FAITH ROGERS: Hello, I am Faith Rogers, host of today's program, COVID-19: Keeping Up with a Moving Target. This is the May 20th 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:

- **Describe immunology factors important in handling viral illness**
- **Review vaccines for coronavirus, potential barriers as well as vaccine development accelerators**
- **Understand the case definition for COVID-19 multisystem inflammatory syndrome in children**

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, and I want to remind everyone this program is only available through the generous support of DKBmed, The Postgraduate Institute for Medicine, and the Institute for Johns Hopkins Nursing. Please see covid19.dkbmed.com for additional resources and educational activities.

As we move through the month of May, there is some sense of almost optimism at times on a number of fronts — medical, social, and economic — that I hope will come to bear as the summer months come.

I want to spend some time, because I think the next few months will be especially preoccupied in the news, with updates on how the vaccine for the novel coronavirus is progressing on so many fronts. As many of you know, because we still don't have a therapeutic tool to treat patients even though remdesivir is there, we don't quite know how well it works. It may only be modest, at least for hospitalized patients, and social distancing clearly has had an effect when it's been performed accurately. But immunization, of course, is the great hope here. If we can sufficiently immunize people, we'll certainly develop herd immunity that will help limit further spread and allow us to get closer to what we think our normal lives were previously.

A little primer without going too deep into this might help you evaluate how these vaccines are being developed and also which ones might actually turn out to be as effective or more effective than others, a little like a horse race. I'll get into that in a moment.

Most of you know that the immune responses to this coronavirus, and any infection, whether a bacteria, fungus, or even a virus, will trigger what's called innate immunity. Think of this as some molecules interacting with the frontline sentries of the immune system, and finally they will alarm and ring a danger signal. This is a very blunt response. But the vaccines we're most interested in activate the adaptive responses. These are generated by B-cells that make antibodies or T-cells that can either help kill virus-infected cells or help coordinate the immune system to eradicate the infection and hopefully have some durable responses as well. Typically, the innate immune responses are first alarmed in the first few days of infection, and at least with many viral infections, by days 7 through 14 and 21 after onset of symptoms, you are turning to the adaptive system.

So what do we know about COVID-19 immunity? There's been so much in the news about antibody tests: are they reliable, what do they actually tell you? Certainly, depending on the quality of the test and whether it's been sufficiently clinically validated, it could tell you probably to a reasonable degree if you've been exposed. I think one of the questions is about the antibody responses that are generated. Are they the kind that will help prevent reinfection? People might say, “well of course if you have antibodies, you're not going to get reinfected.” Well, if you think about it, people can get influenza every year, yet still have some measurable antibodies that are not fully protective. You may not get as severe an illness, but you can still acquire the infection, and perhaps even transmit it, so I think these are the questions.

Also, even after you recover, if you unfortunately have had the coronavirus infection, how long does that immune response last? Because at least some indications from SARS-1, even MERS-CoV, and of course coronaviruses that cause regular respiratory infections, it's not a long-lived immunity like measles for most people.

However, there is some good news. A recent paper published in Nature Medicine closely looked at a cohort of 285 patients who had severe COVID-19, people who needed oxygen and were hospitalized, and it looked like most people indeed developed antibodies by their third week of illness. These were IgM antibodies, the early phase antibodies. IgG appeared to come later, and this is where there's often a lot of focus on durable immunity and whether so-called neutralizing antibodies are present.

A lot of the vaccine manufacturers have been very preoccupied with a certain protein on the coronavirus called the S protein, or spike protein. Some people have said the vaccine manufacturers are very spike-centric: they're focused on this particular molecule. In part because during the first SARS-CoV-1 outbreak, it did appear that neutralizing antibodies were made against this S protein in that coronavirus, so I think it's natural that there's been this focus.

