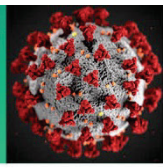
COVID-19 Science Update



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

***** Available on-line at https://www.cdc.gov/library/covid19 *****

Epidemiology

PEER-REVIEWED

Description of COVID-19 in HIV-infected individuals: A single-centre, prospective cohort. Vizcarra *et al.* Lancet HIV (May 28, 2020).

Key findings:

- Among 51 persons with HIV (PWH) diagnosed with COVID-19, median CD4 count near the time of COVID-19 diagnosis was 565 cells/µL (IQR: 296-782); 6 had CD4 counts <200 cells/µL.
- Compared with PWH without COVID-19, PWH with COVID-19 were more likely to:
  - Have higher BMI (OR 1.1, 95% CI 1.0–1.2).
  - Have been prescribed tenofovir (OR 3.7, 95% CI 1.6–8.7).
  - Have comorbidities (OR 6.2, 95% CI 2.6–14.5).
- The laboratory-confirmed COVID-19 infection rate was 1.2% in PWH and 0.96% for the general public.
- COVID-19 illness in terms of clinical, laboratory, and radiological features was similar comparing PWH with the general population.

Methods: A single-center prospective cohort study of 2,873 PWH in Spain to assess clinical, laboratory, and radiological presentation of COVID-19 compared with the general population in the same region. To identify characteristics associated with COVID-19 in PWH, multivariate logistic regression analyses were conducted. *Limitations*: Small sample size of COVID-19-infected PWH limits generalizability; large proportion of COVID-19 cases among PWH were based on clinical or radiological findings and not laboratory confirmed.

Implications: Compared with the general population, PWH with mostly robust CD4 cell counts had a similar risk of SARS-CoV-2 and clinical course of COVID-19 illness.

Does the pathogenesis of SARS-CoV-2 virus decrease at high-altitude? Arias-Reyes *et al.* Respiratory Physiology & Neurobiology (April 22, 2020).

Key findings:

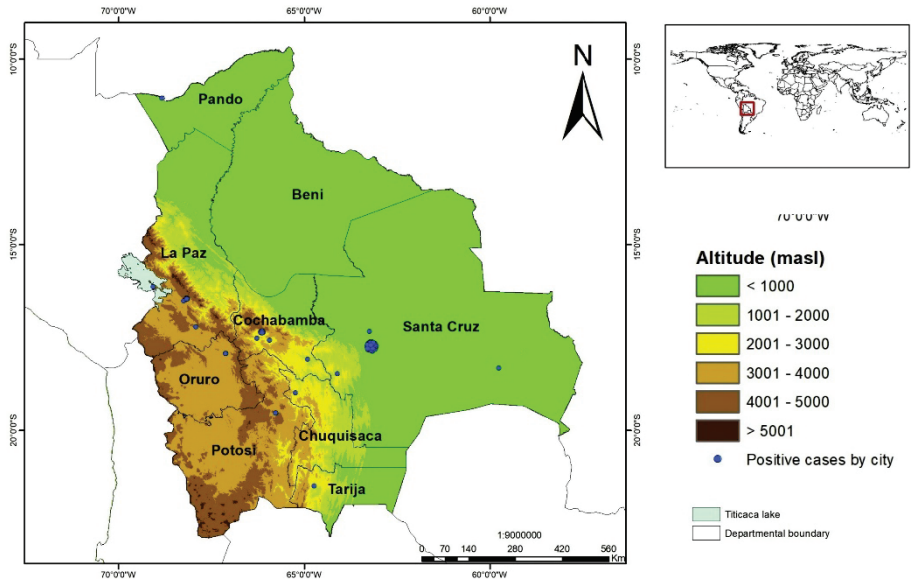
- High-altitude residents were less likely to be infected with SARS-CoV-2 (Figure 1).
  - Bolivia's high-altitude region had nearly three times fewer COVID-19 cases than in the lowlands.
  - COVID-19 infection rates in Ecuador's highlands were almost four-fold less than in the coastal areas (10 vs 35 cases per 100,000 persons).
- Globally, fewer COVID-19 cases occurred at altitudes >3000 meters (Figure 2).

Methods: Epidemiologic analysis that compared infection rates (number of COVID-19 cases divided by population size) in highland and lowland areas of Bolivia and Ecuador. Authors combined geographic COVID-19 data with a previously published elevation model to characterize the global distribution of COVID-19 cases based on altitude.

Limitations: Infection rate calculations did not adjust for confounding, including the well-recognized correlation between elevation and population density.

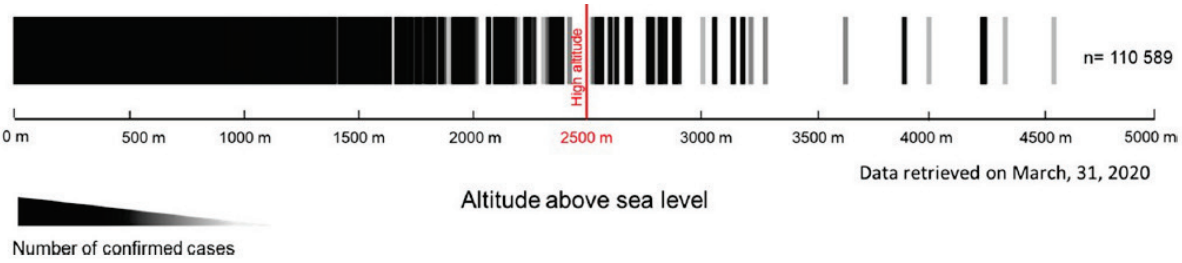
Implications: SARS-CoV-2 acquisition appears to be reduced among high-altitude inhabitants. The intriguing possible contribution of environmental factors (e.g., levels of ultraviolet light, lower air density) and physiological factors, such as reduced concentrations of angiotensin converting enzyme 2 (ACE-2) receptors in persons chronically exposed to low-oxygen conditions, to these findings remains to be elucidated.

