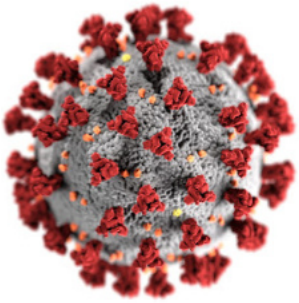

COVID-19 Action Newsletter

UT Southwestern Department of Internal Medicine
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The Situation: Dallas Risk Level Down from 'Red' to 'Orange'

For the first time in the pandemic, Dallas County's risk level has been downgraded from the highest risk red level "Stay Home Stay Safe" to orange "Extreme Caution." The decision was recommended to county leaders by its Public Health Advisory Committee on the basis of sustained improvement in 12 indicators, reviewed in the *Epi Corner* section below.

In the world as of September 4, 2020, a total of 26,347,573 cases of Covid-19 and 869,600 deaths have been confirmed. In the United States, there have been 6,153,735 cases, the most in the world followed in order by Brazil, India, Russia and Peru. China is now 35th in the world with 89,999 cases. Deaths in the U.S. through August 21 have been estimated at 186,834.[1]

From March 10 through August 28, there have been 70,376 confirmed cases of Covid-19 reported from Dallas County with 898 deaths, about 26% of these from long-term facilities.[2] Of hospitalized cases in Dallas County, 70% have been under 65 years of age. Diabetes mellitus has been seen in about one-third of all hospitalized patients. More men than women have died, and 53% of the hospitalized cases have occurred in the Hispanic population. As of 8/28, 898 deaths have been analyzed by race, with 27% occurring in Whites (actual White population 29%), Hispanics 45% (population 41%), Blacks 24% (population 24%), and Asians 3% (population 7%). Specimens submitted for diagnosis of respiratory viruses show continuing positivity rate for SARS-CoV-2 of 11.0% as of 8/22/20, down from a peak value of 30.5% during the week ending 7/4/20.

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Feature Article

Convalescent Plasma in Covid-19: A Literature Review of Safety and Efficacy

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Treatment options are limited at the onset of an epidemic or pandemic, as has been the case during the global pandemic of SARS-Coronavirus 2 (Covid-19). One potential therapy is the use of convalescent plasma, in which plasma collected from individuals following resolution of infection and antibody development, is transfused to a patient. This passive antibody transfer could be used to prevent clinical infection in individuals with recent pathogen exposure or to blunt the severity of disease in symptomatic patients. Convalescent plasma can contain both neutralizing and non-neutralizing antibodies. In the case of Covid-19, neutralizing antibodies recognize and bind to the Receptor Binding Domain (RBD) on the Spike protein to prevent viral fusion and entry into cells. Neutralizing antibodies can also interact with other immune mediators or cells via complement activation, antibody-dependent cellular cytotoxicity or phagocytosis. Although non-neutralizing antibodies bind to pathogens and do not interfere with their ability to replicate, they could contribute to enhanced recovery.

Convalescent serum or plasma has been used for over 100 years as a therapeutic option to combat infectious disease outbreaks. It was first used during the 1918 Spanish flu pandemic. A 21st Century meta-analysis of the 1918 data revealed 21% less mortality in patients treated with convalescent serum.[1] Its use was prevalent until the 1940-1950s, when antibiotics and vaccines became first line therapy to treat and prevent many outbreaks. However, the use of passive antibody transfer has continued through the use of hyperimmune globulin products, such as Anthrasil, CytoGam, VARIZIG and HepaGam B.

There was a resurgence of interest in convalescent plasma use in the 21st Century with the emergence of the SARS respiratory outbreak in 2003 and more recently, the Ebola epidemic. A non-randomized comparative study published in the *New England Journal of Medicine* in January 2016 found that convalescent plasma transfusion with unknown levels of neutralizing antibodies was not associated with a significant improvement of survival.[2] A 2015 meta-analysis of 32 studies of convalescent plasma in treatment of severe viral acute respiratory infections found a lower risk of mortality in the groups treated with convalescent plasma/serum (odds ratio 0.24); however, the authors concluded, "Studies were commonly of low or very low quality, lacked control groups, and [were] at moderate or high risk of bias."[3]

The use of Covid-19 convalescent plasma became readily available when on March 24, 2020, the FDA approved an emergency use authorization. Initially, patients had to be approved individually by the FDA through the emergency investigational device use pathway. The Mayo Clinic worked with the FDA and the Biomedical Advanced Research and Development Authority (BARDA) to create and fund a multicenter, open-label protocol that would facilitate use of convalescent plasma in hospitalized patients. This Expanded Access Program (EAP) had the primary goal of providing access to and assess the safety of Covid-19 convalescent plasma. In addition to EAP or single patient emergency IND, the FDA has allowed for convalescent plasma use in clinical trials, which requires submission through the traditional IND regulatory pathway.

