

COVID-19 Science Update



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Intended for use by public health professionals responding to the COVID-19 pandemic.

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Epidemiology

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[Substantial underestimation of SARS-CoV-2 infection in the United States](#). Wu *et al.* Nature Communications (September 9, 2020).

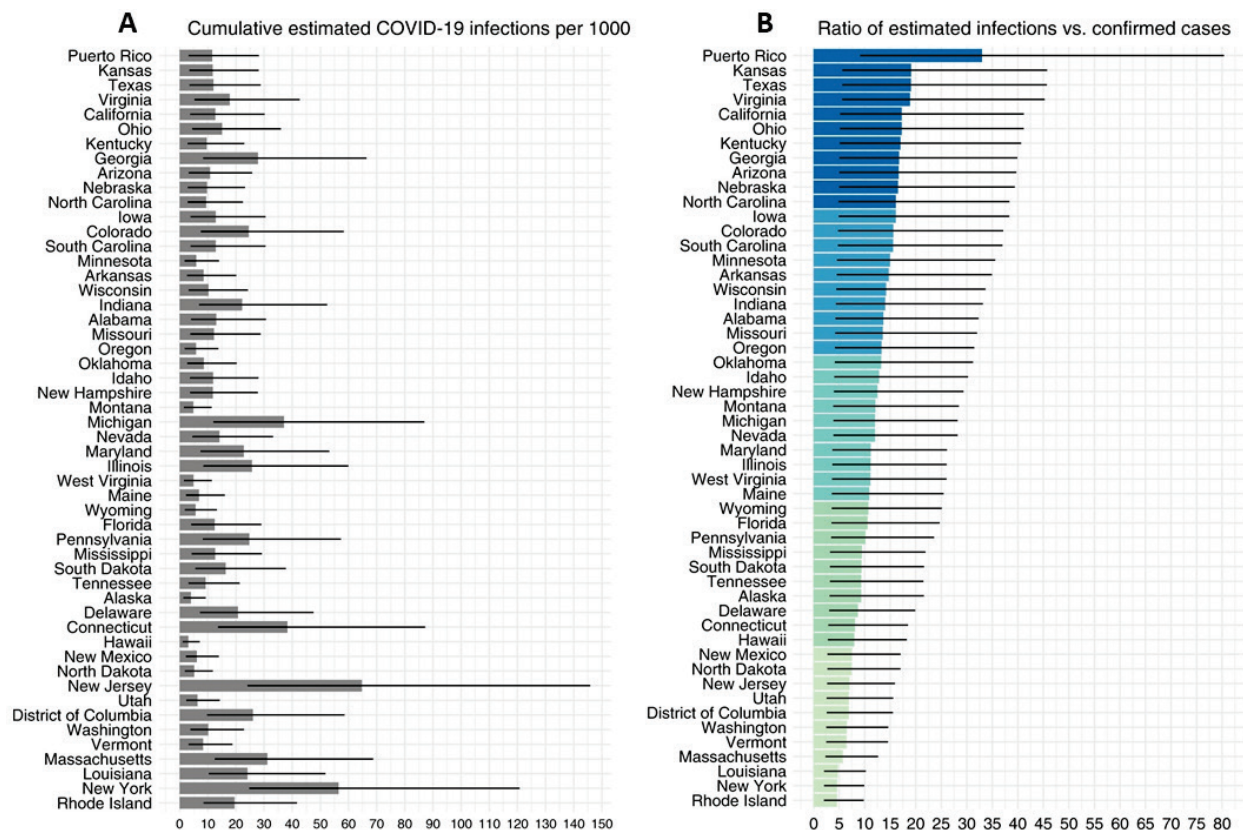
Key findings:

- By April 18, 2020, the *estimated cumulative* SARS-CoV-2 incidence in the US was ~2%.
 - The number of estimated cumulative SARS-CoV-2 infections was 8.6 times the number of *confirmed* infections: 6,454,951 vs 751,245.
 - 84% of the difference between estimated cumulative and reported confirmed cases was due to incomplete testing and 16% was due to test inaccuracy.
- The estimated cumulative infection rate (range: 3.1 to 65.0/1,000) and ratio of estimated cumulative to reported confirmed SARS-CoV-2 infections (range: 5 to 33) varied widely by state (Figure).
 - Differences among states were driven by different transmission rates, testing rates, and test positivity rates in each state rather than modeling assumptions.

Methods: Analysis using data from the [COVID Tracking Project](#) to assess estimated cumulative SARS-CoV-2 infections by state and evaluate contributions of incomplete testing and imperfect test performance. Used daily test counts and confirmed SARS-CoV-2 positive tests in each state from February 28 to April 18, 2020. The 2019 projected state populations from the 2010 US Census were used to calculate rates. Simulation intervals (2.5th and 97.5th percentiles) were computed from the distribution of estimated infections. **Limitations:** States with very low testing rates; positive test probabilities might not predict overall population incidence (e.g., if testing was restricted to patients with severe symptoms); county-level data not available.

