FAITH ROGERS: Hello, I'm Faith Rogers, host of today's program COVID-19: Keeping Up with a Moving Target. This is the May 27 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. 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 COVID-19.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 factors associated with "super spreading" events of SARS-CoV-2**
- **Describe general measures required for safe reopening of offices**
- **Explain the role of endothelial dysfunction in severe COVID-19**

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

DR. AUWAERTER: Thank you, Faith, and I also want to again thank DKBmed, The Postgraduate Institute for Medicine, as well as the Institute for Johns Hopkins Nursing for the support needed to bring you this program. There's also additional resources and educational activities that are available through DKBmed at covid19.dkbmed.com.

Cases across the United States still continue. Some states are decreasing, thankfully, and others increasing. There are concerns that with relaxation we'll see more cases and also some indication that civic unrest, which unfortunately has been occurring across our country, will lead to increases the next few weeks. We'll just have to see here, but a lot of this is a natural experiment. It's making it very hard for the disease modelers to help predict what will happen.

For me, until we have better therapies and an effective vaccine, viral transmission is the key for getting ourselves, our economy, and our country in a better and more functional state. I thought I would focus on this a bit. There is this super-spreader concept. This was talked about very early with the coronavirus because we saw it with the first SARS-CoV-1, and to some degree with the Middle East respiratory syndrome. That conversation faded away as we started to talk about asymptomatic spreaders and other things, but it's fairly clear that large gatherings, especially indoors, are one of the keys. Outbreaks such as those related to church choirs have been one case, also people in tightly organized spaces, often meat processing plants where temperatures are much cooler and humidity levels are fairly constant, the virus loves this as opposed to high heat and humidity.

But these super-spreader events are events where we're now seeing a lot of activity. Early in the pandemic, before rolling out social distancing and staying at home, a number of venues that seemed very prone to spreading the virus were those where large groups of people became infected. The key here, I believe, is that people who were mostly indoors, tightly connected in closed spaces, were

infected much more often than people participating in outdoor activities. But while these super-spreader events can be found through contact tracing, they're still very difficult to understand.

Most of you have heard about the R0, the number of people a single infected person on average then goes on to infect. The average R0 of 3 for novel coronavirus means that one person might infect three if you're not socially distancing, but the reality is that most people probably infect none, and a smaller number of people infect more. It’s not homogeneous, and we also know through asymptomatic spread concerns that healthy people have droplet production even when they're talking, some much more than others.

The other attribute is risk of transmission. Studies in China and Japan show that there's almost a 19% greater increase in transmission in closed areas than in outdoor activities where someone with coronavirus is known to be present. Another factor is people who are very gregarious and have lots of social contacts spread far more disease. We've known this through contract tracing of people who had been to 10 clubs in one night, for example, or visited lots of friends.

I also want to touch on something you may not have heard much about, the K or Kappa factor, the dispersion factor for infection clusters. This value is usually placed on viruses, but it could be any infection, where a lower value means the transmission comes from fewer people, hence the clustering. We know with some of the earlier coronaviruses, the numbers were fairly low, but to give you an example: for Spanish influenza it was 1, meaning lots of people infected lots of people, whereas smaller numbers of people who were infected spread the other coronaviruses. We think — although this is just an estimate based on a study — the current novel coronavirus seems to even be worse than the others, where only about 10% of people go on and infect 80%.

We're not exactly sure of all the factors; is it the extroverts doing this? Is it the people who spray it, not say it? Is it people that are not wearing masks and just sort of doing their thing? Or is it more intrinsic to the virus or the host, the aerosol generation?

There's been a lot more attention now, because honestly I think our strategy now is changing. Initially, of course, it was concern that we didn't have any PPE or didn't have enough, and we thought this would be similar to droplet requirements for influenza, that if you stay away from three to six feet and you wear a surgical mask, you'll be fine, probably won’t get the infection. But the reality is, as people have looked at this much more carefully than studies that were done decades ago, humans produce respiratory droplets of average to large size, mostly in the 5-10 micron range, and they fall to the ground or evaporate; but some people generate droplets below 5 microns, and those are the ones that might be inhaled and bypass the upper airways.

There are also concerns about silent shedders, people who don't know they're ill. Current estimates are all the way up to 79% of silent shedders may account for most of the transmission, often before people even become sick. As you know, not everyone becomes sick, but if they do, they can be shedding virus six days before the onset of symptoms.

The standard six-foot recommendation may not account for these submicron particles, especially when the air circulation is poor. This is something to take in consideration and maybe give people a wider berth. We know for uncovered coughs or sneezes, you can get droplets from 20 feet away. I believe that universal masking is our current best weapon to help limit the spread of this virus. Even surgical masks

or cloth masks can help, by limiting an infected person's droplets from speech or unopposed coughs and sneezes, thereby protecting others. We know from influenza studies that a surgical mask can still cut down 6-8% of acquiring transmissions.

I think this is related to the case fatality rate per location. This means that people may not be getting quite as much infectious inoculum, or the burden of infection. In Hong Kong and Singapore, there is considerably less infection than in other instances that have been much higher. We still don't know exactly why. People can point to other factors, but I think the frequency of adherence to wearing masks is much higher in these two areas, and it is a lesson that we should probably consider and push.

One of my keys as a physician is that I really try to espouse wearing a mask when out in public whenever possible and can't maintain physical distancing, as being the right public health approach, and respecting other people by trying to help diminish transmission.

