FAITH ROGERS: Hello, I am Faith Rogers, host of today's program, COVID-19: Keeping Up with a Moving Target. This is the April 29 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 evenings and Friday mornings. 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/CE information.

To attest for CME/CE credit please visit COVID19.Dkbmed.com. There you will also find all of our previous COVID-19 programs and have access other free CME/CE programs on a range of topics.

Here are the learning objectives:

- **Describe natural history of COVID-19 illness**
- **Discuss risks, management, and precautions associated with COVID-19**
- **Discuss status of antibody testing**

With us today we have Dr. Auwaerter, Clinical Director of the Division of Infectious Diseases at Johns Hopkins School of Medicine. Dr. Auwaerter, thank you for joining us.

DR. AUWAERTER: Thank you, Faith, and I want to remind everyone that this program is only brought about through the generous support of DKBmed, the Postgraduate Institute for Medicine, and also the Institute for Johns Hopkins Nursing. You can find additional CME and educational resources at COVID19.DKBmed.com.

As we are now past our fourth month of knowing about the novel coronavirus, the landscape in the United States has certainly changed dramatically. Always first in urban centers, some areas may be past peak. People who model this infection say that others will not occur until late June, especially in more rural and Midwestern locations, so I think this results in some difficult messaging as a country. We also have competing federal and state governments trying to help give best advisory patterns and recommendations, so I think this is something where, as you talk to your patients and advise them, you have to sort through a lot of information to give advice.

New issues that have come about in the past week have included the Centers for Disease Control updating their symptoms that might be typical of COVID-19. Pretty much from the start, people are quite familiar with the respiratory illness with fever, cough, and any kind of difficulty breathing. That may be up to two weeks after exposure. At this point, with community spread, I don't think the time frame is particularly helpful.

However, what's been added now are other symptoms that are consistent with the flu-like illness which probably most have been screening for at any rate, including chills or shaking chills, myalgia, headache, and then signs of upper respiratory illness such as a sore throat. Although some have also described a kind of runny nose and sinus congestion, it's probably not as frequent as we see with influenza. Not unique to this virus but probably much more common is a new loss of taste or smell, which go hand in

hand. We've certainly seen that in patients in Baltimore and it's something I've even had patients well aware of from news reports that tip them off that they're having evolving coronavirus infection.

One of the reasons for a rapid spread has continued to be the debate about whether there's airborne or aerosolization of the virus vs droplet, but weighing in on the asymptomatic shedding side of the equation is some information that was published recently in the New England Journal from a nursing home which, as you might think about any kind of high-density environment with people at risk for infection, this is quite concerning and similar to what may have been happening on cruise ships and so on. This report found that after the first resident's COVID-19 was diagnosed, two thirds of patients became infected. This was before there was as much awareness and organization for infection control.

The real take-home point here is that over half of people at the time that whole nursing facility was evaluated were without symptoms at the time that they had viral RNA measured on swabs from their nasopharynx. From this time frame, they were able to determine this higher-density environment that the doubling time of infection was only about three and a half days, which was certainly shorter than in the community, and very high copy numbers of the virus were found. I think this speaks to how this virus could spread very rapidly, and we see this in a much grander scale in the New York metropolitan area. Many people feel that the sheer density of people probably has contributed, along with public transportation.

The fatality rate in the home with older residents was very much the same as seen in the intensive care unit, with a fatality rate of about 26%. About 20% of staff, despite using PPE, still tested positive. The conclusion is that it was asymptomatic shedding rather than some kind of aerosolization that probably contributed to this, but that debate is ongoing.

That whole aspect of asymptomatic shedding may also speak to seroprevalence studies, and there is great debate, which we'll launch into momentarily, about how accurate antibody testing is for COVID-19. I think the really important part from some press releases, from the public health department in LA and also New York City, is that a substantial number of people have been noted to be seropositive for COVID-19, even if there is some cross-reaction and false positives.

But what I wanted to get to is, if you look at New York City, almost 20% of their sample size was positive, and a similar number in the suburb on Long Island. But in upstate New York, the confirmed cases are only 4%. So you get the idea that there are no doubt significant amounts of asymptomatic infection. No one knows the precise numbers, but estimates are 25% to 50% or even more may not have symptoms that would identify them as being ill.

When people don't know they're ill, this is no doubt a big magnifier, but many people have looked to antibodies as sort of armor; that is, once you've had the infection you can then go on about your business and feel that you won't be reinfected or expose other people. I think that's *probably* true if you've had confirmed COVID-19, at least for the first couple of years until we learn more about the durability of immunity, which is probably both antibody- and cell-mediated. However, the problem is when people don't know they had COVID-19 and they're asking for antibody testing.

