

TGIF everyone

I hope everyone had a productive and safe week

Today I have chosen a variety of topics. The first two articles highlight infection in college aged people. These reports suggest in addition to enforcement of mask requirements, stricter mitigation measures and comprehensive mitigation strategies are required at colleges and universities. The third article is a meta-analysis on use of tocilizumab in treatment of SARS-CoV-2. All included studies were observational. The next article is a meta-analysis on use of plasma and SARS-CoV-2 infection. This review did include RCTs. Overall the report did not see a benefit, but sub analysis suggested earlier initiation of therapy might decrease the rate of mortality. The next article looks at use of HCQ for prophylaxis. As in other reports there was no benefit. The last article could be a game changer if investigators are correct that early in the pandemic the real R_0 is actually over 4.

Have a great weekend

Ed

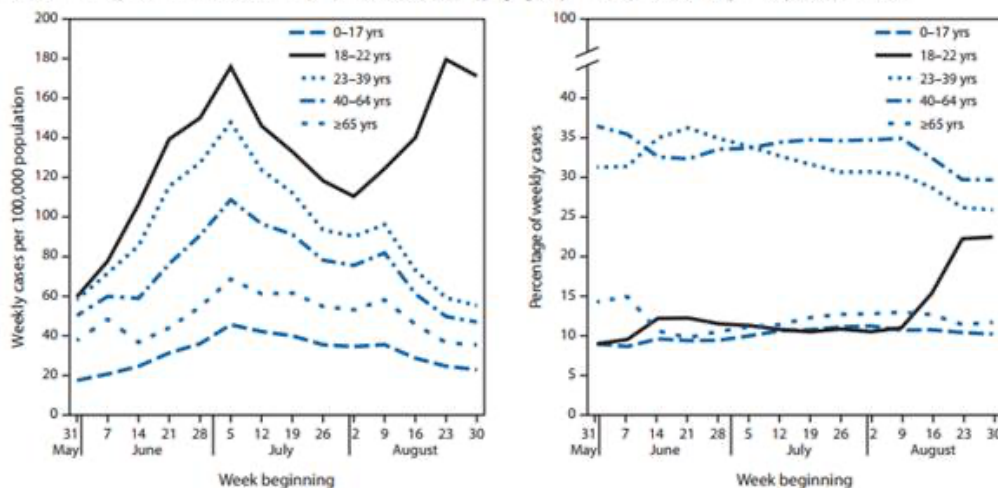
Recent Increase in COVID-19 Cases Reported Among Adults Aged 18–22 Years — United States, May 31–September 5, 2020

MMWR published online September 29, 2020

This CDC report documented weekly COVID-19 incidence among younger adults aged 18–22 was up 55% in August, and more than doubled in the Northeast and Midwest. From Aug. 2 to Sept. 5, the proportion of cases occurring among adults ages 18 to 22 approximately doubled from 10.5% to 22.5%. By U.S. Census region, weekly incidence of COVID-19 rose 144% in the Northeast and 123.4% in the Midwest, with an increase of 43.8% in the South. National weekly incidence of COVID-19 cases among the 18–22 age group increased from 110 to 180 cases per 100,000 from Aug. 2 to Aug. 29, a 62.7% rise, before dipping to 171 per 100,000 from Aug. 30–Sept. 5.

Examining demographic data, the proportion of weekly cases among white adults ages 18 to 22 increased from 33.8% to 50.8% from May 31–June 20, and the proportion of cases from Aug. 2–Sept. 5 grew from 52.1% to 77.3%. However, this report noted incidence in other racial/ethnic groups remained stable or declined.

FIGURE 1. Weekly COVID-19 incidence in case surveillance data,* by age group — United States,† May 31–September 5, 2020



Comment: In the United States, approximately 45% of persons aged 18–22 years were enrolled in colleges and universities in 2019. As these institutions reopen, opportunities for infection increase; therefore, mitigation efforts and monitoring reports of COVID-19 cases among young adults are critical.

