

FAITH ROGERS: Hi, I'm Faith Rogers, host of today's program: COVID-19: Keeping Up with a Moving Target. This is the June 10th update of DKBmed Radio's coronavirus educational series. Thank you for joining us.

As a reminder, we are providing twice weekly 15-minute webcasts and podcasts on Wednesday evenings and Friday mornings featuring the latest news, treatment updates, and clinical considerations as well as answering your questions about COVID-19. Sign up at covid19.dkbmed.com to be sure you get the latest updates. For this week only, we will not have a Friday morning webcast. Friday episodes will resume soon.

Today's program is accredited for ANCC and AMA PRA Category 1 Credits. Please visit our website for complete CME and CE information.

To attest for CME and CE credit, please visit covid19.dkbmed.com. There you'll also find all of our previous COVID-19 programs and have access to other free CME/CE programs on a wide range of topics. The slides for today's webinar and previous webinars can be found under the resource tab. today's learning objectives are:

- **Discuss common misperceptions about COVID-19 preventive measures**
- **Describe the relationship between trust and news and adherence to public health recommendations**
- **Discuss the data pertaining to use of convalescent plasma in people with severe COVID-19.**

With us today we have Dr. Paul Auwaerter, clinical director of the division of infectious disease at Johns Hopkins School of Medicine. Thanks for your time, Dr. Auwaerter.

DR. AUWAERTER: Thank you, Faith. I want to acknowledge that these programs could not continue without the generous support of DKBmed, The Postgraduate Institute for Medicine, and the Institute for Johns Hopkins Nursing. More information about COVID-19 is available at covid19.dkbmed.com if you'd like to look for earlier programs and additional information.

I'm showing the world map here because the WHO and many countries are now acknowledging that the rates in North America and Europe are declining (in many areas, but not all) and it's really elsewhere in the world that is causing the total number of cases to rise, with hotspots that at least we know, especially in Central and South America, especially Brazil, and no doubt in African countries, although testing there is not as robust, and also Asia, for example in India. I think this just speaks to the ongoing and inherently global nature of this pandemic, and especially as people loosen travel restrictions, I think internationally is going to remain a question mark for many parts of the world for a long period of time yet.

I would like to just return to virus transmission. I can emphasize that I think the public knowledge of how this virus is spread and best practices are probably insufficient. I wanted to touch on information that we sort of know now six months into the novel coronavirus pandemic, and then also how people are getting their information.

A recent systematic review and meta-analysis published in Lancet by Chu and colleagues looked at what are going to be observational studies, but many of them reflected over 25,000 patients. None of these were our RCTs, but I don't think any of those who be terribly ethical at this point. They came down to

three findings that are reducing the rate of people infecting others. What they were able to describe is that by staying a meter apart, and probably even two meters, would be better. It's clearly reduced risk, so you're not shoulder-to-shoulder with someone, speaking right in front of one another and so on, and is certainly biologically plausible. The further you're removed, the more likely you have increased protection.

The second is facemask use. There is an 80%+ reduction. Stronger, of course, with the n95 masks which have been in short supply, even for healthcare workers, but even similar masks including surgical masks. Lastly, eye protection also correlates with about an 80% reduction in risk. So, these three, especially if you're using them together most of the time when you're in public, especially if you're indoors or in closed spaces, are really to your best advantage.

Some of this had to do with helping prevent what's called asymptomatic transmission. Sure, people that develop symptoms probably at the highest titers and are coughing are capable of spreading more virus, but there are estimates that up to 79% to people who are asymptotically infected may be contributing to the virus, and in the past couple of days there has been a confusing statement by a WHO official from a small contact tracing study in China that suggested perhaps asymptomatic transmission is not important. That was a small study. I think there's still a lot of controversy about how much aerosol droplet transmission versus asymptomatic transmission or fomite transmission are all contributing, and I think people have lots of opinions. It's clearly respiratory and to what degree, but this asymptomatic component I think unfortunately gives people some credence that wearing masks is not important.

So how do people find out about news and misperceptions? Here are some things that you can just take a look at from the Shorenstein Center at Harvard which did a large survey along with other universities and put together this information. If you just take a look at some of these questions about whether these practices help avoid COVID-19, you can see there's some significant misconceptions. A lot of this also was promulgated early on by false information that was circulated widely on social media and others, so this is not insubstantial as you can see. In a way, interestingly, younger ages were a little more susceptible this information than older ages, and perhaps that's due to social media intake. But yet if you are asked overall where people are getting their information, they cite local television or family and friends and Facebook, which certainly is social media, and then you move on and down and interestingly, government websites or any kind of other information such as in news or radio is significantly less. So, it no doubt bears to mind that social media, I suspect especially the family and friends conveying and retweeting or sharing social information may be important.