This concept of immunity passports, which I think was popularized by several European countries as a mechanism to get people back to work. The key point is that testing accuracy has not evolved to the point where we can guarantee sufficient safety that a positive result truly means someone won't acquire

or spread the virus. I think this is fundamentally important as you talk to patients or patients ask you to give them the test. I am very hesitant to order the test for people because I think it can give them a false impression, and I'll tell you why.

This report is just a preprint, it hasn't been peer reviewed, but it's from a very legitimate group of scientists who have looked at a lot of tests. As you know, the FDA had liberalized the ability to manufacture and issue new commercial tests for COVID without a lot of testing other than analytical testing initially. Compared here are 12 different antibody assays, and the top level news I would tell you is that only two kits did a good job (marked with the stars) at accurately identifying samples from confirmed COVID positive patients. You can see them there.

On the other hand, the false positive rates were about 5% on average with these assays and some of the more poorly performing ones had false positive ranges in 11% to 16%. I don't think this is yet an acceptable range to allow these kinds of tests to stand as immunoprotective tests, but we may get to this point in the next few months. Tests may be further validated and checked to see if there are neutralizing antibodies, but it's also true that cell-mediated immunity, which is much more difficult to check, is also responsible. This checkerboard pattern indicates there's very poor agreement among the tests, which tells you there's a fair amount of variability there.

I would be very careful. If the test is ordered, ask the laboratory which one they're ordering and try to see what kind of clinical data is available. Has it been validated against known samples of COVID-positive patients? Against known negatives? Actually, it'd also be wonderful to check it against people who have had other coronavirus infections, although that's a much harder sample to analyze. This would all be in an effort to see if it's truly accurate of COVID-19 positivity. We know even coronavirus immunity is not terribly cross-protective, if at all, and can cause false positive testing. So, first warning there.

Moving to therapeutics, this gives you an idea, at least as of last week, a graphic showing what we know to date from studies that have either been published or in preprint, and there are many more. I think I've seen over 500 trials at a minimum listed that are in various stages of conception or progress, but at the moment we still don't have clear insights on any drugs that are very helpful, despite what I think is a shotgun process initially for trying so many different strategies, which I think is very appropriate, since we know so little how to handle this virus.

One drug initially last week had some bad news, because the trial in China was halted. They couldn't enroll subjects. The thought was they weren't seeing much of a signal. However, just today a few hours ago, Dr. Anthony Fauci mentioned that a trial sponsored by the NIH was favorable. I haven't looked at the data, but as an antiviral this is promising, and I think you'll see some mixed news. The trials in China have found it difficult to recruit patients, in part because they're already on a number of medications, and so on. When you give an antiviral, it depends how well it works at the stage of illness, and the earlier the better, as we know with influenza; I think that'll be true for this coronavirus infection, as well. Stay tuned, and hopefully we'll update with some additional information next week.

Dealing with the cytokine storm of coronavirus, a number of immune-based strategies are undergoing testing. A trial at the Jenner Institute that looked at an anti il-6 receptor blocker initially in phase 2 was deemed not helpful. This was true for patients who were not yet ill enough to require intubation in the ICU, although people who did have the critical illness in the ICU did have at least positive trend on subset analysis. This is an adaptive trial, so it will continue to study this drug further in the critical care

population. Interestingly, tocilizumab, which is the drug that's been used more off-label for this coronavirus, there is at least a press release of a small, randomized controlled trial from France that reported positive results. We await that information. There are some glimmers of hope, compared to some of the earlier pieces where you had uncontrolled trials and it was very difficult to interpret whether these drugs would be helpful.

Lastly, you'll hear a lot of different information from the federal government, state governments, and other experts as we try to move and open up businesses and move out of lockdowns. Each state will probably behave differently, some more conservative, others less, so I think when we advise our patients, we have to almost do in an individual analysis on patients who are quite at risk. I think there'll be a false sense of security by many that, just because lockdowns are no longer in place, the virus will be less likely to be acquired. That may not be the case, so for the most vulnerable, I would urge people to remain at home and minimize contacts.

Remember, acquiring this virus is strictly a game of numbers. The more people you see, the more likely you have an opportunity to acquire the virus. If you do venture out, masks are very helpful to help prevent spreading the virus to others. If there's an opportunity for better-quality masks, especially for elderly and the very at-risk, I might advise the N95 variety, for example. There are even discussions by the CDC and WHO as we get better supplies of more protective masks about whether there will be a change in recommendations. Of course, with supply chain problems, they did not want the general population trying to get N95 masks which would be needed for first responders, but I think this is under some reconsideration. We shall see.