Multiple COVID-19 Clusters on a University Campus — North Carolina, August 2020

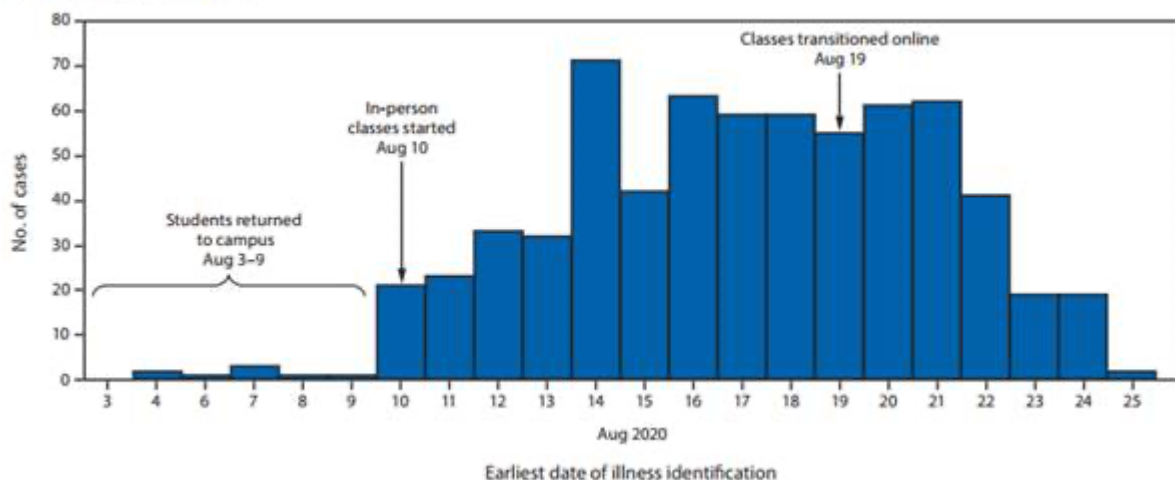
MMWR published online September 29, 2020

Multiple COVID-19 clusters were detected at a university in North Carolina, with 670 laboratory-confirmed cases of COVID-19, 96% of them among patients age 22 or younger. Residence halls were at 65-80% capacity, with most students in double rooms. Undergraduate enrollment was 19,690 students, and 5,800 students resided on campus as of Aug. 10, when in-person classes began.

The university opened on Aug. 3, and over the next 3 weeks, 18 clusters of five or more epidemiologically linked cases within 14 days of each other were reported, and 30% of cases were linked to a cluster, the authors said. Among the 18 case clusters, eight were in residence halls, five were among students belonging to a fraternity or sorority, four were among athletic teams, and one was in off-campus housing. Clusters ranged from 5 to 106 patients, with the largest one linked to a university-associated apartment complex. Among cases in undergraduate students, 36% resided on campus, at least 8% were members of a fraternity or sorority, and 8% were student athletes.

On Aug. 19, all classes transitioned to online, and students living on campus in residence halls were required to return home and instructed to quarantine for 14 days. [I disagree sending students home] As of Aug. 25, no COVID-19 patients from the campus were hospitalized, had reported cases of multi-system inflammatory syndrome in children (MIS-C), or died, though one student was kept for extended observation in the hospital emergency department.

FIGURE. Confirmed COVID-19 cases among university A students, faculty, and staff members (N = 670), by earliest illness identification date — North Carolina, August 2020



Comment: This report suggests in addition to enforcement of mask requirements, stricter mitigation measures and comprehensive mitigation strategies are required at colleges and universities, which would include efforts to reduce the density of on-campus housing, increase testing for SARS-CoV-2, and discourage student gatherings.

Decreased Mortality in COVID-19 Patients Treated with Tocilizumab: A Rapid Systematic Review and Meta-Analysis of Observational Studies

Clin Infect Dis published online September 23, 2020

The authors systematically searched PubMed, PMC PubMed Central, MEDLINE, WHO COVID-19 Database, Embase, Web-of-Science, COCHRANE LIBRARY, Emcare and Academic Search Premier (until June 30th2020). Random effects meta-analysis was used to pool the risk ratio and risk difference of individual studies. Risk of bias was appraised using the MINORS checklist.