Implications: Estimated cumulative SARS-CoV-2 infections were greater than confirmed reported infections, due in part possibly to challenges with testing. Monitoring underestimation of reported confirmed cases can provide more accurate estimates of the cumulative burden of SARS-CoV-2 infection.

Figure:



Note: From Wu *et al.* **A:** Gray bars indicate the median rate of estimated infections. **B:** Ratios of estimated infections to confirmed cases in each state by quintile in descending order, with the darkest shade of blue indicating the largest quintile, and the lightest shade of green indicating the lowest quintile. Horizontal black lines indicate simulation intervals (2.5th and 97.5th percentiles). Licensed under CC-BY 4.0.

[Assessment of mental health of Chinese primary school students before and after school closing and opening during the COVID-19 pandemic.](#) Zhang *et al.* JAMA Network (September 11, 2020).

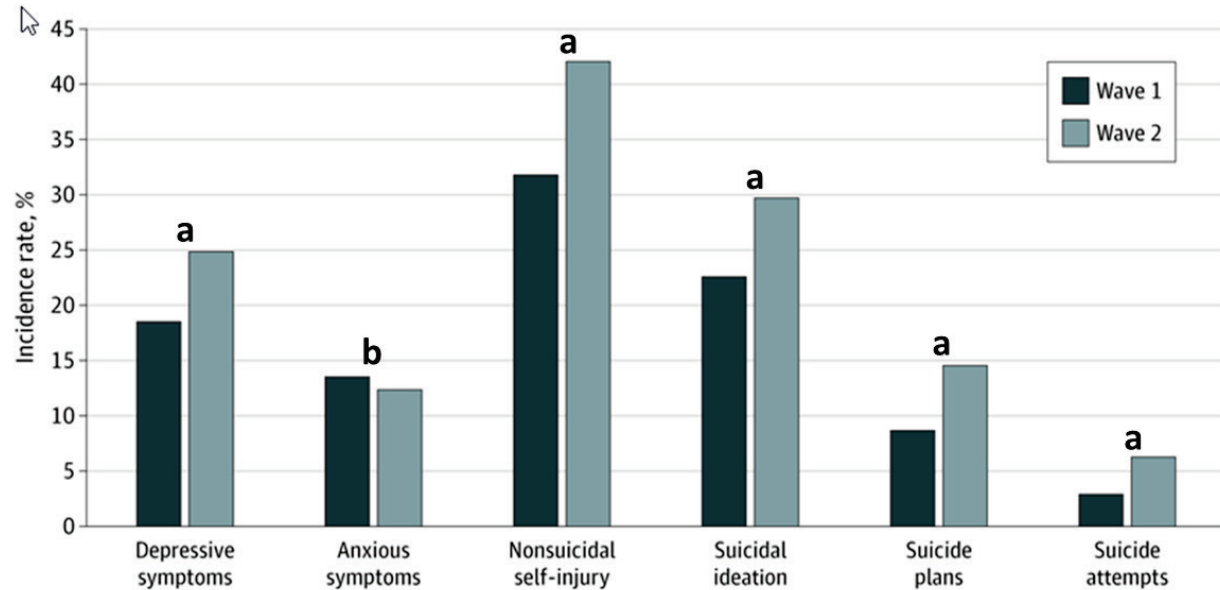
Key findings:

- The prevalence of depression and suicidality increased significantly among students after school closing (Wave 2) from levels before school closing (Wave 1) (Figure).

Methods: Longitudinal cohort study of 1,241 Chinese schoolchildren in grades 4 through 8 comparing physical and mental health factors before the COVID-19 outbreak (Wave 1, early November 2019) with 2 weeks after school reopening (Wave 2, mid-May 2020) in a low risk area of China. **Limitations:** Response and recall bias; unmeasured confounders and measurement errors in mental health outcomes; limited representativeness of the sample.

Implications: School closures adversely affected mental health of students. Healthcare and government agencies need to plan for the impact of prolonged school closures and be prepared to provide increased level of mental health services to the children and their families.

Figure:



Note: Adapted from Zhang *et al.* Incidence of mental health symptoms and suicide behaviors in **Wave 1** before school closures and **Wave 2** after school reopening. **a** $p < 0.001$; **b** $p = 0.09$. Licensed under CC-BY.

Convalescent Plasma

Convalescent plasma (CP) therapy is under evaluation as treatment of COVID-19 and is obtained from persons who have recovered from prior COVID-19. However, not all persons develop the same antibody profile or adequate neutralizing antibody (NAb) titers after SARS-CoV-2 infection. There is a need to determine levels of NABs in CP that are optimal for treatment and prevention. As assays to measure neutralization are complex, determining if other antibody titers such as those to the receptor binding domain (RBD) or the spike protein may be used as a marker of high neutralizing activity is important. The following two studies present recent findings on characteristics of CP.

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A. [Convalescent plasma anti-SARS-CoV-2 spike protein ectodomain and receptor binding domain IgG correlate with virus neutralization](#). Salazar *et al.* Journal of Clinical Investigation (September 10, 2020).