Figure 1



Note: Adapted from Arias-Reyes *et al*. Geographic distribution of COVID-19 cases in Bolivia, by altitude. Cases in high-altitude regions are nearly 3-fold lower than in lowlands.

Figure 2



Note: From Arias-Reyes *et al*. Global distribution of COVID-19 cases, by altitude. Cases drastically decrease in altitudes >3000m. This article was published in Respiratory Physiology & Neurobiology, Vol 277, Arias-Reyes *et al*., Does the pathogenesis of SARS-CoV-2 virus decrease at high-altitude? Page 103443, Copyright Elsevier 2020. This article is currently available at the Elsevier COVID-19 resource center: https://www.elsevier.com/connect/coronavirus-information-center.

No evidence of secondary transmission of COVID-19 from children attending school in Ireland, 2020.

Heavey *et al.* Eurosurveillance (May 28, 2020).

Key findings:

- 6 COVID-19 cases, 3 students aged 10-15 years and 3 teachers were identified; epidemiological data indicated that cases were infected outside of school (e.g., household outbreak or travel).
- Within the school setting, 924 child contacts and 101 adult contacts of cases were identified; none of these contacts were diagnosed with COVID-19.

Methods: Study to trace school contacts of COVID-19 cases diagnosed in March 2020 in Ireland. Cases were identified through a national infectious disease surveillance system. All traced contacts who developed symptoms

consistent with COVID-19 were referred for testing. *Limitations*: Small number of cases; incomplete contact tracing since only symptomatic contacts were tested.

Implications: All 6 cases were infected outside the school setting. No secondary transmission was observed in the school. This study suggests that schools may not be a high-risk setting for COVID-19 transmission.

PREPRINTS (NOT PEER-REVIEWED)

Systemic and mucosal antibody secretion specific to SARS-CoV-2 during mild versus severe COVID-19. Cervia *et al.* bioRxiv (May 23, 2020). Published in Journal of Allergy and Clinical Immunology (November 20, 2020).

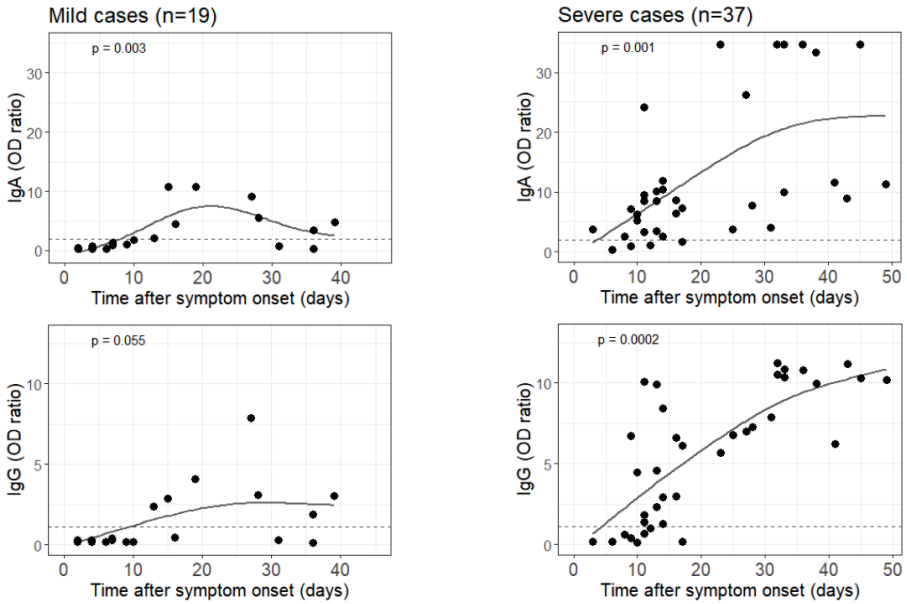
Key findings:

- Persons with severe COVID-19 had significantly higher serum titers of IgG and IgA than those with mild disease.
- IgG titers increased markedly after symptom onset with severe COVID-19, but moderately with mild disease (Figure).
- IgG titers showed a stronger increase over time in cases with mild pneumonia than those with mild disease without pneumonia.
- Among symptomatic healthcare workers (HCW) with positive SARS-CoV-2 RNA results, IgG and IgA titers in serum and in nasal secretions were correlated.

Methods: Assessment of serum SARS-CoV-2-specific IgG and IgA titers in 56 RT-PCR RNA positive cases with mild disease (n = 19; 7 of whom had mild pneumonia) or severe disease (severe pneumonia or ARDS, n = 37) and 109 HCW exposed to SARS-CoV-2. 21 of the 109 HCW tested positive by RT-PCR. Mucosal fluids, including tears, nasal fluid, and saliva were collected from 33 HCW. *Limitations*: Among HCW, small number of laboratory-confirmed cases.

