent symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are needed. The mRNA-1273 vaccine is a lipid-encapsulated mRNA vaccine encoding the prefusion stabilized spike protein of SARS-CoV-2.

CLINICAL TRIAL

A randomized, double-blind trial to evaluate the efficacy and safety of mRNA-1273.

30,420 participants ≥18 years old were assigned to receive either the vaccine or placebo in two intramuscular injections 28 days apart. Participants were followed for safety and the development of laboratory-confirmed, symptomatic Covid-19 over a median of 2 months after the second dose.

RESULTS

Safety:
Vaccine recipients had higher rates of local reactions (e.g., pain, erythema, swelling) and systemic reactions (e.g., headache, fatigue, myalgia) than placebo recipients. Most reactions were mild to moderate and resolved over 1–3 days.

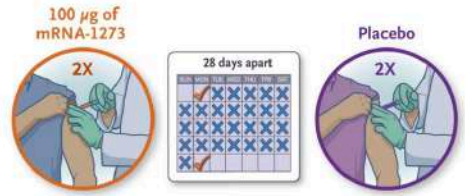
Efficacy:
The incidence of Covid-19 was lower among vaccine recipients than among placebo recipients as early as 14 days after the first dose. Protection in the vaccine group persisted for the period of follow-up.

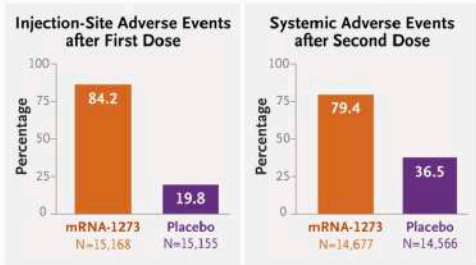
LIMITATIONS AND REMAINING QUESTIONS

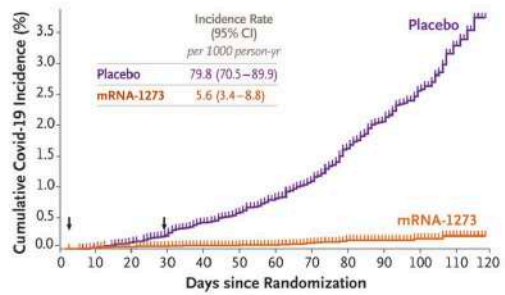
Further study is required to understand the following:

- Safety and efficacy over a longer period of time, in a larger population, and in pregnant women and children.
- Whether the vaccine protects against asymptomatic infection and transmission to unvaccinated persons.
- How to care for those who miss the second vaccine dose.

Links: Full article | NEJM Quick Take | Editorial







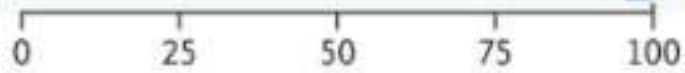
	mRNA-1273 Vaccine N=14,550	Placebo N=14,598
Symptomatic Covid-19	11	185
Severe Covid-19	0	30

Vaccine efficacy of 94.1% (95% CI, 89.3–96.8%; P<0.001)

CONCLUSIONS

Two doses of a SARS-CoV-2 mRNA-based vaccine were safe and provided 94% efficacy against symptomatic Covid-19 in persons 18 or older.

Subgroup	Placebo (N=14,073)	mRNA-1273 (N=14,134)	Vaccine Efficacy (95% CI)
	no. of events/total no.		
All patients	185/14,073	11/14,134	94.1 (89.3–96.8)
Age			
≥18 to <65 yr	156/10,521	7/10,551	95.6 (90.6–97.9)
≥65 yr	29/3552	4/3583	86.4 (61.4–95.2)
Age, risk for severe Covid-19			
18 to <65 yr, not at risk	121/8403	5/8396	95.9 (90.0–98.3)
18 to <65 yr, at risk	35/2118	2/2155	94.4 (76.9–98.7)
≥65 yr	29/3552	4/3583	86.4 (61.4–95.2)
Sex			
Male	87/7462	4/7366	95.4 (87.4–98.3)
Female	98/6611	7/6768	93.1 (85.2–96.8)
At risk for severe Covid-19			
Yes	43/3167	4/3206	90.9 (74.7–96.7)
No	142/10,906	7/10,928	95.1 (89.6–97.7)
Race and ethnic group			
White	144/8916	10/9023	93.2 (87.1–96.4)
Communities of color	41/5132	1/5088	97.5 (82.2–99.7)



CDC Guidance on Allergic Reactions

- If someone has had an immediate type hypersensitivity reaction following the first dose of an mRNA vaccine, whether severe or not severe, they should not get a second dose
- Above includes anaphylaxis, hives, swelling or wheezing
- People with allergies to polyethylene glycol or polysorbate should not get an mRNA COVID vaccine
- People with allergic reactions to other vaccines should discuss whether to get the vaccine with their physician
- People who have other allergic reactions, not IgE mediated, may want to consult with an allergist