Key findings:

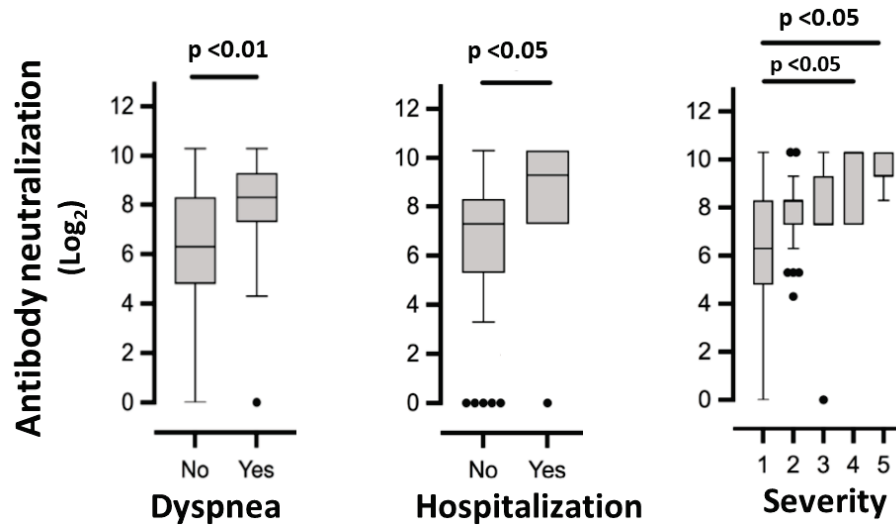
- Most CP donors (43/68; 63%) had high NAb titers ($\geq 1:160$).
 - High NAb titers were associated with dyspnea, hospitalization, and severity at the time of illness in the donor (Figure 1).
- Anti-RBD antibodies and anti-spike ectodomain (ECD) antibodies were strongly correlated with NABs ($p < 0.001$ for each).
- 80% of CP donors had NAb titer $\geq 1:160$ when their anti-RBD or anti-spike ectodomain (ECD) titer (part of the spike protein) was $\geq 1:1,350$ (Figure 2).
 - In a separate survey of antibodies levels in 73 asymptotically infected persons, 27 had anti-RBD or anti-spike ECD titers of $\geq 1:1,350$.

Methods: Retrospective assessment of anti-ECD IgG, anti-RBD IgG, and SARS-CoV-2 NAb titers from 68 CP donors who had symptomatic SARS-CoV-2 infection. Dyspnea, hospitalization, and a severity score at the time of illness

were recorded. IgG titers were also measured in a separate sample of 73 asymptomatic, seropositive individuals.

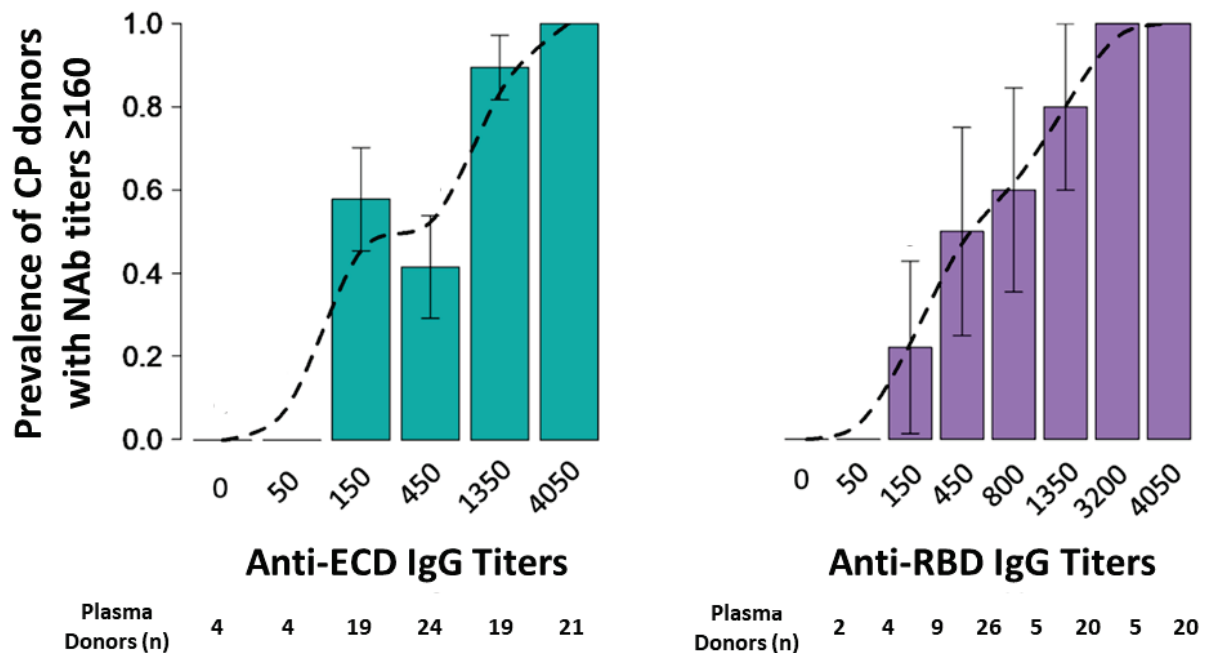
Limitations: Assessed IgG only; findings may not be applicable to all antibody testing platforms or other sample types; relatively small sample size.

