FAITH ROGERS: Hello, I am Faith Rogers, host of today's program, COVID-19: Keeping Up with a Moving Target. This is the May 13th update of DKBmed Radio's coronavirus educational series. Thank you for joining us.

As a reminder, we are now providing twice-weekly, 15-minute webcasts and podcasts featuring the latest news, treatment updates and clinical considerations, as well as answering your questions about COVID-19. These will be available on Wednesday evening and Friday morning. 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*.

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Today's learning objectives are:

- **Discuss the effects of contact tracing**
- **Describe testing modalities for COVID-19 illness**
- **Review data from randomized controlled trials**

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. As a reminder, this program is only possible through the generous support of DKBmed, the Postgraduate Institute for Medicine, and the Institute for Johns Hopkins Nursing. Additional COVID-19 resources and educational activities can be found at COVID19.dkbmed.com.

As we head into mid-May, many states are lifting restrictions. I think many people, at least public health experts and infectious disease people, think that, with this virus, this will generally mean at least a steady to increased number of cases in the forthcoming weeks as perhaps people are not taking as much guard. Already as expected, in Wuhan City in China, despite the fact that they had no cases, there are now clusters. I think with the easy transmissibility of this virus and asymptomatic shedding, this is our future as well. So it's incumbent for us as medical professionals to advise our patients to use whatever techniques possible to try to help limit further spread.

One of the key issues, at least in the United States, has been some confusion. States have their own rules, but the federal responses have often been seen as not being very clear, forthright, and so on. This is by no means scientific, but it interested me because it was a survey of global public relations professionals on which countries, governments, or states issued some of the clearest communications. New Zealand and Germany have both been recognized as handling this in a way that transmission rates and new cases came down much faster and more effectively. A lot of this was attributed to the clear communications from the government, so these probably go to some degree hand in hand. I can't attribute all success to communications, but it does emphasize the importance of people trying to

understand what is possibly accomplishable and the limitations. This is always important messaging, even in our local health systems, but also to our wider societies.

It's important because some states are engaging in contact tracing much more than others: California and Massachusetts, other states as well. If levels can be kept down and there's robust testing, then people can be aware of whether they're infected or whether they need to stay home and isolate themselves. Without these, this kind of unfettered spread would occur, and I'm afraid that this contributes to some mixed messaging along these lines. I think individual states will try their best, but states will have different rules and it will certainly be confusing to many to understand the rationale. People chafe at having their individual liberties curtailed, but at the same time it is for a better benefit.

I want to mention as an advance is growing amounts of evidence that we probably don't have to do the somewhat barbaric nasopharyngeal swab for molecular testing. This was done because it is routine with influenza. Interestingly, coronavirus probably has more predilection to the lower tract, in part because there are many more viral receptors, the ACE 2 receptors, in the lower tract. It is clear that oral spit tests are much more comfortable and are being pursued: one by Rutgers has won FDA approval, and the manufacturing is now increasing. They're in the tens of thousands, and I think this offers a better way to have quick and easy testing that might help institutions and workplaces.

The issue of whether the nasopharyngeal swab is as accurate as the salivary sample has been looked at in a number of papers, but here's one where it looks very equivalent. In fact, they can't say that it's better, but it's certainly not worse and can track relatively well in matching samples and the number of copies that might be identified to reflect so-called viral carriage between the saliva and the swab. My bet is over time, a swab of saliva or spit test will be probably how most tests will be performed, hopefully months moving ahead.

I'd like to focus a bit on the treatment remdesivir, which had been in the news and the focus of last week. We still do not have any data from the NIH trial, so we don’t know anything more than what was announced in late April. But this pivotal trial has adapted, meaning that remdesivir has become the standard of care. Because of that they are now using a combination therapy in this trial with a second drug, an immunomodulator, called baricitinib. This is a JAK1 and JAK2 subtype inhibitor that works at interrupting some key proteins involved in genes that need to be expressed to produce inflammatory molecules. This drug has been used in refractory rheumatoid arthritis. The thought here is that it would have a role if used along with an antiviral to be complementary, especially for patients who might be evolving into a hyperinflammatory or cytokine storm.

One issue that has been in the press has been distribution. Gilead has generously made 1.5 million doses available for treatment throughout the United States. It appears that only half of it will be actually used under the Emergency Use Act that was authorized by the Food and Drug Administration. People who are in trials will get the drug, but distribution to states has not been very transparent. Many people have asked questions. Initially the thought was allocation based on the number of cases. At Johns Hopkins, in our health system, only one of five hospitals has gotten the drug so far, as of this taping on May 13. We've gotten enough vials of remdesivir to treat two patients. There's clearly probably not going to be enough to go around, but how it's being distributed and allocated, what seems to be in phases of distribution, remains to be seen.

A paper came out on a different strategy, one that takes a leaf from how we treated hepatitis C in earlier days with an interferon product, in this case, interferon beta-1b, which was compared in a triple therapy. This was very common in Asian countries who used a protease inhibitor from HIV, the lopinavir/ritonavir, along with ribavirin. This interferon-ribavirin combo was taken from hepatitis C treatment and randomized to just the protease inhibitor alone for 14 days. This phase 2 trial was open label but randomized, and the primary endpoint was following until the nasopharyngeal swab turned negative.

So 127 patients were evaluated, and the combination group had reduced viral carriage; their swabs turned negative at seven days versus 12. There was also a faster alleviation of symptoms by what they called the NEWS-2 score by four days, so I think this is encouraging in fostering an immune response. This is a small study. There are reservations that interferon would only exacerbate potentially immune responses and foster more of the cytokine storm issue. It wasn't identified, with only typical side effects. Some others have criticized the study, as it didn't have a true placebo arm. Their control arm was lopinavir/ritonavir, and many feel that the real drug here that was operative was the interferon, not the ribavirin or the protease inhibitor. I think this approach might have a role potentially with further study, especially if combined, for example, with an antiviral compound such as remdesivir.