While the use of convalescent plasma was evolving in the United States, preliminary data from the Chinese experience were published. On March 18th, a non-comparator study of 10 patients with severe Covid-19 were transfused one dose of 200 ml of convalescent plasma with neutralizing antibody titers >1:640. All 10 patients had improvement in symptoms, and four had significantly decreased oxygen requirements. After transfusion, neutralizing antibody titers either rapidly increased or remained at a high level (>1:640), and viral load became undetectable in seven patients who had prior viremia. Of note, median time for onset of illness to transfusion was 16.5 days.[4] Less than 10 days later, another report of five patients with Covid-19 and acute respiratory distress syndrome demonstrated clinical improvement in patients who received convalescent plasma with a neutralization titer >1:40 between hospital days 10 and 22.[5] These studies, though provocative, lacked a randomized design and sufficient sample size to support definitive conclusions.

A subsequent multicenter randomized control trial was begun in Wuhan, China, in early February to compare clinical improvements in patients with severe and life-threatening Covid-19 treated with standard treatment versus convalescent plasma. However, the study was terminated due to significant containment of the virus and inability to enroll enough patients.

On July 3rd, results of a randomized control trial comparing 300 ml of convalescent plasma with neutralizing antibody titers of at least 1:80 to standard of care in hospitalized patients were published. The trial was prematurely terminated after finding that the majority of patients had pre-existing neutralizing antibody at titers comparable to those found in convalescent plasma, questioning the study's potential benefit. At the study's end, the available data showed no difference between groups in mortality, hospital stay or day-15 disease severity.[6]

The Mayo EAP provided an update of convalescent plasma use in 20,000 hospitalized patients in which, finding no excess risk of complications, they concluded that it is safe for patients with Covid-19.[7] On August 12, 2020, the Mayo EAP published their initial efficacy findings after evaluating data collected from 35,322 patients transfused between April 4 and July 4. They reported that earlier use of convalescent plasma (i.e. within three days of Covid-19 diagnosis) and the use of convalescent plasma with higher antibody levels (>18.45 S/Co) were associated with reduced 7-day and 30-day mortality. The authors acknowledge limitations of the design without a control group and the lack of quantification of antibody titers prior to transfusion.

In early September, the FDA granted Emergency Use Authorization for convalescent plasma. For example, there are questions about optimal timing of convalescent plasma transfusion during disease. Based on prior experiences with convalescent plasma in other outbreaks and the Mayo findings, earlier use in severely ill patients may increase chances of improvement. However, many questions remain regarding efficacy of convalescent plasma. Fortunately, several randomized clinical trials are ongoing in the U.S. Studies are currently evaluating its use as prophylactic treatment in those exposed who have not yet mounted an antibody response or as a treatment in mildly symptomatic outpatients. Additionally, product potency, such as neutralizing antibody titers and amount of convalescent plasma to transfuse, may also affect outcomes. Thus, more studies are needed to draw better conclusions regarding the use of convalescent plasma to treat Covid-19.

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Editorial Note: The Mayo Clinic appraised their 3 month experience with convalescent plasma by concluding that there was a positive benefit of plasma with high titers of antibody was used and that the patients were transfused early in the course of illness.[1] Subsequently, however, an NIH Panel concluded that, whereas the procedure was safe, its efficacy could be questioned due to the lack of a randomized control group. The Panel also questioned the present status of antibody determinations. The Panel concluded that the data were insufficient at present to recommend "for or against the use of convalescent plasma for the treatment of Covid-19".[2]

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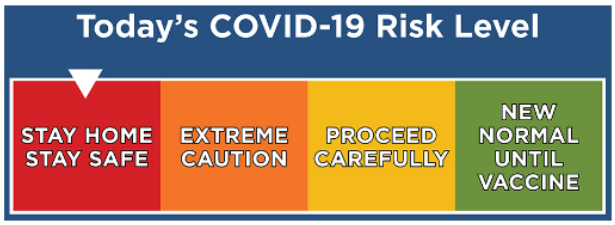
Epi Corner

How Dallas County's Covid-19 Risk Level Is Determined

Last April, County Judge Clay Jenkins appointed a 10-member Public Health Advisory Committee, headed by UT Southwestern's Director of Infectious Diseases and Geographical Medicine, Dr. Trish Perl, to advise the County Government on response to the pandemic. The other members are listed at the end of this article. One of the Committee's main responsibilities has been to develop and manage a system for assessing the level of risk of Covid-19 disease transmission in the county from which to advise county residents on precautions to minimize their risk of getting the illness.