Figure 1



Note: Adapted from Salazar *et al.* Boxplots of interquartile range, showing the log₂ transformed antibody neutralization titer by category in 68 CP donors. **Black dots** are outliers, whisker bars are upper and lower quartiles. Severity- highest severity score during illness. Open access journal; all content freely available.

Figure 2



Note: Adapted from Salazar *et al.* Prevalence of CP donors with NAb titer $\geq 1:160$ by IgG titers of anti-spike ECD and anti-RBD. Dashed line is a curve fitted to probability values. Standard error bars are shown. Open access journal; all content freely available.

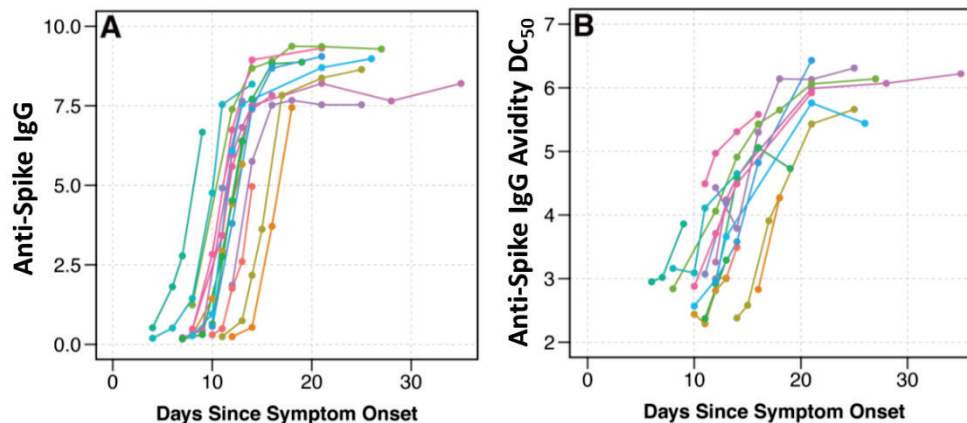
SARS-CoV-2 antibody avidity responses in COVID-19 patients and convalescent plasma donors. Benner *et al.* Journal of Infectious Diseases (September 10, 2020).

Key findings:

- Among hospitalized patients, antibody avidity as well as anti-spike and anti-nucleocapsid IgG titers increased from days 10 to 20 after symptom onset (Figure 1).
- Among CP donors, age correlated with antibody avidity (strength of binding between antibody and antigen) for men ($p = 0.008$) but not women ($p = 0.872$) (Figure 2A).
- CP donors who were hospitalized had stronger anti-spike IgG avidity than donors who were not hospitalized (Figure 2B).
- Neutralizing antibody titers had a positive correlation with anti-spike IgG avidity (Spearman's $\rho = 0.386$; $p < 0.001$) and anti-spike IgG binding (Spearman's $\rho = 0.772$, $p < 0.001$).

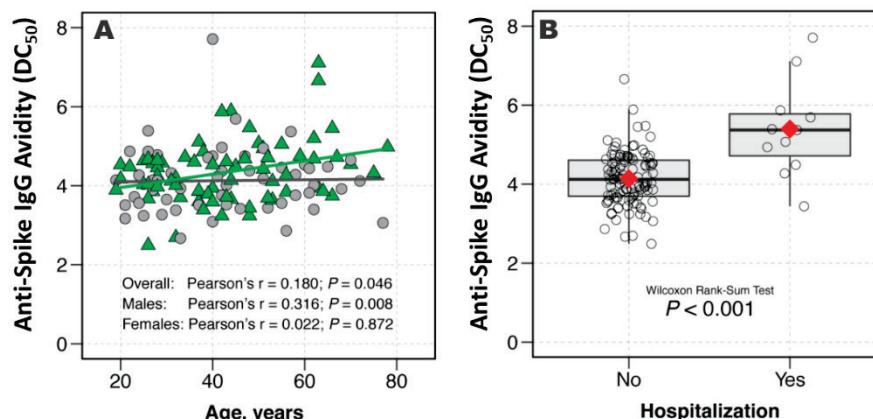
Methods: Samples from hospitalized patients ($n = 16$) with confirmed SARS-CoV-2 infection and CP donors ($n = 130$) were assessed for anti-spike IgG, anti-nucleocapsid IgG titers, and antibody avidity. **Limitations:** Different methods used for anti-spike IgG versus anti-nucleocapsid IgG antibody titers; antibody assays were semi-quantitative; may not be applicable to mild or asymptomatic infections; short observation period.