Yet if you're to ask the question about who do you trust, if you look at that information, hospitals and doctors, scientists and researchers, and even the CDC which has been a bit maligned lately are all at the top, followed by city and state governments. You can see that there's less trust in individual politicians or the news media, so it's interesting that although people have trust in certain entities, that's not necessarily where they're getting their information, or if they are it's quite filtered.

Lastly, belief equals actions. If you think about how people avoid COVID-19, if people believe the news that they read is accurate, they are more likely to follow guidelines. If they think most of what they read is true, then they're doing some of the things like hand hygiene, wearing masks, disinfecting, and doing social distancing. If they don't have that belief, they are swinging in the other direction.

So, who is concerned? I think especially with much attention recently to barriers and increased rates of severity and rates of infection in COVID-19, non-whites are at higher risk. It does show that the messages there are getting through that people need to take care of themselves. You can tell by these rates and also some of the difficulties and concerns that are being voiced. These are very important concerns about receiving appropriate health care, especially to Black people, Hispanics and Latinos, as well as other underrepresented groups.

I think as far as transmission, it's important for all of us as health professionals to really model best practices, to wear masks out in public if we're at risk for being in closer contact, especially indoors. We do have to educate our patients, especially those at higher risk, to continue a social distancing, as well as hygiene and face mask practices. I really hope you continue to work at getting people to do that. It's very difficult, I know, even in my own family.

I'd like to focus on us two papers that came out for COVID-19 therapeutics. So much information has been case series or early reports from China that's guided a lot of decision-making, and we're just beginning to get some prospective trial information to help inform us. One of the high hopes is for convalescent plasma, and this is the first randomized trial which was started in China in the early phases of the epidemic. Unfortunately, it had to end early because they really ran out of new cases to enroll, so they only had 103 patients, so this was an underpowered study. But it was certainly an at-risk population, older in age, 70 being the median, and they either needed to have severe COVID-19, meaning they were hypoxemic or they were critically ill in the ICU.

It was convalescent plasma versus usual care, and just to be clear our usual care often meant that patients there were receiving protease inhibitors, hydroxychloroquine, steroids, traditional Chinese herbal medicines, and so on. This was a negative study because their primary endpoint was 28-day mortality looked at prospectively. It was underpowered. You can see there's wide confidence intervals, so it's hard to judge if the numbers that you see here are meaningful. Patients were often ill for a while before they were enrolled, but the plasma did seem to more readily convert people to no longer having viral carriage, and very few people had reactions. So, it looked at of the group of 103, and the rates of serious reactions were quite small, at least looking towards a safety signal. As I mentioned in panel A, it was a negative study, because it was underpowered and we can't really say if plasma therapy is helpful in a post-hoc subgroup analysis, though those people that were not ill enough to be in the ICU but just on oxygen looked like they improved, and at least in this post-hoc analysis was statistically significant, meaning there is higher rates of improvement in 28 days. But if you look at people in the ICU with life threatening disease, this was not the case, but also with lower numbers. I think in conclusion, although a negative study, there is at least some glimmers that trials which are currently in progress in Europe, North America, and elsewhere that are also examining this therapy may prove to be useful. We'll have to wait and see.

The last paper to mention is a preprint. This has not been yet subject to peer review, however I thought I would bring this out for a couple of reasons. This is about tocilizumab, the anti-interleukin-6 receptor inhibitor that had been proposed early on in China as part of their guidelines for COVID-19 treatment mainly to focus on the so-called hyper inflammatory or what some people call the cytokine release syndrome aspect of the illness. This was a phase 2 trial, very interesting to me, although it was over 1,200 patients it was a single arm trial. What that means is there is no placebo control arm of this prospective trial. The investigators cited that the public demand for interventions was so strong that

they felt they couldn't offer placebo control, which many would argue is not the right approach regarding equipoise or even ethics.

This is how the trial proceeded: with either one or two infusions of the biologic, but because the delivery problems, many people had delays, and much like the other Chinese study many were on concurrent therapies. This just gives you a bit of a picture of the kinds of treatments that patients received as well. Their validation cohort were just identified as those not receiving tocilizumab at the same centers. Interestingly, the validation group had a very similar rate of c-reactive protein elevations as an awfully crude surrogate that they were probably getting people in the inflammatory phases of illness.

