RESEARCHUPDATE
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Research Update is published by the Butler Center for Research to share significant scientific findings from the field of addiction treatment research.

Breaking Research on the Treatment of COVID-19 (SARS-CoV-2)

New evidence calls into question efficacy of Hydroxychloroquine (HCQ; Plaquenil) and Azithromycin (azm; Z-Pak) combo for patients with severe COVID-19 infections:

On March 16, Gautret et al. (2020) published a preprint article containing early results from an open label trial of one of the more promising off-label uses of the antimalarial medication Hydroxychloroquine and the antibiotic Azithromycin for the treatment of severe COVID-19 cases.

- The initial sample included 36 patients: 20 who received the medication combo and 16 no-treatment controls (either who refused the treatment or who met an exclusion criterion). The authors concluded that HCQ alone and the combo of HCQ and azm led to significantly lower levels of patients testing positive for the virus six days after treatment than those in the control group.
- However, inconsistencies in the design and reporting of the data soon emerged, which called into question the validity of the results. As a result, the publisher of the journal released a statement on April 3 that the article does not meet their standard of evidence and therefore should not have been published.
- Molina et al. (2020) conducted a small prospective study of the HCQ/azm combo in 11 patients. In the five days after treatment with the combo began, one patient died, two were transferred to the ICU and one patient discontinued use of HCQ/azm after four days due to negative side effects. Unlike in the Gautret et al. (2020) study, eight of the 10 patients still on the medications on days 5-6 tested positive for SARS-CoV-2.

Key Takeaway #1: There is not enough evidence in controlled research trials to suggest efficacy of the medication combo of HCQ/azm in the treatment of severe cases of COVID-19. Larger randomized, controlled trials are needed to determine if this medication combination improves outcomes for this population in the future.

Key Takeaway #2: The pressure to accelerate findings that will help fight this virus is profound. The peer review process must be undertaken carefully to ensure biased or inaccurate results are not inadvertently influencing treatment and care of patients during a period of frenzied adoption of any therapies that appear to be evidence-based.

Breaking Research on the Novel Coronavirus: Putting All the Pieces Together

COVID-19 is significantly more contagious than SARS was, and individuals seem to be at their most contagious early on in the illness:

Wölfel et al. (2020) conducted a virological analysis of nine hospitalized patients with clinically mild cases of COVID-19 in Germany to determine at what point individuals with upper-respiratory symptoms are most contagious.

- All of the individuals tested were young and had no significant pre-existing conditions; all were first tested when their symptoms were mild or newly present.
- Virus shedding in the throat was very high during the first week of symptoms (reaching a peak on day 4).
- Importantly, the majority of individuals tested seemed to be beyond their peak shedding when first tested, suggesting peak contagiousness may occur when symptoms are most mild and can be attributed to other upper respiratory tract infections.
- Peak concentrations of COVID-19 (SARS-CoV-2) were 1,000 times higher than what was found during the SARS (SARS-CoV) outbreak, suggesting that COVID-19 is not only significantly more contagious than SARS, but that peak contagiousness occurs much earlier (before day 5 vs. seven to 10 days after onset).

Key Takeaway: COVID-19 is an extremely contagious virus and is most contractible early on in the course of the illness. This highlights the importance of preventative tactics, such as social distancing and wearing masks, as a way to prevent the spread of the illness before people may realize they are infected.

Coronavirus infections (including COVID-19, SARS and MERS) in pregnant women found to be associated with a host of negative fetal outcomes:

Di Mascio et al. (2020) conducted a systematic review and meta-analysis of coronavirus spectrum infections, pooling data from 19 small studies of outcomes for pregnant women from all three outbreaks.

- Six studies representing 41 pregnant women who contracted COVID-19 were included in analyses. Over half (56.1%) experienced a pre-term birth (before 34 or 37 weeks), 91% of babies were delivered via cesarean section (c-section) and the rate of perinatal death was 7% (two of 41 cases).
- No maternal deaths were observed with COVID-19, which was significantly lower than what was observed in the studies for SARS and MERS (0% vs. 25.8% vs. 28.6%, respectively).
- 91.68% of pregnant women with COVID-19 had pneumonia.

Key Takeaway: Preliminary evidence based on aggregation of small case studies suggests that COVID-19, like previous coronaviruses, places pregnant women at increased risk for negative pregnancy and perinatal outcomes, including miscarriage, C-section and perinatal death. Larger datasets with additional variables are needed to better understand the full extent of the risk to pregnant mothers.