Figure 1



Note: Adapted from Benner *et al.* **A:** IgG antibody levels. **B:** Antibody avidity against the SARS-CoV-2 spike protein in hospitalized patients. DC₅₀ - 50% dissociation constant. Colored lines indicate individual patients. Because assays used were semi-quantitative, units used were proxies for quantitative measures. Licensed under CC BY 4.0.

Figure 2



Note: Adapted from Benner *et al.* Cross-sectional sampling of recovered patients by age tested for IgG antibody avidity against the SARS-CoV-2 spike protein by age (**A**) and hospitalization status (**B**). DC₅₀ - 50% dissociation constant. Licensed under CC BY 4.0.

Implications for 2 studies (Salazar *et al* & Benner *et al*): Effect of CP in the treatment of COVID-19 likely depends on numerous characteristics including antibody level, avidity, and target as well as neutralization activity. Understanding how to best screen CP donors to identify those with NAb titers and characteristics that may optimize use of CP as treatment may be important.

Clinical Treatment & Management

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Reduced maximal aerobic capacity after COVID-19 in young adult recruits, Switzerland, May 2020.

Cramer *et al.* Eurosurveillance (September 10, 2020).

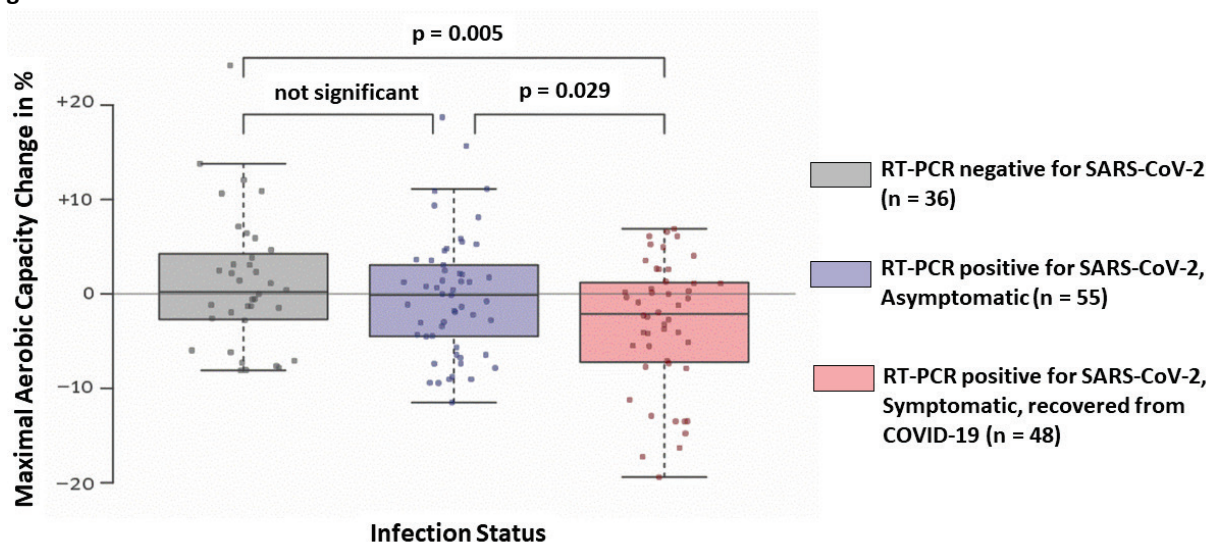
Key findings:

- The VO₂ max (a measure of ability to perform aerobic exercise) was lower in recovered recruits with symptomatic COVID-19 compared with recruits who had not had COVID-19 ($p = 0.02$).
- In recovered recruits, there was a significant decrease in VO₂ max compared with a baseline measure obtained prior to illness (Figure).
 - 19% of recruits with symptomatic COVID-19 had a loss of >10% VO₂ max.

Methods: Cross-sectional study of 199 Swiss Army recruits tested by RT-PCR in May 2020 during a COVID-19 outbreak and divided into 3 groups: RT-PCR positive, symptomatic, RT-PCR positive, asymptomatic, and RT-PCR negative. Endurance and aerobic capacity, including VO₂ max, were measured in all recruits at baseline (coincidentally 3-months prior to COVID-19 outbreak). Complete data at baseline and after the COVID-19 outbreak were available for 139 (70%) of the recruits and assessed for differences. **Limitations:** Timing of testing after the outbreak was unclear.

Implications: A decrease in pulmonary aerobic capacity was observed among military recruits who recovered from COVID-19. Long-term effects on lung function have been noted after mild to moderate influenza infection and may also be present after COVID-19. Additional research to understand the incidence of any long-term consequences is needed.

Figure:



Note: Adapted from Cramer *et al.* Difference in predicted maximal aerobic capacity before and after COVID-19 outbreak ($n = 139$). Licensed under CC BY 4.0

Effect of recombinant human granulocyte colony-stimulating factor for patients with coronavirus disease 2019 (COVID-19) and lymphopenia: A randomized clinical trial. Cheng *et al.* JAMA Internal Medicine (September 10, 2020).