Just in the past few days, hydroxychloroquine and azithromycin, a drug and drug combination, has gotten very early press, with some French investigators claiming that a combination with azithromycin significantly reduced viral load. This is now underway in a placebo- controlled randomized trial in the United States, so there has not yet been any high-quality data regarding this, but I thought it was of interest that this paper appeared in JAMA based on use in New York State and had 1,400 patients. This a retrospective study, and trying to make genuine insights into treatment effect with retrospective use of drugs is very difficult, although somewhat improved by very large numbers.

But as you can see, the adjusted in hospital mortality had no effect and appeared a bit worse in patients who had received hydroxychloroquine, or even worse off with hydroxychloroquine and azithromycin, with about a 35% increased mortality identified with concerns about cardiotoxicity. I wouldn't say azithromycin is protective, the numbers are small, and on the graph the azithromycin line falls below, but the hydroxychloroquine and the “neither” drug lines are superimposed.

Lastly, to date, the information from preprints or published studies were looked at on an interim basis and a meta-analysis. Of course this is a moving target, but I wanted to emphasize that for these antimalarials, this review of drugs found nothing to endorse or refute either hydroxychloroquine or chloroquine. This was the same conclusion reached by the NIH guidelines, which have been most recently updated this past week.

With that Faith, I believe you have some questions?

FAITH ROGERS: Thank you for those updates. We will now continue to the listener Q&A. To submit questions for Dr. Auwaerter, please send questions to qa@dkbmed.com. That’s Q as in question, A as in answer, at DKBmed.com. If we are not able to address your question in this session, we will try to address it in another session.

Dr. Auwaerter, first question: Are recommendations changing surrounding precautions for pregnant women, given the recent articles in Journal of American Medical Association in The Lancet which

showed increased risks of miscarriage, stillbirth, and preterm delivery in mothers who contracted COVID-19?

DR. AUWAERTER: I think everyone initially had concerns about women who were pregnant contracting COVID-19. I think much like in influenza, we have taken a stance that pregnant women should be very cautious with social distancing and avoid situations that could place them at risk for acquiring the virus. I'll also mention that many institutions, even with the emergency use act of the FDA for remdesivir, are prioritizing pregnant women as those who would receive this drug first ahead of others.

FAITH ROGERS: Thank you, next question: It has been discussed recently that there are potentially several different strains of this novel coronavirus. What are the latest research findings related to these different strains?

DR. AUWAERTER: Many people have asked whether the virus may mutate and become either more or less virulent. My take is that the sequencing studies are helping with the epidemiology. We know that strains on the East Coast seem to probably been acquired more from Europe, whereas those from the West Coast from Asia, but this is something that I think is evolving. Many people have questioned whether the virus will mutate significantly to the virus's advantage. If it were to become less virulent even than it is now, it would be to its advantage as even more people would be capable of spreading disease, but whether this will happen with this virus I think is very difficult to say. I think we would probably just plan to think that it will behave as it currently does for the foreseeable future. As an RNA virus, this coronavirus doesn't mutate nearly as much as some others in that arena.

FAITH ROGERS: Thank you, next question: What do we know about the inflammatory condition being seen in children that has been associated with COVID-19?

DR. AUWAERTER: So initially when reports were coming out of China, it was clear that children were not nearly as affected as adults, and in fact, children between 1 and 10 were rarely hospitalized, and adolescents uncommonly unless they had health problems. More recently, though, following experience in Europe also North America and particularly in the mid-Atlantic in New York City area, there have been descriptions of children who have developed Kawasaki disease that occurred after acquiring the novel coronavirus.

Kawasaki has always been a mysterious illness that had autoimmune features and has always been thought to be triggered perhaps by viruses or certain bacteria. We don't yet know why some children are afflicted, but it is yet another aspect where I think we have to be somewhat cautious for reopening schools. Obviously, this is quite rare but it is something that we don't understand. Kawasaki disease can be severe, affecting the heart and causing aneurysms of coronary arteries, and has been treated with a variety approaches, some of which have been postulated for the hyperinflammatory response of COVID-19. Still much to learn as always. This is such a mystifying yet fascinating virus in the many different potential issues it can cause in the human body.

FAITH ROGERS: Okay, our last question is: Could you please comment on Sweden and New Zealand's disparate approaches to COVID-19?

DR. AUWAERTER: I can't say I have great personal knowledge, but I would make the following comments and it wraps into what I said earlier about New Zealand: there was very effective communication. There has been accordance among the population to adhere to this in a very orderly way and they didn't have

so many cases, were able to bring them down, and have been beginning to liberalize their restrictions. Also, discussions of a “travel bubble,” where people could move about between New Zealand and Australia, for example. Similarly, the prime minister has been lauded in this regard for helping direct this in a clear way with cooperation of public health officials.

On the other hand, Sweden has not taken to restrictions. They have practiced social distancing. They did not close down the economy, but I'll also say, at least my last look at the records, they had a higher death rate than in the United States. Of course, their economy was not nearly as severely affected by the measures that other countries have taken. I think it's still too soon to tell in the long run, and also the adherence in Scandinavia may be different than what you might experience in other countries.

FAITH ROGERS: Thank you again for those updates, Dr. Auwaerter.

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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 our listeners, please be on the lookout for our next activity this Friday. We will send out an email when it is available later this week. Any questions can be submitted by sending them to qa@dkbmed.com.

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

DR. AUWAERTER: Thank you, Faith, and I want to thank you all for listening and wish you your families and your colleagues all to stay well and stay safe.