Data Modeling: Helpful Visualizations Related to the Coronavirus

Projections of virus spread continue to improve in short term but often only project a first wave:

The Institute for Health Metrics and Evaluation (IHME), part of the University of Washington, created an interactive model (updated daily) designed to show demand for and existing capacity of

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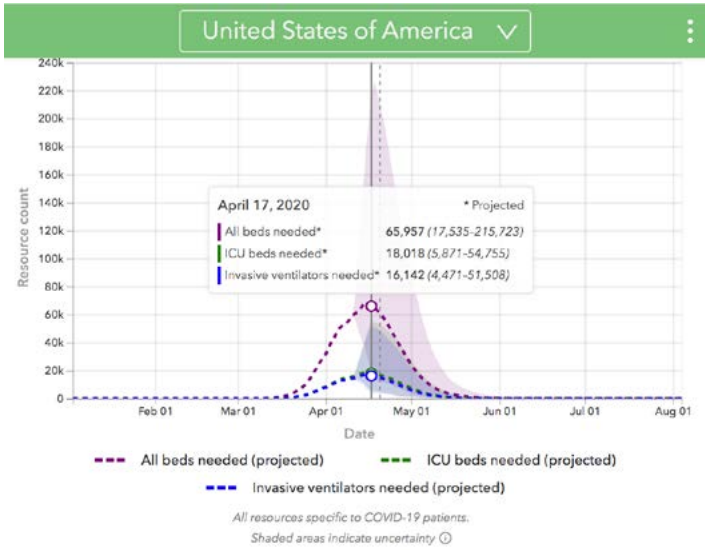
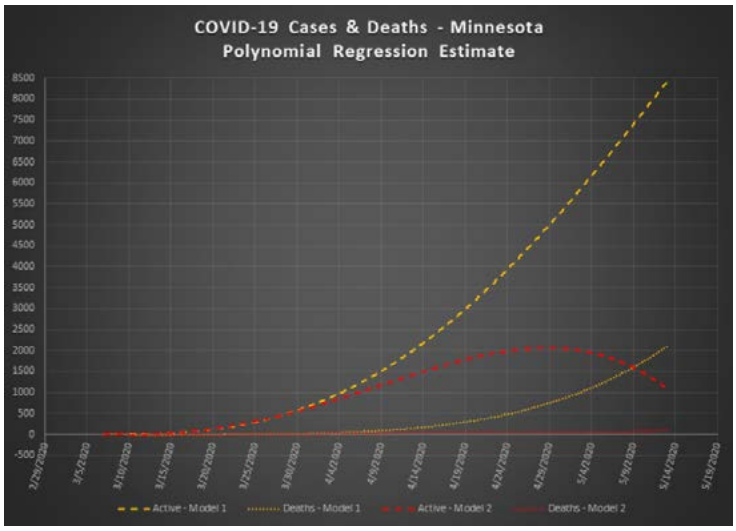
hospital services on both a local and global level during the COVID-19 pandemic.

- It is important to note that this model, along with most others, only seeks to predict the first wave of cases. These models are predicated on a number of assumptions (since the true outcome in the future is still unknown). One of the main assumptions in the IHME model is that full social distancing will occur through May 2020. Any deviations in these, both within and across countries/states, will lead to shifts in the model.
- For example, the model currently predicts that with social distancing through May 2020, the first wave of the epidemic would be over by early June.
- However, our population will continue to be at risk until a vaccine is widely available. After the first wave concludes, IHME estimates that 97% of the U.S. population will still be susceptible to infection, and therefore further measures are necessary to prevent a second wave.
- This could include the maintenance of social distancing, or an approach similar to South Korea, where widespread screening, testing, contract tracing and quarantines are used nationwide to isolate and eliminate localized infections before they are given a chance to spread.

Key Takeaway: We will have to continue to fight the novel coronavirus until a vaccine becomes available, and the amount of social distancing that will be required to stop subsequent waves will depend on how well-coordinated our nationwide containment response is from this summer forward.





Continue Physical Distancing (as much as possible)

There have been many questions regarding the accuracy and utility of data modeling of the spread of COVID-19. Skepticism in regard to these models' accuracy has abounded among the public because of how trajectories have changed over time. Below we explain why modeling is essential and helps officials to determine which courses of actions are most helpful at limiting the worst consequences of the pandemic.

One of our data experts modeled the rate of infection and death using the Johns Hopkins University COVID-19 dataset. Based on this data alone, trend lines forecast where cases and deaths may be in the future based on the rate of growth until the date the model was run. This helps to model if and how environmental changes (such as shelter-in-place mandates) change the course or trajectory of a forecast.