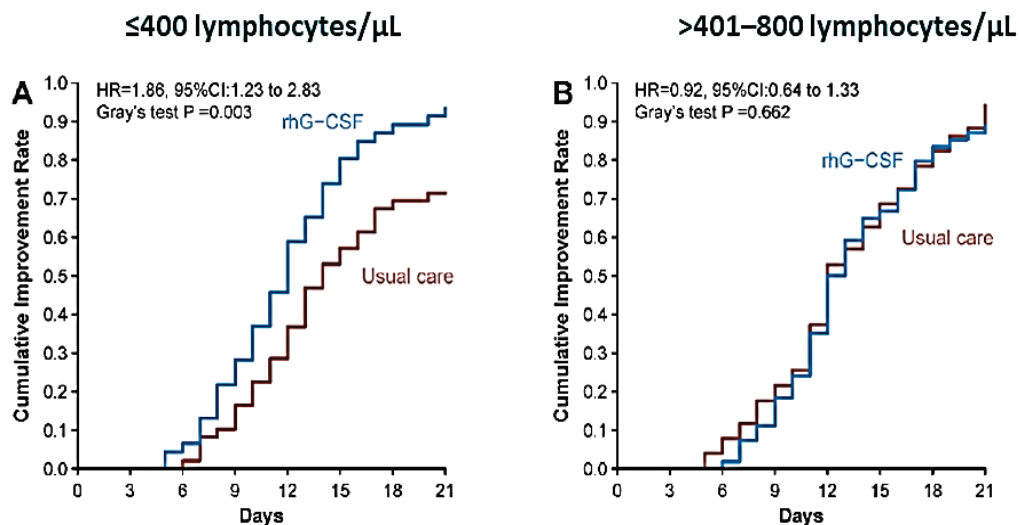
Key findings:

- Treatment of COVID-19 patients experiencing lymphopenia (lower than normal white blood cell levels) with recombinant human granulocyte colony-stimulating factor (rhG-CSF) to promote production of lymphocytes did not affect time to clinical improvement (12 with lymphopenia vs 13 days without, $p = 0.06$).
 - Among patients with peripheral blood lymphocytes ≤ 400 per μL , rhG-CSF treatment reduced time to clinical improvement compared with the usual care group (12 vs 14 days respectively, $p = 0.003$) (Figure).
- The rhG-CSF treatment group were less likely to progress to critical illness (2% vs 15%, difference -13%) and had lower mortality rates (2% vs 10%, hazard ratio 0.19) at Day 21.

Methods: An open-label, randomized clinical trial at three sites in China between February 18 and April 10, 2020 testing the effects of treatment of PCR-confirmed COVID-19 patients with rhG-CSF ($N = 100$) on days 0, 1, and 2 vs usual care ($N = 100$). Eligibility requirements were pneumonia, a blood lymphocyte cell count of 800 per μL or lower, and no comorbidities. Time to clinical improvement, progression to critical conditions and mortality was measured. **Limitations:** Small size and short observational time frame; exclusion of patients with co-morbidities.

Implications: rhG-CSF appears to prevent progression to severe disease and death in COVID-19 patients with lymphocytopenia ≤ 400 lymphocytes/ μL ; larger studies with broader patient inclusion are needed.

Figure:



Note: Adapted from Cheng *et al.* Improvement in patients with peripheral blood lymphocyte counts of $\leq 400/\mu\text{L}$ (A) or $>401-800/\mu\text{L}$ (B). Reproduced with permission from JAMA Intern Med. doi: 10.1001/jamainternmed.2020.5503. Copyright©2020 American Medical Association. All rights reserved.

Phylogenetic Analysis

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[The emergence of SARS-CoV-2 in Europe and North America.](#) Worobey *et al.* Science (September 10, 2020).

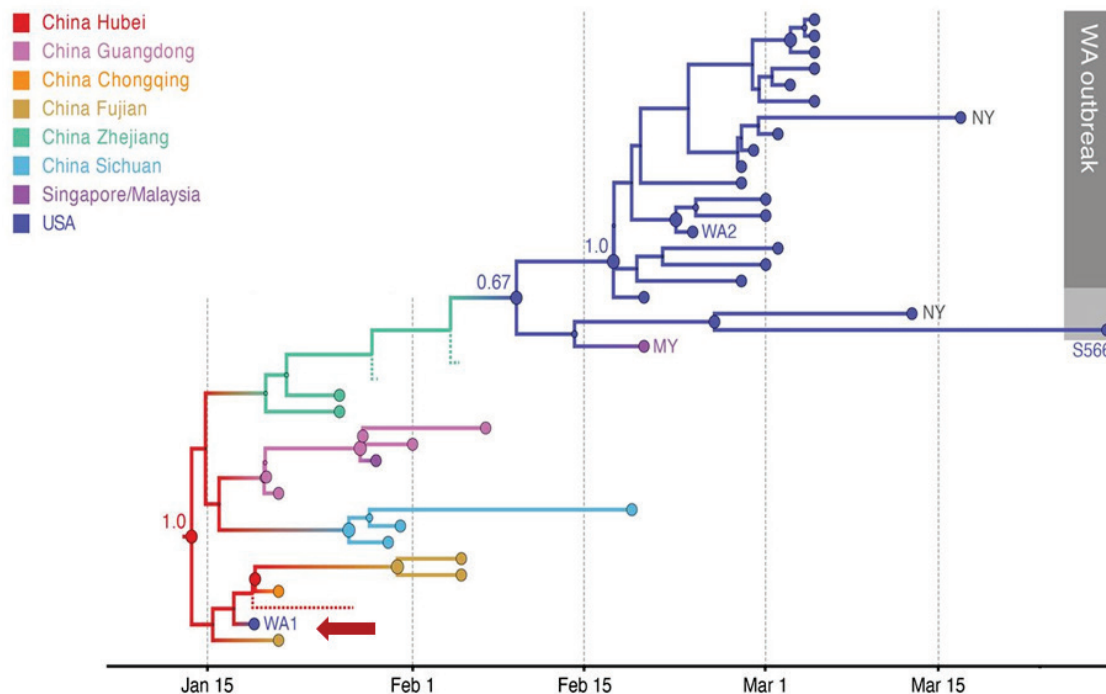
Key findings:

- Epidemic simulations suggest multiple independent entries of SARS-CoV-2 into the US occurred (Figure 1).
 - Models could not identify a scenario in which the viral sequence of the Washington State outbreak beginning February 15, 2020 could have derived from the first known US SARS-CoV-2 case (January 15, 2020).
- Phylogenetic reconstruction also suggests independent viral introduction from China to both Germany and Italy (Figure 2).

Methods: Using 294 SARS-CoV-2 viral genomes from Washington State collected from January 15 to March 15, 2020 through community surveillance for influenza, epidemic simulations were performed to model emergence of mutations of SARS-CoV-2 genome in the US. To determine if Italy's outbreak was initiated by a virus imported from the German outbreak, additional phylogeographic analyses were conducted. **Limitations:** Constraints placed on doubling time; genetic sequence data not available from all countries.

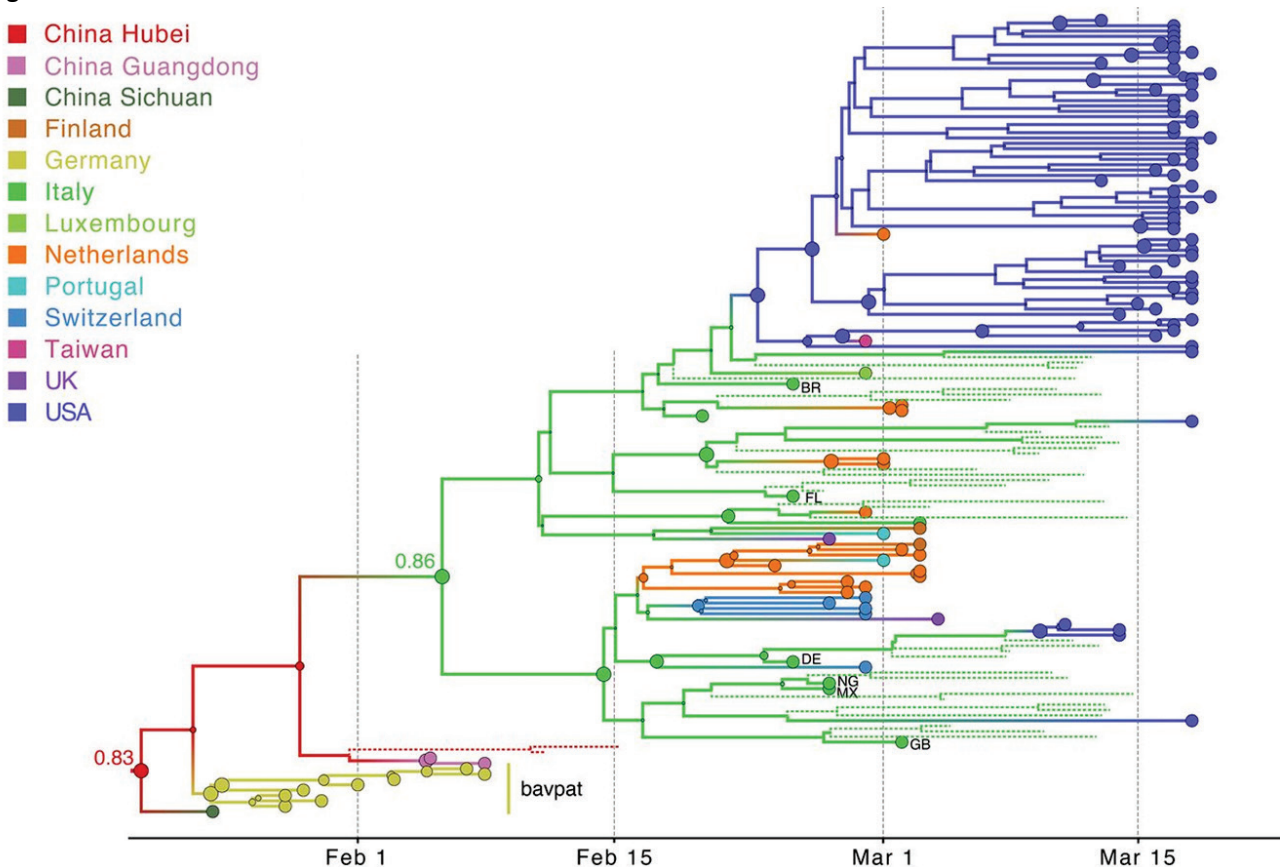
Implications: This study highlights that community-level respiratory virus surveillance combined with genomic analyses can be a useful tool to help distinguish sustained community transmission vs importation of new strains, which helps identify origin of clusters, delineate time and place of outbreak origins and define optimal mitigation measures for potential future outbreaks.