Implications: Antibody responses to SARS-CoV-2 infection correlated with COVID-19 illness severity.

Figure:



Note: Adapted from Cervia *et al*. Modeling of SARS-CoV-2-specific IgA and IgG serum levels as a function of days between reported symptom onset and sample collection in mild (n = 19) versus severe COVID-19 cases (n = 37). Dashed lines indicate borders between positive and borderline or negative serum values of IgA (top) and IgG (bottom).

Mortality Measures

Epidemiologic measures of mortality can help quantify disease severity and burden. The ***case fatality rate***, the proportion of deaths that occur among people with a particular disease, is important in the context of clinical management and treatment. The ***mortality rate***, usually expressed as the number of deaths per population over a specified time period, provides a measure of deaths for an entire population.

In Odone *et al*. (**COVID-19 deaths in Lombardy, Italy: data in context, Lancet Public Health**), regional case fatality and mortality rate data in Italy provide different types of information and enable comparisons across regions to inform public health interventions (Table).

Table.

	Population (million)	Cases	Deaths	Case fatality rate	Mortality (per 100 000)
Lombardy	10·08	62 153	11 377	18·3%	112·9
Veneto	4·90	14 624	940	6·4%	19·2
Rest of Italy	45·39	88 378	9328	10·6%	20·6

Note: From Odone *et al*. COVID-19 case surveillance data, including case fatality rates and mortality rates from Lombardy, Veneto, and other regions of Italy—updated through April 15, 2020. This article was published in Lancet Public Health, Vol 5, Odone *et al*., COVID-19 deaths in Lombardy, Italy: data in context, Page e310, Copyright Elsevier 2020. This article is currently available at the Elsevier COVID-19 resource center: https://www.elsevier.com/connect/coronavirus-information-center.

COVID-19-related mortality can be compared with the expected mortality rate in a population to estimate excess deaths associated with COVID-19. The article below describes how excess mortality rates can be compared by subpopulations to identify potential disparities in COVID-19 severity.

Excess mortality in men and women in Massachusetts during the COVID-19 pandemic. Krieger *et al.* Lancet (May 27, 2020).

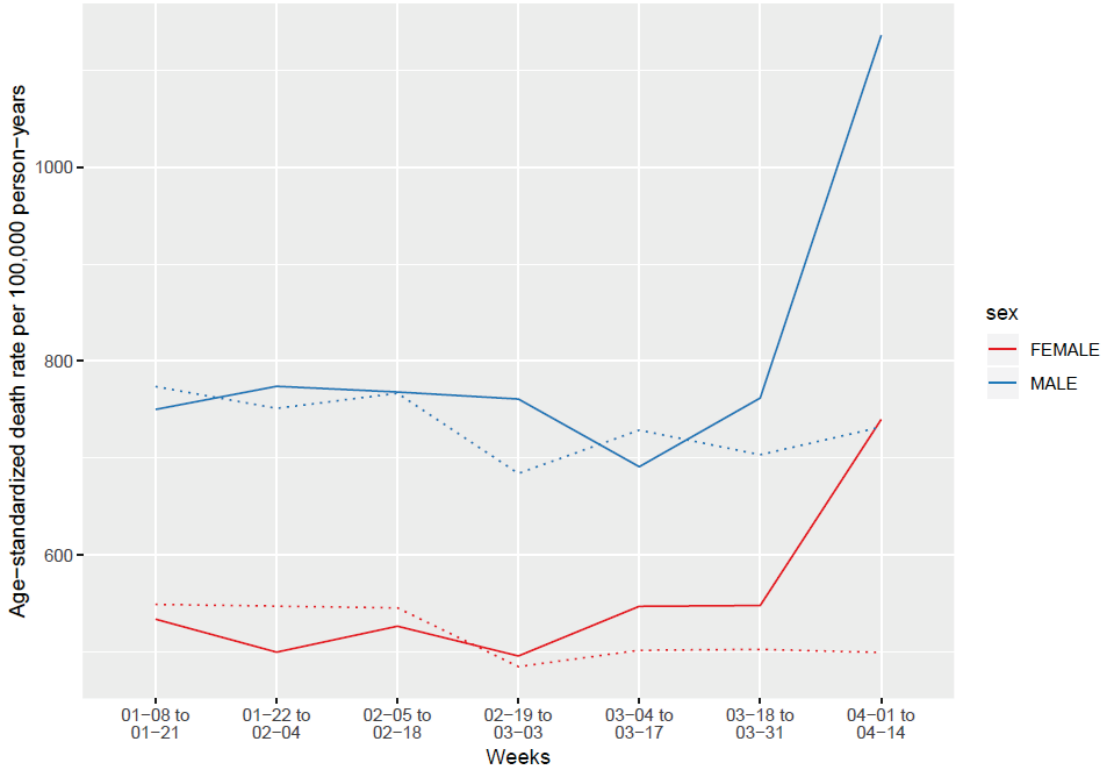
Key findings:

- The 2015–19 age-standardized mortality rate in Massachusetts was 499.3 per 100,000 person-years (95% CI 393.6–605.1) for women and 732.0 (95% CI 578.9–885.0) for men.
- The relative increase in the total number of deaths in Massachusetts during the COVID-19 pandemic was similar among men and women.
    - The age-standardized mortality rate ratio for 2020 versus 2015–19 was 1·48 (95% CI 1.13–1.94) for women and 1.55 (95% CI 1.19–2.03) for men.
- The absolute difference in mortality rates was larger for men than women (Figure).
    - The age-standardized rate difference between 2020 and 2015-19 was 240.4 deaths per 100,000 person-years (95% CI 75.5–404.4) for women and 404.1 per 100,000 person years (95% CI 158.8–648.1) for men.