CDC finally released some of its updated guidance last month for reopening offices and churches, but again it has mixed messages. Look at the guidelines for offices, it's very rigorous, talking about spacing desks apart, no common seating areas, cleaning, and using visual cues for marking, and so on. Also avoiding mass transit. But if you look at houses of worship, language was removed that warned against allowing choirs and singing, and they also deleted information about shared cups, hymnals, and worship rugs. Again, although fomite transmission, or transmission from surfaces, probably doesn't account for a large majority, it still sends a mixed message. Unfortunately, this is one of the communication issues that I think is leaving people a little adrift about how they should proceed.

Lastly I'll just talk about herd immunity, because some people have advocated for it, saying, "Look, we're doing all this shut-down, and it's really not worth it. Better to just let everyone get infected and then everything will be fine and we won't have to wait for a vaccine." For this respiratory virus, the estimates are you need at least 60% herd immunity for this to occur. Sweden was often talked about by those who thought, "We don't need to shut things down, we will develop herd immunity, we'll be far ahead of everyone else." But as of late May, Sweden had a higher death rate than New York City, and only 7.5% or so of people had antibodies, so clearly that is not working. I don't believe it will work as a strategy, and we may experience more health consequences and death.

I'll close on the complete other end. We're not talking about acquiring infection, but for people who are so critically ill. What's happening? What's causing death? A lot has been focused on lung injury. We know there is a cytokine storm that generates intense inflammation and immune responses that cause injury, especially in the lung. There were a number of strategies to deal with that, but there's also been a lot of signs that this viral illness also creates endothelial dysfunction and more clots in addition the hypercoagulable state. I don't know if it's a surprise, but what struck me in this series that's only on a preprint server at the moment, experience at New York's Mount Sinai Hospital suggests that a lot of people with multiorgan-system problems had something like hemophagocytosis, or histiocytosis, Langerhans-like syndrome, and lymphocytic syndrome. This is just one slide from that series of a lung that had a lot of damage, a heart that had fibrosis and ischemic changes, and the spleen had evidence of an HLH-like process. Certain stains showed heightened numbers of macrophages, so macrophage activation is likely at play here as well, and although they didn't fit the typical criteria for HLH, this does seem to be that sort of process. It gives a little information and insight. It'll be interesting to see if any of the anti-inflammatory strategies currently under study in clinical trials might have some impact on this process.

Faith, I think that's all I have for today. I think we have some questions.

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

Our first question: is there a recommendation for routine anticoagulation for hospitalized COVID-19 patients?

DR. AUWAERTER: There are lots of recommendations out there from Europe and health organizations, as well as hospitals in the United States. My sense of it is this: some people who are critically ill often have clots present, and so some have advocated for high-intensity anticoagulation prophylaxis or even full anticoagulation at the onset, especially for the more ill patients, and others have targeted people that they view as higher risk such as sickle cell patients and so on. I don't think we have enough data about having higher levels of anticoagulation, but we clearly know that clots seem to be more common especially in critical care illness. How well these are evidence-based, we're still far away from knowing exactly who we should target.

FAITH ROGERS: Okay, thank you. Our next question: based on what is known from other coronaviruses, are the effects of severe SARS-CoV-2 infection on the heart and kidneys reversible?

DR. AUWAERTER: Especially for those in critical illness, I would say yes and no. Clearly we've seen patients who have shown some improvement, and that may be what we call critical illness cardiomyopathy, but there are also times as you just saw in the autopsy series where there's a lot of fibrosis and ischemia, so in some patients it does not seem — at least in just a few months' experience we have — that ejection fractions, for example, always improve.

The same is true for renal disorders. We've had patients develop dialysis requirements that they still need on discharge, but others seem to show recovery and no longer need dialysis. I'm not sure I can give you great percentages or risk factors for those, but it can be both.

FAITH ROGERS: Thank you, this is our last learner question: can you comment about the vaccines that have some data from clinical trials?

DR. AUWAERTER: This is beginning to come out, and it's early, still in the baby steps, phase 1, looking for certain doses to see if they can generate immune responses. Moderna came under some criticism for only giving data by press release and then issuing a stock offering later in the day. There's some encouraging information there, though. They said eight patients generated antibody responses with neutralizing antibodies against the spike protein, but there are 30-odd other people that we don't know the data for, and honestly we also don't know any of the characteristics of the patients.

For the CanSino product, which I believe is in adenovirus, there were concerns that yes, they were immune responses, but in a larger study this is an adenovirus vector, and a lot of people already have antibodies against the adenovirus. So perhaps you're not going to get as good or as durable an immune response as if you had a completely new immune response to a set of antigens.

I think we're still very early to make any predictions from this. It's encouraging that we're seeing some immune responses, but we really need to wait for the phase 3 studies, or if we do human challenge studies with smaller numbers of patients. Unfortunately, you're going to need thousands and thousands of patients in each vaccine trial to really gauge its efficacy and safety. A lot of times we don't know as much until we really administer the vaccine to tens of thousands of patients.

FAITH ROGERS: Thank you Dr. Auwaerter. As a reminder to claim CME/CE credit please complete the evaluation at Covid19.dkbmed.com and select today's activity. You'll receive your certificate immediately after. Any questions or issues feel free to email us at the address listed.

To submit questions please send them to QA@dkbmed.com. That's Q as in question, A as in answer at DKBmed.com.

Don't forget to access our resource center at COVID19.dkbmed.com. You'll find a range of information including the latest COVID-19 data and statistics, medical society guidelines. and resources in Spanish.

To all of our listeners, please be on the lookout for our next activity this Friday. We will send out an email when it's available later this week.

Again, thanks for joining us and thank you for your dedication to your patients with COVID-19.