- The first example (yellow lines) was the projection for March 30, 2020, for Minnesota. This occurred four days after a shelter-in-place order was enacted, when Minnesota had 576 cases and 10 deaths due to COVID-19. At this point, the cases were projected to continue increasing beyond mid-May to more than 7,500 cases and 1,500 deaths as of May 11, 2020.
- The second example (red lines) is from nine days later, April 8, 2020, when Minnesota had 1,154 cases and 39 deaths due to COVID-19.
- Now 13 days into a shelter-in-place order, the total active cases curve was projected to peak around April 29 (at just over 2,000 cases), and decline through May.
- In the initial model run, the projected number of active cases on May 9, 2020, was approximately 7,500 with 1,500 deaths. In the latest model run, the projected number of active cases for the same date was 1,500, with under 100 deaths.
    - These projections show the effect of the actions taken to help stem the spread of COVID-19 in one state. Had no action been taken (e.g., orders to shelter-in-place), the data would have continued to follow the projected growths in the first (yellow) model. However, because of the shelter-in-place order, the models change to reflect the impact of the order on changes to the rate of infection in the ensuing nine days.

Key Takeaway: The current trajectories show the effectiveness of social distancing; however, given the contagiousness of COVID-19 and potential for rapid spread, the gains could be completely undone in a very short period of time without careful planning in the weeks ahead.

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Updates on Testing for COVID-19 (SARS-CoV-2)

There are two primary types of tests that have been developed to detect the novel coronavirus:

1. The Antigen Test (Polymerise Chain Reaction; PCR)

PCR tests were the first type to be developed for the novel coronavirus and represent the majority of testing being conducted in clinics and hospitals today. PCR tests directly detect the current presence of the virus in the body.

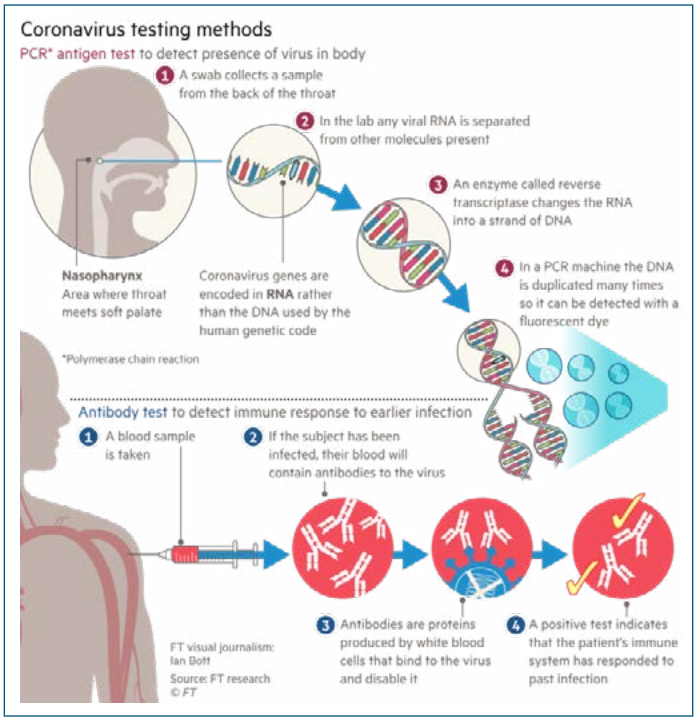
- PCR tests are conducted primarily by nasopharyngeal swab (a deep swab through the nose to the back of the throat)
- Most PCR tests must be sent to a lab in order to convert the virus' RNA-based genetic code to DNA
- Abbott, a medical device company, recently released a real-time PCR test that can detect a positive sample in as little as five minutes. This test requires the use of a small, portable platform, termed ID NOW, that can be used directly by providers in emergency rooms or urgent care clinics
- PCR tests such as the ID NOW test can detect the virus early on in the course of the illness, even when patients may still be asymptomatic.
- False negatives (returning a negative result when a virus is actually present) occur up to 30% of the time with different PCR tests, although the precision of the tests continues to improve.

2. The Antibody Test (Serological Tests)

Antibody tests for COVID-19 have more recently become available and test for past exposure to the virus. This is done through evidence of the antibodies that develop after an individual has been infected by a virus.

- Serology tests are conducted primarily by blood samples, with some tests requiring as little as a finger prick.
- Antibodies are not generated until seven to 10 days after infection, so a serological test is an ineffective indicator of early infection.
- Antibody tests are critical indicators of how many individuals within a population have been infected and will eventually be able to inform if all individuals infected with COVID-19 develop prolonged immunity, as well as how long any immunity lasts (anywhere from a few months to a few years).