Methods: Massachusetts mortality data for the period between January 1 and April 14, 2015-2019 was compared with the same period in 2020 to calculate excess deaths during the COVID-19 pandemic. *Limitations*: Geographically limited; excess deaths during the COVID-19 pandemic could be due to other factors.

Implications: Given higher baseline mortality rates in men, it might be misleading to focus on their higher death counts for COVID-19 relative to women. This study demonstrates that men and women have similar relative risk for death during the period of the COVID pandemic compared to the period before it. Estimates of excess deaths associated with COVID-19 may be useful for monitoring the impact of COVID-19 in different populations.

Figure:



Note: Adapted from Krieger *et al.* (**Supplementary Appendix**). Massachusetts weekly age-standardized death rates for **women** and **men**, 2020 (solid line) and 2015-2019 (dotted line), Jan 8 to April 14. This article was published in Lancet, Vol 395, Krieger *et al*., Excess mortality in men and women in Massachusetts during the COVID-19 pandemic, Page 1829, Copyright Elsevier 2020. This article is currently available at the Elsevier COVID-19 resource center: https://www.elsevier.com/connect/coronavirus-information-center.

Stay-at-Home Orders

As of April 7, stay-at-home orders were issued in 42 states to control COVID-19 spread and limit the strain on the U.S. healthcare system. These papers describe the effect of issuing stay-at-home orders on COVID-19 hospitalizations and infection rates in the US.

PEER-REVIEWED

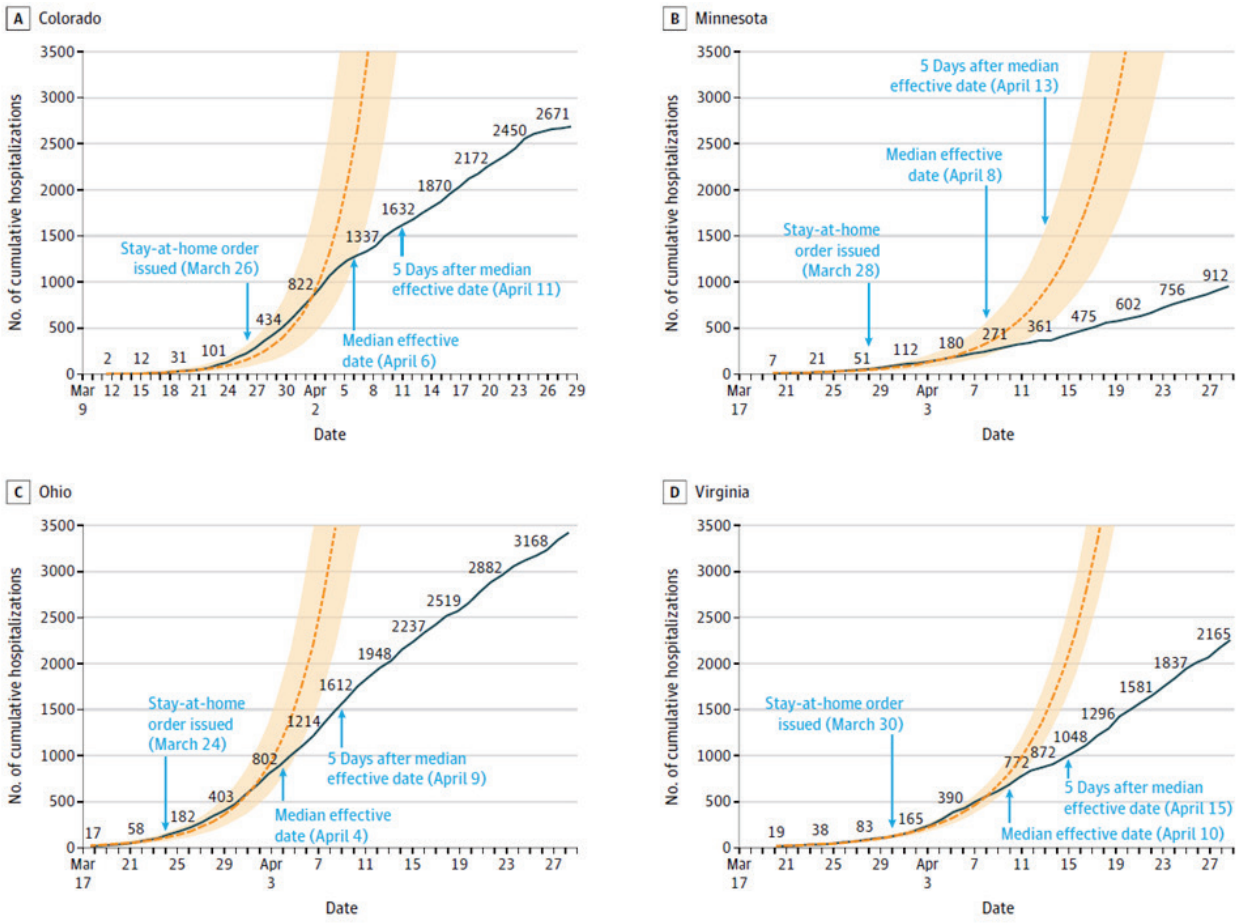
A. **Association of stay-at-home orders with COVID-19 hospitalizations in 4 states.** Sen *et al.* JAMA (May 27, 2020).