Other proteins are also part of the inner part of the virus and nucleocapsid. They are embedded into the membrane, or envelope, as well. This is a trimeric protein that's folded together and the idea is, are you generating spike antibodies that are specific to the coronavirus, that would bind to the virus and/or interfere with that virus's ability to then bind into the ACE2 receptors and enter the host cell.

There are 90 preps now, over a hundred candidates, and it's very interesting because there have been so many approaches that. I will hit on a few just to let you know the real breadth of this kind of vaccinology research. Of the overall menu of vaccines over the years that have been developed and then came to market to be proven efficacious and safe, it's estimated that only about 16% of vaccine candidates actually reach market. This is maybe just marginally higher than drugs that enter clinical

phases of investigation, so this is a high-risk kind of enterprise, and by no means guaranteed. A lot about this virus has surprised us, so although our hopes are up, I would say just given the intensive efforts by many governments and private industry, we're still not exactly guaranteed that this will come to bear.

One prep, for example, is using a weakened viral vector, meaning something that we know something about like measles virus, and then inserting a spike protein into that weakened virus. You give it to the person, the virus replicates, and it also manufactures the spike protein without actually causing a serious viral infection and develop antibodies. This is one method, it could be a number of viruses, and it has been used for the newly approved Ebola vaccine, which has proved successful for helping during immunization practices and try to corral the Ebola outbreak that had been underway earlier in the Democratic Republic of Congo and other areas.

Another approach is nonreplicating viral vectors. This also uses a virus, but the virus isn't meant to reproduce within the body, although it does encode information such that the genes themselves will be slurped up and integrated into cells, or at least manufacture proteins that develop an antibody response. Adenoviruses have been used for gene therapy, but to date no infectious disease vaccine has used this technique.

I'll leave the Moderna one for a moment, but DNA molecules, plasmids, have been constructed, again with the spike protein, by Anova. This one uses a gun to inject this, and hopefully the plasmid is slurped up by cells, it’s transcribed, proteins are made, and you get an immune response. You see the CanSino biologics, which again uses the adenovirus vector we talked about on the last slide.

Another approach is a retroviral vector, lentivirus, by the Shenzhen Genoimmune Medical Institute. Again, the principles are very similar in that it uses the constructed virus with the protein injected and also with some infusions, perhaps to get slightly different responses, including T cells and dendritic cells. This is a different approach, rather than one that's for neutralizing antibodies.

The Sinovac vaccine is a very old-fashioned approach, that's in the lower right-hand corner. That's where the virus is simply grown up, it goes under in an activation protocol much like influenza virus, it is grown in eggs and activated, and then injected to develop immune responses, hopefully without disturbing the protein structures too much to get appropriate responses. That is also in progress right now.

The Moderna one, which has been in the news, is a novel one. There's been no such vaccine before, but this is where message RNA is injected, and in that message is the spike protein. This protein is taken up by cells and then synthesized in much the same way a virus would be, but without the whole viral apparatus.

As I mentioned, there's been so much emphasis on spike proteins and antibodies generated, but a paper was just published earlier this week that I thought was highly interesting. It looked at a group of people who recovered from the coronavirus and found certain “epitope pools” — think of them as similar to antibodies, but for T-cells. These are very specific to this coronavirus, and they found that most patients develop CD4 and helper cells and CD8 cells as part of their recovery. These T-cell responses were not only focused on the spike protein, but also had very strong response to two other proteins made by the virus, including M, N, and others in what are called “open reading frames.” One thought is that a successful virus response from a vaccine might not just make neutralizing antibodies, which has been

such a focus, but perhaps throwing in some of these proteins in hopes of engendering T-cell responses might give a better response.

This week there's been a lot of press, and indeed optimism. The stock market went up. it has been said because of this announcement of this mRNA vaccine by Moderna. I think many of us have given some pause, though, because much like remdesivir, we only have a press release. Everyone's very hungry for information, but I would just tell people to hit the pause button because this is the first phase of vaccine manufacture, and we have very limited information.