Early Recognition of Anaphylaxis

- Respiratory: sensation of throat closing, stridor (high-pitched sound while breathing), shortness of breath, wheeze, cough
- Gastrointestinal: nausea, vomiting, diarrhea, abdominal pain
- Cardiovascular: dizziness, fainting, tachycardia (abnormally fast heart rate), hypotension (abnormally low blood pressure)
- Skin/mucosal: generalized hives, itching, or swelling of lips, face, throat

Observation Following vaccines

- 30 minutes for people with history of an immediate hypersensitivity reaction to an injectable therapy of anaphylaxis from any cause
- 15 minutes for all others

Vaccinating Pregnant and Lactating Patients Against COVID-19

Practice Advisory | December 2020

Search page

Jump to:

Last updated December 21, 2020

This Practice Advisory was developed by the American College of Obstetricians and Gynecologists' Immunization, Infectious Disease, and Public Health Preparedness Expert Work Group in collaboration with Laura E. Riley, MD; Richard Beigi, MD; Denise J. Jamieson, MD, MPH; Brenna L. Hughes, MD, MSc; Geeta Swamy, MD; Linda O'Neal Eckert, MD; Cynthia Gyamfi-Bannerman, MD, MSc; Mark Turrentine, MD; and Sarah Carroll, MPH.

Summary of Key Information and Recommendations

COVID-19 vaccine development and regulatory approval are rapidly progressing. Thus, information and recommendations will evolve as more data are collected about these

ACOG Highlights

- ACOG recommends that COVID-19 vaccines should not be withheld from pregnant individuals who meet criteria for vaccination based on ACIP-recommended priority groups.
- COVID-19 vaccines should be offered to lactating individuals similar to non-lactating individuals when they meet criteria for receipt of the vaccine based on prioritization groups outlined by the ACIP.
- Individuals considering a COVID-19 vaccine should have access to available information about the safety and efficacy of the vaccine, including information about data that are not available. A conversation between the patient and their clinical team may assist with decisions regarding the use of vaccines approved under EUA for the prevention of COVID-19 by pregnant patients. Important considerations include:
- While a conversation with a clinician may be helpful, it should not be required prior to vaccination, as this may cause unnecessary barriers to access.
- Vaccines currently available under EUA have not been tested in pregnant women. Therefore, there are no safety data specific to use in pregnancy. See details about the Food and Drug Administration's (FDA) EUA process below.

ACOG Highlights Continued

- Pregnancy testing should not be a requirement prior to receiving any EUA-approved COVID-19 vaccine.
- Pregnant patients who decline vaccination should be supported in their decision. Regardless of their decision to receive or not receive the vaccine, these conversations provide an opportunity to remind patients about the importance of other prevention measures such as hand washing, physical distancing, and wearing a mask.
- Expected side effects should be explained as part of counseling patients, including that they are a normal part of the body's reaction to the vaccine and developing antibodies to protect against COVID-19 illness.
- The mRNA vaccines are not live virus vaccines, nor do they use an adjuvant to enhance vaccine efficacy. These vaccines do not enter the nucleus and do not alter human DNA in vaccine recipients. As a result, mRNA vaccines cannot cause any genetic changes.


TRAVEL

Testing and International Air Travel

Updated Jan. 26, 2021 Languages Print

To reduce introduction and spread of new variants of SARS-CoV-2, CDC issued an Order effective January 26, 2021. It requires all air passengers arriving to the US from a foreign country to get tested for COVID-19 infection no more than 3 days before their flight departs and to provide proof of the negative result or documentation of having recovered from COVID-19 to the airline before boarding the flight. For more information on this testing requirement, see the Frequently Asked Questions.

These CDC recommendations are based on the latest public health science to inform safer, more responsible international travel during the COVID-19 pandemic. These recommendations are not intended to be requirements for the travel industry. Follow all destination and airline recommendations or requirements.

https://www.cdc.gov/coronavirus/2019-ncov/travelers/testing-air-travel.html

What's different about this pandemic

- No previous infection has spread this quickly throughout the world.
- Never before has so much of the scientific community been focused on finding answers to questions about a single pathogen.
- Diagnostic tests were available more quickly for this virus on a large scale than for any prior disease, but the limitations were also immediately more visible.
- Science has advanced to the point where we have a greater understanding of what we don't know early in the pandemic.

Conclusions

- COVID-19 is not going away. This is going to be with us for a long while.
- Your behavior directly impacts your own health and the health of those around you.
- Realize that what you do also affects those around you.
- Infection Prevention works.
- Know that the guidance will likely continue to change as more information becomes available.