Key findings:

- In Colorado, Minnesota, Ohio, and Virginia, the rate of observed hospitalizations related to COVID-19 slowed following stay-at-home orders.

Methods: Between March 10 and April 28, 2020, COVID-19 hospitalizations were reported in four states that (1) issued stay-at-home orders and (2) had available hospitalization data for ≥7 days prior to, and ≥17 days after, the stay-at-home order issue date. A "best fit" (projected) exponential model was used to determine whether the number of observed hospitalizations deviated from the projected model following the stay-at-home orders. *Limitations*: Data presented for only four states.

Figure:



Note: From Sen *et al*. Number of projected (**orange dotted line** with 95% prediction bands depicted in translucent **orange**) vs observed (**dark blue line**) hospitalizations attributed to COVID-19 before and after stay-at-home orders in four states (A: Colorado; B: Minnesota; C: Ohio; D: Virginia). The median effective date of the stay at home order represented the estimated median incubation period plus the median number of days from illness onset to hospitalization and was defined as ≥12 days after the stay-at-home issue date. Reproduced with permission from JAMA. doi:10.1001/jama.2020.9176.

B. **The effect of state-level stay-at-home orders on COVID-19 infection rates.** Castillo *et al.* American Journal of Infection Control (May 24, 2020).

Key findings:

- COVID-19 infection rates decreased across all 42 states following issued orders.
    - On average, the doubling rate (time it takes for COVID-19 case counts to double) increased from 5–6 days to 14 days following stay-at-home orders.

Methods: For 42 states that implemented stay-at-home orders between March 19 and April 7, 2020, COVID-19 infection rates were calculated before and after the issued orders, and data was combined across states to estimate overall rates of change after orders were issued. *Limitations*: Availability of testing, particularly in the beginning of the outbreak, may have affected case counts.

Implications for 2 studies (Sen *et al*. & Castillo *et al*.): Rates of COVID-19 infection and hospitalization decreased following issued stay-at-home orders and/or other public health interventions implemented around the same time to curb COVID-19, such as school closures, social distancing, and use of masks. Findings demonstrate the utility of these interventions in decreasing disease burden and limiting strain on the healthcare system.

Steroid Therapy

COVID-19 begins with a viremic phase followed by an inflammatory phase. Although WHO advocates against glucocorticosteroid (steroid) use in COVID-19 patients due to increased risk of adverse events, steroids have been used for some COVID-19 patients with moderate to severe disease since therapies to manage the inflammatory phase are limited. Evidence on the safety and effectiveness of steroids in this patient population is emerging.

PREPRINT (NOT PEER-REVIEWED)

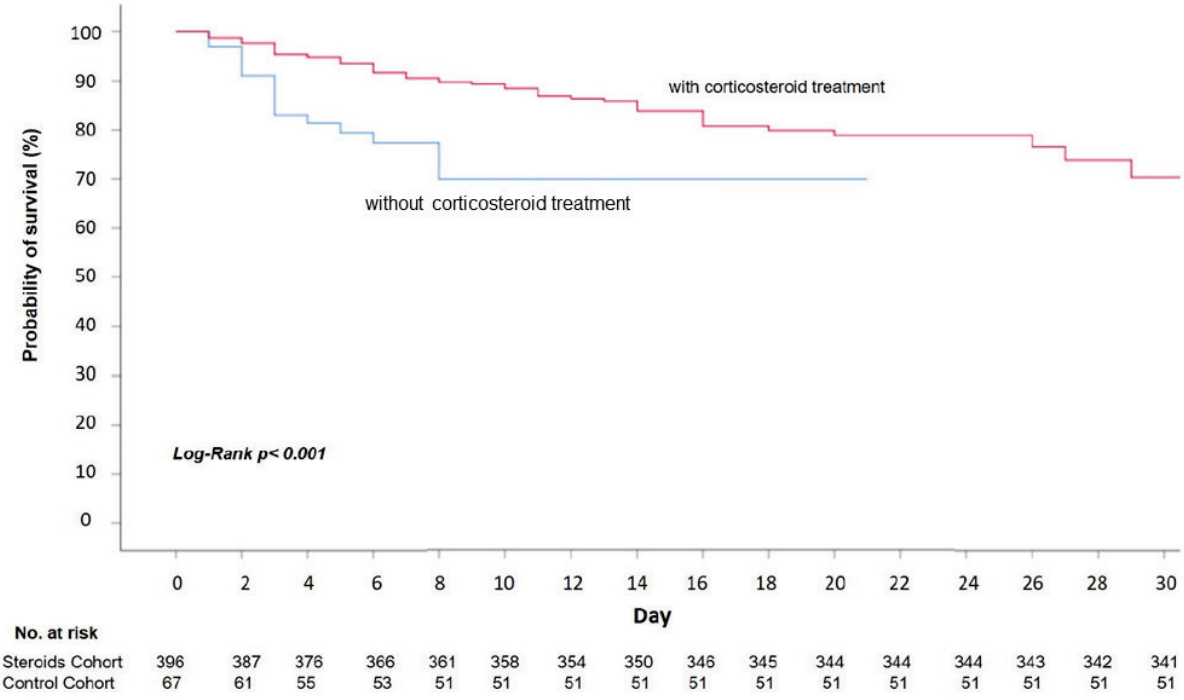
Impact of glucocorticoid treatment in SARS-CoV-2 infection mortality: A retrospective controlled cohort study. Fernández Cruz *et al*. medRxiv (May 26,2020). Published in Antimicrobial Agents and Chemotherapy (June 22, 2020).