In terms of efficacy, the 30-day intention-to-treat did look compared to their validated cohort that the lethality rate in the treatment group was better than the validation group, whereas the 14-day did not look very similar. The other thing they did is they looked at over 43,000 patients and their mortality rates as sort of a comparison to the null hypothesis in terms of impact which show at 30 days, but not at 14.

So, for the 43,000 patients with COVID-19, the 14-day mortality rate was 22% and the 30-day was 27.6%, at least in the active arm of this single center study. Logistic regression analyses suggested the people that benefited most were those that got the tocilizumab before mechanical ventilation, sounding very similar to what happened with the convalescent plasma therapy. These investigators thought there was only one death attributable to complications arising from the tocilizumab, and a small percent had some additional elevations and liver function tests, so I think there's an inability to make any firm conclusions from this. But it is a large study that followed the patients prospectively. I think the reason it's so hard is Italy had one of the highest death rates along with the UK worldwide. Also, obviously, as the study went on, people probably improved their care of COVID-19, so without a true comparison arm, I think it's awfully difficult to say that tocilizumab might be helpful, but you might be hearing this study cited or thinking about it when you're making your own decisions for treatments, so I thought it was important to communicate.

Faith, do we have some questions this week?

FAITH ROGERS: Thank you for those updates. We will now continue to the listener Q&A.

Dr. Auwaerter, our first question: can you comment on whether COVID-19 appears to be weakening as it mutates?

DR. AUWAERTER: This has been brought to me by many patients, even physicians, because I think there have been some news reports and suggestions that this is the case. Actually, our own biologists at Hopkins have been looking at genetic sequences of this virus and finds that it's actually fairly stable. The good news is the stability of the virus actually bodes well for vaccine efforts, meaning unlike influenza, the virus is unlikely to mutate sufficiently so that you'd have to be changing the vaccine year-to-year, but I don't think there's a strong belief or scientific credibility yet that this is the case. The coronaviruses, for an RNA virus, tend to be relatively stable compared to some of their brethren.

FAITH ROGERS: This is our next question: how will infection rates affect the ability of schools to reopen? What criteria should be most important when considering opening schools in the fall?

DR. AUWAERTER: Well, these are really important questions that also so many large institutions such as universities are considering. I think the issues that I would think about if I were a decision-maker or providing advice are: what are the community rates? What's going on in the local community? The second is: how well can both the children attending school as well as teachers continue with proper social distancing and what can be achieved at school during that time? I think people will try in many instances because online learning clearly has not been a homerun success, and there's so many other variables that people have spoken about in terms of insufficient learning and home life, even nutritional issues for children that are dependent on getting lunches at school. These will require careful monitoring, and if things were to continue, I think you'd have to expect cases will occur. There would need to be contact tracing, frequent testing of staff and children when there are cases, and even temporary closures. So, I think we'll just have to see here, and some locations I think will be lucky, some less. I don't think there will be any one model we can look to, and often these will need to be individualized, but I think the messaging and the conduct will need to be fairly clear and repeatedly emphasized.

FAITH ROGERS: Thank you, this is our last learner question: Some reports suggest that blood type may be associated with risk of COVID-19 infection and disease severity, with type-O blood being protective. Can you comment on this?

DR. AUWAERTER: This is highly interesting. There was an early report, retrospective from China, that suggested if you had a type-A blood that you were prone to more severe disease. Conversely, you were protected if you had type-O. That was a clinical study, but recently there have been reports coming out of Germany who've done some human genome sequencing to try to look at whose factors are responsible. We all feel that there must be something in addition to some of the demographics regarding risk factors, regarding comorbidities, because clearly some people sail through with minimal effects. Even an 85-year-old with congestive heart failure in a nursing home may be asymptomatic from infection, and why is that? Everyone placed a lot of emphasis on the viral receptor for coronavirus, ACE-2, but these investigators from Germany did not find any association with genetic variants and ACE-2. What they did find, though, was again in blood, and suggested that those who had severe disease were more likely to have type-A blood. Now of course, they didn't sequence the whole genome so it's not by any means clear that this is the only one, but that was one of the early signals that type-A at least in this study seemed to be a possible risk factor. Not too much you can do about that, but if you know you're type-A, if you start developing symptoms, you may want to seek medical attention a little earlier. Why this is the case I think is unclear and I think this is something we'll certainly be learning more about in future months.