Also, we'll see an increase in COVID-19 cases, there's no doubt, and in some of the states that are liberalizing it's unclear whether they've really had their peak illnesses. I don't think in good conscience there can be large group events, sporting events, stadiums, parades, these sorts of things. Schools and universities represent a very tough aspect of trying to understand how they can go back to normal now. I would not advise going to those, even if somehow they are allowed to occur.

So thanks again for listening. I think we have some questions.

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

The first question asks: is there a standardized questionnaire or noninvasive screening tool that we should be using when screening people? All I see out there are subjective questions about people feeling ill in the past 72 hours and being in contact with someone who's been ill in the past 14 days. Is there anything a little more specific and discriminatory?

DR. AUWAERTER: The standardized screening with the additional symptom items that I outlined from the Centers for Disease Control. Many facilities, including ours, have already incorporated those into a brief questionnaire. This is what we do, screening everybody who comes into a building for example, and I don't know of anything that's more specific. Anyone who's positive, we will check for swab testing. The real question, especially with contact tracing coming up in some states, is that even asymptomatic people in a household might also be screened.

FAITH ROGERS: Thank you. Next question: what is the thinking behind why children seem to not be as vulnerable to this virus?

DR. AUWAERTER: There are a number of theories, and I would outline them as follows: for one, children may not yet have a very significant immune response, in the sense of making them ill, but they seem to handle the virus very similarly to the Epstein-Barr virus, for example, which in younger children doesn't usually cause mononucleosis but becomes a latent virus. That's not the case with this coronavirus, but clearly in children some viruses don't seem to stimulate the vigorous immune responses.

The other aspect of it is that adults have already seen some other coronaviruses and other infections and seem to mount, in some, a much more vigorous response. I believe there may be particular signatures, either from the virus or from certain hosts that might trigger this intense inflammation, which is why most people get ill, unless they have a severe immune deficiency, for example. So children luckily and blessedly are not very ill, but they probably are effective transmitters of the virus because they're not ill and people are not taking such good care around them. It's another reason why this virus is so successful.

FAITH ROGERS: Okay, our next question: other than the respiratory tract secretions, has COVID-19 virus been found in blood or other bodily fluids?

DR. AUWAERTER: This virus has been identified, at least the viral RNA, in feces. The significance of this isn't clear. We don't yet know if it's infectious. I doubt this is a traditional fecal-oral spread to this kind of virus, which is how hepatitis A virus is spread, although I wouldn't rule it out. That's probably fundamentally the one that I think has been most identified.

Some people are wondering whether there's perinatal transmission, I think most people feel this is not routinely the case. Certainly, almost all respiratory viruses, including influenza, don't seem to have any predilection for the fetus. Of course, if the mother is very ill, that can certainly affect a pregnancy, but it doesn't look like there's likely transmission through the placenta.

FAITH ROGERS: Thank you, and this is our last question: can you please comment on the reports of strokes in COVID-19 patients? Whether the clotting is because of direct attack on blood vessel or caused by patients' immune response, and, similarly, clots being found in veins vs arteries?

DR. AUWAERTER: I think there are probably aspects of both. I'm not a hematologist, but there are increasing reports of hypercoagulable states, especially in people in the critical phases of illness, although there's some question whether it's at any higher rate than people who are in similar critical phases of illness from other diseases, but I think the intense inflammation is also contributory. You can see leaks and other things that are probably a consequence of this, as well.

Overall, it's likely combinations of both. Some have advocated in very high-risk populations like sickle-cell disease that they have high-intensity anticoagulation prophylaxis. But this I'll also mention: disseminated intravascular coagulation, or DIC, is another particular attribute that some suffer in critical illness, and this can also lead to paradoxical and abnormal clotting.

FAITH ROGERS: Thank you again, Dr. Auwaerter, for those very important updates. As a reminder, to claim CME or 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.

Don't forget to access our resource center on COVD19.dkbmed.com. There, 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 featuring Sue Hansen, a Clinical Nurse Specialist at Harborview Medical Center in Seattle. We will send out an email when it is available later this week. Any questions for Dr. Auwaerter or Sue Hansen can be submitted by sending to QA@dkbmed.com. Thanks again for joining us and thank you for your dedication to your patients with COVID-19. Thank you, Dr. Auwaerter.

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