Figure 1



Note: Adapted from Worobey *et al.* Phylogenetic tree depicting the evolutionary relationships inferred between **WA1** (the first identified US COVID-19 case, **red arrow**), **the clade associated with the Washington State outbreak** and related viruses (gray box) and closely related viruses identified in Asia. Dotted lines represent branches with unsampled taxa. Numbers next to each node represent the level of support for that node using posterior probabilities, with 1 being the maximum. Licensed under CC BY 4.0.

Figure 2



Note: Adapted from Worobey *et al.* SARS-CoV-2 entry into Europe. A subtree for viruses from **the first outbreak in Europe** (Germany, bavpat), **identical viruses from China**, outbreaks in **Italy** and **New York**, and other locations in Europe. Dotted lines represent branches with unsampled taxa. Numbers next to each node represent the level of support for that node using posterior probabilities, with 1 being the maximum. Licensed under CC BY 4.0.

In Brief

Vaccines

- Persad *et al.* [Fairly prioritizing groups for access to COVID-19 vaccines](#). JAMA. Discusses how ethical values should guide allocation and prioritization of a COVID-19 vaccine to prevent harm, prioritize people who are disadvantaged, and achieve equal treatment. This approach would support prioritizing health care workers, people in high-risk occupations and housing, and people with high-risk conditions. Since these priority populations are likely to exceed initial vaccine quantities, prioritizing within these groups will be necessary.
- Callaway E. [The underdog coronavirus vaccines that the world will need if front runners stumble](#). Nature News. Highlights how the potential of “underdog” vaccines advancing in a slower, more conventional path could be critical. Early vaccines could fail, confer only partial protection, or work poorly in certain age groups; high costs and other barriers might make some of the front runners unsuitable for wide-scale deployment in lower-income countries.

COVID-19 and Influenza

- Miatech *et al.* [A case series of coinfection with SARS-CoV-2 and influenza virus in Louisiana](#). Respiratory Medicine Case Reports. A case series of four SARS-CoV-2 and influenza coinfecting cases in Louisiana. More severe disease in these four coinfecting patients was not shown despite multiple co-morbidities.
- Balakrishnan V. [In preparation for a COVID-19-influenza double epidemic](#). Lancet. Microbe. Strategies for dealing with COVID-19 and influenza as the Northern Hemisphere enters flu season by increasing testing for seasonal respiratory infections and strengthening influenza vaccination programs.

Immunity

- Mantovani *et al.* [Trained innate immunity, epigenetics, and COVID-19](#). NEJM. Describes how exposure to selected vaccines can increase innate immunity and trigger pathogen-agnostic antimicrobial resistance (known as trained innate immunity).
- Edridge *et al.* [Seasonal coronavirus protective immunity is short-lasting](#). Nature Medicine. Provides insights from infections from the four seasonal human coronaviruses that might reveal common characteristics applicable to all human coronaviruses. Describes monitoring of healthy individuals for more than 35 years showing that reinfection with the same seasonal coronavirus occurred frequently at 12 months after infection.
- Stephens *et al.* [COVID-19 and the path to immunity](#). JAMA. Describes immunity to COVID-19 and the key features and evolution of B-cell- and T-cell-mediated adaptive immunity to SARS-CoV-2. These features are important in forecasting COVID-19 outcomes and for developing effective strategies to control the pandemic.

Other Topics

- Viglione G. [How many people has the coronavirus killed?](#) Nature. Describes the impact of the pandemic on deaths in multiple countries and how it has overwhelmed death-registration systems. It highlights, with interesting graphics, how the true cost of the pandemic extends beyond deaths directly due to COVID-19.
- Pitstick *et al.* [A curious case of croup: Laryngotracheitis caused by COVID-19](#). Pediatrics. First documented case of COVID-19-associated croup in a 14-month-old male. Recommends that infants and children presenting with symptoms for croup should be tested for SARS-CoV-2 and appropriate isolation precautions should be taken to limit disease transmission.
- Adyel T. [Accumulation of plastic waste during COVID-19](#). Science. Describes the significant increase in plastic waste during pandemic due to PPE (billions of gloves used) and lifestyle changes. The writer warns the United Nations sustainable development goals may not be met.

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