Key findings:

- Steroid use in COVID-19 patients with ARDS and/or a hyperinflammatory syndrome was associated with lower in-hospital mortality (adjusted odds ratio [aOR] 0.51, 95% CI 0.27-0.96) and increased survival 30 days after treatment initiation (Figure).
- Differences in steroid dosing (initial single dose regimen vs steroid pulses [2-4 intermittent steroid infusions]) did not impact in-hospital mortality (aOR 0.88, 95% CI 0.45-1.73).

Methods: Retrospective cohort study in Spain of 463 persons diagnosed with COVID-19 pneumonia, combined with ARDS and/or hyperinflammatory syndrome (396 receiving steroids; 67 controls). In-hospital mortality and survival probability assessed through multivariable logistic regression, with examination of impact of different doses on mortality. *Limitations*: Differences in baseline characteristics between treatment and control groups, short follow-up period, single center study.

Figure:



Note: Adapted from Fernández Cruz *et al*. Probability of survival in **treatment** and **control** groups. COVID-19 patients with ARDS and/or hyperinflammatory syndrome treated with steroids had higher probability of survival 30 days after treatment initiation.

Implications: This study and an earlier study presented in the May 29, 2020 Science Update by Fadel *et al*. (**Early short course corticosteroids in hospitalized patients with COVID-19, CID**) on the association of steroid use with decreased likelihood of ICU admission, ventilation and death contribute to evidence on the benefits of steroid use in COVID-19 patients with moderate to severe disease. Optimal steroid treatment timing, duration, and dosing still need to be determined, ideally through randomized clinical trials.

In a recent correspondence, Tang *et al.* (**Caution against corticosteroid-based COVID-19 treatment, Lancet**) advised against routine steroid use in COVID-19 patients except in critically ill patients since improper use can increase the risk of osteonecrosis of the femoral head (inadequate blood supply to the head of the thigh bone), which occurred in nearly one-fourth of SARS patients receiving steroids.

Vaccines

PEER-REVIEWED

Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial. Zhu *et al.* Lancet. (May 22, 2020).

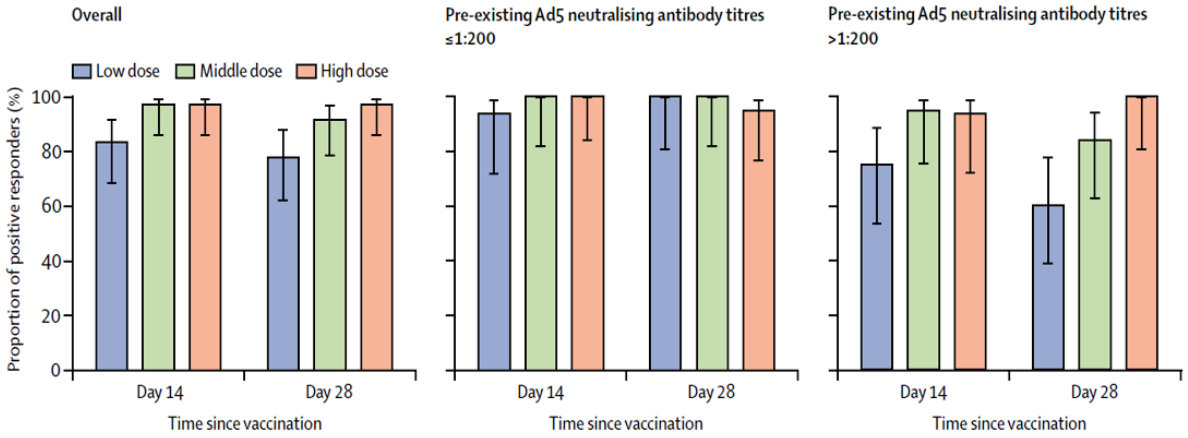
Key findings:

- Of 108 persons given a low, medium or high dose of recombinant adenovirus type-5 (Ad5) vectored COVID-19 vaccine:
  - Majority had specific T-cell responses that peaked 14 days after vaccination (Figure 1).
  - 50-75% generated at least a four-fold increase in antibodies able to neutralize SARS-CoV-2 (neutralizing antibodies) 28 days after vaccination (Figure 2).
  - 81% had at least one adverse event; most events were mild or moderate.
- T-cell and antibody responses were reduced among persons with high pre-existing neutralizing antibodies to Ad5.