The search strategy retrieved 743 unique titles of which 10 studies (all on tocilizumab) comprising 1358 patients were included. Nine out of ten studies were of high quality. Meta-analysis showed that the tocilizumab group had lower mortality than the control group. The risk ratio (RR) was 0.27 95%CI 0.12 to 0.59 and the risk difference (RD) was 12% 95%CI 4.6% to 20% in favor of the tocilizumab group. With only a few studies available there were no differences observed regarding side effects. [some have shown increased risk of bacterial infections]

Comment: This review showed that mortality was 12% lower for COVID-19 patients treated with tocilizumab compared to COVID-19 patients who were not treated with tocilizumab. The number needed to treat was 11, suggesting that for every 11 (severe) COVID-19 patients treated with tocilizumab 1 death is prevented. This report has some limitations. The most important one is the fact that all included studies were observational. Presently there are no published results of randomized controlled trials of tocilizumab. Observational studies have a tendency to overestimate the treatment effect. High quality randomized controlled trials are urgently needed and underway.

Effect of Convalescent Blood Products (CBP) for Patients with Severe Acute Respiratory Infections of Viral Etiology: A Systematic Review and Meta-Analysis

Int J Infect Dis published online September 28, 2020

Up-to-date trials were identified by the authors through searches of Medline, Embase, Cochrane Library, Web of Science, ClinicalTrial.gov, and medRxiv from inception up to 14 September 2020 Meta-analysis was performed using random effects model.

According to observational studies, the cases received CPBs showed a decline of all-cause mortality compared with cases without using (OR 0.36, 95% CI 0.23 to 0.56, $P < 0.00001$). The all-cause mortality in the randomized controlled trials (RCTs) showed no difference between the interventional group and the control group (OR 0.82; 95% CI 0.57 to 1.19; $P = 0.30$). CBPs did not increase the risk of adverse events between these two groups (OR 0.88; 95% CI 0.60-1.29; $P = 0.51$). Using CBPs earlier, compared with using CBPs later, was associated with a significant reduction in all-cause mortality (OR 0.18; 95% CI 0.08- 0.40; $P < 0.0001$)

Comment: Based on the outcomes of RCTs, CBPs did not decrease all-cause mortality. Furthermore, comparing with later initiation of CBP therapy, earlier initiation of therapy might decrease the rate of mortality. This later finding is consistent with the Mayo Clinic results. Not in this review is high titer vs low titer. Clearly more high-quality RCTs with a larger sample size are needed to assess the efficacy, safety, optimal time of initiation, and best dose of CP in COVID-19 patients. NIH has begun an RCT using only high titer CBP in early stage disease in hospitalized patients.

Efficacy and Safety of Hydroxychloroquine vs Placebo for Pre-Exposure SARS-CoV-2 Prophylaxis Among Health Care Workers A Randomized Clinical Trial

JAMA Intern Med published online September 30, 2020

This is a randomized, double-blind, placebo-controlled clinical trial conducted at 2 tertiary urban hospitals, with enrollment from April 9, 2020, to July 14, 2020; follow-up ended August 4, 2020. The trial randomized 132 full-time, hospital-based HCWs (physicians, nurses, certified nursing assistants, emergency technicians, and respiratory therapists), of whom 125 were initially asymptomatic and had negative results for SARS-CoV-2 by nasopharyngeal swab. Hydroxychloroquine, 600 mg, daily, or size-matched placebo taken orally for 8 weeks. At the time of randomization (baseline), 4 weeks, and 8 weeks, participants underwent study-specific NP swab testing for SARS-CoV-2.

Both hospitals had uniform policies for HCW use of PPE (including masks, eyewear, and gowns) as well as patient screening for COVID-19 symptoms. An independent medical monitor, data safety monitoring board (DSMB), and COVID-19 trial steering committee provided oversight of safety and efficacy end points. Health care workers at either study hospital were eligible for inclusion if they (1) worked 20 hours or more per week in hospital-based units, (2) had no known history of SARS-CoV-2 infection, and (3) did not have symptoms suggestive of COVID-19 in the 2 weeks before enrollment. The primary outcome was the rate of conversion to SARS-CoV-2–positive status via NP swab in enrolled participants during the 8 weeks of study participation.

All participants who did contract SARS-CoV-2 were either asymptomatic or had mild disease courses with full recoveries. The trial was terminated early for futility before reaching a planned enrollment of 200 participants.