The first decision was to provide a simple color-coded sign showing 4 risk levels that County residents could easily recognize and interpret. The resulting sign, displayed on the County's Covid-19 webpage, shows the designation of the highest risk level "Stay Home, Stay Safe" where it remained through the huge surge in cases and deaths in June and July. An accompanying table recommends how residents should handle various common situations to remain safe at each risk level. Go to: https://www.dallascounty.org/Assets/uploads/docs/hhs/2019-nCoV/FINAL-POSTED-Updated-Headings-PublicHealth-DallasCounty-COVID19-Guidance-Public-05132020.pdf



From an extended review of potential risk indicators and sources of data to monitor them, early deliberations explored a short list of only 3 or 4 metrics that, when met, would automatically signal a move to the next lower risk level. With further debate, however, it became clear that a legalistic decision from such a short list was likely to result in a decision with which a consensus of experts would disagree. Eventually the Committee arrived at a list of 20 metrics that would provide a comprehensive view of the many determinants of the risks from relaxing precautions. The decision to change the risk level would then be reached by a consensus of the Committee from this broad view of the situation.

The table below lists the 20 metrics the Committee considered to make its decision. They are grouped into 5 categories indicating the dimensions of Covid-19 risk considered.

Metrics for determining the level of Covid-19 risk in Dallas County
COVID-19 Infection Rate • Sustained decline in daily confirmed and probable COVID-19 cases for 14 consecutive days, as reflected in the 7-day rolling average with a 7-day lag • Confirmed and probable cases less than 10 cases per 100,000 population or 270 cases per day over 14 consecutive days with a 7-day lag • Less than 10% of tests conducted over 14 days are positive for COVID-19* • Sustained decline in suspected/confirmed COVID-19 illness seen in the emergency department-trending down over 14 days, as reflected in the 7-day rolling average • Decrease in confirmed COVID-19 hospitalizations per day (census) , as reflected in the 7-day rolling average over 14 days • Sustained decline in confirmed COVID-19 hospital admissions - trending down over 14 days, as reflected in the 7-day rolling average • Sustained decrease in COVID-19 confirmed and probable deaths per capita rates, as reflected in the 7-day rolling average over 14 days **Diagnostic Testing and Surveillance** • All symptomatic, asymptomatic, and high-risk individuals or contacts can access testing (qualitative • Tests are readily available for all essential personnel (qualitative) • Adequate supply of equipment, reagents and testing supplies (qualitative) • Health Department receives 80% of test results within 48 hours (hospital and commercial labs)* **Case and Contact Investigations** • At least 40% of new cases are from identified contacts**

Healthcare Readiness

- COVID-19 patients occupy <20% med/surg (ward) beds and <30% of ICU beds, as reflected in the 7-day rolling average over 14 days
- Sufficient PPE for majority of healthcare facilities, at-risk facilities, and essential personnel for 4 weeks (qualitative)
- 80% of acute-care hospitals with more than 250 beds have adequate staffing without RAC/state support for care (qualitative)

Protecting at-Risk Populations

- Sufficient testing, quarantine, and isolation in long-term care facilities (qualitative)
- Decreasing long-term care, schools, and other congregate facilities (homeless shelters, correctional facilities), and essential workplace (e.g. meatpacking) outbreaks with COVID-19 cases and deaths in residents and staff—report aggregated numbers
- Sufficient PPE for majority long-term care facilities, and essential personnel for 2 weeks (qualitative)
- 80% of long-term care facilities have adequate staffing without RAC/state support for care (qualitative)
- >80% of people wearing masks correctly in public indoor settings (e.g., mass transit, shopping), based on direct observation by a standard, consistent method, by week**

*Metric not met. **Metric could not be assessed.

On September 2, the Committee's review found that 16 metrics were met, 2 were not met, and 2 could not yet be assessed. Judging from which metrics were met and the consistency and rate of improvement in the situation, the Committee concluded that the reduction in the risk level was sufficient to justify the change from level "Red" to level "Orange" on the risk sign. This was transmitted to the County Judge along with the list of conditions still not met and a precautionary warning to the public that extreme caution was still required to prevent another resurgence like what had occurred after the last relaxing of precautions in June. The following day the County Judge exercised his emergency authority to order the change, shown to the right.

The Committee's membership in addition to Dr. Perl includes Debbie Branson, attorney and former head of the Parkland Board; Ruby Blum, health policy and public health advisor to the County Government; Dr. Mark Casanova, President of the Dallas County Medical Society; Dr. Fred Cerise, CEO of Parkland; Dr. Christi Columbus, chief of Infectious Diseases at Baylor University Medical Center; Dr. Robert Haley, Chief of the Epidemiology Division in the Internal Medicine Department at UT Southwestern; Dr. Philip Huang, Director of Dallas County Health and Human Services; W. Stephen Love, CEO of the Dallas-Ft. Worth Hospital Council; and Peter Urbanowicz, health advisor and former Chief of Staff to the Secretary of the U.S. Department of Health and Human Services.

From the Editors

The editors thank Dr. De Simone for her feature article on convalescent plasma.

The aim of this weekly newsletter is to serve as a source of information for the UT Southwestern community which can lead to better understanding and control of a new disease (COVID-19) caused by the pandemic spread of an emerging viral pathogen (SARS-CoV-2). We welcome questions, comments, and suggestions for topics and authors.