Methods: Open-label, non-randomized trial of 108 persons in China given a low, medium or high dose of a recombinant Ad5-vectored COVID-19 vaccine expressing the SARS-CoV-2 spike glycoprotein (36 in each group). Participants were monitored for adverse events for 28 days post-vaccination. Antibody and T-cell responses were assessed 14 and 28 days after vaccination. *Limitations*: Small sample size, short follow-up period, no control group, and no participants older than 60.

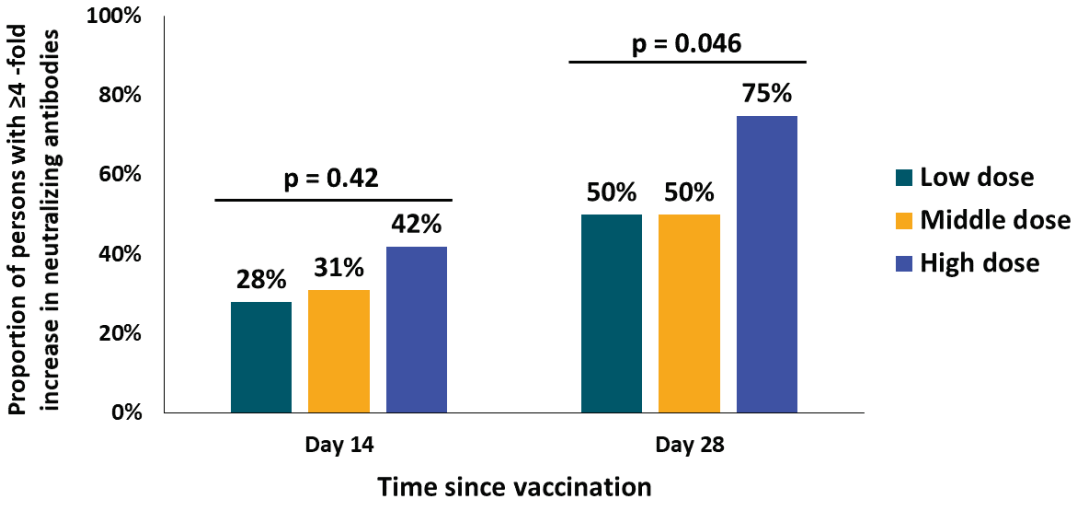
Implications: This first in-human trial demonstrated safety and immunogenicity of an Ad5-vectored COVID-19 vaccine in healthy adults with no underlying conditions. Additional human studies are needed to examine vaccine efficacy, including among older persons and those with underlying conditions who are at increased risk for severe disease.

Figure 1



Note: Adapted from Zhu *et al*. T-cell responses in all immunized persons, as well as stratified by pre-existing adenovirus type-5 (Ad5) neutralizing antibodies. T-cell responses peaked at 14 days after vaccination and were reduced among persons with high pre-existing Ad5 neutralizing antibodies. Proportion of positive responders (y axis) refers to the proportion of persons with samples that had detectable T-cell responses through the enzyme-linked immune absorbent spot assay. This article was published in Lancet, Vol 395, Zhu *et al*., Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial, Page 1845-1854, Copyright Elsevier 2020. This article is currently available at the Elsevier COVID-19 resource center: https://www.elsevier.com/connect/coronavirus-information-center

Figure 2



Note: Adapted from Zhu *et al*. Neutralizing antibodies to SARS-CoV-2 in immunized persons. The proportion of persons with ≥4-fold increase in neutralizing antibodies to live SARS-CoV-2 was highest at 28 days after vaccination and highest in the group receiving the **highest** dose. P values indicate comparison across the three groups of vaccinated persons. This article was published in Lancet, Vol 395, Zhu *et al*., Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial, Page 1845-1854, Copyright Elsevier 2020. This article is currently available at the Elsevier COVID-19 resource center: https://www.elsevier.com/connect/coronavirus-information-center.

Laboratory Science

PEER-REVIEWED

Predicting infectious SARS-CoV-2 from diagnostic samples. Bullard *et al.* Clinical Infectious Diseases (May 22, 2020).

Key findings:

- Of 90 samples that tested positive for SARS-CoV-2 by RT-PCR, 26 (29%) were culture positive consistent with the presence of replication-competent virus.
    - Positive culture samples had lower median Ct values (17 vs 27; Figure 1 – lower Ct value equates to higher viral RNA burden) and a lesser median number of days between symptom onset and RT-PCR test than negative culture samples: 3 vs 7 days (Figure 2).
- None of the samples that had a Ct value >24 or that were tested >8 days after symptom onset yielded a positive culture.

Methods: 90 samples obtained from people who tested RT-PCR positive for SARS CoV-2 were cultured. Relationships between Ct values (number of RT-PCR replication cycles needed to detect SARS-CoV-2), days between symptom onset and RT-PCR test, and positive viral culture were assessed. *Limitations*: Date of symptom onset was based on self-report; presence of replication-competent virus may not indicate infectivity; Ct values across different PCR platforms have not been standardized.

Implications: In the absence of viral culture, samples that test RT-PCR positive for SARS-CoV-2 with low Ct values (in this study <24) or were tested ≤8 days since illness onset could indicate presence of replication-competent virus. Specimens collected after 8 days and with high Ct values may not contain infectious virus.