Comment: Among hospital-based HCWs at potential risk of exposure to SARS-CoV-2, hydroxychloroquine, 600 mg, daily, for 8 weeks did not reduce the incidence of SARS-CoV-2 infection compared with placebo. This result is consistent with another randomized COVID-19 prophylaxis trial published. [N Engl J Med. 2020; 383:517-525] In that study, 821 asymptomatic adults were randomized to hydroxychloroquine or placebo following a postexposure in which participants self-identified as having a significant exposure and were treated with a 5-day course of hydroxychloroquine or placebo. This current study was clearly underpowered. They did not attempt to quantify the frequency of participant exposure or specific timing of exposures.

Global Convergence of COVID-19 Basic Reproduction Number and Estimation from Early-Time SIR Dynamics

PLoS ONE published online September 24, 2020

Researchers used a mathematical model – ‘susceptible-infectious-removed’ (SIR) [not standard infection ratio!] – to look at confirmed cases of the virus in 57 countries between January and March. In the analysis herein, the SIR model is used to uncover generic spread mechanisms observed by COVID-19 dynamics globally, especially in the early phases of infectious spread. During this early period, potential controls were not effectively put in place or enforced in many countries around the world despite early warning signals from China, Iran, and later, Italy. Hence, the early phases of COVID-19 spread in many countries where controls were weak offer a unique perspective on the ensemble-behavior of COVID-19 R_0 .

The investigators found that the average number of new COVID-19 cases caused by an infected patient R_0 – was 4.5, more than twice as many as the initial 2.2 rate estimated by the World Health Organization initially.

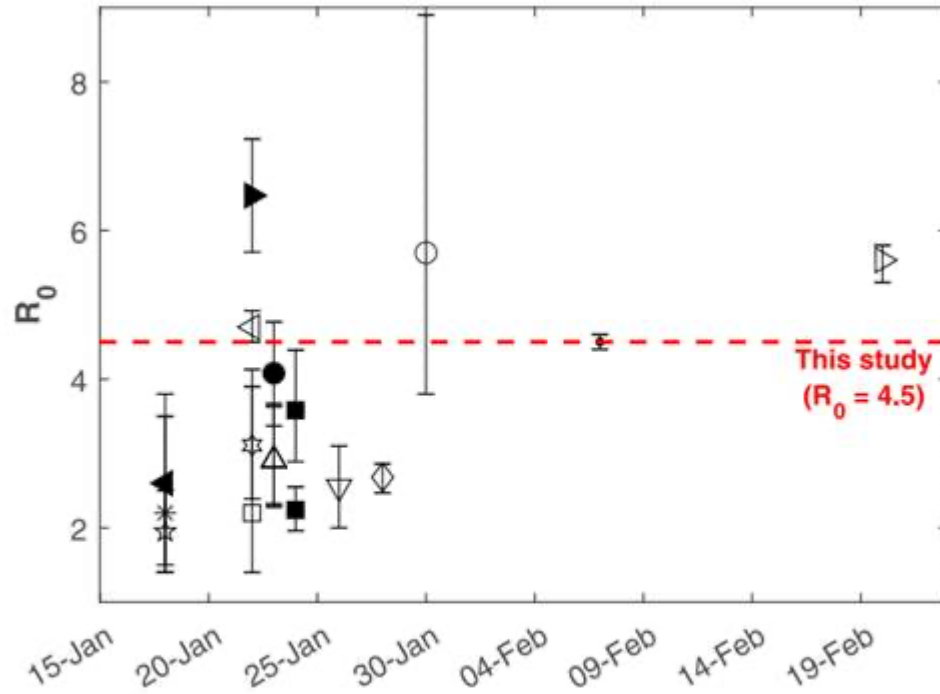


Fig 1. Timeline of the COVID-19 R_0 estimates. Symbols represent studies listed in Appendix (Table 1) while the red dashed line marks $R_0 = 4.5$ derived from this study. An initial $R_0 = 2.2$ was initially adopted by the World Health Organization (WHO).

Comment: The work here has shown a global convergence of $R_0 = 4.5$ when no interventions were taken for COVID-19. [e.g. masks, social distancing etc.] The critical herd immunity level now must be 78% to ensure COVID-19 does not become an epidemic again. This estimate sets a maximum limit on the vaccination required. The models are elegant and attempts to arrive at R_0 before NPI were implemented. In addition, the mutation described by several investigators recently [reviewed in the Daily Briefing last week] suggest the mutated stain may be more contagious than the original pandemic strain.