The press release said that 46 patients received a low dose or a higher dose of the mRNA. They did develop antibody responses, but we are told that only eight developed neutralizing antibodies. These are tests where you need to be in a BSL 3 lab, testing the antibodies to see if they actually help neutralize the virus from killing cells and tissue culture. This is the gold standard for antibodies, and these are the kinds you would like against a viral infection, but we have very limited information.

This is a new vaccine approach in humans. We don't have any safety data yet; in fact we don't have any information on who these volunteers were. Were they young? Were they old? Were the responses uniform? But interestingly, they are jumping ahead, passing through phase 2 to phase 3 with this announcement that they're going to trial this in over 30,000 people. That's quite a large number, and I think it's highly interesting. Remember that to prove safety, you'll want to test the vaccine a large number of patients, so this is very good.

In testing efficacy, you'll want to make sure that these participants are potentially exposed to the virus to prove that you're actually preventing infection compared to people who got a sham vaccine. It's always hard to prove efficacy sometimes, unless you have vast numbers of people, because you'll want to make sure they're circulating the virus, and everyone's trying to avoid getting the virus, so it'll be interesting to see how the efficacy side of this moves ahead. Until we see more information, I wouldn't say there's a cause for unbridled optimism at present. This phase 3 trial is supposed to start in July.

Another approach, besides just jumping ahead to a very large phase 3 trial, is one of the thoughts that the WHO and even the NIH and the CDC said, that hopefully we'll get a vaccine in 12 to 18 months, is the human viral challenge. One of the problems with studies such as phase 3 is to prove the efficacy, people have to be exposed to the virus and have it prevented, and people who didn't get the vaccine still get the illness to prove that it works. The human challenge model is different. Some people have questioned whether it is ethical, but this can significantly shorten the time frame if people are intentionally exposed to the virus after they've been able to mount an antibody response for a couple months and then they're challenged with the virus to see if there's protection.

The advantages are that you can test the vaccine on a much smaller number of people, you can see if it truly works, and then roll it out in much larger phases to phase 3, sort of the reverse of when you've already determined if it's efficacious and now you're looking for safety, whereas the other way, you're sort of determining safety and efficacy at the same time. It's a way that might winnow down if you have 90 or 100 candidates, but it could be very hard to do 30,000-70,000 person vaccine studies well. This is being proposed and discussed, but unfortunately a lot of the vaccine coordination is not at the kind of high level that involves multiple countries, so we'll see how this more fragmented approach goes.

In the closing minutes, I want to briefly discuss the interesting twists that the coronavirus still provides on many facets we're still learning about. We've always thought children and teenagers are not prone to getting severe illness. You can see that of the total cases, and we're not sure we're looking very hard at children. Children have a very low percentage of total cases of coronavirus in many countries. The largest pediatric study I know of was done in China with a little over 2000 patients, and you can see that most patients had very mild illness and only 5-6% had severe or critical illness. Overall, this is a different picture than we tend to see in older patients or those with comorbidities.

What has gotten everyone's attention are reports not only in France, but I think the sheer number of children, over 100, who were reported in New York City who became ill. They seemed to present with a Kawasaki syndrome-like illness, multiple problems, rashes, high fevers, perhaps cardiac dysfunction, and so on. It was interesting in that most of these children no longer had evidence of COVID-19, but had positive antibodies, meaning they probably had an infection a month earlier or six weeks earlier. We may be seeing more of this kind of delayed response, maybe an abnormal immune response, that we do sometimes see with certain viral infections, acute demyelinating encephalitis, encephalomyelitis, is one such condition that is a post-infectious consequence.

The definition, which some people call the COVID-19 inflammatory syndrome in children, others have called it the multisystem inflammatory syndrome in children, or MIS-C.