Key Takeaway: Both antigen and antibody tests will be key in stemming the pandemic. Antigen tests are crucial at point-of-care locations to more swiftly identify those infected with COVID-19. Antibody tests are critical for understanding the extent of the infection in the broader population, in helping to determine who would be safe to return to work due to established immunity and in helping to track the course of the spread of infection.



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Expert Opinions

Is COVID-19 seasonal, with infections likely to ebb in the summer months?

Experts believe this is unlikely. In a rapid expert consultation published by the National Academies of Sciences, Engineering, and Medicine, the Committee on Emerging Infectious Diseases and 21st Century Health Threats addressed the potential seasonality of COVID-19.

- Data is still quite preliminary, but there is some indication from controlled lab tests that SARS-CoV-2 might survive and remain infectious in warm air as an aerosol longer than the influenza virus or the first SARS virus.
- While seasonal influenza strains follow a seasonal pattern (peaking in the winter, decreasing substantially in the summer), each of the ten influenza pandemics over the last 250 years have not: each one recorded a second wave peak of cases approximately six months after the virus emerged in the human population, regardless of what time of year each pandemic started.

Key Takeaway: The committee concluded that the highly infectious nature of COVID-19 in a population with no natural immunity to the virus would override any potential seasonality, suggesting cases will not decline in the summer months without continued aggressive mitigation tactics.

Ways to be a Part of the Solution: Join a Research Study

- **For anyone:** Researchers at the University of California-San Francisco aim to enroll a million individuals over the age of 18 in a research study that aims to gain insight into how the coronavirus spreads and identify new ways to predict and prevent future infections.

  o Download the Eureka Research App for your smartphone, and log into the app daily to fill out a one-minute survey.

- **For those in the U.S. who have a recent known exposure to COVID-19 without symptoms or who have a confirmed case within four days of the onset of symptoms:** Researchers at the University of Minnesota are testing Hydroxychloroquine as a preventative/early treatment of COVID-19. All assessments are completed online, and the medication is mailed directly to your home.

References

Di Mascio, D., Khalil, A., Saccone, G., Rizzo, G., Buca, D., Libarati, M., Vecchiet, J., Nappi, L., Scambia, G., Berghella, V., & D'Antonio, F. (2020). Outcome of Coronavirus spectrum infections (SARS, MERS, COVID 1 -19) during pregnancy: a systematic review and meta-analysis. *American Journal of Obstetrics & Gynecology MFM.* Advanced online publication. doi.org/10.1016/j.ajogmf.2020.100107

Gautret, P., Lagier, J.-C., Parola, P., Hoang, V. T., Meddeb, L., Mailhe, M., Doudier, B., Courjon, J., Giordanengo, V., Vieira, V. E., Dupont, H. T., Honoré, S., Colson, P., Chabrière, E., La Scola, B., Rolain, J.-M., Brouqui, P., & Raoult, D. (2020). Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial. *International Journal of Antimicrobial Agents.* Advanced online publication. doi.org/10.1016/j.ijantimicag.2020.105949

Institute for Health Metrics and Evaluation. (2020). *Hospital resource use* [Data set]. Retrieved April 9, 2020, from covid19.healthdata.org/united-states-of-america

Molina, J. M., Delaugerre, C., Le Goff, J., Mela-Lima, B., Ponscarme, D., Goldwirt, L., & de Castro, N. (2020). No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. *Médecine et Maladies Infectieuses.* Advanced online publication. doi.org/10.1016/j.medmal.2020.03.006

National Academies of Sciences, Engineering, and Medicine. (2020). *Rapid expert consultation on SARS-CoV-2 survival in relation to temperature and humidity and potential for seasonality for the COVID-19 pandemic (April 7, 2020).* nap.edu/read/25771/chapter/1

Voss, A. (2020, April 3). *Statement on IJAA paper.* International Society of Antimicrobial Chemotherapy. isac.world/news-and-publications/official-isac-statement

Wölfel, R., Corman, V. M., Guggemos, W., Sellmater, M., Zange, S., Müller, M. A., Niemeyer, D., Jones, T. C., Vollmar, P., Rothe, C., Hoelscher, M., Blelcker, T., Brünink, S., Schnelder, J., Ehmann, R., Zwirglmaler, K., Drosten, C., & Wendtner, C. (2020). Virological assessment of hospitalized patients with COVID-2019. *Nature.* Advanced online publication. doi.org/10.1038/s41586-020-2196-x

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