Figure 1

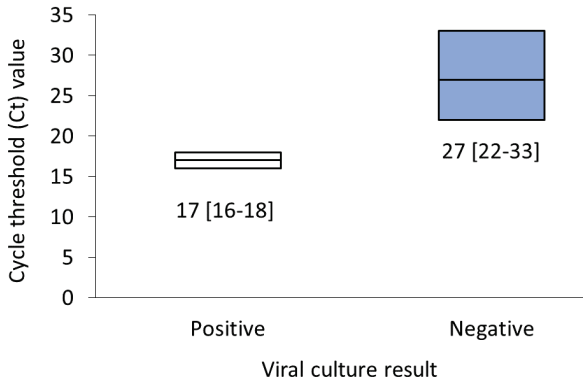
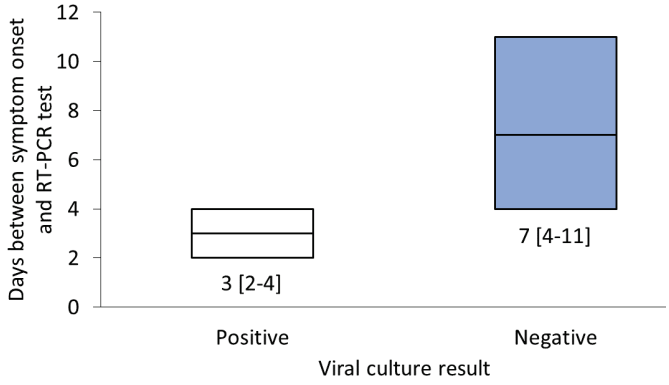


Figure 2



Note: Adapted from Bullard *et al*. **Figure 1**. Median and interquartile range of Ct values among SARS-CoV-2 RT-PCR positive samples that were culture positive (**white**; n=26) and culture negative (**blue**; n=64). **Figure 2**. Median and IQR of number of days between symptom onset and RT-PCR test among SARS-CoV-2 RT-PCR positive samples that were culture positive (**white**) and culture negative (**blue**). Available via Oxford University Press Public Health Emergency Collection through PubMed Central.

In Brief

Clinical Management

- Liu *et al*. **The pulmonary sequalae in discharged patients with COVID-19: A short-term observational study**. Respiratory Research. Of patients hospitalized with COVID-19 pneumonia, lung lesions resolved within three weeks after discharge in over half of patients; lesions in younger patients were more likely to be resolved within this period.
- Beach *et al*. **Delirium in COVID-19: A case series and exploration of potential mechanisms for central nervous system involvement**. General Hospital Psychiatry. A case series of 4 COVID-19 patients ≥70 years in which delirium/altered mental status was the only presenting symptom.
- Sandhu *et al*. ***Clostridioides difficile* in COVID-19 patients, Detroit, Michigan, USA, March-April 2020**. 9 patients co-infected with SARS-CoV-2 and *C. difficile*; highlights importance of prudent antibiotic use for treatment of severe COVID-19.

Contact Tracing

- Amit *et al*. **Mass-surveillance technologies to fight coronavirus spread: The case of Israel**. Nature Medicine. Israel successfully implemented a cell phone-based system to identify contacts of SARS-CoV-2-infected persons and isolate/quarantine as needed. Authors address privacy concerns related to digital contact tracing.
- Kleinman *et al*. **Digital contact tracing for COVID-19**. Canadian Medical Association Journal. Strengths and limitations of digital contact tracing; suggests an integrated approach of digital and traditional contact tracing to identify contacts of SARS-CoV-2-infected persons.

Non-Pharmaceutical Interventions

- Kupferschmidt K. **Why do some COVID-19 patients infect many others, whereas most don't spread the virus at all?** Science. Provides possible reasons some people may transmit COVID-19 while others do not, including variability in viral shedding and social distancing.
- Gilbert *et al*. **Preparing for a responsible lockdown exit strategy**. Nature Medicine. A framework for a "lockdown exit strategy" that emphasizes continued social distancing, increasing testing capacity, and implementing contact tracing to limit transmission as businesses and schools open up.
- Werner *et al*. **Long-Term care policy after COVID-19 - Solving the nursing home crisis**. NEJM. Nursing homes and long-term care facilities lack the resources needed to protect residents and staff from COVID-19; the US needs to invest in a safe and effective long-term care system.

Vaccine Development and Clinical Trials

- Lakdawala *et al*. **The search for a COVID-19 animal model**. Science. Animal models play a critical role in determining effectiveness of proposed SARS-CoV-2 therapeutic agents and vaccines. Non-human primates may be optimal for determining the best vaccine candidates, while cats and ferrets could be useful for studying transmissibility.
- Raabe *et al*. **Importance of pediatric inclusion in COVID-19 therapeutic trials**. Clinical Infectious Diseases. Authors urge researchers to include pediatric patients in COVID-19 therapeutic trials as they may have clinical presentations and medication responses that differ from adults.
- Trogen *et al*. **Adverse consequences of rushing a SARS-CoV-2 vaccine: Implications for public trust**. JAMA. Cautions against rushing a SARS-CoV-2 vaccine to market; highlights the importance of having enough data, including clinical trials, for vaccine development.