It's young adults, teenagers, and children with fever and evidence of inflammation, high sedimentation rate, ferritin, and so on. Multisystem illness, meaning that it's targeting not just the lung, but other organs with no conceivable other diagnosis. There is at least some evidence either of a positive PCR assay, although most of these children don't have it or, by history at least, if they don't have it at that time, but probably more that the serology is positive suggests recent infection. Much more to be learned about the pathogenesis and whether some of the treatments that Kawasaki syndrome uses, like intravenous immunoglobulin or other immunomodulators, may be useful here. It remains to be played out, but it seems to be a rare problem overall. It's interesting that even children who aren't at risk for severe health problems may have issues.

So, Faith, I think we have time for some questions.

FAITH ROGERS: Thank you for those updates! We will now continue to the listener Q&A. To submit questions, please send them 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.

Okay, Dr. Auwaerter, first question: why are nasal swabs for COVID-19 still being done if a saliva test is a better look at the lower respiratory tract, the saliva test has equal reliability to the nasal swab test, and when the nasal swab test is extremely uncomfortable compared to a saliva test?

DR. AUWAERTER: I think because the nasopharyngeal swab is sort of the respiratory gold standard. It's been used for influenza for a long time, and other respiratory viruses. I think a lot of institutions are very comfortable with this approach. People have been trained, systems have been validated, and so on. The saliva tests require that institutions validate studies to make sure that it's as reliable as commercial labs, so I think until that comes on board and is much more reliable, this is something that still is not widespread, but I think will replace the NP swab at least for COVID-19. Now I will say as we move into

the respiratory season in the fall, I think we'll be back to the NP swab because you'll have to look for influenza and respiratory syncytial virus as well. I'll also mention it's clear that for COVID-19 at least, lower respiratory secretions have somewhat better yield it seems, but many institutions haven't validated sputum tests. We have at Johns Hopkins, a few other places have as well, but we're left with the NP swab in many areas.

FAITH ROGERS: Thank you. Next question: is there any consensus about antibody testing, such as which test is reliable and what the utility of antibody testing is?

DR. AUWAERTER: I'm not sure there's a consensus. Clearly, some tests have been clinically validated with higher numbers and look more accurate. I do think whatever lab you're using for this, you want to be very sure that it's using a reliable test. For me, I think if you see a positive value and you know someone's had a COVID-19 type illness, it can give you some accurate information. Where people have been a little hesitant is understanding whether people are generating the kind of protective antibody responses. I think in all likelihood they are, or if they were to reacquire that illness, it probably wouldn't be as severe, but we don't yet have the ability to say that a certain test means that people will be completely protected partially protected. That's only going to come with more experience. No tests I know of have been recommended by any guideline authorities yet.

FAITH ROGERS: Great. Our next learner question: is there any possible association between vitamin D deficiency and COVID-19 as hypothesized recently?

DR. AUWAERTER: You know, this is an interesting area because I still do a little bit of internal medicine and patients often have low vitamin D levels. I think this will need to play out a bit more. People as they age often have lower vitamin D levels. Whether it's truly deficiency is hotly debated among many endocrinologists, so stay tuned. I certainly wouldn't take extra vitamin D at this stage. A lot of these associations are being worked out, so I think it's too early to give you much information on that.

FAITH ROGERS: Okay, thank you, and this is our last question: the CDC announced the childhood vaccinations are down significantly based on purchasing data. Should all routine vaccinations, including the shingles vaccine, be carried out on schedule regardless of local COVID-19 activity?

DR. AUWAERTER: I think there is a risk now, if children are not back in school or day care, the risks are not as high, but this is going to lead to a backlog. For adults, many offices yet aren't fully open. I'm a big fan of immunizations, including the shingles vaccine, and of course that's not a pediatric vaccine; it's for adults over age 50. I think we should play catch-up on that. I think the message here is that, because offices have been closed, don't forget about where your children are in the vaccine schedule. Some of them will have to have some make-ups performed, so that just shouldn't be lost.

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 of 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.